Targeted Immune Modulators for Rheumatoid Arthritis and Ankylosing Spondylitis: Update

Systematic Review

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Executive Summary

Background

Targeted immune modulators (TIMs) are a category of medications used to treat certain types of immunological and inflammatory diseases, including rheumatoid arthritis (RA) and ankylosing spondylitis.[1]

TIMs work by selectively blocking mechanisms involved in the inflammatory and immune response, although the specific mechanism varies by TIM.[2] There are 5 predominant mechanisms of action in this class of drugs approved by the US Food and Drug Administration (FDA) for treatment of RA and ankylosing spondylitis[2]:

- Tumor necrosis factor-alpha (TNF-α) inhibitors: adalimumab (Humira), certolizumab pegol (Cimzia), etanercept (Enbrel), golimumab (Simponi/Simponi ARIA), and infliximab (Remicade)
- Interleukin receptor blockers: anakinra (Kineret), sarilumab (Kevzara), secukinumab (Cosentyx), and tocilizumab (Actemra)
- Janus kinase (JAK) inhibitors: baricitinib (Olumiant), tofacitinib (Xeljanz/Xeljanz XR), and upadacitinib (Rinvoq)
- T-cell costimulation inhibitor: abatacept (Orencia)
- CD20 antibody: rituximab (Rituxan)

The FDA recently approved biosimilar agents for adalimumab, etanercept, and infliximab.[3] ABBV-3373,[4] bimekizumab,[5] and peficitinib[6] are pipeline drugs under investigation but not yet approved for the treatment of RA or ankylosing spondylitis. ABBV-3373 is an antibody drug conjugate, bimekizumab an interleukin-17 receptor inhibitor, and peficitinib a JAK inhibitor. JAK inhibitors are the only TIMs that can be administered orally.[2]

In most cases, TIMs are used for the treatment of patients with RA or ankylosing spondylitis who did not achieve an adequate response with conventional disease-modifying antirheumatic drugs.[7,8] Patients who do not achieve adequate symptom relief during a first-line treatment with a TIM agent are usually switched to a TIM agent with a different mechanism of action (second-line treatment).[7,8]

PICOS and Key Questions

This report identifies comparative randomized controlled trials (RCTs) and cohort studies (with sample size and study quality limits modified for this update) evaluating the effectiveness and harms of TIM agents FDA-approved for the treatment of RA and ankylosing spondylitis. Outcomes of interest are measures of clinical improvement and disease remission, quality of life (QoL), adverse events (AEs), serious adverse events (SAEs), and other health outcome measures. This report also evaluates the effectiveness and harms (compared with placebo) of selected pipeline TIM agents.

This review addresses 4 key questions (KQs): the effectiveness and harms of TIMs for RA and ankylosing spondylitis (KQ1 and KQ2), whether outcomes differ by personal characteristics (KQ3), and ongoing studies (KQ4).

Methods

We describe our complete methods in Appendix A. Briefly, for this update, we searched Ovid MEDLINE, Cochrane Library, ClinicalTrials.gov, International Standard Randomised Controlled Trials Number (ISRCTN) registry from January 1, 2019 through July 22, 2021, and several other websites to identify eligible published and ongoing studies.

We rated the risk of bias (RoB) of eligible studies using standard instruments adapted from national and international quality standards.[9-13] We used OpenEpi (version 3.01) to calculate effect estimates and associated 95% confidence intervals (CIs) based on data provided in the study, when not reported by authors. We rated the certainty of evidence (CoE) for each comparison and indication (RA and ankylosing spondylitis) for each major outcome (i.e., QoL, clinical improvement or response, disease remission, overall AEs, and SAEs) using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach.[14,15] The previous Drug Effectiveness Review Project (DERP) systematic review on TIMs was segmented into 3 reports. This report is an update involving only medications for RA and ankylosing spondylitis.

Key Findings

We identified 9 new studies (in 11 articles)[16-24] and carried forward 51 studies[25-76] from the previous report for a total of 60 eligible studies in this update. We identified 2 additional publications on patient-reported outcomes of 2 already included studies.[77,78] All RCTs (except for 2)[20,25] and cohort studies (except for 2)[61,71] evaluated TIM agents among participants with RA. One RCT[25] evaluated TIM agents and another pipeline[20] for ankylosing spondylitis; 2 cohort studies[61,71] assessed TIMs in a mixed population that included participants with RA and ankylosing spondylitis.

Of the 60 eligible studies, 35 were RCTs[17-21,25-32,36,39-59] and 25 were cohort studies.[16,22-24,33-35,37,38,60-76] Among the 35 RCTs, we rated 8 studies[17,21,25,32,36,42,46,56] as high RoB, 3 studies[18-20] as low RoB, and the others as moderate RoB. Among the 25 cohort studies, we rated 1 study[72] as high RoB, 3 studies[23,65,74,75] as low RoB, and the rest as moderate RoB. Outcomes selected for GRADE ratings ranged from very low to high CoE; the majority was low. Generally, outcomes were downgraded for RoB and imprecision (i.e., wide CI because of small sample size).

For the Key Findings section, text displayed in **purple** indicates no differences between the intervention and comparison; **orange** text indicates the intervention was significantly less effective or more harmful than the comparison; and **blue** text indicates the intervention was significantly more effective or less harmful. Appendix D summarizes instruments used to measure outcomes in RA and ankylosing spondylitis trials.

Rheumatoid Arthritis

TIMs as First-line Treatments

- We identified 19 RCTs[18,21,29,30,43-55,77,78] with 15 different head-to-head comparisons and 2 comparisons of combination treatments with monotherapy.
    - *Abatacept vs. adalimumab* (1 RCT[43]): **No significant differences** in response (American College of Rheumatology [ACR] 50), remission (ACR70), or improvements in functional

capacity (Health Assessment Questionnaire-Disability Index [HAQ-DI]) at 48 weeks (moderate CoE for response; low CoE for remission).

- *Abatacept vs. certolizumab pegol* (1 RCT[18]): **No significant differences** in response (European League Against Rheumatism [EULAR] response) or remission (Clinical Disease Activity Index [CDAI] remission) at 24 weeks (moderate CoE for response and remission).
- *Abatacept vs. infliximab* (1 RCT[44]): **No significant differences** in response (ACR50), remission (ACR70), or improvements in functional capacity (HAQ-DI) at 24 weeks (low CoE for response and remission).
- *Abatacept vs. tocilizumab* (1 RCT[18]): **No significant differences** in response (EULAR response) or remission (CDAI remission) at 24 weeks (moderate CoE for response and remission).
- *Adalimumab vs. baricitinib* (1 RCT[29]): Adalimumab was **significantly less effective** than baricitinib for achieving response (ACR20, 61% vs. 70%) and improvements in functional capacity (HAQ-DI of ≥ 0.22, 58% vs. 68%) at 52 weeks. **No significant differences** in remission (Simplified Disease Activity Index [SDAI] < 3.3); high CoE for response; low CoE for remission).
- *Adalimumab vs. certolizumab pegol* (1 RCT[45]): **No significant differences** in response (ACR20) and remission (ACR70) at 12 weeks (high CoE for response; data not reported for remission).
- *Adalimumab vs. etanercept* (2 RCTs[46,47]): **No significant differences** in disease activity and improvements in functional capacity (HAQ-DI, Disease Activity Score-28 [DAS28], Patient Global Assessment) at 24 weeks (very low CoE).
- *Adalimumab vs. sarilumab* (1 RCT[48,79]): Adalimumab was **significantly less effective** than sarilumab for achieving response (ACR50, 30% vs. 46%), remission (CDAI, 3% vs. 7%), improvements in functional capacity (HAQ-DI, −0.43 vs. −0.61), and QoL (Short Form 36-item Health Survey [SF-36], 6.09 vs. 8.75) at 24 weeks (moderate CoE for QoL and response; low CoE for remission).
- *Adalimumab vs. tocilizumab* (2 RCTs[47,49]): Adalimumab was **significantly less effective** than tocilizumab for achieving response (ACR50, 28% vs. 47%) and remission (ACR70, 18% vs. 33%) at 24 weeks. **No significant differences** in QoL at 24 weeks (SF-36, low CoE for all 3 measures). Tocilizumab was also used at a higher dose than FDA-approved.
- *Adalimumab vs. tofacitinib* (3 RCTs[50-52,78]): **No significant difference** in response (ACR50), remission (ACR70), and improvements in functional capacity (HAQ-DI) at 24 weeks (high CoE for response and remission).
- *Adalimumab vs. upadacitinib* (1 RCT[30,77]): Adalimumab was **significantly less effective** than upadacitinib for achieving response (ACR50, 29% vs. 45%), remission (DAS28 < 2.6, 18% vs. 21%), and improvements in functional capacity (HAQ-DI, −0.49 vs. −0.60; $P < .01$) at 12 weeks (high CoE for response and remission).
- *Anakinra vs. TNF-α inhibitors* (1 RCT[21]): **No significant differences** in response (EULAR response, 95% vs. 63%) and remission (EULAR, 50% vs. 25%) at 24 weeks (very low CoE for response and remission).
- *Certolizumab pegol vs. tocilizumab* (1 RCT[18]): **No significant differences** in response (EULAR response) or remission (CDAI remission) at 24 weeks (moderate CoE for response and remission).

- *Etanercept vs. infliximab* (1 RCT[53]): Etanercept was **significantly more effective** than infliximab for achieving response (ACR20, 74% vs. 60%) and improving functional capacity (HAQ-DI, −32.30 vs. −21.60) at 54 weeks. No dose increase was allowed for infliximab (very low CoE for response).
- *Etanercept vs. tocilizumab* (1 RCT[47]): **No significant differences** in clinical improvement (DAS28) and improvement in functional capacity (HAQ-DI) at 24 weeks (very low CoE for clinical improvement).
- *Combination strategies* (2 RCTs[54,55]): **No additional benefits** (response, remission) from the combination of etanercept with abatacept or anakinra compared with etanercept monotherapy (moderate CoE).

TIMs as Second-line Treatments

- We identified 7 RCTs[17,19,32,42,56,57,59] that provided evidence for 6 different head-to-head comparisons of TIM agents and 2 comparisons of TIM combination treatment with TIM monotherapy.
  - *Abatacept vs. TNF-α inhibitors* (adalimumab, etanercept, infliximab, golimumab or certolizumab pegol; (2 RCTs[42,56]): **No significant differences** in clinical improvement (DAS28) and QoL (SF-36) at 52 weeks (very low CoE for QoL; low CoE for clinical improvement).
  - *Abatacept vs. rituximab* (2 RCTs[42,56]): **No significant differences** in clinical improvement (DAS28) and QoL (SF-36) at 52 weeks (very low CoE for QoL; low CoE for clinical improvement).
  - *Abatacept vs. tocilizumab* (1 RCT[32]): **No significant differences** in clinical improvement (DAS28) and functional capacity (HAQ-DI) at 24 weeks (low CoE for clinical improvement).
  - *Abatacept vs. upadacitinib* (1 RCT[19]): Abatacept was **significantly less effective** than upadacitinib for achieving response (DAS28-C-reactive protein [CRP] mean change from baseline, −2 vs. −2.52) and remission (DAS28-CRP < 2.6, 12% vs. 28%) at 24 weeks (high CoE for response; moderate CoE for remission).
  - *Rituximab vs. tocilizumab* (1 RCT[17]): **No significant differences** in clinical improvement (CDAI 50% improvement) at 16 weeks (very low CoE for response).
  - *TNF-α inhibitors (adalimumab, certolizumab pegol, etanercept, infliximab) vs. other TIMs* (1 RCT[57]): Non-TNF-α inhibitors were **significantly more effective** than TNF-α inhibitors for achieving response (odds ratio, 2.06; 95% CI, 1.27 to 3.37) and remission (DAS28 < 2.6, 27% vs. 14%) at 52 weeks (low CoE for both).
  - *Combination therapy (rituximab plus adalimumab or etanercept*; 1 RCT[59]): Combination treatment was **significantly more effective** than TNF-α inhibitor maintenance treatment for achieving response (ACR50, 12% vs. 6%) and remission (DAS28 < 2.6, 18% vs. 6%) at 24 weeks (low CoE for both).
  - *Combination therapy (abatacept plus other TIM vs. other TIM;* 1 RCT[58]): **No significant differences** in functional capacity (HAQ-DI) at 52 weeks (low CoE).

Pipeline Therapies

- We included 5 RCTs that assessed the efficacy and harms of peficitinib compared with placebo for the treatment of RA[26-28,40,41]; 1 RCT also compared peficitinib with etanercept.[40] In addition, we included 1 comparison of combination treatments with monotherapy.[39]
  - *Peficitinib vs. placebo* (5 RCTs[26-28,40,41]): Peficitinib was **significantly more efficacious** than placebo for achieving response (ACR20, 64% vs. 22%) and remission (DAS28-erythrocyte sedimentation rate [ESR] < 2.6, 35% vs. 8%) at 12 weeks. **No significant difference** in overall AEs and SAEs (high CoE for response and remission; moderate CoE for AEs and SAEs).
  - *Peficitinib vs. etanercept* (1 RCT[40]): Peficitinib was **less effective** than etanercept in achieving response (ACR20, 75% vs. 84%) at 52 weeks. **No significant difference** in overall AEs and SAEs (moderate CoE for response; low CoE for AEs and SAEs).
  - *Combination therapies vs. monotherapy* (1 RCT[39]): Combination treatment was **more effective** than monotherapy for achieving response (DAS28-CRP < 3.2, 46% vs. 29%) and remission (DAS28-CRP < 2.6, 26% vs. 8%). **Significantly higher incidence** of overall AEs (79% vs. 59%), but **fewer** SAEs with combination treatment than monotherapy (low CoE for all outcomes).
- For comparative harms (KQ2), we identified 23 RCTs[18,19,21,29-32,36,42-46,48-52,54-56,58,59] with 17 different head-to-head comparisons and 4 comparisons of TIM combination treatment with TIM monotherapy; in addition, we identified 25 cohort studies.[16,22-24,33-35,37,38,60-76] Overall, we observed few differences in harms in head-to-head RCT comparisons of TIM agents. In the following bullets, we focus on statistically significant differences observed in included studies.
  - *Abatacept vs. infliximab* (1 RCT[44]): **Significantly fewer** SAEs with abatacept than infliximab (5% vs. 12%; *P* value not reported) at 24 weeks. **No significant differences** in overall AEs (low CoE for SAEs and moderate CoE for overall AEs).
  - *Abatacept vs. tocilizumab* (1 RCT[18], first-line treatment): **Significantly lower** incidence of overall AEs (80% vs. 95%) for abatacept than tocilizumab at 24 weeks. **No significant differences** in SAEs (low CoE for overall AEs and very low CoE for SAEs).
  - *Abatacept vs. tocilizumab* (1 RCT[32], second-line treatment): **Significantly lower** incidence of overall AEs (28% vs. 60%) for abatacept than tocilizumab at 24 weeks. **No significant differences** in SAEs (low CoE for overall AEs and very low CoE for SAEs).
  - *Adalimumab vs. baricitinib* (1 RCT[29]): **Significantly fewer** SAEs with adalimumab than baricitinib (4% vs. 8%) at 52 weeks. **No significant differences** in overall AEs (low CoE for SAEs and high CoE for overall AEs).
  - *Certolizumab pegol vs. tocilizumab* (1 RCT[18]): **Significantly fewer** overall AEs with certolizumab pegol than tocilizumab (83% vs. 95%) at 24 weeks. **No significant differences** in SAEs (moderate CoE for overall AEs and low CoE for SAEs).
  - *Tocilizumab vs. sarilumab* (1 RCT[36]): **No significant differences** in overall AEs and SAEs at 24 weeks (low CoE for overall AEs and very low CoE for SAEs).
  - *Combination therapies vs. monotherapy* (4 RCTs[54,55,58,59]): Combination of etanercept with abatacept or anakinra resulted in more SAEs (11% vs. 3%) compared with etanercept monotherapy, but **no significant differences** (moderate CoE). Abatacept plus other TIM (adalimumab, anakinra, etanercept, or infliximab) resulted in more SAEs (22% vs. 13%)

compared with other TIM alone but **no significant difference** (low CoE). **Higher proportion of overall AEs** (94% vs. 83%) for combination of rituximab with TNF-α inhibitors compared with TNF-α inhibitor maintenance therapy (low CoE for overall AEs and SAEs).

- For differences in effectiveness and harms in subgroups (KQ3), we identified no relevant subgroup analyses or secondary publications on subgroups.

Ankylosing Spondylitis

- For comparative effectiveness and harms, we identified 1 head-to-head trial.[25]
  - Etanercept *vs. infliximab* (1 RCT[25]): Etanercept was **significantly less effective** for clinical improvement than infliximab (Bath Ankylosing Spondylitis Activity Index [BASDAI], 5.9 vs. 4.8) at 12 weeks. **No significant differences** in weeks 54 and 104 (very low CoE). The RCT reported on discontinuation due to AEs, but it did not provide the overall number of participants with at least 1 AE or SAE.
- The 1 eligible RCT did not report on differences by subgroups (KQ3).
- For efficacy and safety of pipeline drugs, we identified 1 new placebo-controlled trial[20] assessing the efficacy of bimekizumab compared with placebo for the treatment of ankylosing spondylitis.[20]
  - Bimekizumab *vs. placebo* (1 RCT[20]): Bimekizumab 16 mg, 64 mg, 160 mg, and 320 mg were **more effective** than placebo for achieving clinical improvement (BASDAI, −1.7 vs. −2.7 vs. −2.5 vs. −2.9 vs. −1.0)[20] and improvement of functional ability (Bath Ankylosing Spondylitis Functional Index [BASFI], −1.4 vs. −1.9 vs. −1.7 vs. −2.2 vs. −0.6) at 12 weeks (moderate CoE). **No significant difference** in overall AEs and SAEs (low CoE).

Ongoing Studies

- For RA, we identified 16 ongoing comparative effectiveness trials of TIM agents and 1 ongoing placebo-controlled trial of peficitinib.
- For ankylosing spondylitis, we identified 4 eligible ongoing comparative trials

Conclusions

The evidence for the comparative effectiveness and harms for TIM agents provided data on 17 comparisons of TIMs as first-line treatments (including 2 treatment combinations) and 9 comparisons as second-line treatments (including 2 treatment combinations) for RA. Most comparisons were limited to single trials. The CoE for many outcomes was very low or low, precluding definitive conclusions. Evidence rated as moderate or high CoE indicated that baricitinib, sarilumab, and upadacitinib were more effective than adalimumab, and that etanercept was more effective than peficitinib as first-line treatments for RA. As a second-line treatment, abatacept was less effective than upadacitinib (high to moderate CoE). High and moderate CoE indicated lower incidence of overall AEs and SAEs with abatacept and certolizumab pegol than tocilizumab. Significant differences for the incidence of AEs or SAEs of some comparisons were rated as very low or low CoE and need to be interpreted with caution.

The evidence on ankylosing spondylitis was sparse. We identified only 1 high-RoB RCT, which does not allow for definitive conclusions about the comparative effectiveness of etanercept and

infliximab. In addition, 1 placebo-controlled trial indicated general efficacy of the pipeline drug bimekizumab for the treatment of ankylosing spondylitis.

Twenty-one studies of head-to-head comparisons of TIM agents for the treatment of RA (17 studies) and ankylosing spondylitis (4 studies) are currently in progress; 6 will be completed before 2023. Nine studies have been completed, but results have not yet been published. These additional ongoing studies, if published, will likely address important gaps in the evidence and potentially increase our certainty in the evidence for relevant outcomes.

List of Brand Names and Generics

Table 1. Included Drugs and Biosimilars for Treatment of RA and Ankylosing Spondylitis

Generic Name	Trade Name	Mechanism	Route	Approved Population[a]
Approved therapies				
Abatacept	Orencia	CD80/86–CD28 T-cell costimulation modulator	IV, SC	RA
Adalimumab	Humira	TNF-α inhibitor	SC	RA
			SC	Ankylosing spondylitis
Adalimumab-adaz	Hyrimoz	TNF-α inhibitor	SC	Ankylosing spondylitis
			SC	RA
Adalimumab-adbm	Cyltezo	TNF-α inhibitor	SC	Ankylosing spondylitis
			SC	RA
Adalimumab-afzb	Abrilada	TNF-α inhibitor	SC	RA
			SC	Ankylosing spondylitis
Adalimumab-atto	Amjevita	TNF-α inhibitor	SC	RA
			SC	Ankylosing spondylitis
Adalimumab-bwwd	Hadlima	TNF-α inhibitor	SC	RA
			SC	Ankylosing spondylitis
Adalimumab-fkjp	Hulio	TNF-α inhibitor	SC	RA
			SC	Ankylosing spondylitis
Anakinra	Kineret	IL-1 inhibitor	SC	RA
Baricitinib	Olumiant	JAK inhibitor	PO	RA
Certolizumab pegol	Cimzia	TNF-α inhibitor	SC	RA
			SC	Ankylosing spondylitis
Etanercept	Enbrel	TNF-α inhibitor	SC	RA
			SC	Ankylosing spondylitis

Generic Name	Trade Name	Mechanism	Route	Approved Population[a]
Etanercept-szzs	Erelzi	TNF-α inhibitor	SC	RA
			SC	Ankylosing spondylitis
Golimumab	Simponi	TNF-α inhibitor	SC	RA
			SC	Ankylosing spondylitis
Golimumab	Simponi ARIA	TNF-α inhibitor	IV	RA
			IV	Ankylosing spondylitis
Infliximab	Remicade	TNF-α inhibitor	IV	RA
			IV	Ankylosing spondylitis
Infliximab-abda	Renflexis	TNF-α inhibitor	IV	RA
			IV	Ankylosing spondylitis
Infliximab-dyyb	Inflectra	TNF-α inhibitor	IV	RA
			IV	Ankylosing spondylitis
Infliximab-qbtx	Ixifi	TNF-α inhibitor	IV	RA
			IV	Ankylosing spondylitis
Rituximab	Rituxan	Anti-CD20 antibody	IV	RA
Sarilumab	Kevzara	IL-6 receptor inhibitor	SC	RA
Secukinumab	Cosentyx	IL-17A receptor inhibitor	SC	Ankylosing spondylitis
Tocilizumab	Actemra	IL-6 receptor inhibitor	IV, SC	RA
Tofacitinib	Xeljanz	JAK inhibitor	PO	RA
Tofacitinib	Xeljanz XR	JAK inhibitor	PO	RA
Upadacitinib	Rinvoq	JAK inhibitor	PO	RA
Pipeline therapies				
ABBV-3373	NA	TNF-α inhibitor	IV	Under investigation for RA
Bimekizumab	NA	IL-17A and IL-17F receptor inhibitor	IV	Under investigation for ankylosing spondylitis
Peficitinib[b]	NA	JAK inhibitor	PO	Under investigation for RA or ankylosing spondylitis

Notes. [a] *Details of approved indications for each drug can be found in the full prescribing information;* [b] *submitted for FDA approval.*
Abbreviations. IL: interleukin; IV: intravenous; JAK: Janus kinase; NA: not applicable; PO: per os (oral); RA: rheumatoid arthritis; SC: subcutaneous; TNF-α: tumor necrosis factor-alpha; XR: extended release.

Background

Targeted immune modulators (TIMs) are a category of medications used in the treatment of certain types of immunologic and inflammatory diseases, including rheumatoid arthritis (RA), ankylosing spondylitis, psoriatic arthritis, Crohn disease, ulcerative colitis, and plaque psoriasis.[1] The US Food and Drug Administration (FDA) first approved a TIM, infliximab, in 1998, and numerous additional agents including biosimilar TIM agents since then.[2] Table 1 summarizes currently available TIMs approved in the US for RA and ankylosing spondylitis.

TIMs work by selectively blocking mechanisms involved in the inflammatory and immune response.[2] Of the TIMs evaluated for use in RA and ankylosing spondylitis, adalimumab, certolizumab pegol, etanercept, golimumab, and infliximab all bind to both the circulating and transmembrane forms of tumor necrosis factor-alpha (TNF-α), inhibiting its biological activity.[2] Biosimilars are available for adalimumab, etanercept, and infliximab.[3]

Interleukin (IL) -1 and IL-17A, naturally occurring cytokines, have immune and proinflammatory actions.[2] Anakinra is a human recombinant protein and the therapeutic version of a naturally occurring cytokine that competitively blocks the IL-1 receptor, thus blocking various inflammatory and immunological responses.[2] Secukinumab is a human immunoglobulin (Ig) G1 monoclonal antibody that selectively binds to the IL-17A cytokine and inhibits the release of proinflammatory cytokines and chemokines.[2]

The immunosuppressant agent abatacept exerts its immune regulation by interfering with T-lymphocyte activation.[2] Abatacept is a soluble fusion protein consisting of the extracellular domain of human cytotoxic T lymphocyte-associated antigen (CTLA-4) and the modified Fc portion of IgG1.[2]

Rituximab, a chimeric rodent/human monoclonal antibody, works by binding to the CD20 antigen found on the surface of B lymphocytes, which play a role in autoimmune and inflammatory processes.[80] Tocilizumab is a recombinant humanized monoclonal antibody against the IL-6 receptor.[2] Sarilumab, another IL-6 targeted biologic drug, is a fully human monoclonal antibody.[2] Interleukin-6 is a proinflammatory cytokine produced by a variety of cell types including T-cells and B-cells, lymphocytes, monocytes, and fibroblasts.[2]

Baricitinib, tofacitinib, and upadacitinib are orally administered TIMs that act as Janus kinase (JAK) inhibitors.[2,81] Janus kinase are intracellular enzymes that mediate signaling by surface receptors for several important cytokines with pivotal roles in propagation of inflammation.[2]

In addition to the TIMs approved with an indication for RA and ankylosing spondylitis, we considered 3 pipeline drugs in this update. Bimekizumab is an IL-17 receptor inhibitor currently under investigation for the treatment of ankylosing spondylitis.[5] Peficitinib is an orally administered JAK inhibitor; peficitinib has been approved for the treatment of RA in Japan and Korea (but is still under review by the FDA in the US) and targets primarily JAK subtype 3.[82] ABBVIE-3373 is a TNF-α inhibitor under investigation for RA.[4]

State Medicaid program administrators are interested in an updated review of the evidence of the effectiveness and harms of TIMs for RA and ankylosing spondylitis to aid in managing this drug class as the FDA continue to provide additional approvals. The previous review the Drug

Effectiveness Review Project (DERP) commissioned on this topic was completed in April 2020. Further details on RA and ankylosing spondylitis are below.

Rheumatoid Arthritis

RA is an autoimmune disease that affects about 1% of the population worldwide.[83] The exact etiology of RA is not completely understood, but genetic susceptibility factors have been described in certain populations.[83] The hallmarks of the disease are inflammation of the joint lining tissues, with progressive erosion of bone leading to imperfect alignment of the joint and, in most cases, disability.[84] TNF-α plays a central role in the pathobiology of RA.[84,85]

The diagnosis of RA is primarily clinical.[84] Constitutional symptoms, such as fatigue and low-grade fevers, are common before the onset of joint swelling and pain.[84] Joint stiffness is almost always present and is frequently most severe after periods of prolonged rest.[84] The disease tends to affect the small joints of the hands and feet first in a symmetric pattern, but other joint patterns are often seen.[84] Severe disease may be complicated by involvement of the eyes, lungs, nerves, and the cardiovascular system.[84]

Ankylosing Spondylitis

Ankylosing spondylitis is a chronic inflammatory arthritis with primary involvement of the axial skeleton and prominent involvement of the spine and sacroiliac joints.[86] Peripheral joint disease can occur and may be destructive in some cases.[86] The sacroiliac joints are usually the first joints involved, and the disease is characterized by progressive involvement of the spine.[86] Enthesitis, inflammation of the insertion of ligaments and tendons on bones, is one of the hallmarks of the disease.[86]

Existing diagnostic criteria are relatively insensitive and have limited utility in clinical practice.[87] Radiographs of the sacroiliac joints, when abnormal, can be useful in assessing the presence of ankylosing spondylitis; however, the frequently appear normal in early disease.[87] Over time, patients with ankylosing spondylitis develop progressive fusion of the spine with resultant deformity and disability.[86] Because TNF-α has been implicated in the pathophysiology of ankylosing spondylitis, biologic agents targeting TNF-α are now recommended as part of the standard treatment approach.[8,88]

PICOS

Population

- Adult outpatients with moderate to severe RA
- Adult outpatients with ankylosing spondylitis (axial spondyloarthropathy)

Interventions

- Table 1 presents the TIMs and respective biosimilars that have been approved by the FDA for the treatment of RA and ankylosing spondylitis, along with select pipeline drugs likely to be approved in the near future.

Comparators

- For FDA-approved drugs: another listed TIM intervention (head-to-head comparison)
- For pipeline drugs: any listed TIM, standard of care, placebo

Outcomes

- Health outcomes
  - Quality of life (QoL)
  - Functional capacity
  - Productivity, ability to sustain employment
  - Clinical improvement
  - Disease remission
  - Pain
  - Reduction in the number of swollen or tender joints
  - Reduction in disease-related hospitalizations
  - Reduction in disease-specific mortality
  - Rebound/flare
  - Joint destruction
  - Steroid withdrawal
  - Dose escalation
- Harm outcomes
  - Overall adverse events (AEs)
  - Withdrawals due to AEs
  - Overall serious adverse events (SAEs)
  - Specific AEs and SAEs (e.g., serious infectious diseases)
  - Mortality

Study Designs

- RCTs with ≥ 12-week study duration
- Retrospective and prospective cohort studies comparing an intervention type to another for harms outcomes
  - Minimum study duration of 12 weeks
  - Minimum total sample size of 10,000
  - Statistical analysis adjusted for any confounders
  - Studies providing direct statistical comparisons between drugs

Key Questions

1. What is the comparative effectiveness of TIMs to treat RA or ankylosing spondylitis?
2. What are the comparative harms of TIMs to treat RA or ankylosing spondylitis?
3. Do the included drugs differ in their effectiveness or harms in the following subgroups: age and racial groups, gender, patients with comorbidities, patients taking other commonly prescribed drugs, or in patients with early vs. established disease?
4. What are the characteristics of ongoing studies for TIMs to treat RA or ankylosing spondylitis?

Methods

We describe our complete methods in Appendix A. Briefly, for this update, we searched Ovid MEDLINE, Cochrane Library, ClinicalTrials.gov, International Standard Randomised Controlled Trials Number (ISRCTN) registry from January 1, 2019, through July 22, 2021, and several other websites to identify eligible published and ongoing studies. We rated the risk of bias (RoB) of eligible studies using standard instruments adapted from national and international quality standards.[9-13] We used OpenEpi (version 3.01) to calculate risk difference (RD), risk ratio (RR), and associated 95% confidence intervals (CIs) based on data provided in the study when not reported by authors. We rated the certainty of evidence (CoE) for each drug and indication (RA or ankylosing spondylitis) for up to 5 selected outcomes (i.e., disease remission, clinical improvement or response, QoL, AEs, SAEs) using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach.[14,15] The previous DERP systematic review on TIMs was segmented into 3 reports; this report is an update only involving medications for indications for RA and ankylosing spondylitis.

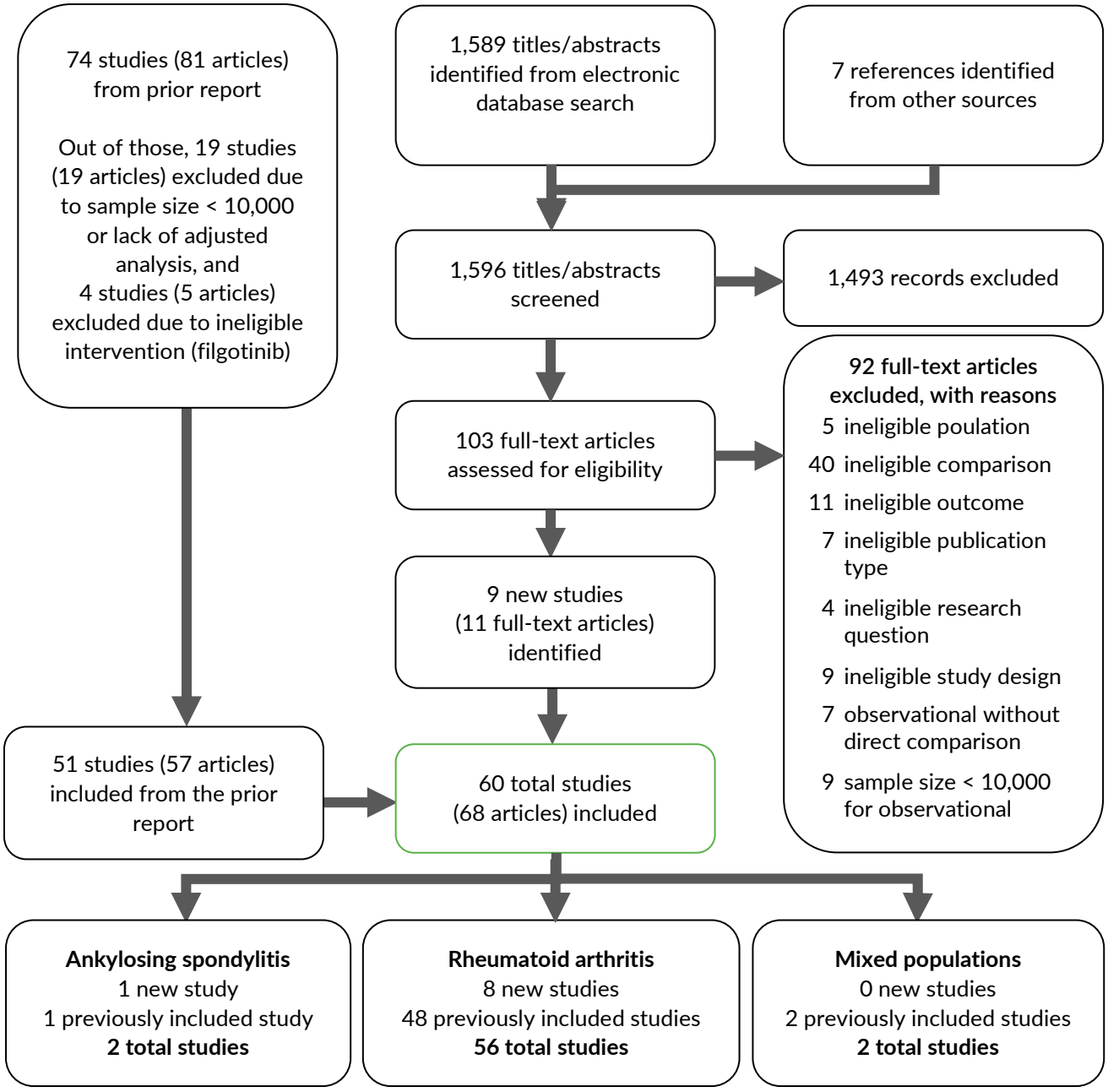
Findings

For this update we included 9 new studies (in 11 publications). Of these 9, 4 were new head-to-head RCTs (in 4 publications[17-19,21]) on the comparative effectiveness and harms of TIM agents that are approved for the treatment of RA or ankylosing spondylitis. We carried forward 24 RCTs[25,29-32,36,42-59] from the prior report for a total of 28 RCTs in this update. We also identified 2 additional publications on patient-reported outcomes of 2 already included studies.[77,78] In addition, we included 1 new placebo-controlled trial[20] and carried forward 6 trials[26-28,40,41] from the previous report on peficitinib and bimekizumab. One of these studies also compared peficitinib with etanercept.[40] In addition, we identified 1 head-to-head trial on bimekizumab (not yet FDA-approved for treatment of RA or ankylosing spondylitis) in combination with certolizumab pegol, compared with certolizumab pegol alone.[39]

Overall, this updated report includes 35 RCTs out of 60 included studies (Figure 1), providing evidence for 25 head-to-head comparisons for the treatment of RA (including 4 combination treatments) and 1 head-to-head comparison[25] for the treatment of ankylosing spondylitis. We rated 8 RCTs[17,21,25,32,36,42,46,56] as high RoB, 3 RCTs[18-20] as low RoB, and the others as moderate RoB, primarily because of extensive manufacturer involvement in study design, execution, and reporting.

We did not identify any studies addressing differences in effectiveness or harms by subgroup (Key Question [KQ] 3). Appendix G. Bibliography of Excluded Studies provides the bibliography of studies identified in the update search but that we excluded at the full-text review stage.

Figure 1. Literature Flow Diagram



Rheumatoid Arthritis

The following sections first present the comparative effectiveness of TIMs as first-line treatments (i.e., no prior treatment with TIMs) and then as second-line treatments (i.e., at least 1 inadequate response to a TIM). All studies enrolled participants with moderate-to-severe RA despite treatment with disease-modifying antirheumatic drugs (DMARDs). Following results of comparative effectiveness studies, we present placebo-controlled evidence on pipeline drugs.

Comparative Efficacy as First-line Treatment (KQ1)

For this update, we identified 2 new RCTs with data on response and remission.[18,21] Overall, we describe findings of 17 RCTs evaluating the comparative effectiveness of TIMs as a first-line treatment.[18,21,29,30,43-55] These studies provided evidence on 15 head-to-head comparisons of TIM agents and 2 comparisons of combination TIM treatment with TIM monotherapy. Appendix B, Table B1 and Table B3 provide detailed study characteristics and results from the included RCTs. The Summary of Findings (GRADE) for these comparisons are presented in Table 2 with detailed evidence profiles in Appendix C. Evidence Grade ProfilesThe rest of this section describes each of the comparisons. Table 3 presents a summary of efficacy outcomes, and Appendix D summarizes instruments used to measure outcomes in RA trials.

Table 2. Summary of Effectiveness Findings (GRADE) for TIMs for First-line Treatment of RA

Outcome Number of Studies / Number of Participants	Certainty of Evidence	Relationship	Rationale
Abatacept vs. adalimumab			
Clinical improvement or response 1 RCT[43] / 646	Low ●●○○	No difference between groups	Downgraded 1 level for RoB and 1 level for imprecision
Disease remission 1 RCT[43]) / 646	Low ●●○○	No difference between groups	Downgraded 1 level for RoB and 1 level for imprecision
Abatacept vs. certolizumab pegol			
Clinical improvement or response 1 RCT[18] / 407	Moderate ●●●○	No difference between groups	Downgraded 1 level for imprecision
Disease remission 1 RCT[18] / 407	Moderate ●●●○	No difference between groups	Downgraded 1 level for imprecision
Abatacept vs. infliximab			
Clinical improvement or response 1 RCT[44] / 321	Low ●●○○	No difference between groups	Downgraded 2 levels for very serious imprecision
Disease remission 1 RCT[44] / 321	Low ●●○○	No difference between groups	Downgraded 2 levels for very serious imprecision
Abatacept vs. tocilizumab			
Clinical improvement or response 1 RCT[18] / 392	Moderate ●●●○	No difference between groups	Downgraded 1 level for imprecision
Disease remission 1 RCT[18] / 392	Moderate ●●●○	No difference between groups	Downgraded 1 level for imprecision
Adalimumab vs. baricitinib			
Clinical improvement or response 1 RCT[29]) / 817	High ●●●●	Lower proportion improved with adalimumab than baricitinib	Not downgraded
Disease remission 1 RCT[29]/ 817	Low ●●○○	No difference between groups	Downgraded 2 levels for very serious imprecision

Outcome Number of Studies / Number of Participants	Certainty of Evidence	Relationship	Rationale
Adalimumab vs. certolizumab pegol			
Clinical improvement or response 1 RCTs[45] / 915	High ●●●●	No difference between groups	Not downgraded
Adalimumab vs. etanercept			
Clinical improvement or response 2 RCTs[46,47] / 190	Very low ●○○○	No difference between groups	Downgraded 1 level for RoB and 2 levels for very serious imprecision
Adalimumab vs. sarilumab			
Quality of life 1 RCT[48] / 369	Moderate ●●●○	Smaller improvements for adalimumab than sarilumab	Downgraded 1 level for imprecision
Clinical improvement or response 1 RCT[48] / 369	Moderate ●●●○	Lower proportion improved with adalimumab than sarilumab	Downgraded 1 level for imprecision
Disease remission 1 RCT[48] / 369	Low ●●○○	Lower proportion with remission with adalimumab than sarilumab	Downgraded 2 levels for very serious imprecision
Adalimumab vs. tocilizumab			
Quality of life 1 RCT[49] / 326	Low ●●○○	Similar between groups	Downgraded 1 level for indirectness and 1 level for imprecision
Clinical improvement or response 2 RCTs[47,49] / 369	Low ●●○○	Lower proportion improved with adalimumab than tocilizumab	Downgraded 1 level for indirectness and 1 level for imprecision
Disease remission 2 RCTs[47,49] / 369	Low ●●○○	Lower proportion with remission with adalimumab than tocilizumab	Downgraded 1 level for indirectness and 1 level for imprecision
Adalimumab vs. tofacitinib			
Clinical improvement or response 3 RCTs[50-52] / 2,247	High ●●●●	No difference between groups	Not downgraded
Disease remission 2 RCTs[50,52] / 1,863	High ●●●●	No difference between groups	Not downgraded
Functional capacity 1 RCT[52,78] / 1,146	High ●●●●	No difference between groups	Not downgraded
Adalimumab vs. upadacitinib			
Quality of life and functional capacity 1 RCT[30,77] / 978	High ●●●●	Less improvement with adalimumab than upadacitinib	Not downgraded
Clinical improvement or response 1 RCT[30] / 978	High ●●●●	Lower proportion improved with	Not downgraded

Outcome Number of Studies / Number of Participants	Certainty of Evidence	Relationship	Rationale
		adalimumab than upadacitinib	
Disease remission 1 RCT[30] / 978	High ●●●●	Lower proportion with remission for adalimumab than upadacitinib	Not downgraded
Anakinra vs. TNF-α inhibitors			
Clinical improvement or response 1 RCT[21] / 39	Very low ●○○○	No differences between groups	Downgraded 1 level for Rob and 2 levels for very serious imprecision
Disease remission 1 RCT[21] / 39	Very low ●○○○	No difference between groups	Downgraded 1 level for RoB and 2 levels for very serious imprecision
Certolizumab pegol vs. tocilizumab			
Clinical improvement or response 1 RCT[18] / 391	Moderate ●●●○	No difference between groups	Downgraded 1 level for imprecision
Disease remission 1 RCT[18] / 391	Moderate ●●●○	No difference between groups	Downgraded 1 level for imprecision
Etanercept vs. infliximab			
Clinical improvement or response 1 RCT[53] / 32	Very low ●○○○	Relationship cannot be determined	Downgraded 1 level for RoB and 2 levels for very serious imprecision,
Etanercept vs. tocilizumab			
Clinical improvement or response 1 RCT[47] / 43	Very low ●○○○	No difference between groups	Downgraded 1 level for RoB and 2 levels for very serious imprecision
TIM combination therapies vs. TIM monotherapy			
Clinical improvement or response 2 RCTs[54,55] / 365	Moderate ●●●○	No additional clinical benefit of combined therapy	Downgraded 1 level for imprecision

Abbreviations. GRADE: Grading of Recommendations, Assessment, Development, and Evaluation approach; RA: rheumatoid arthritis; RCT: randomized controlled trial; RoB: risk of bias; TIM: targeted immune modulator; TNF-α: tumor necrosis factor-alpha.

Table 3. Brief Evidence Table for Efficacy Outcomes in Adults for TIMs as First-line Treatment for RA

Authors, Year Trial Name	Study Design Number of Participants[a]	Duration	Comparisons	Primary Outcome	Secondary Outcomes	Population	Results	Risk of Bias
Abatacept vs. adalimumab								
Weinblatt et al., 2013[43] Schiff et al., 2014[89] Fleischmann et al., 2015[90] AMPLE	Open-label RCT 646	48 and 104 weeks	• Abatacept 125 mg QW SC + MTX • Adalimumab 40 mg Q2W SC + MTX	ACR20	ACR50, ACR70, DAS28, HAQ	Active RA for less than 5 years; had failed MTX treatment; mean disease duration: 1.8 years	No difference in efficacy for abatacept and adalimumab	Moderate
Abatacept vs. certolizumab pegol								
Hetland et al., 2020[18] NORD-STAR	Pragmatic, open-label RCT 812	24 weeks	• Abatacept 125 mg QW SC+ MTX • Certolizumab pegol 200 mg Q2W SC (loading dose 400 mg at week 0, 2, and 4) + MTX • Tocilizumab 8 mg/kg QM IV or 162 mg QW SC + MTX • Active conventional treatment	CDAI after 24 weeks	CDAI after 12 weeks, DAS28, SDAI, EULAR response	Treatment-naïve participants with moderate to severe early (less than 2 years) RA	No difference in efficacy for abatacept and certolizumab pegol	Low
Abatacept vs. infliximab								
Schiff et al., 2008[44] ATTEST	RCT 431	24 weeks	• Abatacept ~10 mg QM IV +MTX • Infliximab 3 mg Q2M IV +MTX • Placebo + MTX	DAS28	ACR 20/50/70, HAQ, SF-36	Active RA for at least 1 year; had failed MTX treatment; mean disease duration, 7.9 years	No difference in efficacy for abatacept and infliximab after 6 months. Greater response for abatacept than infliximab after 12 months (note: no	Moderate

Authors, Year Trial Name	Study Design Number of Participants[a]	Duration	Comparisons	Primary Outcome	Secondary Outcomes	Population	Results	Risk of Bias
							dose adjustment allowed for infliximab)	
Abatacept vs. tocilizumab								
Hetland et al., 2020[18] NORD-STAR	Pragmatic, open-label RCT 812	24 weeks	• Abatacept 125 mg QW SC+ MTX • Tocilizumab 8 mg/kg QM IV or 162 mg QW SC + MTX • Certolizumab pegol + MTX 200 mg Q2W SC (loading dose 400 mg at week 0, 2, and 4) • Active conventional treatment	CDAI after 24 weeks	CDAI after 12 weeks, DAS28, SDAI, EULAR response	Treatment-naïve participants with moderate to severe early RA (less than 2 years) RA	No difference in efficacy for abatacept and tocilizumab	Low
Adalimumab vs. baricitinib								
Taylor et al., 2017[29] RA-BEAM	RCT 1,305	52 weeks	• Adalimumab 40 mg Q2W SC + MTX • Baricitinib 4 mg QD PO + MTX • Placebo +MTX	ACR20 after 12 weeks	ACR50/70, DAS28-CRP, HAQ-DI, SDAI, CDAI	Active RA with inadequate response to MTX; mean disease duration, 10 years	Adalimumab less effective than baricitinib	Moderate
Adalimumab vs. certolizumab pegol								
Smolen et al., 2016[45] EXXELERATE	RCT 915	12 weeks	• Adalimumab 40 mg Q2W + MTX • Certolizumab pegol 400 mg Q2W SC + MTX until week 4, then 200 mg Q2W SC + MTX until week 12	ACR20	ACR50/70, DAS28-ESR, HAQ-DI	Active RA with inadequate response to MTX; prognostic factors for severe disease progression; mean disease	No difference in efficacy for adalimumab and certolizumab pegol	Moderate

Authors, Year Trial Name	Study Design Number of Participants[a]	Duration	Comparisons	Primary Outcome	Secondary Outcomes	Population	Results	Risk of Bias
						duration, 5.8 to 6.0 years		
Adalimumab vs. etanercept								
Jobanputra et al., 2012[46] NR	Pragmatic, open-label RCT 125	52 weeks	• Adalimumab 40 mg Q2W SC + MTX[b] • Etanercept 50 mg QW SC + MTX[a]	Treatment continuation	DAS28-CRP, EQ-5D, PtGA	Active RA with lack of response to at least 2 DMARDs; mean disease duration: 6.0 years	No difference in efficacy for adalimumab and etanercept	High
Kume et al., 2011[47] NR	Open-label RCT 64	26 weeks	• Adalimumab 20 mg Q2W SC • Etanercept 25 mg BIW SC • Tocilizumab 8 mg QM SC	Arterial stiffness	DAS28-ESR, HAQ-DI	Active RA; mean disease duration: 10 months	No difference in efficacy for adalimumab and etanercept	Moderate
Adalimumab vs. sarilumab								
Burmester et al., 2017[48,79] MONARCH	RCT 369	24 weeks	• Adalimumab 40 mg Q2W SC • Sarilumab 200 mg Q2W SC	DAS28-ESR	ACR 20/50/70, FACIT, CDAI, HAQ-DI, SF-36	Active RA with inadequate response or intolerability to MTX and prognostic factors for severe disease progression; mean disease duration, 6.6 to 8.1 years	Adalimumab less effective than sarilumab	Moderate

Authors, Year Trial Name	Study Design Number of Participants[a]	Duration	Comparisons	Primary Outcome	Secondary Outcomes	Population	Results	Risk of Bias
Adalimumab vs. tocilizumab								
Gabay et al., 2013[49] ADACTA	RCT 326	26 weeks	• Adalimumab 40 mg Q2W SC • Tocilizumab 8 mg/kg QM SC	DAS28	HAQ, EULAR, ACR 20/50/70, SF-36	Active RA in participants who did not tolerate MTX; mean disease duration, 6.8 years	Adalimumab less effective than tocilizumab (note: tocilizumab was administered at a higher dose than FDA approved)	Moderate
Kume et al., 2011[47] NR	Open-label RCT 64	26 weeks	• Adalimumab 20 mg Q2W SC • Etanercept 25 mg BIW SC • Tocilizumab 8 mg QM IV	Arterial stiffness	DAS28, HAQ	Active RA; mean disease duration: 10 months	No difference in efficacy for adalimumab and tocilizumab	Moderate
Adalimumab vs. tofacitinib								
van Vollenhoven et al., 2012[50,91] ORAL Standard	RCT 717	48 weeks	• Adalimumab 40 mg Q2W SC +MTX • Tofacitinib 5 mg BID PO + MTX • Tofacitinib 10 mg BID PO + MTX • Placebo + MTX	ACR20	ACR50/70, DAS28, HAQ, SF-36	Active RA with an inadequate response to MTX treatment; mean disease duration, 6.9 to 9.0 years	No difference in efficacy for adalimumab and tofacitinib	Moderate
Fleischmann et al., 2012[51] NR	RCT 384	12 weeks	• Adalimumab 40 mg Q2W SC • Tofacitinib 1 mg BID PO/Tofacitinib 3 mg BID PO • Tofacitinib 5 mg BID PO/Tofacitinib 10 mg BID PO • Tofacitinib 15 mg BID PO • Placebo	ACR20	ACR50/70, DAS28, HAQ, SF-36	Active RA with an inadequate response to MTX treatment; mean disease duration, 7.7 to 10.8 years	Adalimumab less efficacious than tofacitinib	Moderate

Authors, Year Trial Name	Study Design Number of Participants[a]	Duration	Comparisons	Primary Outcome	Secondary Outcomes	Population	Results	Risk of Bias
Fleischmann et al., 2017[52] Strand et al., 2019[78] ORAL Strategy	RCT 1,146	48 and 24 weeks	• Adalimumab 40 mg Q2W SC + MTX • Tofacitinib 5 mg BID PO + MTX • Tofacitinib 5 mg BID PO	ACR50	ACR 20/70, DAS28, CDAI, HAQ, PtGA, Pain, HAQ-DI, FACIT-F, SF-36 PCS and MCS	Active RA with an inadequate response to MTX treatment; mean disease duration, 5.4 to 6.1 years	No difference in efficacy for adalimumab and tofacitinib	Moderate
Adalimumab vs. upadacitinib								
Fleischmann et al., 2019[30] Strand et al., 2021[77] SELECT-COMPARE	RCT 1,629	12 weeks	• Adalimumab 40 mg Q2W SC + MTX • Upadacitinib 15 mg QD PO + MTX • Placebo + MTX	ACR20, DAS28-CRP < 2.6	ACR50, DAS28-CRP < 3.2, Pain VAS, HAQ-DI, PtGA, FACIT-F, SF-36, AM stiffness, RA-WIS	Active RA with an inadequate response to MTX treatment; mean disease duration, 8 years	Adalimumab less effective than upadacitinib	Moderate
Anakinra vs. TNF-α inhibitors								
Ruscitti et al.,2019[21] TRACK	Open-label RCT 39	24 weeks	• Anakinra 100 mg QD SC + MTX • TNF-α (adalimumab, certolizumab pegol, etanercept, infliximab, or golimumab) + MTX	Change in HbA1c% levels	DAS28, SDAI, EULAR clinical response and remission, PGA	Moderate to severe RA with inadequate response to MTX and affected by type 2 diabetes mellitus	Anakinra more effective than TNF- α inhibitors	High

Authors, Year Trial Name	Study Design Number of Participants[a]	Duration	Comparisons	Primary Outcome	Secondary Outcomes	Population	Results	Risk of Bias
Certolizumab pegol vs. tocilizumab								
Hetland et al., 2020[18] NORD-STAR	Pragmatic, open-label RCT 812	24 weeks	• Certolizumab pegol 200 mg Q2W SC (loading dose 400 mg at week 0, 2, and 4) + MTX • Tocilizumab 8 mg/kg QM IV or 162 mg QW SC + MTX • Abatacept 125 mg QW SC+ MTX • Active conventional treatment	CDAI after 24 weeks	CDAI after 12 weeks, DAS28, SDAI, EULAR response	Treatment naïve participants with moderate to severe early (less than 2 years) RA	No difference in efficacy for certolizumab pegol and tocilizumab	Low
Etanercept vs. infliximab								
De Filippis et al., 2006[53] NR	Open-label RCT 32	52 weeks	• Etanercept 25 mg BIW SC +MTX • Infliximab 3 mg at 0, 2, and 6 weeks and then every 2 months IV +MTX	ACR20	ACR50/70, HAQ-DI	Active RA for at least 2 years; had failed MTX treatment; mean disease duration, NR	Etanercept more effective than infliximab (Note: no dose adjustment allowed for infliximab)	Moderate
Etanercept vs. tocilizumab								
Kume et al., 2011[47] NR	Open-label RCT 64	26 weeks	• Adalimumab 20 mg Q2W SC • Etanercept 25 mg BIW SC • Tocilizumab 8 mg QM SC	Arterial stiffness	DAS28-ESR, HAQ-DI	Active RA; mean disease duration, 10 months	No difference in efficacy for etanercept and tocilizumab	Moderate

Authors, Year Trial Name	Study Design Number of Participants[a]	Duration	Comparisons	Primary Outcome	Secondary Outcomes	Population	Results	Risk of Bias
Combination strategies								
Genovese et al., 2004[54] NR	RCT 244	26 weeks	• Etanercept 25 mg BIW SC + MTX • Etanercept 25 mg BIW SC + Anakinra 100 mg QD SC + MTX • Etanercept 25 mg QW SC + Anakinra 100 mg QD SC + MTX	ACR50	ACR 20/70, SF-36	Active RA for at least 6 months; stable MTX regimen; mean disease duration, 10 years	No additional benefit from etanercept + anakinra vs. etanercept monotherapy	Moderate
Weinblatt et al., 2007[55] NR	RCT 121	26 weeks	• Abatacept 2 mg days 1, 15, and 30 and then every 4 weeks IV + etanercept 25 mg SC BIW • Etanercept 25 mg SC BIW + placebo	ACR20	ACR50/70, HAQ-DI	Chronic RA; on etanercept for at least 3 months; mean disease duration, 12.9 years	Limited additional benefit from abatacept + etanercept vs. etanercept monotherapy	Moderate

Notes. [a] Total number of randomized participants; [b] Because this was a pragmatic trial, not all participants were on methotrexate background therapy. Abbreviations. ACR 20/50/70: American College of Rheumatology, numbers refer to percentage improvement; AM stiffness: morning stiffness; BID: dose delivered twice daily; BIW: dose delivered twice weekly; CDAI: Clinical Disease Activity Index; DAS28: 28-joint Disease Activity Score; DAS28-CRP: 28-joint Disease Activity Score using C-reactive protein; DAS28-ESR: 28-joint Disease Activity Score using erythrocyte sedimentation rate; DMARD: disease-modifying antirheumatic drug; EULAR: European League Against Rheumatism; EQ-5D: European Quality of Life-5 Dimensions Questionnaire; FACIT(-F): Functional Assessment of Chronic Illness Therapy (-Fatigue); FDA: US Food and Drug Administration; HAQ (-DI): Health Assessment Questionnaire (-Disability Index); HbA1c: glycated hemoglobin; IV: intravenous administration; kg: kilogram; mg: milligram; MTX: methotrexate; NORD-STAR: Nordic Rheumatic Disease Strategy Trials and Registries; PGA: Physician Global Assessment; PtGA: Patient Global Assessment; PO: per os (oral administration); Q2M: dose delivered every 2 months; Q2W: dose delivered every 2 weeks; QD: dose delivered daily; QM: dose delivered monthly; QW: dose delivered weekly; RA: rheumatoid arthritis; RA-WIS: Work Instability Scale for rheumatoid arthritis; RCT: randomized controlled trial; SC: subcutaneous administration; SDAI: Simple Disease Activity Index; SF-36: Short Form 36-item Health Survey; SF-36 MCS: Short Form 36-item Health Survey mental component summary; SF-36 PCS: Short Form 36-item Health Survey physical component summary; TIM: targeted immune modulator; VAS: Visual Analog Scale; vs.: versus.

Abatacept vs. Adalimumab

We did not identify any new RCTs for this update.

One moderate-RoB, open-label, noninferiority, RCT (AMPLE [Abatacept versus Adalimumab Comparison in Biologic-Naïve RA Subjects with Background Methotrexate], N = 646) compared abatacept (125 mg weekly) to adalimumab (40 mg every other week) in combination with methotrexate.[43] The study was funded by the manufacturer of abatacept.[43] The primary outcome measure was the American College of Rheumatology 20% improvement (ACR20) response at 12 months.[43] At study endpoint, ACR20 response rates were similar between participants treated with abatacept and adalimumab (65% vs. 63%; *P* value not reported [NR]).[43]

Other efficacy outcomes were also similar for participants in the 2 treatment groups. At 1 year, participants in both groups had similar ACR50 (50% improvement in ACR measure; 46% vs. 46%; *P* value NR) and ACR70 (70% improvement in ACR measure; 29% vs. 26%; *P* value NR) responses.[43] Likewise, participants treated with abatacept had similar improvements on Disease Activity Score 28 (DAS28; −2.30 vs. −2.27) and the Health Assessment Questionnaire-Disability Index (HAQ-DI; −0.60 vs. 0.58) compared with participants on adalimumab.[43]

At 2 years, the ACR50 (45% vs. 47%; *P* value NR) and ACR70 (31% vs. 29%; *P* value NR) responses were still similar between participants receiving abatacept and those treated with adalimumab.[89] Disease activity (assessed with DAS28, Clinical Disease Activity Index [CDAI]), physical functioning (HAQ-DI), and other patient-reported outcomes such as pain, fatigue, or the ability to perform work were also similar between treatment groups at year 2.[89,90]

Abatacept vs. Certolizumab Pegol

We identified 1 new, low-RoB RCT.[18] The Nordic Rheumatic Diseases Strategy Trials and Registries (NORD-STAR) was a multicenter, pragmatic, observer-blinded trial, that enrolled treatment-naïve participants from 29 rheumatology departments in Denmark, Finland, Iceland, the Netherlands, and Sweden.[18] NORD-STAR compared various treatment strategies (including conventional DMARDs and TIMs), 2 of which were abatacept (125 mg subcutaneously weekly; N = 204) and certolizumab pegol (200 mg every other week; N = 203).[18] Participants in both treatment groups received up to 25 mg methotrexate background therapy per week.[18] The primary outcome of the trial was remission (CDAI < 2.8) at 24 weeks.[18] Participants treated with abatacept or certolizumab pegol achieved similar remission rates at endpoint (56.3% vs. 52.6%; *P* value NR).[18] Secondary endpoints, such as DAS28 remission (74.0% vs. 77.2%, *P* value NR) or EULAR good response (84.9% vs. 86.7%; *P* value NR), were also similar.[18]

Abatacept vs. Infliximab

We did not identify any new RCTs for this update.

The ATTEST (Abatacept or infliximab compared with placebo, a Trial for Tolerability, Efficacy, and Safety in Treating RA) study, was a moderate-RoB RCT that allocated 431 participants to abatacept (10 mg/kg every 4 weeks), infliximab (3 mg/kg every 8 weeks), or placebo.[44] All participants were on methotrexate background therapy.[44] The primary outcome (DAS28-CRP [C-reactive protein]) yielded similar reductions in scores between participants treated with abatacept or infliximab at 6 months (−2.53 vs. −2.25; *P* value NR).[44] ACR50 (40% vs. 37%;

P value NR) and ACR70 (21% vs. 24%; *P* value NR) response rates were also not significantly different between treatment groups.[44] Likewise, improvements in physical functioning between participants treated with abatacept or adalimumab were not significantly different.[44]

After a double-blind extension phase of up to 1 year, significantly more participants achieved an ACR20 response on abatacept than on infliximab (72% vs. 56%; *P* value NR); ACR50 and ACR70 responses were numerically improved for participants on abatacept than infliximab, but differences did not reach statistical significance (ACR50, 46% vs. 36%; *P* value NR; ACR70, 26% vs. 21%; *P* value NR).[44] Likewise, measures of physical functioning and health-related QoL measures (HAQ-DI, Short Form 36-item Health Survey [SF-36]) improved statistically significantly more with abatacept than with infliximab treatment.[44] However, we note that infliximab was administered at a fixed-dose regimen throughout the entire study whereas infliximab efficacy trials have shown that up to 30% of participants require dose increases.

Abatacept vs. Tocilizumab

We identified 1 new RCT (NORD-STAR) that we rated as low RoB, and described in more detail in the abatacept vs. certolizumab pegol section above.[18] NORD-STAR compared various treatment strategies in treatment-naïve participants with early RA, 2 of which were abatacept (125 mg subcutaneously weekly; N = 204) and tocilizumab (8 mg/kg every 4 weeks intravenously or 162 mg every week subcutaneously; N = 188).[18] Participants in both treatment groups received up to 25 mg methotrexate background therapy per week.[18] Participants treated with abatacept or tocilizumab achieved similar remission rates (CDAI < 2.8) at endpoint (56.3% vs. 48.7%; *P* value NR) after 24 weeks.[18] Secondary endpoints, such as DAS28 remission (74.0% vs. 73.0%, *P* value NR) or EULAR good response (84.9% vs. 82.2%; *P* value NR), were also similar.[18]

Adalimumab vs. Baricitinib

We did not identify any new RCTs for this update.

The previous report included 1 moderate-RoB RCT for this update. The RA-BEAM trial, a multinational phase 3, double-blind study, randomized 1,305 participants to adalimumab (40 mg every other week), baricitinib (4 mg once daily), or placebo.[29] All participants received background therapy with methotrexate. The study was funded by the manufacturer of baricitinib and lasted 52 weeks.[29] The primary endpoint was the ACR20 response at week 12.[29] Significantly fewer participants in the adalimumab than baricitinib treatment group achieved a response (61% vs. 70%; *P* = .01) at endpoint.[29] Likewise, participants treated with adalimumab had significantly lower changes from baseline in DAS28-CRP than participants in the baricitinib group (−1.95 vs. −2.24; *P* < .001).[29] Additionally, significantly fewer achieved HAQ-DI score improvements of at least 0.22 at 52 weeks (58% vs. 68%; *P* < .01).[29] Remission rates (Simplified Disease Activity Index [SDAI] ≤ 3.3; 7% vs. 8%; *P* value NR) and HAQ-DI score improvement of at least 0.22 at 12 weeks (71% vs. 75%; *P* value NR) were not different between the 2 treatment groups[29] The statistically significant differences between treatment groups were maintained through week 52.[29]

Adalimumab vs. Certolizumab Pegol

We did not identify any new RCTs for this update.

The EXXELERATE study randomized 915 participants with active disease despite methotrexate treatment who had prognostic factors for severe disease progression (positive rheumatoid factor or anticyclic citrullinated peptide antibody or both) to adalimumab (40 mg once every 2 weeks) or certolizumab pegol (400 mg at weeks 0, 2, and 4, then 200 mg once every 2 weeks).[45] All participants remained on methotrexate background treatment.[45] The study, sponsored by the manufacturer of certolizumab pegol, was rated as moderate RoB.[45] After 12 weeks, participants in the adalimumab and the certolizumab pegol groups had similar ACR20 (71% vs. 69%; *P* = .47), ACR50 (data NR), and ACR70 (data NR) response rates.[45] The study did not report any outcomes data for functional capacity at 12 weeks.[45] After 12 weeks, nonresponders in each treatment arm were switched to the opposite treatment[45] (see section on effectiveness of TIMs as second-line treatments).

Adalimumab vs. Etanercept

We did not identify any new RCTs for this update.

The previous reviews included 2 open-label RCTs, 1 rated as moderate RoB[47] and the other as high RoB[46] comparing adalimumab with etanercept.

The moderate-RoB study was a small (N = 64), open-label, RCT comparing adalimumab monotherapy (40 mg every 2 weeks), etanercept monotherapy (25 mg twice a week), and tocilizumab monotherapy (8 mg/kg every 4 weeks) to assess changes in arterial stiffness.[47] As secondary outcomes, this study assessed changes on the HAQ-DI and the DAS28-ESR (erythrocyte sedimentation rate) after 24 weeks of treatment.[47] The statistical analysis was performed as a "completers analysis" only; however, only few participants dropped out of the study (2 people in the adalimumab group and 1 person in the etanercept group).[47] Consequently, results of the completers analysis are probably similar to an intention-to-treat analysis. After 24 weeks, participants in the adalimumab and the etanercept groups had similar improvements on the HAQ-DI score (0.69 vs. 0.68; *P* value NR) and the DAS28-ESR (−2.12 vs. −2.84; *P* value NR).[47] The study did not report response or remission rates.[47]

The second trial (N = 125) was a pragmatic, open-label RCT that we rated as high RoB because of a high loss to follow-up.[46] After 52 weeks, participants in the adalimumab and etanercept groups had similar improvements in the Patient Global Assessment (PtGA) and DAS28-CRP.[46]

Adalimumab vs. Sarilumab

We did not identify any new RCTs for this update.

The previous report included 1 RCT, the MONARCH trial.[48,79] MONARCH was a moderate-RoB, double-blinded, phase 3 RCT that enrolled 369 participants with active RA who were intolerant to methotrexate or had an inadequate response to methotrexate treatment.[48,79] We rated the study as moderate RoB because of extensive manufacturer involvement in study design, execution, and reporting.[48] Participants were randomized to adalimumab monotherapy (40 mg once every 2 weeks) or sarilumab monotherapy (200 mg once every 2 weeks).[48] Participants did not receive methotrexate background therapy. The manufacturer of sarilumab funded the study.[48] After 24 weeks, participants treated with adalimumab had statistically significantly lower changes on the DAS28-ESR than participants who received sarilumab (−2.20 vs. −3.28;

P < .001).[48] Likewise, participants on adalimumab monotherapy had significantly lower ACR50 response rates (30% vs. 46%; *P* = .002) and CDAI remission rates (3% vs. 7%; *P* = .047) than participants assigned to sarilumab monotherapy.[48]

This study also assessed differences for several patient-reported outcomes that measure functional capacity or QoL.[79] Adalimumab monotherapy resulted in smaller improvements for most patient-reported outcomes than sarilumab monotherapy.[79] For example, for the HAQ-DI (−0.43 vs. −0.61; *P* < .005) and the SF-36 physical component score ([PCS], 6.09 vs. 8.75; *P* < .001), participants on adalimumab monotherapy had significantly smaller improvements than participants on sarilumab.[79]

Adalimumab vs. Tocilizumab

We did not identify any new RCTs for this update.

The previous report included 2 moderate-RoB trials, a double-blinded RCT[49] and a small, open-label RCT[47]; both compared adalimumab monotherapy (40 mg every 2 weeks) with tocilizumab monotherapy (8 mg/kg every 4 weeks).

The manufacturer of tocilizumab funded the ADACTA (ADalimumab ACTemrA) trial; this trial enrolled 326 participants who were unable to tolerate methotrexate.[49] The primary endpoint was the change in DAS28-ESR from baseline to week 24.[49] After 24 weeks, participants treated with adalimumab had statistically significantly smaller improvements on the DAS28-ESR than participants treated with tocilizumab (−1.8 vs. −3.3; *P* < .001).[49] Likewise, fewer participants treated with adalimumab achieved remission (DAS28-ESR < 2.6, 11% vs. 40%; *P* < .001), ACR50 response (28% vs. 47%; *P* < .001), or ACR70 response (18% vs. 33%; *P* = .002) than participants on tocilizumab.[49] Mean changes on the HAQ-DI (−0.5 vs. −0.7; *P* = .07) and the SF-36 PCS (7.6 vs. 9.2; *P* = .16) were similar between the adalimumab and tocilizumab groups.[49] We note that in this trial tocilizumab was used at a higher dosage than the FDA has approved.[49] Because the dosing equivalence is questionable, findings should be interpreted cautiously.

Results of the small, open-label RCT showed no difference between participants treated with adalimumab or tocilizumab.[47] After 24 weeks, participants in the adalimumab and the tocilizumab groups had no difference in improvements on the HAQ-DI (0.69 vs. 0.70; *P* value NR) and the DAS28-ESR (−2.12 vs. −2.10; *P* value NR).[47] The statistical analysis was a completers analysis only; however, only a few participants dropped out of the study (2 people in the adalimumab group and 1 person in the tocilizumab group).[47]

Adalimumab vs. Tofacitinib

We did not identify any new RCTs for this update, but included a new publication on patient-reported outcomes of the Oral Rheumatoid Arthritis Trial (ORAL) Strategy trial.[78]

The previous report included 3 moderate-RoB, double-blinded, RCTs[50-52] that assessed the comparative benefits and harms of adalimumab and tofacitinib in participants with RA who had an inadequate response to methotrexate treatment. The manufacturer of tofacitinib funded all 3 trials; 1 trial was a phase 2b dose-ranging study.[51] We rated the studies as moderate RoB because of extensive manufacturer involvement in study design, execution, and reporting.[51]

The largest of the 3 RCTs (ORAL Strategy trial) was a noninferiority, moderate-RoB, double-blinded RCT that enrolled 1,146 participants with active RA despite treatment with conventional DMARDs.[52,78] The study randomized participants to 1 year of treatment with adalimumab (40 mg every 2 weeks plus methotrexate), tofacitinib (5 mg twice daily plus methotrexate), or tofacitinib monotherapy (5 mg twice daily).[52] The primary outcome was ACR50 response after 6 months.[52] At 6 months, participants treated with adalimumab and tofacitinib in combination with methotrexate achieved similar ACR50 response rates (44% vs. 46%; *P* value NR); ACR50 response for participants with tofacitinib monotherapy was numerically lower (38%; *P* value NR).[52] The combination treatment of tofacitinib and methotrexate reached formal noninferiority compared with adalimumab and methotrexate combination treatment (noninferiority boundary: −13 percentage points).[52] Tofacitinib monotherapy did not achieve noninferiority (i.e., no combination with methotrexate).[52] At 12 months, 46% of participants in the adalimumab and 48% in the tofacitinib combined with methotrexate groups had an ACR50 response.[52] Likewise, similar proportions reported remission (DAS28-ESR < 2.6) at 6 months (28% vs. 31%; *P* value NR) and 12 months (35% vs. 30%; *P* value NR).[52] The publication by Strand and colleagues assessed differences for several patient-reported outcomes that measured functional capacity (HAQ-DI) or pain after 6 months.[78] Adalimumab or tofacitinib plus methotrexate and tofacitinib monotherapy resulted in similar improvements for most patient-reported outcomes.[78] The change from baseline in Functional Assessment of Chronic Illness Therapy–Fatigue scores was significantly smaller in participants in the adalimumab plus methotrexate group than the tofacitinib plus methotrexate group (−6.07 vs. −7.59; *P* < .05).[78]

Two other moderate-RoB, double-blinded RCTs reported on the comparative benefits and harms of adalimumab and tofacitinib in participants with RA who had an inadequate response to methotrexate treatment.[50,51] The ORAL Standard trial enrolled 717 participants with active RA who experienced an incomplete response to methotrexate treatment and were randomized to adalimumab (40 mg every other week), tofacitinib 5 mg (twice daily), tofacitinib 10 mg (twice daily), or placebo.[50,91] Tofacitinib 10 mg twice daily is not an FDA-approved dosage. All treatment groups received methotrexate background therapy.[50,91] At 6 months, participants treated with adalimumab or the 2 tofacitinib regimens had similar ACR20 response rates (adalimumab, 47%; tofacitinib 5 mg, 52%; tofacitinib 10 mg, 53%).[50] ACR50 and ACR70 responses and HAQ-DI changes were also similar among the 3 treatment groups.[50]

The dose-ranging study reported substantially lower ACR20 response rates after 12 weeks of treatment for participants treated with adalimumab than for those on tofacitinib 5 mg or 10 mg (36% vs. 59% vs. 71%; *P* value NR).[51]

Adalimumab vs. Upadacitinib

We did not identify any new RCTs for this comparison, but included a new publication of the SELECT-COMPARE trial summarizing patient-reported outcomes.[77]

The SELECT-COMPARE trial was a global, phase 3, double-blinded, moderate-RoB RCT that enrolled 1,629 patients with active RA despite treatment with methotrexate.[30] The study randomized participants to adalimumab (40 mg every other week), upadacitinib (15 mg once daily), or placebo.[30] All participants received methotrexate background therapy. The manufacturer of upadacitinib funded the study, which lasted 52 weeks.[30] The primary endpoints

were the proportion with ACR20 response and the proportion of participants achieving a DAS28-CRP score of < 2.6 after 12 weeks of treatment.[30] At week 12, adalimumab was significantly less effective than upadacitinib in both primary endpoints (ACR20, 63% vs. 71%; *P* < .05; DAS28-CRP < 2.6, 18% vs. 29%; *P* < .001).[30] Likewise, participants treated with adalimumab had significantly lower ACR50 response rates (29% vs. 45%; *P* < .001) and changes from baseline on HAQ-DI (−0.49 vs. −0.60; *P* < .01) than participants treated with upadacitinib.[30] Adalimumab was also statistically significantly less effective than upadacitinib to improve most patient-reported outcomes (Functional Assessment of Chronic Illness Therapy–Fatigue scale, HAQ-DI, PtGA, Pain Visual Analogue Scale, SF-36 PCS).[77]

Anakinra vs. TNF-α Inhibitors

We included 1 new, high-RoB, open-label RCT for this update.[21] The trial enrolled 39 participants with type 2 diabetes mellitus who had moderate to severe RA and an inadequate response to methotrexate.[21] The trial did not receive any funding. Patients were randomly assigned to weekly subcutaneous anakinra 100 mg (N = 22) or TNF-α inhibitors (N = 17; adalimumab, certolizumab pegol, etanercept, golimumab, or infliximab; dosages not reported).[21] The primary outcome for effectiveness was the change in percent glycated hemoglobin (HbA1c) levels.[21] We rated the study as high RoB because outcome assessors, participants, and investigators were not blinded.[21]

At 24 weeks, participants treated with anakinra achieved numerically higher response (EULAR response, 95.0% vs. 62.5%; odds ratio [OR], 1.47; 95% CI, 0.95 to 2.26) and remission (EULAR remission 50% vs. 25%; OR, 1.93; 95% CI, 0.73 to 5.10) than TNF-α inhibitors, but the difference did not reach statistical significance.[21] Likewise, the differences in changes from baseline in SDAI and DAS28 scores were not statistically significant between groups (−27.09 vs. −20.93 and −2.72 vs. −2.12, respectively; *P* values NR).[21]

Certolizumab Pegol vs. Tocilizumab

We identified 1 new RCT (NORD-STAR), rated as low RoB and described in more detail above.[18] NORD-STAR compared various treatment strategies in treatment-naïve participants with early RA, 2 of which were certolizumab pegol (200 mg subcutaneously every other week; N = 203) and tocilizumab (8 mg/kg every 4 weeks intravenously or 162 mg every week subcutaneously; N = 188).[18] Participants in both treatment groups received up to 25 mg methotrexate background therapy per week.[18] The primary outcome of the trial was remission (CDAI < 2.8) at 24 weeks.[18] Participants treated with certolizumab pegol or tocilizumab achieved similar remission rates at endpoint (52.6% vs. 48.7%; *P* value NR).[18] Secondary endpoints, such as DAS28 remission (77.2% vs. 73.0%, *P* value NR) or EULAR good response (86.7% vs. 82.2%; *P* value NR), were also similar.[18]

Etanercept vs. Infliximab

We did not identify any new RCTs for this update.

The previous report included a moderate-RoB, small (N = 32), open-label RCT comparing etanercept (25 mg twice weekly) with infliximab (3 mg/kg, weeks 0, 2, 6, and every 2 months).[53] Participants in this trial had confirmed RA for longer than 2 years, did not respond adequately to DMARDs, and were on a stable dose of methotrexate.[53] Although infliximab had a faster onset of action than etanercept, more participants on etanercept achieved ACR20 response after 54

weeks (74% vs. 60%; *P* value NR); changes were similar for the HAQ-DI (−32.3 vs. −21.6; *P* value NR).[53] The trial did not report data on ACR50 or ACR70 response rates.[53] We note that in this trial, the dosage of infliximab (3 mg/kg) was fixed for 54 weeks at the lower end of the recommended regimen (3 to 10 mg/kg), while infliximab efficacy trials have shown that up to 30% of participants require dose increases. Therefore, results should be interpreted with caution.

Etanercept vs. Tocilizumab

We did not identify any new RCTs for this update.

The previous report included a small (N = 64), moderate-RoB, open-label RCT comparing etanercept monotherapy (25 mg twice weekly), tocilizumab monotherapy (8 mg/kg every 4 weeks), and adalimumab monotherapy (40 mg every other week) to assess changes in arterial stiffness.[47] As secondary outcomes, this trial also assessed changes on the HAQ-DI and the DAS28-ESR after 24 weeks of treatment.[47] Statistical analyses were completers analyses only; however, only a few participants dropped out of this trial (1 person each in the etanercept and tocilizumab group).[47] Consequently, results of the completers analyses are probably similar to an intention-to-treat-analysis. After 24 weeks, participants in the etanercept and the tocilizumab groups had similar improvements on the HAQ-DI score (0.68 vs. 0.70; *P* value NR) and the DAS28-ESR (−2.84 vs. −2.10; *P* value NR).[47]

Combination Therapies

We did not identify any new RCTs for this update.

The previous report included 2 trials that determined the potential for additive or synergistic effects of combination therapies of 2 TIMs; together, they provide data on 363 total participants.[54,55] The larger study, a moderate-RoB, 24-week RCT, did not detect any synergistic effects for treatment with a combination of etanercept (25 mg/week or 50 mg/week) and anakinra (100 mg/day) compared with monotherapy etanercept (25 mg twice per week).[54] Overall, 242 participants on stable doses of methotrexate treatment were enrolled. At endpoint, combination treatment did not lead to greater efficacy than etanercept alone (ACR50, 31% vs. 41%; *P* = .91).[54]

The second trial, examining a combination of abatacept (2 mg/kg on days 1, 15, and 30 and every 4 weeks thereafter) and etanercept (25 mg twice weekly) compared with abatacept monotherapy (2 mg/kg), reached similar conclusions.[55] The combination was associated with increased SAEs but only limited additional clinical benefit (ACR50, 26% vs. 19%; *P* value NR).[55]

Comparative Efficacy as Second-line Treatments (KQ1)

We identified 7 RCTs evaluating the comparative effectiveness of TIMs as a second-line treatment.[17,19,32,42,56,57,59] These studies provided evidence on 6 head-to-head comparisons of TIM agents and 2 comparisons of TIM combination treatment against TIM monotherapy. The Summary of Findings (GRADE) for these comparisons are in Table 4, with detailed evidence profiles in Appendix C; Table 5 presents a summary of efficacy outcomes. Appendix B, Table B1 and Table B3 provide detailed study characteristics and results from the included RCTs. The rest of this section describes each of the comparisons.

Table 4. Summary of Effectiveness Findings (GRADE) for TIMs for Second-line Treatment of RA

Outcome Number of Studies / Number of Participants	Certainty of Evidence	Relationship	Rationale
Abatacept vs. TNF-α inhibitors			
Quality of life 1 RCT[56]) / 93	Very low ●○○○	No difference between groups	Downgraded 1 level for RoB and 2 levels for very serious imprecision
Clinical improvement 2 RCTs[42,56] / 176	Low ●●○○	No difference between groups	Downgraded 2 levels for very serious imprecision
Abatacept vs. rituximab			
Quality of life 1 RCT[56] / 93	Very low ●○○○	No difference between groups	Downgraded 1 level for RoB and 2 levels for very serious imprecision
Clinical improvement 2 RCTs[42,56] / 174	Low ●●○○	No difference between groups	Downgraded 1 level for RoB and 1 level for imprecision
Abatacept vs. tocilizumab			
Clinical improvement 1 RCT[32] / 132	Low ●●○○	No difference between groups	Downgraded 1 level for RoB and 1 level for imprecision
Functional capacity 1 RCT[32] / 132	Low ●●○○	No difference between groups	Downgraded 1 level for RoB and 1 level for imprecision
Abatacept vs. upadacitinib			
Clinical improvement 1 RCT[19] / 612	High ●●●●	Greater clinical improvement with upadacitinib than abatacept	Not downgraded
Remission 1 RCT[19] / 612	Moderate ●●●○	Higher proportion of remission with upadacitinib than abatacept	Downgraded 1 level for imprecision
Rituximab vs. tocilizumab			
Clinical improvement 1 RCT[17] / 164	Very low ●○○○	No difference between groups	Downgraded 1 level for RoB and 2 levels for very serious imprecision
TNF-α inhibitors vs. other TIMs			
Clinical improvement 1 RCT[57] / 300	Low ●●○○	Higher proportion of improvement with non-TNF-α inhibitors than TNF-α inhibitors	Downgraded 1 level for RoB and 1 level for imprecision
Remission 1 RCT[57] / 300	Low ●●○○	Higher proportion of remission with non-TNF-α inhibitors than TNF-α inhibitors	Downgraded 1 level for RoB and 1 level for imprecision
Combination therapies (rituximab + adalimumab or etanercept)			
Clinical improvement 1 RCT[59] / 54	Low ●●○○	Higher proportion of response with combination therapy than TNF-α inhibitor maintenance therapy	Downgraded 2 levels for very serious imprecision

Outcome Number of Studies / Number of Participants	Certainty of Evidence	Relationship	Rationale
Remission 1 RCT[59] / 54	Low ●●○○	Higher proportion of remission with combination therapy than TNF-α inhibitor maintenance therapy	Downgraded 2 levels for very serious imprecision
Combination therapies (abatacept + other TIMs vs. another TIM alone)			
Functional capacity 1 RCT[58] / 167	Low ●●○○	No difference between groups	Downgraded 2 levels for very serious imprecision

Abbreviations. GRADE: Grading of Recommendations, Assessment, Development, and Evaluation approach; RA: rheumatoid arthritis; RCT: randomized controlled trial; RoB: risk of bias; TIM: targeted immune modulator; TNF-α: tumor necrosis factor-alpha; vs.; versus.

Abatacept vs. TNF-α inhibitors

We did not identify any new RCTs for this update.

The previous report included 2 high-RoB RCTs.[42,56] The larger trial, a pragmatic, open-label study, was conducted in the Netherlands with patients who had failed TNF-α inhibitor treatment.[56] The trial compared abatacept, rituximab, and TNF-α inhibitors as second-line treatments and enrolled 144 patients who had moderate-to-high disease activity despite previous treatment with different TNF-α inhibitors.[56] The only exclusion reason in this pragmatic trial was a contraindication for treatment (e.g., pregnancy, presence of a serious infection).[56] Patients were randomly assigned to intravenous abatacept every 4 weeks (N = 43; dosage based on body mass: patients under 60 kg received 500 mg, patients between 60 kg and 100 kg received 750 mg, and patients over 100 kg received 1,000 mg), rituximab (N = 50; 1,000 mg at weeks 0 and 2, and after 6 months if indicated), or TNF-α inhibitors (N = 51; adalimumab, certolizumab pegol, etanercept, golimumab, or infliximab, according to approved dosages).[56] The primary outcome for effectiveness was the DAS28-ESR over time.[56] We rated the study as high RoB because outcome assessors were not blinded and the rate of crossovers and loss to follow-up was high. Overall, 42% of patients stopped their assigned medication or switched to a different medication.[56]

At 12 months, DAS28-ESR scores were similar between treatment groups (3.8 for abatacept, 3.5 for TNF-α inhibitors; *P* value NR).[56] Likewise, health-related QoL measures (HAQ, SF-36) did not show any statistically significant differences among treatment groups.[56]

The second trial, SWITCH, is described in more detail below (in the section on abatacept compared with rituximab).[42] It did not formally compare the abatacept (N = 41; 125 mg subcutaneously per week) and TNF-α inhibitor arms (N = 41; based on recommended dosages) in its statistical analyses.[42] Changes in DAS28-ESR scores; however, were similar between abatacept and TNF-α inhibitors (−1.20 vs. −1.47; *P* value NR).[42]

Table 5. Brief Evidence Table for Efficacy Outcomes in Adults for TIMs as Second-line Treatment for RA

Authors, Year Trial Name	Study Design Number of Participants	Duration	Comparisons	Primary Outcome	Secondary Outcomes	Population	Results	Risk of Bias
Abatacept vs. TNF-α inhibitors and rituximab								
Brown et al., 2018[42] NR	Open-label RCT 81	24 weeks	• Abatacept 125 mg SC QW • Rituximab 1,000 mg at days 0 and 15 and every 6 months if indicated	DAS28-ESR	ACR 20/50/70	Active RA with moderate-to-high disease activity, with inadequate response to TNF-α inhibitor; mean disease duration: 6.7 years	No difference in efficacy for abatacept and rituximab	High
Manders et al., 2015[56] NR	Open-label RCT 144	52 weeks	• Abatacept 500 mg < 60 kg, 750 mg 60 to 100 kg, 1,000 mg > 100 kg QM IV • Rituximab 1,000 mg IV, weeks 0 and 2 • TNF-α inhibitors (adalimumab 40 mg Q2W, etanercept 50 mg QW or 25 mg BIW, infliximab 3 mg Q2M after a loading dose given at weeks 0, 2 and 6, golimumab 50 mg QM, certolizumab pegol 400 mg weeks 0, 2 and 4, followed by 200 mg Q2W)	DAS28-ESR	HAQ-DI, SF-36	Active RA with moderate-to-high disease activity, had failed a TNF-α inhibitor; mean disease duration, 6.3 years	No difference in efficacy for abatacept, rituximab, and TNF-α inhibitors	High

Authors, Year Trial Name	Study Design Number of Participants	Duration	Comparisons	Primary Outcome	Secondary Outcomes	Population	Results	Risk of Bias
Abatacept vs. tocilizumab								
Elmedany et al., 2019[32] NR	Open-label RCT 132	24 weeks	• Abatacept 500–1,000 mg IV QM + MTX • Tocilizumab 8 mg/kg IV QM + MTX	NR	DAS28-ESR, HAQ, HAQ-DI	Females with active RA and moderate-to-high disease activity, with inadequate response to TNF-α inhibitor; mean disease duration: 7.0 to 8.0 years	No difference in efficacy for abatacept and tocilizumab	High
Abatacept vs. upadacitinib								
Rubbert-Roth et al., 2020[19] NR	Double-blinded RCT 613	24 weeks	• Abatacept 500–1,000 mg IV QM + MTX • Upadacitinib 15 mg QD + MTX	DAS28-CRP	Remission	Active RA with moderate-to-high disease activity, had failed a TIM; mean disease duration, 12.4 and 11.8 years	Better efficacy for upadacitinib	Low
Rituximab vs. tocilizumab								
Humby et al., 2021[17]	Open-label RCT 164	16 weeks	• Rituximab 1,000 mg IV Q2W • Tocilizumab 8 mg/kg IV QM	CDAI 50% improvement after 16 weeks	CDAI remission, DAS28-ESR, DAS28-CRP	Adults with RA and inadequate response to anti-TNF-α therapy	Better efficacy for tocilizumab	High

Authors, Year Trial Name	Study Design Number of Participants	Duration	Comparisons	Primary Outcome	Secondary Outcomes	Population	Results	Risk of Bias
TNF-α inhibitors vs. other TIMs								
Gottenberg et al., 2016[57] NR	Open-label RCT 300	52 weeks	• TNF-α inhibitors according to approved dosages (adalimumab, certolizumab pegol, etanercept, golimumab, infliximab) • Non-TNF-α inhibitor TIMs according to approved dosages (abatacept, rituximab, tocilizumab)	EULAR response	DAS28-ESR remission, HAQ	Active RA with moderate-to-high disease activity, with inadequate response to TNF-α inhibitor; mean disease duration: 10.0 years	Better efficacy for non-TNF-α inhibitors	Moderate
Combination therapies								
Greenwald et al., 2011[59] TAME[59]	RCT 54	24 weeks	• Rituximab 500 mg day 1 and 15 IV+ adalimumab 40 mg Q2W SC day 1 and 15 or etanercept 50 mg QW SC day 1 and 15 + MTX • Adalimumab 40 mg Q2W SC or etanercept 50 mg QW SC + MTX	Serious infections	Other SAEs, ACR 20/50/70, HAQ, DAS28-ESR, EULAR	Active RA despite treatment with adalimumab or etanercept + MTX for at least 12 weeks; mean disease duration, 10.5 years	Better efficacy for combination treatment than TNF-α inhibitor maintenance treatment	Moderate

Authors, Year Trial Name	Study Design Number of Participants	Duration	Comparisons	Primary Outcome	Secondary Outcomes	Population	Results	Risk of Bias
Weinblatt et al., 2006[58] NR	RCT 167	52 weeks	• Abatacept 10 mg/kg IV, days 1, 15, and 29, and every 4 weeks thereafter + other TIMs (anakinra, etanercept, infliximab, and adalimumab) • Other TIM alone (anakinra, etanercept, infliximab, and adalimumab)	AEs, SAEs, discontinuations due to AEs, death,	HAQ-DI, Pain, Patient's global assessment, Physician's global assessment	Active RA despite treatment with a TIM for at least 3 months; mean disease duration, 10.3 years	No difference in efficacy for combination treatment than TIM monotherapy	Moderate

Abbreviations. ACR 20/50/70: American College of Rheumatology, percentage improvement; AE: adverse event; BIW: dose delivered twice weekly; DAS28-CRP: Disease Activity Score 28 using C-reactive protein; DAS28-ESR: Disease Activity Score 28 using erythrocyte sedimentation rate; EULAR: European League Against Rheumatism; HAQ: Health Assessment Questionnaire; HAQ-DI: Health Assessment Questionnaire-Disability Index; IV: intravenous administration; kg: kilogram; mg: milligram; MTX: methotrexate; NR: not reported; Q2M: dose delivered every 2 months; Q2W: dose delivered every 2 weeks; QD: dose delivered once a day; QM: dose delivered monthly; QW: dose delivered weekly; RA: rheumatoid arthritis; RCT: randomized controlled trial; SAE: serious adverse event; SC: subcutaneous administration; SF-36: Short Form 36-item Health Survey; TIM: targeted immune modulator; TNF-α: tumor necrosis factor-alpha; vs.; versus.

Abatacept vs. Rituximab

We did not include any new RCTs for this update.

The previous report included 2 high-RoB RCTs[42,56] assessing the comparative effectiveness of abatacept and rituximab in participants who had an inadequate response to a TNF-α inhibitor. Overall, the studies provide data on 174 participants.[42,56]

A high-RoB, open-label pragmatic trial conducted in the Netherlands and described above (in abatacept vs. TNF-α inhibitors) also compared abatacept with rituximab.[56] At 12 months, DAS28-ESR scores were similar between treatment groups (3.8 for abatacept, 3.4 for rituximab; *P* value NR).[56] Likewise, health-related QoL measures (HAQ, SF-36) did not show any statistically significant differences between treatment groups.[56]

The second trial, SWITCH, was a publicly funded, open-label, noninferiority trial in the United Kingdom.[42] The study intended to enroll 477 participants to determine the noninferiority of an alternative TNF-α inhibitor (according to approved dosages) or abatacept (125 mg subcutaneously per week) compared with rituximab (1,000 mg at days 0 and 15, and every 6 months if indicated) after 24 weeks of treatment (noninferiority margin: −0.6 units on the DAS28-ESR).[42] Because funding was withdrawn after 2 years, the study enrolled only 122 participants (TNF-α inhibitor: n = 41; abatacept: n = 41; rituximab: n = 40).[42] Consequently, statistical analyses were likely underpowered and rendered nonstatistically significant, giving uncertain results.[42] For example, after 24 weeks, the difference in changes on the DAS28-ESR between abatacept and rituximab was −0.4 units (95% CI, −0.72 to 0.79 units; *P* = .93).[42]

Abatacept vs. Tocilizumab

We did not find any new RCTs for this update.

The previous report included a high-RoB, open-label RCT that enrolled 132 female participants in Saudi Arabia with moderate-to-severe RA despite treatment with TNF-α inhibitors.[32] The study randomized participants to abatacept (500 mg to 1,000 mg [depending on body weight] intravenously on days 1, 15, 29, and then every 40 weeks) or tocilizumab (8 mg/kg every 4 weeks) for 24 weeks.[32] All participants were on methotrexate background therapy. The study did not report a registered protocol, primary outcomes, or the funding source.[32] After 24 weeks, participants in the abatacept and the tocilizumab groups had similar DAS28-ESR (2.8 vs. 2.5; *P* = .06) and HAQ-DI scores (1.01 vs. 0.89; *P* = .56).[32]

Abatacept vs. Upadacitinib

We included 1 new RCT for this comparison.[19] A multinational (28 countries), double-blinded RCT rated as low RoB enrolled 613 participants with moderate-to-severe RA, despite treatment with a TIM for at least 3 months.[19] The study randomized participants to 24 weeks of abatacept (500 to 1,000 mg [depending on body weight] intravenously on day 1 and weeks 2, 4, 8, 12, 16, and 20) or upadacitinib (15 mg once daily).[19] All participants were on stable DMARD background therapy. The primary endpoint was the DAS28-CRP at week 12, tested for noninferiority of upadacitinib to abatacept.[19] The study was funded by the producer of upadacitinib.[19]

After 12 weeks of treatment, the mean changes on the DAS28-CRP were statistically significantly lower for participants treated with abatacept compared with those in the

upadacitinib group (−2.00 vs. −2.52; $P < .01$ for noninferiority and $P < .001$ for superiority).[19] The percentage of participants who achieved remission was 13.3% for abatacept and 30.0% for upadacitinib ($P < .001$ for superiority).[19]

Rituximab vs. Tocilizumab

We included 1 new, high-RoB, open-label, noninferiority RCT for this comparison.[17] This multinational (5 countries) trial enrolled 164 participants with RA, despite treatment with a-TNF-α inhibitor therapy (duration NR).[17] The study randomized participants to 16 weeks of rituximab (1,000 mg every 2 weeks intravenous) or tocilizumab 8 mg/kg every month intravenous) stratified into 4 blocks according to a histological classification of baseline synovial biopsy.[17] All participants were on stable DMARD background therapy (methotrexate).[17] The primary endpoint was the proportion of participants who achieved a 50% or greater improvement on the CDAI.[17] The study was funded by the National Institute for Health Research.[17]

After 16 weeks of treatment, the percentage of participants who achieved clinical improvement was similar between groups (45.2% vs. 55.7%; OR, 0.81; 95% CI, 0.59 to 1.10).[17]

TNF-α Inhibitors vs. Other TIMs

We did not find any new RCTs for this update.

The previous report included a pragmatic RCT that assessed the comparative effectiveness of an alternative TNF-α inhibitor and TIM agents with a different mechanism in participants who had an inadequate response to a TNF-α inhibitor.[57]

This multicenter, publicly funded, open-label effectiveness trial in France enrolled 300 patients with an inadequate response to a TNF-α inhibitor (etanercept: 54%, adalimumab: 29%, infliximab: 14%, golimumab 3%).[57] The study randomized patients to another TNF-α inhibitor (adalimumab, certolizumab pegol, etanercept, infliximab, or golimumab, according to approved dosages) or to a TIM with a different mechanism of action (abatacept, rituximab, or tocilizumab, according to approved dosages) as a second-line treatment.[57] The choice of the treatment within each randomized group was left to the treating clinician.[57] The study did not analyze comparisons of individual treatments.[57]

After 24 weeks of treatment, patients receiving a second-line treatment with abatacept, rituximab, or tocilizumab had statistically significantly higher European League Against Rheumatism (EULAR) response rates than patients treated with a TNF-α inhibitor (69% vs. 52%; OR, 2.06; 95% CI, 1.27 to 3.37).[57] At 24 weeks, the difference in DAS28-ESR remission rates were numerically larger for abatacept, rituximab, or tocilizumab over TNF-α inhibitors, but did not reach statistical significance (27% vs. 19%; $P = .08$).[57] However, at 52 weeks, patients treated with abatacept, rituximab, and tocilizumab had significantly higher remission rates than patients receiving TNF-α inhibitors (27% vs. 14%; $P < .01$).[57]

Combination Therapies

We did not include any new RCTs for this update.

The previous report included two moderate-RoB RCTs that assessed the comparative effectiveness of combination therapies in participants who had an inadequate response to a TIM treatment.[58,59] The TAME (Randomized, Double-Blinded, Placebo-Controlled Study to Evaluate the Tolerability and Safety of Rituximab when given in combination with Methotrexate and Etanercept or Methotrexate and Adalimumab) trial assessed benefits and harms of adding rituximab (2 infusions of 500 mg, 2 weeks apart) to the treatment regimen of 54 patients who had active RA despite treatment with adalimumab or etanercept combined with methotrexate.[59] The control group maintained the adalimumab and etanercept therapies and received placebo infusions.[59] The primary endpoint of the study was the proportion of patients developing at least 1 serious infection during 24 weeks of treatment.[59] The study also assessed efficacy as a secondary outcome.[59] After 24 weeks, more participants in the combination group with rituximab achieved ACR20 (30% vs. 17%; *P* value NR) and ACR50 (12% vs. 6%; *P* value NR) response rates than in the combination group with placebo.[59] Likewise, DAS28-ESR remission rates (< 2.6) were higher for the rituximab combination group (18% vs. 6%; *P* value NR).[59]

The second study, a multinational, multicenter, double-blind RCT, assessed benefits and harms of adding abatacept (10 mg/kg on days 1, 15, and 29, and every 4 weeks thereafter) to the treatment regimen of 167 patients with active RA despite treatment with a TIM.[58] The control group maintained the TIM therapy and received placebo infusions.[58] The primary endpoint of the study was the safety of adding abatacept to an existing TIMs regimen after 52 weeks of treatment.[58] The study assessed efficacy as a secondary outcome.[58] After 52 weeks, participants in the combination and monotherapy groups had similar improvements on the HAQ-DI score (0.33 vs 0.22; *P* value NR).[58]

Effectiveness and Harms of Pipeline TIM Agents

We did not identify new studies evaluating the effectiveness and risk of harms of pipeline TIM agents for the treatment of RA.

The previous report included 6 RCTs evaluating effectiveness and harms of pipeline TIM agents for the treatment of RA.[26-28,39-41] These studies provided evidence on peficitinib compared with placebo,[26-28,40,41] peficitinib compared with etanercept,[40] and 1 combination treatment of certolizumab pegol plus bimekizumab compared with certolizumab pegol monotherapy.[39] For this update, we excluded studies assessing filgotinib because the producer of filgotinib withdrew the drug application from the FDA. Appendix B, Table B1 and Table B3 provide detailed study characteristics and results from the included RCTs. The Summary of Findings (GRADE) for these comparisons are in Table 6, with detailed evidence profiles in Appendix C. Table 7 presents a summary of efficacy and harms outcomes. The rest of this section describes each of the comparisons.

Table 6. Summary of Findings (GRADE) for Pipeline TIMs for Treatment of RA

Outcome Number of Studies / Number of Participants	Certainty of Evidence	Relationship	Rationale
Peficitinib vs. placebo			
Clinical improvement 5 RCTs[26-28,40,41] / 1,977	High ●●●●	Higher proportion with improvement for peficitinib than placebo	Not downgraded
Disease remission 4 RCTs[26,27,40,41] / 1,598	High ●●●●	Higher proportion of remission with peficitinib than placebo	Not downgraded
Overall AEs 5 RCTs[26-28,40,41] / 1,977	Moderate ●●●○	No difference between groups	Downgraded 1 level for imprecision
SAEs 5 RCTs[26-28,40,41] / 1,977	Moderate ●●●○	No difference between groups	Downgraded 1 level for imprecision
Peficitinib vs. etanercept			
Clinical improvement 1 RCT[40] / 509	Moderate ●●●○	Lower proportion with improvement for peficitinib than etanercept	Downgraded 1 level for RoB
Disease remission 1 RCT[40] / 509	Moderate ●●●○	Lower proportion with remission for peficitinib than etanercept	Downgraded 1 level for RoB
Overall AEs 1 RCT[40] / 509	Low ●●○○	No difference between groups	Downgraded 1 level for imprecision; downgraded 1 level for RoB
SAEs 1 RCT[40] / 509	Low ●●○○	No difference between groups	Downgraded 1 level for imprecision; downgraded 1 level for RoB
Combination therapy (certolizumab pegol + bimekizumab vs. certolizumab pegol alone)			
Clinical improvement 1 RCT[39] / 79	Low ●●○○	Higher proportion of response for combination therapy than certolizumab pegol alone	Downgraded 2 levels for very serious imprecision
Disease remission 1 RCT[39] / 79	Low ●●○○	Higher proportion of remission with combination therapy than certolizumab pegol alone	Downgraded 2 levels for very serious imprecision
Overall AEs 1 RCT[39] / 79	Low ●●○○	Higher proportion of overall AEs for combination therapy than certolizumab pegol alone	Downgraded 2 levels for very serious imprecision
SAEs 1 RCT[39] / 79	Low ●●○○	Lower proportion of SAEs for combination therapy than certolizumab pegol alone	Downgraded 2 levels for very serious imprecision

Abbreviations. AE: adverse event; GRADE: Grading of Recommendations, Assessment, Development, and Evaluation approach; RA: rheumatoid arthritis; RCT: randomized controlled trial; RoB: risk of bias; SAE: serious adverse event; TIM: targeted immune modulator; vs.;versus.

Table 7. Evidence Table for Efficacy and Harm Outcomes from RCTs for Pipeline TIMs in RA

Authors, Year Trial Number Trial Name	Dose, Frequency N Randomized	Primary Study Endpoint: Difference From Comparator	N (%) With at Least 1 SAE	N (%) With AE Leading to Discontinuation	Risk of Bias
Peficitinib vs. placebo					
Takeuchi et al., 2019[41] NCT02305849 RAJ 4	Peficitinib 100 mg, or 150 mg QD + MTX; Placebo + MTX Total N = 519	ACR20 response at 12 weeks/ET: • Peficitinib 100 mg: 102 of 174 (58.6%), *P* < .001 • Peficitinib 150 mg: 112 of 174 (64.4%), *P* < .001 • Placebo: 37 of 170 (21.8%) mTSS25—change from baseline at 28 weeks/ET: • Peficitinib 100 mg: 1.62, *P* < .001 • Peficitinib 150 mg: 1.03, *P* < .001 • Placebo: 3.37	• Peficitinib 100 mg: 5 of 174 (2.9%) • Peficitinib 150 mg: 3 of 174 (1.7%) • Placebo: 4 of 170 (2.4%)	• Peficitinib 100 mg: 5 of 174 (2.9%) • Peficitinib 150 mg: 5 of 174 (2.9%) • Placebo: 7 of 170 (4.1%)	Moderate
Tanaka et al., 2019[40] NCT02308163 RAJ 3	Peficitinib 100mg, or 150mg QD + MTX; Placebo + MTX Total N = 509	ACR20 response at 12 weeks/ET: • Peficitinib 100 mg: 60 of 104 (57.7%), *P* < .001 • Peficitinib 150 mg: 76 of 102 (74.5%), *P* < .001 • Placebo: 31 of 101 (30.7%)	• Peficitinib 100 mg: 3 of 104 (2.9%) • Peficitinib 150 mg: 2 of 102 (2%) • Placebo: 4 of 101 (4.0%)	• Peficitinib 100 mg: 6 of 104 (5.8%) • Peficitinib 150 mg: 3 of 102 (2.9%) • Placebo: 4 of 101 (4.0%)	Moderate
Kivitz et al., 2017[28] NCT01554696	Peficitinib 25 mg, 50 mg, 100 mg, or 150 mg QD + MTX; Placebo + MTX Total N = 379	ACR20 response at 12 weeks: • Peficitinib 100 mg: 39 of 84 (46.4%) • Peficitinib 150 mg: 45 of 78 (57.7%) • Placebo: 32 of 72 (44.4%) • *P* values NR	• Peficitinib 100 mg: 2 of 84 (2.4%) • Peficitinib 150 mg: 1 of 78 (1.3%) • Placebo: 0 of 72 (0%)	• Peficitinib 100 mg: 3 of 84 (3.6%) • Peficitinib 150 mg: 4 of 78 (5.1%) • Placebo: 1 of 72 (1.4%)	Moderate
Genovese et al., 2017[27] NCT01565655	Peficitinib 25 mg, 50 mg, 100 mg, or 150 mg QD; Placebo Total N = 289	ACR20 response at 12 weeks: • Peficitinib 100 mg: 28 of 58 (48.3%); *P* < .05 • Peficitinib 150 mg: 36 of 64 (56.3%); *P* < .01 • Placebo: 15 of 51 (29.4%)	• Peficitinib 100 mg: 4 of 58 (6.9%) • Peficitinib 150 mg: 2 of 64 (3.1%) • Placebo: 2 of 51 (3.9%)	• Peficitinib 100 mg: 1 of 58 (1.7%) • Peficitinib 150 mg: 2 of 64 (3.1%) • Placebo: 0 of 51 (0.0%)	Moderate

Authors, Year Trial Number Trial Name	Dose, Frequency N Randomized	Primary Study Endpoint: Difference From Comparator	N (%) With at Least 1 SAE	N (%) With AE Leading to Discontinuation	Risk of Bias
Takeuchi et al, 2015[26] NCT01649999	Peficitinib 25 mg, 50 mg, 100 mg, or 150 mg QD; Placebo Total N = 281	ACR20 response at 12 weeks: • Peficitinib 100 mg: 30 of 55 (54.5%); *P* < .001 • Peficitinib 150 mg: 38 of 58 (65.5%); *P* < .001 • Placebo: 6 of 56 (10.7%)	• Peficitinib 100 mg: 3 of 55 (5.5%) • Peficitinib 150 mg: 0 of 58 (0%) • Placebo: 1 of 56 (1.8%)	• Peficitinib 100 mg: 6 of 55 (10.9%) • Peficitinib 150 mg: 4 of 58 (6.9%) • Placebo: 10 of 56 (17.9%)	Moderate
Peficitinib vs. etanercept					
Tanaka et al., 2019[40] NCT02308163 RAJ 3	Peficitinib 100 mg, or 150 mg QD + MTX; Etanercept 50 mg QW Total N = 509	ACR20 response at 12 weeks/ET: • Peficitinib 100 mg: 60 of 104 (57.7%), • Peficitinib 150 mg: 76 of 102 (74.5%), • Etanercept 50 mg: 167 of 200 (83.5%) • *P* values NR	Overall period (52 weeks): • Peficitinib 100 mg: 7 of 104 (6.7%) • Peficitinib 150 mg: 8 of 102 (7.8%) • Etanercept 50 mg: 18 of 200 (9%)	Overall period (52 weeks): • Peficitinib 100 mg: 13 of 104 (12.5%) • Peficitinib 150 mg: 6 of 102 (5.9%) • Etanercept 50 mg: 13 of 200 (6.5%)	Moderate
Combination therapy					
Glatt et al., 2019[39] NCT02430909	Certolizumab pegol 200 mg Q2W + bimekizumab 240 mg LD then 120 mg Q2W; certolizumab pegol + placebo Total N = 79	DAS28-CRP < 3.2 at 12 weeks: • Certolizumab pegol 200 mg + bimekizumab 240 mg: 21 of 52 (46%) • Certolizumab pegol 200 mg+ placebo: 7 of 27 (29%) • *P* values NR	• Certolizumab pegol 200 mg + bimeki-zumab 240 mg: 2 of 52 (4%) • Certolizumab pegol 200 mg+ placebo: 3 of 27 (11%)	• Certolizumab pegol 200 mg + bimeki-zumab 240 mg: 4 of 52 (8%) • Certolizumab pegol 200 mg + placebo: 3 of 27 (11%)	Moderate

Abbreviations. ACR20: American College of Rheumatology, 20% improvement; AE: adverse event; DAS28-CRP: 28-Joint Disease Activity Score, using C-reactive protein; ET: early termination; mg: milligram; LD: loading dose; mTSS25: van der Heijde-modified total Sharp score; MTX: methotrexate; NCT: US National Clinical Trial; NR: not reported; Q2W: dose delivery every 2 weeks; QD: dose delivered daily; QW: dose delivered weekly; RA: rheumatoid arthritis; RCT: randomized controlled trial; SAE: serious adverse event; TIM: targeted immune modulator. .

Peficitinib vs. Placebo

We did not identify new RCTs for this update.

The previous report included 5 double-blinded, randomized, placebo-controlled trials with data on 1,977 participants assessing the benefits and harms of peficitinib in patients with RA.[26-28,40,41] Three trials were phase 2 studies,[26-28] and 2 trials were phase 3 studies.[40,41] We rated all 5 studies as moderate RoB because of extensive manufacturer involvement in study design, execution, and reporting.[26-28,40,41] All studies included participants with moderate-to-severe RA for at least 6 months.[26-28,40,41] Two studies included participants with inadequate response to or intolerance of at least 1 DMARD agent[27,40]; in the other 2 studies, participants had an inadequate response to methotrexate.[28,41]

The phase 3 double-blinded multicenter RCTs (RAJ 4 and RAJ 3 trials) enrolled 1,028 participants with active RA.[40,41] Participants were randomized to 12 weeks of treatment with peficitinib (100 mg or 150 mg once daily), or placebo.[40,41] All participants from 1 study[41] and 59% from the other[40] received concomitant methotrexate. The primary outcome was the ACR20 response after 12 weeks.[40,41] As secondary outcomes, those trials assessed ACR50/70 responses, changes on the HAQ-DI, DAS28-CRP, DAS28-ESR, CDAI, and SDAI, Subject's Global Assessment of disease activity, Subject's Global Assessment of pain, and Physician's Global Assessment of disease activity (PGA) after 12 weeks of treatment.[40,41] Both studies reported similar results.[40,41] After 12 weeks, significantly more participants in the intervention group achieved an ACR20 response compared with participants in the placebo group (peficitinib 100 mg, 59% of participants in RAJ 4 study and 58% in RAJ 3; peficitinib 150 mg, 64% and 75%; placebo, 22% and 31%; $P < .001$ for all comparisons with placebo).[40,41] Higher proportions of remission as defined by DAS28-CRP < 2.6 were achieved with peficitinib than placebo (peficitinib 100 mg, 25% and 31%; peficitinib 150 mg, 35% and 35%; placebo, 8% and 5%; $P < .001$ for all comparisons with placebo).[40,41]

Two of the three phase 2 studies reported similar significant results for response, remission, and functional capacity as the phase 3 trials.[26,27] The third phase 2 study did not identify statistically significant clinical improvements for peficitinib 100 mg and 150 mg compared with placebo.[28]

All 5 RCTs assessed general and specific AEs at 12 weeks.[26-28,40,41] Findings related to any or serious treatment-emergent AEs were consistent across the 5 studies.[26-28,40,41] No significant differences were found between peficitinib and placebo groups in AEs or SAEs.[26-28,40,41]

Peficitinib vs. Etanercept

We did not identify new RCTs for this update.

The previous report included 1 moderate-RoB double-blinded multicenter RCT assessing the efficacy and harms of peficitinib compared with open-label etanercept in participants with RA.[40] Participants were randomized to peficitinib 100 mg, peficitinib 150 mg, etanercept 50 mg, or placebo for 52 weeks.[40] The primary endpoint was the response rate according to ACR20 at 12 weeks.[40] Key secondary endpoints were ACR50/70 responses, changes from baseline in 28-joint disease activity score, rates of remission, changes from baseline in tender joint count at 68 joints and swollen joint count at 66 joints, changes from baseline in CDAI, SDAI, patient- and physician-reported outcomes [40] At 12 weeks, a numerically lower proportion of participants in

peficitinib groups achieved an ACR20 response compared with participants in the etanercept group (peficitinib 100 mg, 58%; peficitinib 150 mg, 75%; etanercept 50 mg, 84%; *P* value NR).[40] Treatment with etanercept also appeared to provide numerically greater improvements than either peficitinib 100 mg or 150 mg, across all outcomes measured.[40]

Combination Therapy (Certolizumab Pegol vs. Certolizumab Pegol + Bimekizumab)

We did not identify new RCTs for this update.

The previous report included 1 moderate-RoB double-blinded RCT assessing the efficacy and harms of adding bimekizumab 240 mg to the treatment regimen of 79 patients who had active RA despite treatment with certolizumab pegol 200 mg.[39] The control group was maintained on the certolizumab pegol 200 mg therapy and also received placebo.[39] The primary endpoint was the change in DAS28-CRP at 12 weeks of treatment.[39] Key secondary endpoints were DAS28-CRP < 2.6 and ACR20/50/70 responses, together with safety outcomes.[39] After 12 weeks of treatment, significantly more participants in the combination group with bimekizumab than in the certolizumab pegol monotherapy group achieved reductions of DAS28-CRP < 3.2 (46% vs. 29%; *P* value NR).[39] Likewise, DAS28-CRP remission rates (< 2.6) were higher for the bimekizumab combination group (26% vs.8%; *P* value NR).[39] Significantly more participants experienced treatment-emergent AEs in the combination group compared with the certolizumab pegol monotherapy group (79% vs. 59%; *P* value NR).[39]

Comparative Harms (KQ2)

In this section, we describe harm findings of RCTs and cohort studies. Appendix B, Table B1 and Table B3 provide detailed study characteristics and results from the included RCTs, and Appendix B, Table B5 provides detailed study characteristics and results from the included cohort studies

This section is structured as follows: We first address the general tolerability of TIMs, relying on data from included RCTs; we then present findings on specific SAEs such as malignancies, serious infections, or cardiovascular events based on data from observational studies. The short durations and small sample sizes of RCTs limited the validity of AE assessment with respect to rare SAEs. Because of their larger sample sizes, observational studies allow for a more adequate number of cases than randomized trials to make sensible head-to-head comparisons. Finally, we address the risk of harms for TIMs when used as combination therapies.

General Tolerability Findings From RCTs

For this update, we identified 3 new RCTs with data on the overall incidence of AEs, discontinuation due to AEs, and SAEs.[18,19,21] Overall, we describe harm findings of 23 included RCTs.[18,19,21,29-32,36,42-46,48-52,54-56,58,59] Of these, 4 RCTs evaluated combination strategies.[54,55,58,59] Table 8 presents the Summary of Findings (GRADE) for comparisons with data on harms. Appendix C. Evidence Grade Profiles Table C1 and Table C2 provide detailed evidence profiles.

Table 8. Summary of Harm Findings (GRADE) for TIMs for Treatment of RA

Outcome Number of Studies / Number of Participants	Certainty of Evidence	Relationship	Rationale
First-line treatments			
Abatacept vs. adalimumab			
Overall AEs 1 RCT[43] / 646	Low ●●○○	No difference between groups	Downgraded 1 level for RoB and 1 level for imprecision
SAEs 1 RCT[43] / 646	Very low ●○○○	No difference between groups	Downgraded 1 level for RoB and 2 levels for very serious imprecision
Abatacept vs. certolizumab pegol			
Overall AEs 1 RCT[18] / 407	Moderate ●●●○	No difference between groups	Downgraded 1 level for imprecision
SAEs 1 RCT[18] / 407	Low ●●○○	No difference between groups	Downgraded 2 levels for very serious imprecision
Abatacept vs. infliximab			
Overall AEs 1 RCT[44] / 321	Moderate ●●●○	No difference between groups	Downgraded 1 level for imprecision
SAEs 1 RCT[44] / 321	Low ●●○○	Lower proportion of SAEs with abatacept than infliximab	Downgraded 2 levels for very serious imprecision
Abatacept vs. tocilizumab			
Overall AEs 1 RCT[18] / 392	Moderate ●●●○	Lower proportion of overall AE for abatacept than tocilizumab	Downgraded 1 level for imprecision
SAEs 1 RCT[18] / 392	Low ●●○○	No difference between groups	Downgraded 2 levels for very serious imprecision
Adalimumab vs. baricitinib			
Overall AEs 1 RCT[29] / 817	High ●●●●	No difference between groups	Not downgraded
SAEs 1 RCT[29] / 817	Low ●●○○	Lower proportion of SAEs with adalimumab than baricitinib	Downgraded 2 levels for very serious imprecision
Adalimumab vs. certolizumab pegol			
Overall AEs 1 RCT[45] / 915	High ●●●●	No difference between groups	Not downgraded
SAEs 1 RCT[45] / 915	Low ●●○○	No difference between groups	Downgraded 2 levels for very serious imprecision
Adalimumab vs. etanercept			
SAEs 1 RCT[46]) / 125	Very low ●○○○	No difference between groups	Downgraded 1 level for RoB and 2 levels for very serious imprecision
Adalimumab vs. sarilumab			
Overall AEs 1 RCT[48] / 369	Moderate ●●●○	No difference between groups	Downgraded 1 level for imprecision
SAEs 1 RCT[48] / 369	Low ●●○○	No difference between groups	Downgraded 2 levels for very serious imprecision

Outcome Number of Studies / Number of Participants	Certainty of Evidence	Relationship	Rationale
Adalimumab vs. tocilizumab			
Overall AEs 1 RCT[49] / 326	Low ●●○○	No difference between groups	Downgraded 1 level for indirectness and 1 level imprecision
SAEs 1 RCT[49] / 326	Low ●●○○	No difference between groups	Downgraded 1 level for indirectness and 1 level imprecision
Adalimumab vs. tofacitinib			
Overall AEs 3 RCTs[50-52] / 2,247	High ●●●●	No difference between groups	Not downgraded
SAEs 3 RCTs[50-52] / 2,247	Moderate ●●●○	No difference between groups	Downgraded 1 level for imprecision
Adalimumab vs. upadacitinib			
Overall AEs 1 RCT[30] / 978	High ●●●●	No difference between groups	Not downgraded
SAEs 1 RCT[30] / 978	Low ●●○○	No difference between groups	Downgraded 2 levels for very serious imprecision
Anakinra vs. TNF-α inhibitors			
SAEs 1 RCT[21] / 39	Very low ●○○○	No difference between groups	Downgraded 1 level for RoB and 2 levels for very serious imprecision
Certolizumab pegol vs. tocilizumab			
Overall AEs 1 RCT[18] / 391	Moderate ●●●○	Lower proportion of overall AEs for certolizumab pegol than tocilizumab	Downgraded 1 level for imprecision
SAEs 1 RCT[18] / 391	Low ●●○○	No difference between groups	Downgraded 2 levels for very serious imprecision
Etanercept vs. tocilizumab			
SAEs 1 RCT[31] / 3,080	Moderate ●●●○	No difference between groups	Downgraded 1 level for RoB
First-line combination therapies			
Etanercept + abatacept vs. etanercept; etanercept + anakinra vs. etanercept			
Overall AEs 2 RCTs[54,55] / 365	Moderate ●●●○	No difference between groups	Downgraded 1 level for imprecision
SAEs 2 RCTs[54,55] / 365	Low ●●○○	More SAEs for combination of etanercept and abatacept or anakinra than etanercept alone	Downgraded 2 levels for very serious imprecision
Second-line treatments			
Abatacept vs. rituximab			
Overall AEs 2 RCTs[42,56] / 174	Low ●●○○	No difference between groups	Downgraded 1 level for RoB and 1 level for imprecision
SAEs 1 RCT[42] / 81	Very low ●○○○	No difference between groups	Downgraded 1 level for RoB and 2 levels for very serious imprecision

Outcome Number of Studies / Number of Participants	Certainty of Evidence	Relationship	Rationale
Abatacept vs. tocilizumab			
Overall AEs 1 RCT[32] / 132	Low ●●○○	Lower proportion of overall AEs for abatacept than tocilizumab	Downgraded 1 level for RoB and 1 level for imprecision
SAEs 1 RCT[32] / 132	Very low ●○○○	No difference between groups	Downgraded 1 level for RoB and 2 levels for very serious imprecision
Abatacept vs. upadacitinib			
Overall AEs 1 RCT[19] / 612	Moderate ●●●○	No difference between groups	Downgraded 1 level for imprecision
SAEs 1 RCT[19] / 612	Low ●●○○	No difference between groups	Downgraded 2 levels for very serious imprecision
Tocilizumab vs. sarilumab			
Overall AEs 1 RCT[36] / 153	Low ●●○○	No difference between groups	Downgraded 1 level for RoB and 1 level for serious imprecision
SAEs 1 RCT[36] / 153	Very low ●○○○	No difference between groups	Downgraded 1 level for RoB and 2 level for serious imprecision
Second-line combination therapies			
Rituximab + adalimumab; etanercept vs. adalimumab alone; etanercept alone			
Overall AEs 1 RCT[59] / 54	Low ●●○○	No difference between groups	Downgraded 2 levels for very serious imprecision
SAEs 1 RCT[59] / 54	Low ●●○○	More SAEs for combination of rituximab with TNF-α inhibitors than TNF-α inhibitor maintenance	Downgraded 2 levels for very serious imprecision
Abatacept + other TIMs (adalimumab, anakinra, etanercept, or infliximab) vs. another TIM alone			
Overall AEs 1 RCT[58] / 167	Low ●●○○	No difference between groups	Downgraded 2 levels for very serious imprecision
SAEs 1 RCT[58] / 167	Low ●●○○	No difference between groups	Downgraded 2 levels for very serious imprecision

Abbreviations. AE: adverse event; GRADE: Grading of Recommendations, Assessment, Development, and Evaluation approach; RA: rheumatoid arthritis; RCT: randomized controlled trial; RoB: risk of bias; SAE: serious adverse event; TIM: targeted immune modulator; TNF-α: tumor necrosis factor-alpha; vs.; versus.

The pharmaceutical industry funded the majority of RCTs included for this KQ. Table 9 summarizes harm findings from included RCTs, including calculated RRs for general tolerability. In the majority of studies, head-to-head comparisons did not show statistically significant differences in the incidence of overall AEs, discontinuation because of AEs, or SAEs. For 6 comparisons, studies reported some statistically significant differences (see Table 9).[18,29,32,36,44,89] However, these findings are all based on single trials, some of which had high RoB. Therefore, findings should be interpreted with caution.

We identified 4 RCTs that randomized patients to a combination of TIMs.[54,55,58,59] The combination of TNF-α inhibitors with a TIM of a different mechanism of action substantially increased the frequency of SAEs.[54,55,59] For example, in a moderate-RoB RCT of 244 patients with RA, a combination of anakinra and etanercept 50 mg led to a substantially higher rate of SAEs than etanercept 50 mg monotherapy (14.8% for 50 mg etanercept plus anakinra, 4.9% for 25 mg etanercept plus anakinra, and 2.5% for 50 mg etanercept only; *P* value NR).[54]

Similarly, 2 moderate-RoB studies revealed that combination therapies were associated with a substantial increase in SAEs.[55,58] One 1 RCT compared a combination of abatacept (2 mg/kg) and etanercept (25 mg twice weekly) to etanercept monotherapy (25 mg twice weekly).[55] The combination was associated with a substantial increase in SAEs (16.5% vs. 2.8%; *P* value NR).[55] The second RCT studied the addition of abatacept to another TIM (background adalimumab, anakinra, etanercept, or infliximab) compared with a background TIM agent and placebo in 167 RA patients.[58] SAEs and serious infections were higher in the combination group (22.3% vs. 12.5%, and 5.8% vs. 1.6%, respectively).[58]

In a small, moderate-RoB trial of rituximab added to either etanercept or adalimumab for RA, the combination therapy resulted in 6% of patients with SAEs compared with 0% in the control group and 5.5% withdrawing due to AEs compared with 0%.[59] The difference in AEs appeared to be related to differences in the rate of infusion reactions, although the 24-week duration of the study may not have been adequate to identify other differences.[59]

Specific Serious Adverse Events Findings From Cohort Studies

For this update, we identified 4 new cohort studies reporting on specific SAEs.[16,22-24] Overall, we describe harm findings of 25 included cohort studies.[16,22-24,33-35,37,38,60-76] Many of the observational studies were independently funded (e.g., government-funded). Table 10 summarizes harm outcomes from observational studies. The majority of studies were conducted in cohorts of participants with RA. Two studies also included other populations.[61,71] Appendix B, Table B5 presents detailed characteristics and findings of individual studies.

Table 9. Summary of Adverse Events (General Tolerability) From RCTs in Adults Receiving TIMs for RA

Authors, Year Trial Name	Number of Randomized Patients (Without Placebo Arms)	Duration	Overall AEs RR (95% CI)[a]	Discontinuation Due to AEs RR (95% CI)[a]	SAEs RR (95% CI)[a]	Summary of Results	Risk of Bias
Abatacept vs. adalimumab							
Weinblatt et al., 2013[43] AMPLE	646	48 weeks	1.02 (0.98 to 1.05)	0.57 (0.28 to 1.16)	1.10 (0.69 to 1.77)	No significant differences	Moderate
Schiff et al., 2014[89] AMPLE		96 weeks	1.01 (0.97 to 1.06)	0.40 (0.21 to 0.76)	0.84 (0.58 to 1.21)	Incidence of discontinuation due to AE significantly lower for abatacept vs. adalimumab	
Abatacept vs. certolizumab pegol							
Hetland et al., 2020[18]	812	24 weeks	0.97 (0.88 to 1.06)	0.44 (0.14 to 1.39)	0.58 (0.27 to 1.24)	No significant differences	Low
Abatacept vs. infliximab							
Schiff et al., 2008[44,92] ATTEST	321	24 weeks	0.97 (0.88 to 1.07)	0.44 (0.16 to 1.22)	0.45 (0.20 to 0.99)	Incidence of SAEs significantly lower for abatacept vs. infliximab	Moderate
Abatacept vs. rituximab							
Manders et al., 2015[56]	93	52 weeks	1.14 (0.65 to 2.02)	NR	NR	No significant differences	High
Brown et al., 2018[42] SWITCH	81	48 weeks	0.98 (0.77 to 1.24)	0.49 (0.09 to 2.52)	0.98 (0.26 to 3.64)	No significant differences	High
Abatacept vs. tocilizumab							
Elmedany et al., 2019[32]	132	24 weeks	0.48 (0.31 to 0.74)	0.42 (0.14 to 1.29)	0.42 (0.14 to 1.29)	Incidence of AEs significantly lower with abatacept vs. tocilizumab	High
Hetland et al., 2020[18]	812	24 weeks	0.84 (0.78 to 0.92)	0.36 (0.12 to 1.13)	1.00 (0.42 to 2.41)	Incidence of overall AEs significantly lower with abatacept vs. tocilizumab	Low

Authors, Year Trial Name	Number of Randomized Patients (Without Placebo Arms)	Duration	Overall AEs RR (95% CI)[a]	Discontinuation Due to AEs RR (95% CI)[a]	SAEs RR (95% CI)[a]	Summary of Results	Risk of Bias
Abatacept vs. upadacitinib							
Rubbert-Roth et al., 2020[19] SELECT-CHOICE	612	24 weeks	0.89 (0.79 to 1.00	0.63 (0.28 to 1.43)	0.49 (0.17 to 1.42)	No significant differences	Low
Adalimumab vs. baricitinib							
Taylor et al., 2017[29] RA-BEAM	817	52 weeks	0.97 (0.90 to 1.05)	0.53 (0.29 to 0.99)	0.50 (0.27 to 0.93)	Incidence of discontinuation due to AEs and SAEs significantly lower for adalimumab vs. baricitinib	Moderate
Adalimumab vs. certolizumab pegol							
Smolen et al., 2016[45] EXXELERATE	915	12 weeks	0.98 (0.91 to 1.05)	0.96 (0.69 to 1.32)	0.85 (0.61 to 1.19)	No significant differences	Moderate
Adalimumab vs. etanercept							
Jobanputra et al., 2012[46] RED SEA	125	52 weeks	NR	0.83 (0.39 to 1.78)	0.86 (0.31 to 2.40)	No significant differences	High
Adalimumab vs. sarilumab							
Burmester et al., 2017[48] MONARCH	369	24 weeks	0.99 (0.85 to 1.16)	1.18 (0.54 to 2.57)	1.33 (0.58 to 3.09)	No significant differences	Moderate
Adalimumab vs. tocilizumab							
Gabay et al., 2013[49] ADACTA	326	24 weeks	1.01 (0.91 to 1.11)	1.11 (0.46 to 2.66)	0.84 (0.45 to 1.58)	No significant differences	Moderate
Adalimumab vs. tofacitinib							
van Vollenhoven et al., 2012[50] ORAL Standard	609	12 weeks	0.99 (0.82 to 1.19[b]	0.71 (0.32 to 1.57)[b]	0.42 (0.15 to 1.16)[b]	No significant differences	Moderate

Authors, Year Trial Name	Number of Randomized Patients (Without Placebo Arms)	Duration	Overall AEs RR (95% CI)[a]	Discontinuation Due to AEs RR (95% CI)[a]	SAEs RR (95% CI)[a]	Summary of Results	Risk of Bias
Fleischmann et al., 2012[51]	325	24 weeks	0.92 (0.64 to 1.33)[b]	3.70 (0.43 to 31.96)[b]	Not estimable[e]	No significant differences	Moderate
Fleischmann et al., 2017[52] ORAL Strategy	1,146	48 weeks	1.07 (0.96 to 1.19)	1.39 (0.86 to 2.24)	0.87 (0.51 to 1.47)	No significant differences	Moderate
Adalimumab vs. upadacitinib							
Fleischmann et al., 2019[30] SELECT-COMPARE	1,629	12 weeks	0.94 (0.85 to 1.04)	1.73 (0.96 to 3.10)	1.16 (0.61 to 2.21)	No significant differences	Moderate
Anakinra vs. TNF-α inhibitors							
Ruscitti et al., 2019[21] TRACK	39	24 weeks	NR	Not estimable[e]	Not estimable[e]	No significant differences	High
Certolizumab pegol vs. tocilizumab							
Hetland et al., 2020[18]	812	24 weeks	0.87 (0.81 to 0.93)	0.82 (0.34 to 1.97)	1.72 (0.79 to 3.76)	Incidence of overall AEs significantly lower with certolizumab pegol vs. tocilizumab	Low
Etanercept vs. tocilizumab							
Giles et al., 2019[31] ENTRACTE	3,080	24 weeks	NR	0.87 (0.68 to 1.12)[c]	0.91 (0.78 to 1.06)[c]	No significant differences	Moderate
Tocilizumab vs. sarilumab							
Emery et al., 2018[36] ASCERTAIN	202	24 weeks	0.94 (0.75 to 1.18)[d]	0.25 (0.08 to 0.79)[d]	1.17 (0.31 to 4.32)[d]	Incidence of discontinuation due to AEs significantly lower for tocilizumab vs. sarilumab 200 mg	High

Authors, Year Trial Name	Number of Randomized Patients (Without Placebo Arms)	Duration	Overall AEs RR (95% CI)[a]	Discontinuation Due to AEs RR (95% CI)[a]	SAEs RR (95% CI)[a]	Summary of Results	Risk of Bias
Combination Therapies							
Anakinra + etanercept vs. etanercept alone							
Genovese et al., 2004[54]	244	24 weeks	1.06 (0.97 to 1.15)[e]	Not estimable[e]	1.98 (0.37 to 10.48)[e]	No significant differences	Moderate
Abatacept + etanercept vs. etanercept alone							
Weinblatt et al., 2007[55]	121	52 weeks	1.05 (0.92 to 1.19)	4.24 (0.56 to 31.87)	5.93 (0.81 to 43.42)	No significant differences	Moderate
Abatacept + other TIM[f] vs. other TIM[f] alone							
Weinblatt et al., 2006[58]	167	52 weeks	1.07 (0.97 to 1.18)	2.80 (0.62 to 12.53)	1.79 (0.85 to 3.75)	No significant differences	Moderate
Rituximab + adalimumab or etanercept vs. adalimumab alone or etanercept alone							
Greenwald et al., 2011[59] TAME	54	24 weeks	1.13 (0.90 to 1.41)	Not estimable[e]	Not estimable[e]	No significant differences	Moderate

Notes. [a] Data were extracted from publications of trials and from www.clinicaltrials.gov; the relative risks with confidence intervals were calculated by the authors of this report unless otherwise stated. [b] RR was calculated for adalimumab vs. tofacitinib 5 mg as approved by the FDA. [c] Hazard ratio obtained from publication and direction of comparison reversed. [d] RR was calculated for tocilizumab vs. sarilumab 200 mg. [e] RR not estimable with OpenEpi due to no events in 1 or both group(s). [f] Included adalimumab, anakinra, etanercept, or infliximab.

Abbreviations. AE: adverse event; CI: confidence interval; mg: milligram; NR: not reported; RA: rheumatoid arthritis; RCT: randomized controlled trial; RR: risk ratio; SAE: serious adverse event; TIM: targeted immune modulator; TNF-α: tumor necrosis factor-alpha; vs.: versus.

Table 10. Summary of Specific SAEs from Observational Studies in Adults Receiving TIMs for RA

Authors, Year Registry Name, Country	Number of Participants	Follow-up	Comparison	Population	Outcome	Results	Risk of Bias
Mortality							
Kim et al., 2018[33] IMS PharMetrics, MarketScan and Medicare	20,922	16,280 pys	Tocilizumab vs. abatacept	RA	Mortality	No significant differences	Moderate
Serious infections							
Patel et al., 2021[16] Medicare, US	30,439 (TIMs naïve)	36 months	Pooled TNF-α inhibitors (adalimumab, certolizumab pegol, etanercept, golimumab, infliximab) vs. abatacept	RA	Serious infections	Significantly higher for pooled TNF-α inhibitors vs. abatacept (aHR, 1.59; 95% CI, 1.43 to 1.77)	Moderate
	16,647 (prior TNF-α inhibitor exposure)					Significantly higher for pooled TNF-α inhibitors vs. abatacept (aHR, 1.48; 95% CI, 1.26 to 1.75)	
Pawar et al., 2020[23] IMS PharMetrics, MarketScan, Medicare and Optum, US	130,718	100,790 pys	Tofacitinib vs. abatacept, adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, tocilizumab	RA	Serious infections	Significantly higher for tofacitinib vs. etanercept (aHR, 1.41; 95% CI, 1.15 to 1.73) No significant differences for tofacitinib vs. other drugs	Low
Pawar et al., 2019[38] IMS PharMetrics, MarketScan and Medicare	49,183	42,139 pys	Tocilizumab vs. pooled TNF-α inhibitors	RA	Serious infections	No significant differences	Moderate
	20,828	17,693 pys	Tocilizumab vs. abatacept			Significantly higher for tocilizumab vs. abatacept (aHR, 1.40; 95% CI, 1.20 to 1.63)	

Authors, Year Registry Name, Country	Number of Participants	Follow-up	Comparison	Population	Outcome	Results	Risk of Bias
Rutherford et al., 2018[37] BSRBR, UK	19,282	46,771 pys	Adalimumab, infliximab, certolizumab, tocilizumab, or rituximab vs. etanercept	RA	Serious infections	Significantly higher for tocilizumab vs. etanercept (aHR, 1.22; 95% CI, 1.02 to 1.47) Significantly lower with certolizumab pegol vs. etanercept (aHR, 0.75; 95% CI, 0.58 to 0.97)	Moderate
Yun et al., 2015 and 2016[74,75] Medicare, US	189,326	NR	Adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, rituximab, or tocilizumab, vs. abatacept	RA	Serious infections	Significantly higher risk for etanercept (aHR, 1.24; 95% CI, 1.07 to 1.45), infliximab (aHR, 1.39; 95% CI, 1.21 to 1.60), and rituximab (aHR, 1.36; 95% CI, 1.21 to 1.53) vs. abatacept	Low
Curtis et al., 2012[63] Medicare, US	11,657	10,240 pys	Adalimumab vs. etanercept vs. infliximab	RA	Serious infections	Significantly higher for infliximab vs. adalimumab (aHR, 1.49; 95% CI, 1.05 to 2.10) and for infliximab vs. etanercept (aHR, 1.52; 95% CI, 1.08 to 2.12	Moderate
Galloway et al., 2011[66] BSRBR, UK	11,881	NR	Adalimumab vs. etanercept vs. infliximab	RA	Serous septic arthritis	No significant differences	Moderate
Galloway et al., 2013[67] BSRBR, UK	11,181	17,048 pys	Adalimumab vs. etanercept vs. infliximab	RA	Serious skin and soft tissue infections	No significant differences	Moderate
Galloway et al., 2011[65] BSRBR, UK	11,798	Median 3.9 years	Adalimumab vs. etanercept vs. infliximab	RA	Serious infections	No significant differences	Low

Authors, Year Registry Name, Country	Number of Participants	Follow-up	Comparison	Population	Outcome	Results	Risk of Bias
Grijalva, et al., 2011[68] SABER, US	10,242	NR	Adalimumab vs. etanercept vs. infliximab	RA	Serious infections	Significantly higher for infliximab (aHR 1.23; 95% CI 1.02 to 1.48) and etanercept (aHR 1.26; 95% CI 1.07 to 1.47) vs. adalimumab	Moderate
Tuberculosis							
Rutherford et al., 2018[35] BSRBR, UK	19,282	106,347 pys	Rituximab or tocilizumab vs. pooled TNF-α inhibitors	RA	Tuberculosis	Significantly lower for rituximab vs. pooled TNF-α inhibitors (aHR, 0.16; 95% CI, 0.04 to 0.67)	Moderate
	7,243	21,015 pys	Etanercept vs. rituximab			Significantly higher for etanercept vs. rituximab (aHR, 4.63; 95% CI, 1.06 to 20.2)	
Arkema et al., 2015[60] SWEDISH, Sweden	10,800	48,228 pys; mean 4.5 ± 2.8 years	Adalimumab, infliximab, rituximab vs. etanercept	RA	Tuberculosis	No significant differences	Moderate
Dixon et al., 2010[64] BSRBR, UK	10,712	34,025 pys	Adalimumab or infliximab vs. etanercept	RA	Tuberculosis	Significantly higher for adalimumab (aIRR, 4.2; 95% CI, 1.4 to 12.4) and infliximab vs. etanercept (aIRR, 3.1; 95% CI, 1.0 to 9.5)	Moderate
Opportunistic infections							
Pawar et al., 2019[38] IMS PharMetrics, MarketScan and Medicare	49,183	42,139 pys	Tocilizumab vs. pooled TNF-α inhibitors	RA	Opportunistic infections	No significant differences	Moderate
Rutherford et al., 2018[35] BSRBR, UK	19,282	106,347 pys	Rituximab or tocilizumab vs. pooled TNF-α inhibitors	RA	Opportunistic infections	No significant differences	Moderate

Authors, Year Registry Name, Country	Number of Participants	Follow-up	Comparison	Population	Outcome	Results	Risk of Bias
Baddley et al., 2014[61] SABER, US	24,384	NR	Adalimumab or infliximab vs. etanercept	RA and other indications	Opportunistic infections	Significantly higher for infliximab vs. etanercept (aHR, 2.9; 95% CI, 1.5 to 5.4)	Moderate
Varicella zoster							
Pawar et al., 2020[23] IMS PharMetrics, MarketScan, Medicare and Optum, US	130,718	100,790 pys Median: 168 to 182 days	Tofacitinib vs. abatacept, adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, tocilizumab	RA	Herpes zoster	Significantly higher for tofacitinib vs. abatacept (aHR, 1.94; 95% CI, 1.53 to 2.44), adalimumab (aHR, 1.99; 95% CI, 1.63 to 2.43), certolizumab pegol (aHR, 2.24; 95% CI, 1.68 to 2.99), etanercept (aHR, 2.12; 95% CI, 1.73 to 2.58), golimumab (aHR, 1.84; 95% CI, 1.35 to 2.50), infliximab (aHR, 1.94; 95% CI, 1.51 to 2.50), tocilizumab (aHR, 2.14; 95% CI, 1.53 to 2.99)	Low
Chen et al., 2020[24] MarketScan, US	10,019	8,373 pys	Pooled TNF-α inhibitors, rituximab, tocilizumab, or tofacitinib, vs. abatacept	RA	Herpes zoster	Significantly higher for rituximab vs. abatacept (aHR, 1.82; 95% CI, 1.02 to 3.24), tocilizumab vs. abatacept (aHR, 1.98; 95% CI, 1.06 to 3.68), and tofacitinib vs. abatacept (aHR, 2.16; 95% CI, 1.09 to 4.28)	Moderate

Authors, Year Registry Name, Country	Number of Participants	Follow-up	Comparison	Population	Outcome	Results	Risk of Bias
Curtis et al., 2016[62] MarketScan and Medicare, US	69,726	44,987 pys	Adalimumab, certolizumab, pegol, etanercept, golimumab, infliximab, rituximab, tocilizumab, or tofacitinib, vs. abatacept	RA	Herpes zoster and herpes simplex	Significantly higher for tofacitinib vs. abatacept (aHR, 1.40; 95% CI, 1.09 to 1.81)	Moderate
Galloway et al., 2013[67] BSRBR, UK	11,881	17,048 pys	Adalimumab vs. etanercept vs. infliximab	RA	Shingles	Significantly higher for infliximab vs. adalimumab (aHR, 1.5; 95% CI, 1.1 to 2.0)	Moderate
Winthrop et al., 2013[71] SABER, US	33,324	28,392 pys	Adalimumab or etanercept vs. infliximab	RA and other indications	Herpes zoster	No significant differences	Moderate
Malignancies							
Kim et al., 2019[34] IMS PharMetrics, MarketScan and Medicare	16,930	14,491 pys	Tocilizumab vs. abatacept	RA	Malignancy (excluding nonmelanoma skin cancer)	No significant differences	Moderate
Nonmelanoma and melanoma skin cancer							
Mercer, et al., 2012[69] BSRBR, UK	13,784	43,798 pys	Adalimumab or etanercept vs. infliximab	RA	Basal cell carcinoma	No significant differences	Moderate

Authors, Year Registry Name, Country	Number of Participants	Follow-up	Comparison	Population	Outcome	Results	Risk of Bias
Cardiovascular events and congestive heart failure							
Kim et al. 2018[33] IMS PharMetrics, MarketScan and Medicare	20,922	16,280 pys	Tocilizumab vs. abatacept	RA	Composite of hospitalization for myocardial infarction or stroke Myocardial infarction, stroke, acute coronary syndrome, coronary revascularization, heart failure	No significant differences	Moderate
Zhang et al., 2016[76] Medicare, US	47,193	15 months	Adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, rituximab, or tocilizumab vs. abatacept	RA	Composite of myocardial infarction, PCI, or CABG Myocardial infarction	Significantly higher for etanercept vs. abatacept (aHR, 1.33; 95% CI, 1.01 to 1.76) and infliximab vs. abatacept (aHR, 1.30; 95% CI, 1.03 to 1.64) No significant differences for abatacept vs. other drugs	Moderate
Wolfe et al., 2004[72] National Databank for Rheumatic Diseases, US	13,171	2 years	Etanercept vs. infliximab	RA	Heart failure	No significant differences	High

Authors, Year Registry Name, Country	Number of Participants	Follow-up	Comparison	Population	Outcome	Results	Risk of Bias
Gastrointestinal perforations							
Monemi et al., 2016[70] MarketScan, US	27,255	Mean: 535 days	Pooled TNF-α inhibitors (adalimumab, certolizumab pegol, etanercept, golimumab, infliximab) vs. tocilizumab	RA	Lower gastrointestinal tract perforations; perforations of the entire gastrointestinal tract	Significantly higher for tocilizumab vs. any TNF-α inhibitor (aIRR, 4.0; 95% CI, 1.1 to 14.1) No significant differences for Tocilizumab vs. any TNF-α inhibitor	Moderate
Xie et al., 2016[73] MarketScan and Medicare, US	167,113	TNF-α inhibitors: 130 324 pys; abatacept: 39,227 pys; tocilizumab: 10,293; tofacitinib: 2,329; rituximab: 4,134 pys	Pooled TNF-α inhibitors (adalimumab, certolizumab, etanercept, golimumab, infliximab) vs. abatacept, tocilizumab, tofacitinib, or rituximab	RA	Lower gastrointestinal tract perforation	Significantly higher for tocilizumab vs. any TNF-α inhibitor (aHR, 2.51; 95% CI, 1.31 to 4.80)	Moderate
Venous thromboembolism							
Desai et al. 2021[22] MarketScan, Medicare, and Optum, US	87,653	Tofacitinib: 5,301 pys, TNF-α inhibitors: 75,824 pys	Tofacitinib vs. pooled TNF-α inhibitors (adalimumab, certolizumab, etanercept, golimumab, infliximab)	RA	Venous thrombo-embolism (pulmonary embolism or deep venous thrombosis)	No significant differences.	Moderate

Abbreviations. aHR: adjusted hazard ratio; aIRR: adjusted incidence rate ratio; BSRBR: British Society for Rheumatology biologics register; CABG: coronary artery bypass graft; CI: confidence interval; NR: not reported; PCI: percutaneous coronary intervention; pys: patient-years; RA: rheumatoid arthritis; SABER: Safety Assessment of Biologic Therapy; SAE: serious adverse event; SWEDISH: Swedish Inpatient Register, the Swedish Outpatient Register, the Swedish Early RA Register, the Swedish National Population Registers, Swedish Tuberculosis Register, and the Swedish Biologics; TIM: targeted immune modulator; TNF-α: tumor necrosis factor-alpha; UK: United Kingdom; US: United States; vs.: versus.

Mortality

We located 1 publication of comparative data from observational studies on mortality.[33] This US multidatabase (IMS PharMetrics, MarketScan, and Medicare), retrospective cohort study included 20,922 patients (16,280 patient-years) and found no difference in all-cause mortality for tocilizumab compared with abatacept (aHR, 0.99; 95% CI, 0.62 to 1.60).[33]

Serious Infections

We identified 10 observational studies containing data on the comparative risk of TIMs for serious infections.[16,23,37,38,63,65-68,74,75] Most of these retrospective studies used data from registries. Definitions of serious infections were typically deaths, hospitalizations, and use of intravenous antibiotics associated with infections. For this outcome, we located comparative data on abatacept, rituximab, tocilizumab, tofacitinib, and the TNF-α inhibitors adalimumab, certolizumab pegol, etanercept, golimumab, and infliximab. Table 11 presents results from studies that conducted direct comparisons of TIMs with adjustment for baseline confounding factors. In the majority of studies, infliximab was associated with the highest incidence of serious infections.[23,63,68,74,75]

The largest cohort study analyzed data of more than 130,000 patients (more than 100,0000 patient-years of follow-up) from 3 US databases (Medicare, Optum, and MarketScan) for the comparison of tofacitinib and TNF-α inhibitors, abatacept, or tocilicumab.[23] Authors combined data from the 3 databases and adjusted analyses for more than 60 potential confounders.[23] Risk of serious infections (bacterial, viral, or opportunistic infections requiring hospital admission) was significantly higher for tofacitinib compared with etanercept (aHR, 1.41; 95% CI, 1.15 to 1.73).[23] However, the study did not find any statistically significant differences for the comparison of tofacitinib and other TNF-α inhibitors (adalimumab, certolizumab pegol, golimumab, infliximab), tocilizumab, or abatacept.[23]

A recent observational study using propensity score-matched data of more than 49,000 patients from 3 US databases (IMS LifeLink PharMetrics Plus, MarketScan, and Medicare) reported no statistically significant difference in serious infections for tocilizumab (N = 16,074) compared with TNF-α inhibitors (N = 33,109; 3 databases combined: hazard ration (HR), 1.05; 95% CI, 0.95 to 1.16).[38] Propensity matching was applied to control for more than 70 baseline covariates (i.e., potential prognostic factors or confounders) within each database.[38] Serious infections included bacterial, viral, or opportunistic infection based on discharge diagnoses.[38] The authors also reported a statistically significant higher risk of serious infections in patients treated for RA with tocilizumab (N = 10,414) compared with abatacept (N = 10,414; 3 databases combined: HR, 1.40; 95% CI, 1.20 to 1.63).[38]

A cohort study used data from more than 19,000 patients (more than 46,000 patient-years of follow-up) from the British BSRBR-RA (British Society for Rheumatology Biologics Register for Rheumatoid Arthritis) registry.[37] Authors reported that compared with etanercept, the incidence of serious infections was statistically significant higher for tocilizumab (HR, 1.22; 95% CI, 1.02 to 1.47) but lower for certolizumab pegol (HR, 0.75; 95% CI, 0.58 to 0.97).[37] However, the authors found no statistically significant differences for infliximab, adalimumab, or rituximab compared with etanercept.[37]

Table 11. Serious Infections in Adults With RA: Head-to-head Comparisons of TNF-α Inhibitors With One Another, Abatacept, Rituximab, or Head-to-head Comparison of TIMs Other Than TNF-α inhibitors

Authors, Year	Result	Risk of Bias
TNF-α inhibitor vs. TNF-α inhibitor		
Adalimumab vs. etanercept		
Galloway et al., 2011[65]	No significant difference	Low
Rutherford et al., 2018[37]	No significant difference	Moderate
Adalimumab vs. infliximab		
Galloway et al., 2011[65]	No significant difference	Low
Grijalva et al., 2011[68]	Significantly lower for adalimumab vs. infliximab (aHR, 0.81; 95% CI, 0.68 to 0.98)	Moderate
Curtis et al., 2012[63]	Significantly lower for adalimumab vs. infliximab (aHR, 0.67; 95% CI, 0.48 to 0.95)	Moderate
Etanercept vs. infliximab		
Galloway et al., 2011[65]	No significant difference	Low
Grijalva et al., 2011[68]	Significantly lower for etanercept vs. infliximab (aHR, 0.79; 95%, 0.68 to 0.93)[a]	Moderate
Curtis et al., 2012[63]	Significantly lower for etanercept vs. infliximab (aHR, 0.66; 95% CI, 0.47 to 0.93)[a]	Moderate
Rutherford et al., 2018[37]	No significant differences	Moderate
Certolizumab pegol vs. etanercept		
Rutherford et al., 2018[37]	Significantly lower for certolizumab pegol vs. etanercept (aHR, 0.75; 95% CI, 0.58 to 0.97)	Moderate
TNF-α inhibitor vs. abatacept		
Adalimumab vs. abatacept		
Yun et al., 2016[75]	No significant difference	Low
Certolizumab pegol vs. abatacept		
Yun et al., 2016[75]	No significant difference	Low
Etanercept vs. abatacept		
Yun et al., 2016[75]	Significantly higher for etanercept vs. abatacept (aHR, 1.24; 95% CI, 1.07 to 1.45)	Low
Golimumab vs. abatacept		
Yun et al., 2016[75]	No significant difference	Low
Infliximab vs. abatacept		
Yun et al., 2016[75]	Significantly higher for infliximab vs. abatacept (aHR, 1.39; 95% CI, 1.21 to 1.60)	Low
Pooled TNF-α inhibitors vs. abatacept		
Patel et al., 2021[16]	First-line: Significantly higher for pooled TNF-α inhibitors vs. abatacept (aHR, 1.59; 95% CI, 1.43 to 1.77) Second-line: Significantly higher for pooled TNF-α inhibitors vs. abatacept (aHR, 1.48; 95% CI, 1.26 to 1.75)	Moderate

Authors, Year	Result	Risk of Bias
TNF-α inhibitor vs. rituximab		
Etanercept vs. rituximab		
Curtis et al., 2014[93]	No significant difference	Low
Rutherford et al., 2018[37]	No significant difference	Moderate
TNF-α inhibitor vs. tocilizumab		
Etanercept vs. tocilizumab		
Rutherford et al., 2018[37]	Significantly lower for etanercept vs. tocilizumab (aHR, 0.82; 95% CI, 0.68 to 0.98)[a]	Moderate
Pooled TNF-α inhibitors vs. tocilizumab		
Pawar et al., 2019[38]	No significant differences	Moderate
TNF-α inhibitor vs. tofacitinib		
Pawar et al., 2020[23]	Significantly higher for tofacitinib vs. etanercept (aHR, 1.41; 95% CI, 1.15 to 1.73)	Low
Non-TNF-α inhibitor vs. non-TNF-α inhibitor		
Abatacept vs. rituximab		
Yun et al., 2016[75]	Significantly lower for abatacept vs. rituximab (aHR, 0.73; 95% CI, 0.65 to 0.83)[a]	Low
Tocilizumab vs. abatacept		
Yun et al., 2016[75]	No significant difference	Low
Pawar et al. 2019[38]	Significantly higher for tocilizumab vs. abatacept (aHR, 1.40; 95% CI, 1.20 to 1.63)	Moderate
Tofacitinib vs. tocilizumab		
Pawar et al., 2020[23]	No significant difference	Low

Note. [a] Direction of comparison was reversed vs. how it was reported in the study publication.
Abbreviations. aHR: adjusted hazard ratio; CI: confidence interval; RA: rheumatoid arthritis; TIM: targeted immune modulator; TNF-α: tumor necrosis factor-alpha; vs.: versus.

A large retrospective observational study using Medicare data (more than 31,000 new treatment episodes) consisted of patients with RA who started a new course of treatment with abatacept, adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, rituximab, or tocilizumab following a previous treatment with a different TIM agent.[75] The outcome of interest was the first hospitalized infection during 12 months of follow-up.[75] Overall, 2,530 patients were hospitalized for infections, yielding a crude incidence rate of 15.3 infections per 100 person-years (95% CI, 14.7 to 15.9).[75] In adjusted analyses, patients on etanercept (1.24; 95% CI, 1.07 to 1.45), infliximab (1.39; 95% CI, 1.21 to 1.60), and rituximab (1.36; 95% CI, 1.21 to 1.53) had statistically significantly higher HRs for serious infections than patients on abatacept.[75] No statistically significant differences could be detected among other TIM agents.[75] A subgroup analysis of patients who were previously hospitalized because of an infection confirmed a higher risk of infliximab compared with abatacept and etanercept.[74]

Another observational study analyzed Medicare data with more than 40,000 patients with RA who were either naïve to TIMs treatment and received a TNF-α inhibitor or abatacept or switched from TNF-α inhibitors to a second-line treatment (other TNF-α inhibitor or

abatacept).[16] In the TIMs-naïve RA patients, authors found a statistically significantly higher risk of infection-related hospitalization in patients treated with a TNF-α inhibitor (considered as a class) compared with abatacept (N = 30,439; aHR, 1.59; 95% CI, 1.43 to 1.77).[16] Likewise for second-line treatments, TNF-α inhibitor were associated with a higher risk of serious infections than abatacept (N = 11,397; aHR, 1.48; 95% CI, 1.26 to 1.75).[16]

Tuberculosis

We located 3 retrospective studies that reported on the comparative risk of tuberculosis in patients taking TIMs.[35,60,64] Studies provided data on 10,712[64] and 19,282[35] RA patients from the British Society for Rheumatology Biologics Register, and 10,800 RA patients from Swedish registers.[60]

The British registry study of more than 10,000 RA patients treated with adalimumab, etanercept, or infliximab, 40 cases of tuberculosis occurred in more than 28,000 patient-years of follow-up (rate, 95 per 100,000 patient-years; 95% CI, 63 to 138).[64] A comparative analysis showed a statistically significant increased risk of tuberculosis for patients treated with adalimumab compared with those on etanercept (adjusted incidence rate ratio [aIRR], 4.2; 95% CI, 1.4 to 12.4).[64] The incidence rate of tuberculosis was higher for infliximab than etanercept; IRR almost reached statistical significance (3.1; 95% CI, 1.0 to 9.5).[64] The median time to event was 13.4 months from start of therapy.[64] Considering that the rates of tuberculosis infection in Britain are higher than in the US, the absolute rates may be lower, but it is unlikely that the relative rates across the drugs would differ.[94,95]

Another study based on British registry data found significantly lower incidence of tuberculosis for patients receiving rituximab (12 events per 100,000 patient-years) compared with those treated with TNF-α inhibitors (65 events per 100,000 patient-years; aHR, 0.16; 95% CI, 0.04 to 0.67).[35]

Data from Swedish registers (National Population Registers, Tuberculosis Register, Biologics Register) with 10,800 RA patients starting their first biological drug compared the risk of tuberculosis for abatacept, adalimumab, anakinra, certolizumab pegol, etanercept, golimumab, infliximab, rituximab, and tocilizumab.[60] The crude incidence rates for tuberculosis per 100,000 person-years were numerically highest for infliximab (67.2; 95% CI, 29.0 to 132.4), followed by adalimumab (52.4; 95% CI, 19.2 to 114.1), rituximab (29.0; 95% CI, 0.7 to 161.7), and etanercept (15.7; 95% CI, 3.2 to 46.0).[60] In these databases, no cases of tuberculosis were seen in patients treated with abatacept, anakinra, certolizumab pegol, golimumab, and tocilizumab.[60] Adjusted HRs did not detect any statistically significant differences in the risk for tuberculosis among any of the treatments.[60] However, these results might be due to lack of statistical power, as this study analyzed fewer patient-years than the studies reported above.

Opportunistic Infections

Three cohort studies provided data on opportunistic infections.[35,38,61] The moderate-RoB SABER study (SAfety Assessment of Biologic ThERapy) included US patients with different autoimmune diseases treated with TNF-α inhibitors.[61] An analysis of data of 24,384 patients treated for RA indicated a higher incidence of nonviral opportunistic infections for infliximab than etanercept (aHR, 2.9; 95% CI, 1.5 to 5.4).[61] In the same study the difference between adalimumab and

etanercept was not statistically significant (aHR, 1.8; 95% CI, 0.8 to 4.0).[61] Overall, 67 opportunistic infections were diagnosed in TNF-α drug users.[61]

The authors of 2 large observational studies including more than 69,000 patients reported no statistically significant difference for TNF-α inhibitors (different pooled drugs) compared with tocilizumab or rituximab.[35,38] In general, the number of opportunistic infections was low.[35,38] For example, authors of 1 observational study that analyzed 19,282 patient data from the BSRBR-RA in the United Kingdom found no significant difference in rates of opportunistic infections (excluding tuberculosis) in patients treated with TNF-α inhibitors (adalimumab, certolizumab pegol, etanercept, infliximab) compared with rituximab (aHR, 0.96; 95% CI, 0.62 to 1.50) or tocilizumab (aHR, 0.52; 95% CI, 0.17 to 1.65).[35] Overall, the incidence of opportunistic infections (excluding tuberculosis) was 134 per 100,000 patient-years.[35] The most common were herpes zoster (n = 54), pneumocystis jirovecii (n = 15), and legionella (n = 11).[35]

Varicella Zoster

Five observational studies provided evidence on the comparative risk of varicella zoster virus infections (herpes zoster, chicken pox, or shingles) in more than 100,000 RA patients.[23,24,62,67,71] All studies performed statistical adjustment for baseline risk including age, sex, race, residence, disease duration, disease severity, and others.[23,24,62,67,71]

Three studies found the numerically highest risk for herpes zoster in patients treated with tofacitinib.[23,24,62] Incidence rates per 100 person-years were 3.72 (95% CI, 3.12 to 4.40),[23] 7.61 (95% CI, 6.06 to 9.55),[62] and 36.8 (95% CI, 22.2 to 61.0).[24] The study with the highest risk included only patients with RA and diabetes.[24]

The largest of these 3 cohort studies analyzed data of more than 130,00 patients (1,952 herpes zoster, 100,541 patient-years of follow-up) from 3 US databases (MarketScan, Medicare, and Optum Clinformatics).[23] In adjusted analysis, authors found a statistically significant higher risk of herpes zoster for tofacitinib compared with different TNF-α inhibitors (adalimumab: aHR, 1.99; 95% CI, 1.63 to 2.43; certolizumab pegol: aHR, 2.24; 95% CI, 1.68 to 2.99; etanercept: aHR, 2.12; 95% CI, 1.73 to 2.58; golimumab: aHR, 1.84; 95% CI, 1.35 to 2.50; infliximab: aHR, 1.94; 95% CI, 1.51 to 2.50); tocilizumab (aHR, 2.14; 95% CI, 1.53 to 2.99); or abatacept (aHR, 1.94; 95% CI, 1.53 to 2.44). [23]

Another study that used MarketScan and Medicare data of almost 58,000 patients with RA[62] assessed the risk for herpes zoster and herpes simplex in patients treated with abatacept, adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, rituximab, tocilizumab, and tofacitinib.[62] Compared with abatacept, the risk for tofacitinib was significantly higher (aHR, 1.40, 95% CI, 1.09 to 1.81).[62] The study used abatacept as the reference drug for all comparisons.[62] Risks of all other drugs were not significantly different than the risk of abatacept.[62] Nevertheless, results should be interpreted with caution because only 74 patients treated with tofacitinib had a herpes zoster or herpes simplex infection.[62]

A smaller study that analyzed MarketScan data of 10,019 patients with RA and diabetes mellitus observed a significantly higher risk of herpes zoster with tofacitinib (aHR, 2.16; 95% CI, 1.09 to 4.28), tocilizumab (aHR, 1.98; 95% CI, 1.06 to 3.68), and rituximab (aHR, 1.82; 95% CI, 1.02 to 3.24) compared with abatacept. The risk of TNF-α inhibitors as a class was not significantly

higher than the risk of abatacept (aHR, 1.48; 95% CI, 0.88 to 2.49).[24] However, the overall number of events was low.[24]

Two studies focused on the comparative risks of the TNF-α inhibitors adalimumab, etanercept, and infliximab.[67,71] Adalimumab had the lowest HR for herpes zoster,[67,71] and this difference was significant for the comparison with infliximab in 1 study (HR, 1.5; 95% CI, 1.1 to 2.0).[67] Two studies found no significant difference between etanercept and infliximab (HR, 1.09; 95% CI, 0.82 to 1.45).[67,71]

Malignancies

We found 1 large observational study with pooled data from 3 US databases (IMS LifeLink PharMetrics Plus, MarketScan, and Medicare) analyzing the incidence of any malignancy (excluding melanoma or nonmelanoma skin cancer) in patients with RA.[34] Authors found no significant difference for the risk of malignancy for tocilizumab compared with abatacept.[34]

Nonmelanoma and Melanoma Skin Cancer

We found 1 publication reporting on incidence of nonmelanoma skin cancers for patients receiving the TNF-α inhibitors adalimumab, etanercept, or infliximab.[69] The risk of basal cell carcinoma was not significantly different for adalimumab and etanercept compared with infliximab.[69]

Cardiovascular Events and Congestive Heart Failure

Three studies reported on the comparative risks of cardiovascular events in patients treated with TIMs.[33,72,76] The largest study, a retrospective cohort study, used data from more than 47,000 Medicare patients with RA.[76] The study assessed the risk of cardiovascular events in patients treated with abatacept compared with patients on other TIMs (adalimumab, certolizumab pegol, etanercept, infliximab, rituximab, tocilizumab, golimumab).[76] TNF-α inhibitors, in general, had higher risks of cardiovascular events than abatacept.[76] The differences reached statistical significance for myocardial infarction, with higher risks for etanercept (HR, 1.33; 95% CI, 1.01 to 1.76) and infliximab (HR, 1.30; 95% CI, 1.03 to 1.64) compared with abatacept.[76]

A retrospective analysis of 3 US databases (IMS LifeLink PharMetrics Plus, MarketScan, and Medicare) with about 21,000 propensity score–matched patients (16,280 person-years) found no significant difference for incidence of the composite cardiovascular endpoint hospitalization due to myocardial infarction or stroke for tocilizumab compared with abatacept (combined HR, 0.82; 95% CI, 0.55 to 1.22).[33] However, the number of events in this study was low (tocilizumab, 32 events; abatacept, 112 events).[33] One retrospective cohort study with high RoB did not detect significant differences in risk for incident heart failure between etanercept and infliximab.[72]

Gastrointestinal Perforations

Two retrospective cohort studies examined the comparative risk for lower gastrointestinal perforations.[70,73] Both studies showed a significantly higher incidence of lower gastrointestinal perforations in patients using tocilizumab compared with any TNF-α inhibitor (aHR, 2.51; 95% CI, 1.31 to 4.80;[73] aIRRs, 4.0; 95% CI, 1.1 to 14.1[70]). One study used MarketScan and Medicare data for 167,113 patients with RA, of whom 106 patients experienced lower gastrointestinal perforations.[73] Authors of a second study using data from the US health care

claims database MarketScan analyzed the incidence rates of gastrointestinal perforations, including 27,255 patients with RA.[70] In addition to the higher risk for lower gastrointestinal perforations in patients using tocilizumab compared with any TNF-α inhibitor, the authors found no significant differences among the drugs for perforations in the entire gastrointestinal tract.[70] However, depending on the definition of the condition, only 16 to 23 cases of lower gastrointestinal perforations occurred in this study.[70] We did not find any information on the number of participants experiencing these events.[70]

Venous Thromboembolism

One cohort study provided data on the incidence of venous thromboembolism (composite endpoint of pulmonary embolism or deep venous thrombosis).[22] The study analyzed data of 87,653 patients (81,125 person-years) included in 3 US databases (MarketScan, Medicare, and Optum Clinformatics).[22] Overall, 365 cases of venous thromboembolism were diagnosed in 80,879 patients treated with a TNF-α inhibitor (incidence rate 0.48 per 100 person-years) and 29 in 6,774 participants receiving tofacitinib (incidence rate 0.55 per 100 person-years).[22] In propensity score weighted analysis, authors found no significant difference for the incidence of venous thromboembolism for tofacitinib compared with any TNF-α inhibitor (combined HR, 1.13; 95% CI, 0.77 to 1.65).[22]

Ankylosing Spondylitis

Comparative Efficacy (KQ1)

We identified 1 open-label, head-to-head study[25] for the treatment of ankylosing spondylitis. The Summary of Findings (GRADE) for these comparisons are in Table 12, with a detailed evidence profile in Appendix C, Table C4. Table 13 presents a summary of efficacy outcomes. Appendix B, Table B1 and Table B3 provide detailed study characteristics and results from the included RCT. Appendix D summarizes instruments used to measure outcomes in ankylosing spondylitis trials.

Table 12. Summary of Findings (GRADE) for TIMs for the Treatment of Ankylosing Spondylitis

Outcome	Certainty of Evidence	Relationship	Rationale
Etanercept vs. infliximab			
Clinical improvement (1 RCT[25])	Very Low ●○○○	Higher proportion of improvement for infliximab than etanercept	Downgraded 1 level for RoB and 2 levels for very serious imprecision

Abbreviations. GRADE: Grading of Recommendations, Assessment, Development, and Evaluation approach; RCT: randomized controlled trial; RoB: risk of bias; TIM: targeted immune modulator.

Etanercept vs. Infliximab

We included 1 high-RoB open-label RCT of 50 enrolled participants with ankylosing spondylitis who had not responded to nonsteroidal antiinflammatory drugs (NSAIDs).[25] All patients were naïve to DMARDs and TIMs.[25] Participants were randomized to etanercept (50 mg weekly) or infliximab (5 mg/kg at weeks 0, 2, 6, and every 6 weeks) for a follow-up period of 102 weeks.[25] Authors do not report whether dose adjustments for infliximab were allowed.[25] The primary endpoints were the Assessment of SpondylArthritis International Society (ASAS) 20 and ASAS 40 responses at 12, 54, and 102 weeks.[25] After 12 weeks, fewer participants on etanercept than on infliximab achieved ASAS 20 (60% vs. 75%; *P* value NR) and ASAS 40 responses (43% vs. 55%; *P* value NR).[25] The Bath Ankylosing Spondylitis Activity Index (BASDAI; 4.8 vs. 5.9; $P < .005$) was significantly lower for etanercept than infliximab. No significant differences were reported at weeks 54 and 102.[25]

Table 13. Brief Evidence Table for Efficacy Outcomes in Adults for TIMs for Ankylosing Spondylitis

Authors, Year	Study Design Number of Participants	Duration	Comparisons	Outcomes	Population	Results	Risk of Bias
Etanercept vs. infliximab							
Giardina et al., 2010[25]	Open-label RCT 50	12 and 102 weeks	Etanercept 50 mg weekly SC vs. infliximab 5 mg/kg every 6 weeks IV	Primary: ASAS 20, ASAS 40 Secondary: BASDAI, BASFI	Active ankylosing spondylitis without response to nonsteroidal antiinflammatory drugs; mean duration of disease: 15 years	Better efficacy for infliximab than etanercept	High

Abbreviations. ASAS: Assessment of SpondylArthritis International Society, numbers refer to percentage improvement; BASDAI: Bath Ankylosing Spondylitis Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; IV: intravenous administration; kg: kilogram; mg: milligram; RCT: randomized controlled trial; SC: subcutaneous administration; TIM: targeted immune modulator; vs: versus.

Effectiveness and Harms of Pipeline TIM Agents

We identified 1 new placebo-controlled, double-blind RCT on bimekizumab for the treatment of ankylosing spondylitis.[20] Appendix B, Table B1 and Table B3 provide detailed study characteristics and results from the included RCT. The Summary of Findings (GRADE) for this comparison is in

Table 14 with detailed evidence profiles in Appendix C, Table C4 and Table C5. Table 15 presents a summary of efficacy and harms outcomes.

Table 14. Summary of Findings (GRADE) for Pipeline Drugs for the Treatment of Ankylosing Spondylitis

Outcome	Certainty of Evidence	Relationship	Rationale
Bimekizumab vs. placebo			
Clinical improvement (1 RCT[20])	Moderate ●●●○	Higher proportion of improvement for bimekizumab than placebo	Downgraded 1 level for imprecision
Functional ability (1 RCT[20])	Moderate ●●●○	Higher proportion of increased functional ability for bimekizumab than placebo	Downgraded 1 level for imprecision
Overall AEs (1 RCT[20])	Low ●●○○	No difference between groups	Downgraded 2 levels for imprecision
SAEs (1 RCT[20])	Low ●●○○	No difference between groups	Downgraded 2 levels for imprecision

Abbreviations. AE: adverse events; GRADE: Grading of Recommendations, Assessment, Development, and Evaluation approach; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus.

Bimekizumab vs. Placebo

One new low-RoB RCT, the BE AGILE (no acronym) trial, assessed the efficacy and harms of bimekizumab compared with placebo in 303 participants who had active ankylosing spondylitis for at least 3 months.[20] The study randomized participants to bimekizumab 16 mg SC every 4 weeks, bimekizumab 64 mg SC every 4 weeks, bimekizumab 160 mg SC every 4 weeks, bimekizumab 320 mg SC every 4 weeks, or placebo.[20] The primary outcome was the change from baseline to week 12 in ASAS 40 response.[20] After 12 weeks, more participants treated with bimekizumab 16 mg, bimekizumab 64 mg, bimekizumab 160 mg, and bimekizumab 320 mg, than on placebo achieved ASAS 20 (41.0% vs. 62.3% vs. 58.3% vs. 72.1% vs. 28.3%; *P* value NR) and ASAS 40 response (29.5% vs. 42.6% vs. 46.7% vs. 45.9% vs. 13.3%; *P* value NR).[20]

Participants in the bimekizumab groups also showed greater clinical improvement on the BASDAI score than participants treated with placebo (bimekizumab 16 mg: −1.7; bimekizumab 64 mg: −2.7; bimekizumab 160 mg: −2.5; bimekizumab 320 mg: −2.9; placebo: −1.0; *P* = NR). Likewise, participants in the bimekizumab groups improved in functional ability, which was measured by the BASFI (bimekizumab 16 mg, −1.4; bimekizumab 64 mg, −1.9, bimekizumab 160 mg, −1.7; bimekizumab 320 mg, −2.2; placebo, −0.6; *P* value NR).[20]

The incidence of treatment-emergent AEs was similar in the bimekizumab groups compared with placebo (bimekizumab 16 mg: RR, 1.97; 95% CI, 0.18 to 21.13; bimekizumab 64 mg: RR, 1.03; 95% CI, 0.07 to 16.15; bimekizumab 160 mg: RR, 0.95; 95% CI, 0.06 to 14.89; bimekizumab 320 mg: RR, 1.97; 95% CI, 0.18 to 21.13). Likewise, the incidence of treatment-emergent SAEs was similar in the bimekizumab groups compared with placebo (bimekizumab 16 mg: not estimable; bimekizumab 64 mg: RR, 1.03; 95% CI, 0.15 to 7.10; bimekizumab 160 mg: RR, 0.48; 95% CI, 0.04 to 5.12; bimekizumab 320 mg: not estimable).[20]

Table 15. Efficacy and Harm Outcomes from RCTs for Pipeline TIMs in Ankylosing Spondylitis

Authors, Year Trial Number Trial Name	Dose, Frequency N Randomized	Primary Study Endpoint; Difference From Comparator (95% CI, or SD and P-Value)	SAEs RR (95% CI)	Discontinuation Due to AEs RR (95% CI)	Risk of Bias
Bimekizumab vs. placebo					
van der Heijde et al., 2020[20] NCT02963506 BE AGILE	• Bimekizumab 16 mg SC every 4 weeks • Bimekizumab 64 mg every 4 weeks • Bimekizumab 160 mg every 4 weeks • Bimekizumab 320 mg every 4 weeks • Placebo every 4 weeks	ASAS40 response at 12 weeks: • Bimekizumab 16 mg: 18 of 61 (29.5%) • Bimekizumab 64 mg: 26 of 61 (42.6%) • Bimekizumab 160 mg: 28 of 60 (46.7%) • Bimekizumab 320 mg: 28 of 61 (45.9%) • Placebo: 8 of 60 (13.3%)	• Bimekizumab 16 mg: not estimable[a] • Bimekizumab 64 mg: 1.03 (0.15 to 7.10) • Bimekizumab 160 mg: 0.48 (0.04 to 5.12) • Bimekizumab 320 mg: not estimable[a]	• Bimekizumab 16 mg: 1.97 (0.18 to 21.13) • Bimekizumab 64 mg: 1.03 (0.07 to 16.15) • Bimekizumab 160 mg: 0.95 (0.06 to 14.89) • Bimekizumab 320 mg: 1.97 (0.18 to 21.13)	Low

Authors, Year Trial Number Trial Name	Dose, Frequency N Randomized	Primary Study Endpoint; Difference From Comparator (95% CI, or SD and P-Value)	SAEs RR (95% CI)	Discontinuation Due to AEs RR (95% CI)	Risk of Bias
	Total N = 303	• Bimekizumab 16 mg vs. placebo: OR, 2.6 (95% CI: 1.0 to 6.5) • Bimekizumab 64 mg vs. placebo: OR, 4.5 (95% CI: 1.8 to 10.9) • Bimekizumab 160 mg vs. placebo: OR, 5.5 (95% CI: 2.3 to 13.5) • Bimekizumab 320 mg vs. placebo: OR, 5.3 (95% CI: 2.2 to 12.9)			

Note. [a] RR not estimable with OpenEpi due to no events in 1 group.
Abbreviations. AE: adverse event; ASAS40: ≥ 40% improvement in the Assessment of SpondyloArthritis international Society measure; CI: confidence interval; mg: milligram; OR: odds ratio; RCT: randomized controlled trial; RR: risk ratio; SAE: serious adverse event; SC: subcutaneous; SD: standard deviation; TIM: targeted immune modulator; vs: versus.

Comparative Harms (KQ2)

General Tolerability Findings from RCTs

In the previous report, we identified 1 RCT that reported on general tolerability; the study had no discontinuations due to AEs, but overall AEs and SAEs were not reported (Table 16).[25] Appendix B, Table B1 and Table B3 provide detailed study characteristics and results from the included RCT.

Specific Serious Adverse Events Findings from Cohort Studies

We did not identify any eligible comparative cohort studies for ankylosing spondylitis.

Table 16. Summary of AEs From RCTs in Adults Receiving TIMs for Ankylosing Spondylitis

Authors, Year	Number of Participants Randomized (Without Placebo Arms)	Duration	Overall AEs RR (95% CI)[a]	Discontinuation Due to AEs RR (95% CI)[a]	SAEs RR (95% CI)	Summary of Results	Risk of Bias
Etanercept vs. infliximab							
Giardina et al., 2010[25]	50	102 weeks	NR	Not estimable	NR	No significant differences.	High

Note. [a] RR not estimable with OpenEpi due to no events in both groups.
Abbreviations. AE: adverse event; CI: confidence interval; NR: not reported; RCT: randomized controlled trial; RR: risk ratio; SAE: serious adverse event; TIM: targeted immune modulator; vs.: versus.

Ongoing Studies (KQ4)

We identified 20 ongoing head-to-head studies evaluating the comparative effectiveness or harms of TIM agents[96-115], and 1 ongoing placebo-controlled trial on pipeline drugs[116] (Table 17) for RA and ankylosing spondylitis. Of the 21 ongoing studies, 19 are RCTs[96-100,103-116] and 2 are retrospective cohort designs[101,102]. Seventeen ongoing studies[96,101-116] include participants with RA and 4 include participants with ankylosing spondylitis[97-100]. The pharmaceutical industry is funding almost all of the identified RCTs[96-100,103-116], while both cohort studies are nonindustry funded.[101,102]

Table 17. Ongoing Studies of Comparative Effectiveness or Harms of TIMs in RA and Ankylosing Spondylitis

Registration Number Trial Name Phase	Treatment Groups; Blinded vs. Open	N Estimated[a] or Actual Enrollment (Status) Treatment Duration	Study Completion Date[b]	Primary Outcome(s)
Abatacept vs. adalimumab [RA]				
NCT03619876[103] Effects of Abatacept on Myocarditis in RA (AMiRA) Phase 4	Abatacept adalimumab Open	N = 20 (Recruiting) 16 weeks	December 2022 (Estimated)	Change in myocardial FDG uptake at 16 weeks
NCT04909801[104] A Randomized, Head-to-head, Single-blind Study to Compare the Response to Treatment With Subcutaneous Abatacept vs Adalimumab, on Background Methotrexate, in Adults With Early, Seropositive Rheumatoid Arthritis Who Have "Shared Epitope" HLA Class II Risk Alleles and Have an Inadequate Response to Methotrexate Phase 3	Abatacept, adalimumab Blinded	N = 300 (Recruiting) 24 weeks	May 2025 (Estimated)	Proportion of shared epitope-positive (SE+) participants meeting 50% improvement in ACR50 response at week 24
Abatacept vs. certolizumab pegol vs. tocilizumab [RA]				
NCT01491815[105] A Multicenter, Randomized, Open-label, Blinded-assessor, Phase 4 Study in Patients With Early RA to Compare Active Conventional Therapy Versus Three Biologic Treatments, and Two De-escalation Strategies in Patients Who Respond to Treatment Phase 4	Abatacept 125 mg, certolizumab pegol 200 mg, tocilizumab (4 weekly infusions at dosage 8 mg/kg or 162 mg in solution every week) Open	N = 812 (Active, not recruiting) 56 weeks	December 2021 (Estimated)	Remission according to CDAI at week 24
ABBV-3373 vs. adalimumab vs. placebo [RA]				
NCT03823391[106 c] A Randomized, Double-Blind, Double-Dummy, Active-Controlled Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Efficacy of ABBV-3373 in Subjects With Moderate-to-Severe RA Phase 2	ABBV-3373, adalimumab, placebo Blinded	N = 48 (Completed) 22 weeks	August 2020 (Actual)	Change in DAS28-CRP from baseline for ABBV-3373 and adalimumab at 12 weeks

Registration Number Trial Name Phase	Treatment Groups; Blinded vs. Open	N Estimated[a] or Actual Enrollment (Status) Treatment Duration	Study Completion Date[b]	Primary Outcome(s)
Abatacept vs. tocilizumab [RA]				
NCT03227419[107] Abatacept Versus Tocilizumab by Subcutaneous Administration for the Treatment of RA in TNF-α inhibitor Inadequate Responder Patients: A Randomized, Open-labelled, Superiority Trial (SUNSTAR) Phase 4	Abatacept, tocilizumab Open	N = 224 (Recruiting) 52 weeks	November 2022 (Estimated)	Change of the CDAI at 6 months
Adalimumab vs. baricitinib vs. etanercept [RA]				
NCT03915964[108] A Randomized, Active-Controlled, Parallel-Group, Phase 3b/4 Study of Baricitinib in Patients With RA (RA-BRIDGE) Phase 4	Adalimumab, baricitinib, etanercept Open	N = 2,600 (Active, not recruiting) 5.5 years	February 2026 (Estimated)	Time from first dose of study treatment to first event of venous thrombo-embolism
Adalimumab vs. etanercept vs. tofacitinib [RA]				
NCT02092467[109c] Phase 3b/4 Randomized Safety Endpoint Study of 2 Doses of Tofacitinib in Comparison to a Tumor Necrosis Factor (TNF) inhibitor in Subjects With RA Phase 4	Adalimumab, etanercept, tofacitinib Open	N = 4,414 (Completed) 5 years	September 2020 (Actual)	Malignancies, excluding non-melanoma skin cancer at 5 years
Baricitinib vs. adalimumab [RA]				
NCT04870203[110] Combination of Baricitinib and Adalimumab vs. Baricitinib in Patients With Rheumatoid Arthritis: a Randomized Placebo-controlled Phase III Trial (CRI-RA) Phase 3	Adalimumab, baricitinib, placebo NR	N = 178 (Recruiting) 4 years	July 2025 (Estimated)	Proportion of patients who achieve an ACR50 response at week 24
Baricitinib vs. etanercept [RA]				
EudraCT number: 2018-004558-30[111] Synovial ultrasound as Primary Outcome in a 3-Arm, Randomized, Open-Label, Parallel Active-Controlled,	Baricitinib, etanercept Open	N = 186 (NR)	NR	Decrease in joint inflammation detected by

Registration Number Trial Name Phase	Treatment Groups; Blinded vs. Open	N Estimated[a] or Actual Enrollment (Status) Treatment Duration	Study Completion Date[b]	Primary Outcome(s)
Multicenter International Study Comparing Baricitinib, Alone and Combined With MTX Versus TNF-α inhibitor in RA Patients: Searching for Synovium Predictors of Response Phase 4		24 weeks		Musculoskeletal ultrasound (B-mode and doppler mode synovitis)
Baricitinib vs. TNF-α inhibitor [RA]				
NCT04086745[112] A Randomized, Controlled Pragmatic Phase 3b/4 Study of Baricitinib in Patients With Rheumatoid Arthritis (RA-BRANCH) Phase 4	Baricitinib, TNF-α inhibitor (Etanercept, adalimumab) Open	N = 1,300 (Recruiting) 5.5 years	December 2024 (Estimated)	Time from first dose of study treatment to first event of venous thrombo-embolism
Etanercept vs. tofacitinib [RA]				
NCT03976245[113 c] Advanced Therapeutics in RA Phase 4	Etanercept, tofacitinib Open	N = 144 (Unknown) 24 months	September 2021 (Estimated)	Retention rates at 24 months
Etanercept vs. rituximab vs. tocilizumab [RA]				
ISRCTN43336433[114 c] Stratification of biologic Therapies for RA by Pathobiology: A Randomised, Open-Labelled Biopsy-Driven Stratification Trial in DMARD Inadequate Responder Patients Randomised to Etanercept, Tocilizumab or Rituximab (STRAP-EU) NR	Etanercept, rituximab, tocilizumab Open	N = 226 (Completed) 48 weeks	January 2021 (Actual)	Response using ACR20 at week 16
ISRCTN10618686[115 c]; EudraCT number: 2014-003529-16 Stratification of Biologic Therapies for RA by Pathobiology (STRAP): A Randomised, Open-Labelled Biopsy-Driven Stratification Trial in DMARD Inadequate Responder Patients Randomised to Etanercept, Tocilizumab or Rituximab,	Etanercept, rituximab, tocilizumab Open	N = 219 (Completed) 48 weeks	January 2021 (Actual)	Response using ACR20 at week 16

Registration Number Trial Name Phase	Treatment Groups; Blinded vs. Open	N Estimated[a] or Actual Enrollment (Status) Treatment Duration	Study Completion Date[b]	Primary Outcome(s)
Phase 3				
Peficitinib vs. placebo [RA]				
NCT03660059[116] [c] A Randomized, Double-Blind, Placebo-Controlled Confirmatory Study of the Safety and Efficacy of ASP015K in Patients With Rheumatoid Arthritis (RA) Who Had an Inadequate Response or Intolerance to MTX, Phase 3	Peficitinib (ASP015K), placebo Blinded	N = 385 (Completed) 24 weeks	November 2021 (actual)	ACR20 response rate at week 24
Tocilizumab vs. TNF-α inhibitor [RA]				
NCT03100253[96] Open-label, Randomized Controlled Trial Comparing Tocilizumab to Anti-TNF Treatment and Discovery of Biomarkers for Treatment Selection in RA Patients With Inadequate Response to a First Anti-TNF (RAFTING), Phase 4	Tocilizumab, TNF-α inhibitor (etanercept, infliximab, adalimumab, golimumab, certolizumab pegol) Open	N = 400 (Recruiting) 96 weeks	December 2023 (Estimated)	Proportion of patients with good EULAR at 24 weeks
Adalimumab vs. secukinumab [ankylosing spondylitis]				
NCT03906136[97] A Randomized, Open-Label Multicenter Trial to Investigate the Efficacy of a Treat-to-Target Treatment Strategy With Secukinumab (AIN457) as a First-Line Biologic Compared to a Standard-of-Care Treatment Over 36 Weeks in Patients With Active Axial Spondyloarthritis (axSpA) – Ascalate Phase 3	Adalimumab, secukinumab 150 mg, secukinumab 300 mg, standard-of-care (NR) Open	N = 300 (Active, not recruiting) 36 weeks	September 2022 (Estimated)	Clinical response assessments in ASAS 40 at week 24
NCT03259074[98] [c] A Randomized, Partially-blinded Study of Secukinumab to Demonstrate Reduction of Radiographic Progression Versus GP2017 (Adalimumab Biosimilar) at 104 Weeks and to Assess the Long-Term Safety, Tolerability and Efficacy up	Adalimumab, secukinumab 150 mg, secukinumab 300 mg Blinded	N = 860 (Completed) 104 weeks	November 2021 (Actual)	Radiographic progression as measured by mSASSS at week 104

Registration Number Trial Name Phase	Treatment Groups; Blinded vs. Open	N Estimated[a] or Actual Enrollment (Status) Treatment Duration	Study Completion Date[b]	Primary Outcome(s)
to 2 Years in Patients With Active Ankylosing Spondylitis (SURPASS) Phase 3				
Bimekizumab vs. certolizumab pegol [ankylosing spondylitis]				
NCT03215277[99] [c] A Multicenter, Phase 2A, Randomized, Investigator-Blind, Subject-Blind, Parallel-Group Study to Evaluate the Efficacy and Safety of Bimekizumab and Certolizumab Pegol in Subjects With Active Ankylosing Spondylitis Phase 2	Bimekizumab, certolizumab pegol, placebo Blinded	N = 76 (Completed)	May 2020 (Actual)	Change from baseline in ASDAS at week 12
Secukinumab vs. TNF-α inhibitor [ankylosing spondylitis]				
NCT03445845[100] Rotation or Change of Biotherapy After TNF-Blocker Treatment Failure for Axial Spondyloarthritis (ROC-SPA) Phase 4	Secukinumab, TNF-α inhibitor (infliximab, etanercept, adalimumab, certolizumab, golimumab) Blinded	N = 300 (Recruiting) 52 weeks	November 2023 (Estimated)	Clinical response assessments in ASAS 40 at week 24
Various biologic treatments evaluated through cohort studies [RA]				
NCT04798287[101] Safety of Tofacitinib in Routine Care Patients With Rheumatoid Arthritis (STAR-RA)-Cancer Endpoints,	Tofacitinib, TNF-α inhibitor (infliximab, adalimumab, certolizumab pegol, etanercept golimumab)	N = 105,711 (Active, not recruiting) Up to 9 years	December 2021 (Estimated)	Time to second outpatient or inpatient diagnosis of any cancer (excluding non-melanoma skin cancer and any carcinoma in situ diagnosis)

Registration Number Trial Name Phase	Treatment Groups; Blinded vs. Open	N Estimated[a] or Actual Enrollment (Status) Treatment Duration	Study Completion Date[b]	Primary Outcome(s)
NCT04772248[102] Safety of Tofacitinib in Routine Care Patients With Rheumatoid Arthritis (STAR-RA)- Cardiovascular Endpoints	Tofacitinib, TNF-α inhibitor (infliximab, adalimumab, certolizumab pegol, etanercept golimumab)	N = 105,711 (Active, not recruiting) Up to 9 years	December 2021 (Estimated)	Time to first composite cardiovascular endpoint consisting of myocardial infarction or stroke

Note. [a]Estimated number of participants for trials during recruitment; [b] As reported in ClinicalTrials.gov,[117] the European Clinical Trials Register,[118] or the International Clinical Trials Registry Platform[119]; [c]Indicates completed, but not published yet.
Abbreviations. ACR20/50: American College of Rheumatology, 20% improvement/50% improvement; ASAS 40: Assessment of SpondylArthritis International Society, 40% improvement; ASDAS, Ankylosing Spondylitis Disease Activity Score; CDAI: Clinical Disease Activity Index; DAS28-CRP: 28-Joint Disease Activity Score, using C-reactive protein; DMARD: disease-modifying antirheumatic drug; EULAR: European League Against Rheumatism response; FDG: F-fluorodeoxyglucose; HLA: human leukocyte antigen; mg: milligram; mSASSS: modified Stroke Ankylosing Spondylitis Spine Score; MTX: methotrexate; N: number of participants; NCT: US National Clinical Trial; NR: not reported; RA: rheumatoid arthritis; SE: shared epitope; TIM: targeted immune modulator; TNF-α: tumor necrosis factor alpha; vs: versus.

Discussion

The evidence for the comparative effectiveness and harms of TIM agents included in this review consists of data for 17 comparisons of TIMs as first-line treatments and 9 comparisons as second-line treatments for the treatment of RA. Most comparisons are limited to single RCTs. The CoE for many outcomes is very low or low, precluding definitive conclusions. Evidence rated as moderate- or high-CoE indicated that baricitinib, sarilumab, and upadacitinib were more efficacious than adalimumab and etanercept was more effective than peficitinib as first-line treatments for RA. As second-line treatment, abatacept was less effective than upadacitinib (high to moderate CoE). QoL and functional capacity outcomes were usually consistent with the direction of response and remission outcomes, but few trials actually assessed QoL. Moderate and high CoE indicated lower incidence of overall AEs and SAEs with abatacept and certolizumab pegol than tocilizumab. Significant differences in AEs and SAEs for the incidence of some comparisons were rated as very low or low CoE and need to be interpreted with caution. However, large observational studies suggest differences in some specific SAEs. In the majority of studies, for example, infliximab was associated with a higher incidence of serious infections than other TIM agents. Some studies also indicated a higher incidence of opportunistic infections, tuberculosis, and varicella zoster infections with infliximab than with other TNF-α inhibitors. Two observational studies reported a higher incidence of gastrointestinal perforations with tocilizumab than with TNF-α inhibitors. Even in these large observational studies, the number of events was generally low and findings need to be interpreted cautiously. The majority of observational studies reported no significant differences in mortality, malignancies, and cardiovascular events or congestive heart failure.

We did not find any evidence that assessed differences in efficacy or effectiveness in subgroups based on age and racial groups, gender, patients with comorbidities, patients taking other commonly prescribed drugs, or in patients with early disease compared to established disease.

For ankylosing spondylitis, the only head-to-head evidence we identified was 1 high-RoB RCT.

Two pipeline drugs (bimekizumab and peficitinib), in 6 published trials, showed superior efficacy for the treatment of RA (peficitinib) or ankylosing spondylitis (bimekizumab) compared with placebo. In addition, 21 ongoing head-to-head studies or placebo-controlled trials of pipeline drugs highlight the rapidly evolving scientific dynamic in this field; 6 will be completed before 2023. Eight studies have been completed, but results have not yet been published.

Data From Network Meta-analyses

We note some of the limitations of network meta-analysis, including that not all available treatments can be compared because of limited studies within the network. Further, important assumptions about the studies included must be met for results from a network meta-analysis to be valid, including similar study and intervention characteristics among studies within the network and consistency between direct and indirect evidence.

Rheumatoid Arthritis

For this update, we identified 1 new relevant network meta-analysis by Weng and colleagues that provided indirect comparisons of TIM agents in patients with RA.[120] Overall, we describe findings of 6 network meta-analyses evaluating the comparative efficacy and harms of TIM

agents.[120-125] The search periods in these studies were up to April 2020. Appendix E summarizes the detailed results of indirect comparisons for the various outcomes. We present findings only for comparisons for which no direct head-to-head evidence were available. If 2 network meta-analyses reported results on the same comparison, we present the comparison with the most recent literature search.

The 3 most comprehensive network meta-analyses used a Bayesian approach; 2 reported results as ORs with corresponding 95% credible intervals (CrIs),[120,122] while the other reported ORs with 95% CIs.[121]

The most recent network meta-analysis by Weng and colleagues analyzed 88 RCTs with data on abatacept, adalimumab, baricitinib, certolizumab pegol, etanercept, golimumab, infliximab, rituximab, tocilizumab, tofacitinib, and upadacitinib.[120] The authors searched publications in 3 databases (PubMed, Embase and Cochrane Central Register of Controlled Trials), from inception to 2020. Overall, discontinuation due to AEs was similar among evaluated treatments.[120]

The network meta-analyses included in the previous report yielded few statistically significant differences between abatacept, adalimumab, anakinra, baricitinib, certolizumab pegol, etanercept, golimumab, infliximab, tocilizumab and tofacitinib.[121,122] Compared with tocilizumab, remission rates were significantly lower for abatacept (OR, 0.15; 95% CrI, 0.03 to 0.87), etanercept (OR, 0.13; 95% CrI, 0.02 to 0.65), golimumab (OR, 0.22; 95% CrI, 0.05 to 0.98), and infliximab (OR, 0.15; 95% CrI, 0.02 to 0.86).[122] Certolizumab pegol was significantly less efficacious in achieving an ACR50 response compared with anakinra (OR, 0.36; 95% CI, 0.14 to 0.89).[121]

Patients taking abatacept plus methotrexate had fewer SAEs compared with certolizumab pegol plus methotrexate (OR, 0.51; 95% CrI, 0.24 to 0.99) and golimumab plus methotrexate (OR, 0.35; 95% CrI 0.14 to 0.78).[122] Because of limitations inherent in network meta-analyses, results should be interpreted with caution.[122]

Ankylosing Spondylitis

No new relevant network meta-analysis was identified for this update. One network meta-analysis identified for the previous report provided indirect comparisons of TNF-α inhibitors for treatment of ankylosing spondylitis.[126] The literature was searched up to March 31, 2016; Appendix E summarizes the detailed results (mean difference with 95% CrI) of indirect comparisons for 2 efficacy outcomes, BASDAI and BASFI.[126] Wang and colleagues analyzed 18 placebo-controlled trials and 2 head-to-head comparison trials to assess the efficacy of TNF-α inhibitors in patients with ankylosing spondylitis, of which 11 trials were included in the analysis of relative efficacy at 24 weeks.[126] None of the comparisons yielded statistically significant differences between TNF-α inhibitors in reducing BASDAI or BASFI at 24 weeks.[126]

Limitations of the Evidence

Although the evidence base for head-to-head comparison of TIM agents includes numerous studies, few comparisons were evaluated by more than 1 or 2 studies. Furthermore, gaps remain for specific head-to-head comparisons because of the number of TIM agents that are available (see Table 1). Drug manufacturers sponsored nearly all included RCTs, and although the extent

to which the manufacturer's involvement influenced study execution or reporting is not definitively known, findings from a Cochrane systematic review suggest that industry sponsorship is associated with more favorable results than sponsorship by other sources.[127] Most observational studies addressing harms were of retrospective design and based on national registries; the quality and completeness of these databases cannot be determined. The only head-to-head RCT that we included for ankylosing spondylitis is of high RoB and does not allow for definitive conclusions about the comparative efficacy of TIMs for the treatment of ankylosing spondylitis.

Limitations of This Review

This review has several limitations. First, we did not include RCTs shorter than 12 weeks in duration, cohort studies with fewer than 10,000 participants, analysis not adjusted for confounders, or studies published in languages other than English. We included only studies published in the peer-reviewed literature; we did not use data presented in press releases or conference abstracts. This review represents a cumulative synthesis of the evidence; thus, studies included in the prior DERP review on this topic were carried forward into this update if they continued to meet eligibility criteria, but data from these studies were not rechecked against the original sources for accuracy. Further, we carried forward RoB ratings of previously included studies with the exception of considering substantive conflicts of interest, which were previously not evaluated as an RoB.

In conclusion, although the CoE for many outcomes was very low or low, evidence rated as moderate or high CoE indicated that baricitinib, sarilumab, and upadacitinib were more effective than adalimumab, and etanercept was more effective than peficitinib as first-line treatments for RA. High and moderate CoE indicated lower incidence of overall AEs and SAEs with abatacept and certolizumab pegol than tocilizumab. When reviewing this report, state Medicaid administrators might consider using the findings and conclusions as a tool in their evidence-based decision-making process, such as clarifying place in therapy for TIM agents, particularly for populations who require first- or second-line treatments for RA. Except for 1 RCT that compared peficitinib with etanercept, the body of evidence for pipeline therapies is limited to placebo-controlled trials, which will introduce challenges for determining place in therapy, if additional evidence is not published ahead of FDA approval.

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Appendix A. Methods

Search Strategy

We searched Drug Effectiveness Review Project (DERP) clinical evidence sources to identify systematic reviews (with and without meta-analyses), technology assessments, randomized controlled trials (RCTs), and cohort studies (for harms) using terms for the conditions (*RA*, *ankylosing spondylitis*), the interventions (*Abatacept*, *Adalimumab*, *Adalimumab-adaz*, *Adalimumab-adbm*, *Adalimumab-afzb*, *Adalimumab-atto*, *Adalimumab-bwwd*, *Adalimumab-fkip*, *Anakinra*, *Baricitinib*, *Certolizumab pegol*, *Etanercept*, *Etanercept-szzs*, *Golimumab*, *Infliximab*, *Infliximab-abda*, *Infliximab-dyyb*, *Infliximab-qbtx*, *Rituximab*, *Sarilumab*, *Secukinumab*, *Tocilizumab*, *Tofacitinib*, *Upadacitinib*, *ABBV-3373*, *Bimekizumab*, *Peficitinib*), and study designs (if appropriate). We limited searches of bibliographic databases to citations published since January 1, 2019, through July 22, 2021. Trials register searches were limited to the search dates of the Surveillance Report until July 22, 2021.

Searches of other sources were last conducted in October 2021.

We searched the following DERP evidence sources:

- Bibliographic databases:
  - Ovid MEDLINE
  - Cochrane Library (Wiley Interscience)
  - Embase.com
  - Trials registers:
  - Clinical Trials.gov
  - ISRCTN
- Other sources:
  - Google.com
  - Google Scholar (scholar.google.com)
  - Evidence-based Practice Centers (EPC) Reports
  - Effective Health Care (EHC) Program
  - Canadian Agency for Drugs and Technologies in Health (CADTH)
  - Institute for Clinical and Economic Review (ICER)/California Technology Assessment Forum (CTAF)
  - National Institute for Health and Care Excellence (NICE)
  - Veterans Administration Evidence-based Synthesis Program (ESP)

Ovid MEDLINE Search Strategy

Ovid MEDLINE ALL 1946 to July 21, 2021

ID	Searches
1	exp Arthritis, Rheumatoid/
2	Spondylitis, Ankylosing/
3	rheumatoid arthritis.ti,ab,kf.
4	(ankylosing adj1 (arthritis or spondyl*)).ti,ab,kf.
5	or/1-4
6	Biological Products/
7	(biologic therap* or biologics).ti,ab.

ID	Searches
8	Tumor Necrosis Factor-alpha/ai [Antagonists & Inhibitors]
9	((tumor necrosis factor alpha or TNF-alpha) adj2 (inhibitor? or anti or block* or antagonist?)).ti,ab.
10	exp Receptors, Interleukin/ai [Antagonists & Inhibitors]
11	(interleukin adj2 (inhibitor? or anti or block* or antagonist?)).ti,ab.
12	exp Janus Kinases/ai [Antagonists & Inhibitors]
13	((janus kinase or JAK?) adj2 (inhibitor? or anti or block* or antagonist?)).ti,ab.
14	antibodies, monoclonal/ or antibodies, monoclonal, humanized/
15	monoclonal antibod*.ti,ab.
16	Abatacept/
17	(Abatacept or Orencia).mp.
18	(ABBV-3373 or ABBV3373).af.
19	Adalimumab/
20	(adalimumab or Humira or Amjevita or Hyrimoz or Cyltezo).mp.
21	Interleukin 1 Receptor Antagonist Protein/
22	(Anakinra or Kineret).mp.
23	(Baricitinib or Olumiant or "INCB 028050" or INCB028050 or LY 3009104 or LY3009104).af.
24	(Bimekizumab or UCB-4940 or UCB4940 or CDP-4940 or CDP4940).af.
25	Certolizumab Pegol/
26	(Certolizumab or Cimzia).mp.
27	Etanercept/
28	(Etanercept or Enbrel or Erelzi).mp.
29	(Filgotinib or Jyseleca or GLPG-0634 or GLPG0634 or GS-6034 or GS6034).af.
30	(golimumab or simponi or CNTO148 or "CNTO 148").af.
31	Infliximab/
32	(infliximab or Remicade or Renflexis or Inflectra or Ixifi).mp.
33	(Peficitinib or Smyraf or ASP015K or JNJ-54781532).af.
34	Rituximab/
35	(Rituximab or Rituxan).mp.
36	(Sarilumab or Kevzara or "REGN 88" or REGN88 or "SAR 153191" or SAR153191).af.
37	(Secukinumab or Cosentyx or "AIN 457" or AIN457).af.
38	(Tocilizumab or Actemra or Atlizumab or RoActemra or "R 1569" or R1569).af.
39	(Tofacitinib or Xeljanz or "CP 690550" or CP690550).af.
40	(Upadacitinib or Rinvoq or ABT494 or "ABT 494").af.
41	or/6-40
42	5 and 41
43	limit 42 to yr="2019 -Current"
44	exp animals/ not humans/
45	43 not 44
46	exp age groups/ not exp adult/
47	45 not 46
48	Systematic Review.pt.
49	(systematic or structured or evidence or trials).ti. and ((review or overview or look or examination or update* or summary).ti. or review.pt.)
50	(0266-4623 or 1469-493X or 1366-5278 or 1530-440X).is.
51	meta-analysis.pt. or Network Meta-Analysis/ or (meta-analys* or meta analys* or metaanalys* or meta synth* or meta-synth* or metasynth*).tw,hw.
52	review.pt. and ((medline or medlars or embase or pubmed or scisearch or psychinfo or psycinfo or psychlit or psyclit or cinahl or electronic database* or bibliographic database* or computeri#ed database* or online database* or pooling or pooled or mantel haenszel or peto or dersimonian or der simonian or fixed effect or ((hand adj2 search*) or (manual* adj2 search*))).tw,hw. or (retraction

ID	Searches
	of publication or retracted publication).pt.)
53	((systematic or meta) adj2 (analys* or review)).ti,kf. or ((systematic* or quantitativ* or methodologic*) adj5 (review* or overview*)).tw,hw. or (quantitativ$ adj5 synthesis$).tw,hw.
54	(integrative research review* or research integration).tw. or scoping review?.ti,kf. or (review.ti,kf,pt. and (trials as topic or studies as topic).hw.) or (evidence adj3 review*).ti,ab,kf.
55	48 or 49 or 50 or 51 or 52 or 53 or 54
56	55 not (case report/ or letter.pt.)
57	47 and 56
58	randomized controlled trial.pt. or random*.mp. or placebo.mp.
59	47 and 58
60	exp Antirheumatic Agents/ae [Adverse Effects]
61	exp Antibodies, Monoclonal/ae [Adverse Effects]
62	Biological Products/ae [Adverse Effects]
63	"Drug-Related Side Effects and Adverse Reactions"/
64	Long Term Adverse Effects/
65	((adverse or dangerous or harmful or indirect or injurious or secondary or side or undesirable) adj2 (effect* or event* or consequence* or impact* or outcome* or reaction*)).ti,ab.
66	(drug adj (survival or retention or longevity or adherence)).ti,ab.
67	(harms or safety or complication?).ti.
68	(toxicity or ((injection site or infusion) adj reaction?) or mortality or infection? or tuberculosis or herpes or malignan* or skin cancer? or heart failure or heart disease? or cardiovascular risk or lung disease? or ((gastrointestinal or gastro-intestinal) adj perforation?)).ti.
69	or/60-68
70	47 and 69
71	57 or 59 or 70

Cochrane Library Search Strategy

Cochrane Library (Wiley) – July 22, 2021

ID	Search
#1	[mh "Arthritis, Rheumatoid"]
#2	[mh ^"Spondylitis, Ankylosing"]
#3	"rheumatoid arthritis":ti,ab,kw
#4	(ankylosing NEAR/1 (arthritis or spondyl*)):ti,ab,kw
#5	{or #1-#4}
#6	[mh ^Abatacept]
#7	(Abatacept:ti,ab,kw OR Orencia:ti,ab,kw)
#8	(ABBV-3373 OR ABBV3373):ti,ab,kw
#9	[mh ^Adalimumab]
#10	(adalimumab:ti,ab,kw OR Humira:ti,ab,kw OR Amjevita:ti,ab,kw OR Hyrimoz:ti,ab,kw OR Cyltezo:ti,ab,kw)
#11	[mh ^"Interleukin 1 Receptor Antagonist Protein"]
#12	(Anakinra:ti,ab,kw OR Kineret:ti,ab,kw)
#13	(Baricitinib OR Olumiant OR "INCB 028050" OR INCB028050 OR "LY 3009104" OR LY3009104):ti,ab,kw
#14	(Bimekizumab OR UCB-4940 OR UCB4940 OR CDP-4940 OR CDP4940):ti,ab,kw
#15	[mh ^"Certolizumab Pegol"]
#16	(Certolizumab:ti,ab,kw OR Cimzia:ti,ab,kw)
#17	[mh ^Etanercept]
#18	(Etanercept:ti,ab,kw OR Enbrel:ti,ab,kw OR Erelzi:ti,ab,kw)

ID	Search
#19	(Filgotinib OR GLPG-0634 OR GLPG0634 OR GS-6034 OR GS6034):ti,ab,kw
#20	(golimumab OR simponi OR CNTO148 OR "CNTO 148"):ti,ab,kw
#21	[mh ^Infliximab]
#22	(infliximab:ti,ab,kw OR Remicade:ti,ab,kw OR Renflexis:ti,ab,kw OR Inflectra:ti,ab,kw OR Ixifi:ti,ab,kw)
#23	(Peficitinib OR Smyraf OR ASP015K OR JNJ-54781532):ti,ab,kw
#24	[mh ^Rituximab]
#25	(Rituximab:ti,ab,kw OR Rituxan:ti,ab,kw)
#26	(Sarilumab OR Kevzara OR "REGN 88" OR REGN88 OR "SAR 153191" OR SAR153191):ti,ab,kw
#27	(Secukinumab OR Cosentyx OR "AIN 457" OR AIN457):ti,ab,kw
#28	(Tocilizumab OR Actemra OR Atlizumab OR RoActemra OR "R 1569" OR R1569):ti,ab,kw
#29	(Tofacitinib OR Xeljanz OR "CP 690550" OR CP690550):ti,ab,kw
#30	(Upadacitinib OR ABT494 OR "ABT 494"):ti,ab,kw
#31	{or #6-#30}
#32	#5 and #31
#33	[mh "age groups"] not [mh adult]
#34	#32 NOT #33
#35	#34 with Cochrane Library publication date Between Jan 2019 and Jul 2021
#36	(clinicaltrials or trialsearch or ANZCTR or ensaiosclinicos or chictr or cris or ctri or registroclinico or clinicaltrialsregister or DRKS or IRCT or rctportal or JapicCTI or JMACCT or jRCT or UMIN or trialregister or PACTR or REPEC or SLCTR):so
#37	"conference abstract":pt or abstract:so
#38	#36 or #37
#39	#35 not #38

Embase Search Strategy

Embase.com (Elsevier) – July 22, 2021

ID	Query
#1	'rheumatoid arthritis'/exp
#2	'ankylosing spondylitis'/exp
#3	'rheumatoid arthritis':ti,ab,kw
#4	(ankylosing NEAR/1 (arthritis OR spondyl*)):ti,ab,kw
#5	#1 OR #2 OR #3 OR #4
#6	'abatacept'/exp/mj
#7	abatacept:ti,ab,kw OR orencia:ti,ab,kw
#8	'abbv 3373':ti,ab,kw OR abbv3373:ti,ab,kw
#9	'adalimumab'/exp/mj
#10	adalimumab:ti,ab,kw OR humira:ti,ab,kw OR amjevita:ti,ab,kw OR hyrimoz:ti,ab,kw OR cyltezo:ti,ab,kw
#11	'anakinra'/exp/mj
#12	anakinra:ti,ab,kw OR kineret:ti,ab,kw
#13	'baricitinib'/exp/mj
#14	baricitinib:ti,ab,kw OR olumiant:ti,ab,kw OR 'incb 028050':ti,ab,kw OR incb028050:ti,ab,kw OR 'ly 3009104':ti,ab,kw OR ly3009104:ti,ab,kw
#15	'bimekizumab'/exp/mj
#16	bimekizumab:ti,ab,kw OR 'ucb 4940':ti,ab,kw OR ucb4940:ti,ab,kw OR 'cdp 4940':ti,ab,kw OR cdp4940:ti,ab,kw
#17	'certolizumab pegol'/exp/mj
#18	certolizumab:ti,ab,kw OR cimzia:ti,ab,kw

ID	Query
#19	'etanercept'/exp/mj
#20	etanercept:ti,ab,kw OR enbrel:ti,ab,kw OR erelzi:ti,ab,kw
#21	'filgotinib'/exp/mj
#22	filgotinib:ti,ab,kw OR 'glpg 0634':ti,ab,kw OR glpg0634:ti,ab,kw OR 'gs 6034':ti,ab,kw OR gs6034:ti,ab,kw
#23	'golimumab'/exp/mj
#24	golimumab:ti,ab,kw OR simponi:ti,ab,kw OR cnto148:ti,ab,kw OR 'cnto 148':ti,ab,kw
#25	'infliximab'/exp/mj
#26	infliximab:ti,ab,kw OR remicade:ti,ab,kw OR renflexis:ti,ab,kw OR inflectra:ti,ab,kw OR ixifi:ti,ab,kw
#27	'peficitinib'/exp/mj
#28	peficitinib:ti,ab,kw OR smyraf:ti,ab,kw OR asp015k:ti,ab,kw OR 'jnj 54781532':ti,ab,kw
#29	'rituximab'/exp/mj
#30	rituximab:ti,ab,kw OR rituxan:ti,ab,kw
#31	'sarilumab'/exp/mj
#32	sarilumab:ti,ab,kw OR kevzara:ti,ab,kw OR 'regn 88':ti,ab,kw OR regn88:ti,ab,kw OR 'sar 153191':ti,ab,kw OR sar153191:ti,ab,kw
#33	'secukinumab'/exp/mj
#34	secukinumab:ti,ab,kw OR cosentyx:ti,ab,kw OR 'ain 457':ti,ab,kw OR ain457:ti,ab,kw
#35	'tocilizumab'/exp/mj
#36	tocilizumab:ti,ab,kw OR actemra:ti,ab,kw OR atlizumab:ti,ab,kw OR roactemra:ti,ab,kw OR 'r 1569':ti,ab,kw OR r1569:ti,ab,kw
#37	'tofacitinib'/exp/mj
#38	tofacitinib:ti,ab,kw OR xeljanz:ti,ab,kw OR 'cp 690550':ti,ab,kw OR cp690550:ti,ab,kw
#39	'upadacitinib'/exp/mj
#40	upadacitinib:ti,ab,kw OR abt494:ti,ab,kw OR 'abt 494':ti,ab,kw
#41	#6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40
#42	#5 AND #41
#43	#42 AND [2019-2021]/py
#44	'animal'/exp NOT 'human'/exp AND [2019-2021]/py
#45	#43 NOT #44
#46	'groups by age'/exp NOT 'adult'/exp
#47	#45 NOT #46
#48	'systematic review'/exp OR 'meta analysis'/exp
#49	(((systematic OR 'state of the art' OR scoping OR umbrella) NEXT/1 (review* OR overview* OR assessment*)):ti,ab,kw) OR 'review* of reviews':ti,ab,kw OR 'meta analy*':ti,ab,kw OR metaanaly*:ti,ab,kw OR (((systematic OR evidence) NEAR/1 assess*):ti,ab,kw) OR 'research evidence':ti,ab,kw OR metasynthe*:ti,ab,kw OR 'meta synthe*':ti,ab,kw
#50	#48 OR #49
#51	#47 AND #50
#52	'randomized controlled trial'/exp OR random*:ti,ab,kw OR placebo:ti,ab,kw
#53	#47 AND #52
#54	'bimekizumab'/exp/dd_ae OR 'filgotinib'/exp/dd_ae OR 'baricitinib'/exp/dd_ae OR 'upadacitinib'/exp/dd_ae OR 'tofacitinib'/exp/dd_ae OR 'secukinumab'/exp/dd_ae OR 'etanercept'/exp/dd_ae OR 'abatacept'/exp/dd_ae OR 'tocilizumab'/exp/dd_ae OR 'sarilumab'/exp/dd_ae OR 'rituximab'/exp/dd_ae OR 'anakinra'/exp/dd_ae OR 'infliximab'/exp/dd_ae OR 'golimumab'/exp/dd_ae OR 'certolizumab pegol'/exp/dd_ae OR 'adalimumab'/exp/dd_ae OR 'peficitinib'/exp/dd_ae
#55	'adverse drug reaction'/de

ID	Query
#56	((adverse OR dangerous OR harmful OR indirect OR injurious OR secondary OR side OR undesirable) NEAR/2 (effect* OR event* OR consequence* OR impact* OR outcome* OR reaction*)):ti,ab,kw
#57	(drug NEXT/1 (survival OR retention OR longevity OR adherence)):ti,ab,kw
#58	harms:ti OR safety:ti OR complication$:ti
#59	toxicity:ti OR ((('injection site' OR infusion) NEXT/1 reaction$):ti) OR mortality:ti OR infection$:ti OR tuberculosis:ti OR herpes:ti OR malignan*:ti OR "skin cancer$":ti OR 'heart failure':ti OR "heart disease$":ti OR 'cardiovascular risk':ti OR "lung disease$":ti OR (((gastrointestinal OR 'gastro intestinal') NEXT/1 perforation$):ti)
#60	#54 OR #55 OR #56 OR #57 OR #58 OR #59
#61	#47 AND #60
#62	#51 OR #53 OR #61
#63	#62 NOT 'conference abstract'/it

Ongoing Studies

We searched the following DERP sources for ongoing studies. We selected search terms depending on the information source (see below):

- ClinicalTrials.gov – July 22, 2021

Search
"Rheumatoid Arthritis" OR "Ankylosing Spondylitis" | adalimumab OR Humira OR Amjevita OR Hyrimoz OR Cyltezo OR Certolizumab OR Cimzia OR golimumab OR simponi OR CNTO148 OR "CNTO 148" OR infliximab OR Remicade OR Renflexis OR Inflectra OR Ixifi OR Anakinra OR Kineret | Adult, Older Adult | Last update posted from 02/01/2021 to 07/22/2021
"Rheumatoid Arthritis" OR "Ankylosing Spondylitis" | Rituximab OR Rituxan OR Sarilumab OR Kevzara OR "REGN 88" OR REGN88 OR "SAR 153191" OR SAR153191 OR Tocilizumab OR Actemra OR Atlizumab OR RoActemra OR "R 1569" OR R1569 OR Abatacept OR Orencia OR Etanercept OR Enbrel OR Erelzi | Adult, Older Adult | Last update posted from 02/01/2021 to 07/22/2021
"Rheumatoid Arthritis" OR "Ankylosing Spondylitis" | Secukinumab OR Cosentyx OR "AIN 457" OR AIN457 OR Tofacitinib OR Xeljanz OR "CP 690550" OR CP690550 OR Upadacitinib OR Rinvoq OR ABT494 OR "ABT 494" OR Baricitinib OR Olumiant OR "INCB 028050" OR INCB028050 OR LY 3009104 OR LY3009104 | Adult, Older Adult | Last update posted from 02/01/2021 to 07/22/2021
"Rheumatoid Arthritis" OR "Ankylosing Spondylitis" | Filgotinib OR Jyseleca OR GLPG-0634 OR GLPG0634 OR GS-6034 OR GS6034 OR ABBV-3373 OR ABBV3373 OR Bimekizumab OR UCB-4940 OR UCB4940 OR CDP-4940 OR CDP4940 OR Peficitinib OR Smyraf OR ASP015K OR JNJ-54781532 | Adult, Older Adult | Last update posted from 02/01/2021 to 07/22/2021

- ISRCTN Registry – July 22, 2021

Search
adalimumab OR Humira OR Amjevita OR Hyrimoz OR Cyltezo OR Certolizumab OR Cimzia OR golimumab OR simponi OR CNTO148 OR "CNTO 148" OR infliximab OR Remicade OR Renflexis OR Inflectra OR Ixifi OR Anakinra OR Kineret Remove filter within Condition: " Rheumatoid Arthritis" OR " Ankylosing Spondylitis" Remove filter Participant age range: Adult Remove filter Date applied: from: 01/02/2021 Remove filter Date applied: to: 22/07/2021 Remove filter
Rituximab OR Rituxan OR Sarilumab OR Kevzara OR "REGN 88" OR REGN88 OR "SAR 153191" OR SAR153191 OR Tocilizumab OR Actemra OR Atlizumab OR RoActemra OR "R 1569" OR R1569 OR Abatacept OR Orencia OR Etanercept OR Enbrel OR Erelzi Remove filter within Condition: " Rheumatoid Arthritis" OR " Ankylosing Spondylitis" Remove filter Participant age range: Adult Remove filter Date applied: from: 01/02/2021 Remove filter Date applied: to: 22/07/2021 Remove filter
Secukinumab OR Cosentyx OR "AIN 457" OR AIN457 OR Tofacitinib OR Xeljanz OR "CP 690550" OR CP690550 OR Upadacitinib OR Rinvoq OR ABT494 OR "ABT 494" OR Baricitinib OR Olumiant OR "INCB 028050" OR INCB028050 OR "LY 3009104" OR LY3009104 Remove filter within Condition: " Rheumatoid Arthritis" OR " Ankylosing Spondylitis" Remove filter Participant age range: Adult Remove filter Date applied: from: 01/02/2021 Remove filter Date applied: to: 22/07/2021 Remove filter
Filgotinib OR Jyseleca OR "GLPG 0634" OR GLPG0634 OR "GS 6034" OR GS6034 OR "ABBV 3373" OR ABBV3373 OR Bimekizumab OR "UCB 4940" OR UCB4940 OR "CDP 4940" OR CDP4940 OR Peficitinib OR Smyraf OR ASP015K OR "JNJ 54781532" Remove filter within Condition: " Rheumatoid Arthritis" OR " Ankylosing Spondylitis" Remove filter Participant age range: Adult Remove filter Date applied: from: 01/02/2021 Remove filter Date applied: to: 22/07/2021 Remove filter

Other Sources

Source	Search Terms
Google	Rheumatoid arthritis OR ankylosing spondylitis Since: 2019 Rheumatoid arthritis OR ankylosing spondylitis AND (ABBV-3373 OR Bimekizumab OR Filgotinib OR Jyseleca OR Peficitinib OR Smyraf) Rheumatoid arthritis OR ankylosing spondylitis AND (Abatacept OR Orencia OR Adalimumab OR Humira OR Adalimumab OR Hyrimoz OR Cyltezo OR Amgevita OR GP2017 OR BI 695501 OR ABP 501 OR Anakinra OR Kineret OR Baricitinib OR Olumiant OR Certolizumab pegol OR Cimzia OR Etanercept OR Enbrel OR Etanercept-szzs OR Erelzi OR GP2015 OR Golimumab OR Simponi OR Infliximab OR Remicade OR Renflexis OR Inflectra OR Ixfi OR Rituximab OR Rituxan OR Sarilumab OR Kevzara OR Secukinumab OR Cosentyx OR Tocilizumab OR Actemra OR Tofacitinib OR Xeljanz OR Upadacitinib OR Rinvoq OR Ustekinumab) Since: 2019
Google Scholar	Rheumatoid arthritis OR ankylosing spondylitis Since: 2019 Rheumatoid arthritis OR ankylosing spondylitis AND (Abatacept OR Orencia) Since: 2019 Rheumatoid arthritis OR ankylosing spondylitis AND (ABBV-3373 OR Bimekizumab OR Filgotinib OR Jyseleca OR Peficitinib OR Smyraf) Since: 2019

Source	Search Terms
	Rheumatoid arthritis OR ankylosing spondylitis AND (Abatacept OR Orencia OR Adalimumab OR Humira OR Adalimumab OR Hyrimoz OR Cyltezo OR Amgevita OR GP2017 OR BI 695501 OR ABP 501 OR Anakinra OR Kineret OR Baricitinib OR Olumiant OR Certolizumab pegol OR Cimzia OR Etanercept OR Enbrel OR Etanercept-szzs OR Erelzi OR GP2015 OR Golimumab OR Simponi OR Infliximab OR Remicade OR Renflexis OR Inflectra OR Ixfi OR Rituximab OR Rituxan OR Sarilumab OR Kevzara OR Secukinumab OR Cosentyx OR Tocilizumab OR Actemra OR Tofacitinib OR Xeljanz OR Upadacitinib OR Rinvoq OR Ustekinumab) Since: 2019
Agency for Healthcare Research and Quality (AHRQ) – EPC Reports	Rheumatoid arthritis AND ankylosing spondylitis Since: 2019
Agency for Healthcare Research and Quality (AHRQ) – Effective Health Care Program	Rheumatoid arthritis AND ankylosing spondylitis Since: 2019
Canadian Agency for Drugs and Technologies in Health (CADTH)	Rheumatoid arthritis OR ankylosing spondylitis Since: 2019
Institute for Clinical and Economic Review (ICER)/California Technology Assessment Forum (CTAF)	Rheumatoid arthritis OR ankylosing spondylitis Since: 2019
National Institute for Health and Care Excellence (NICE) - Evidence	Rheumatoid arthritis OR ankylosing spondylitis Since: 2019 Search filter: primary research, systematic reviews, evidence summaries
Veterans Administration Evidence-based Synthesis Program (ESP)	Rheumatoid arthritis OR ankylosing spondylitis Since: 2019

Inclusion Criteria

Population

- Adult outpatients with moderate to severe rheumatoid arthritis (RA)
- Adult outpatients with ankylosing spondylitis (axial spondyloarthropathy)

Interventions

- In the list of brand names and generics (Table 1) are presented the TIMs and respective biosimilars that have been approved by the US Food and Drug Administration (FDA) for the treatment of RA and ankylosing spondylitis and select pipeline drugs likely to be approved in the near future.

Comparators

- For FDA-approved drugs: another listed targeted immune modulator (TIM) intervention (head-to-head) comparison
- For pipeline drugs: any listed TIM, standard of care, placebo

Outcomes

- Health Outcomes
  - Quality of life
  - Functional capacity
  - Productivity, ability to sustain employment
  - Clinical improvement
  - Disease remission
  - Pain
  - Reduction in the number of swollen or tender joints
  - Reduction in disease-related hospitalizations
  - Reduction in disease-specific mortality
  - Rebound/flare
  - Joint destruction
  - Steroid withdrawal
  - Dose escalation
- Harms Outcomes
  - Overall adverse events (AEs)
  - Withdrawals due to adverse events
  - Overall serious adverse events (SAEs)
  - Specific AEs and SAEs (e.g., serious infectious diseases)
  - Mortality

Study Designs

- Randomized controlled trials (RCTs) with ≥ 12-week study duration
- Retrospective and prospective cohort studies comparing an intervention type to another for harms outcomes
  - Minimum study duration of 12 weeks
  - Minimum total sample size of 10,000
  - Statistical analysis adjusted for confounders
  - Studies providing direct statistical comparisons between drugs.

Exclusion Criteria

We excluded studies if they were not published in English. We also excluded conference abstracts and data reported in press releases.

Screening

Two experienced researchers independently screened all titles and abstracts of identified documents. In cases where we disagreed about eligibility, we resolved the disagreement through discussion. We repeated this method for full-text review of documents that we could not exclude by title and abstract screening.

Data Abstraction

One experienced researcher abstracted and entered data from eligible studies in a standardized way using DistillerSR. A second experienced researcher reviewed all the data entered. We resolved discrepancies through discussion.

Quality Assessment: Risk of Bias of Included Studies

We assessed the risk of bias (RoB) of the included RCTs and cohort studies using standard instruments developed and adapted by DERP that are modifications of instruments used by national and international standards for quality.[9-13] Two experienced researchers independently rated all included studies. In cases in which there was disagreement about the RoB of a study, a third rater resolved the disagreement.

Randomized Controlled Trials

Low RoB RCTs include a clear description of the population, setting, intervention, and comparison groups; a random and concealed allocation of patients to study groups; low dropout rates; and intention-to-treat analyses. Low RoB RCTs also have low potential for bias from conflicts of interest and funding source(s). Moderate RoB RCTs have incomplete information about methods that might mask important limitations or a meaningful conflict of interest. High RoB RCTs have clear flaws that could introduce significant bias.

Cohort Studies

Low RoB cohort studies include a sample that is representative of the source population, have low loss to follow-up, and measure and consider relevant confounding factors. Low-RoB cohort studies also list their funding source(s) and have a low potential of bias from conflicts of interest. Moderate RoB cohort studies might not have measured all relevant confounding factors or adjusted for them in statistical analyses, have loss to follow-up that could bias findings, consist of a sample that is not representative of the source population, or have potential conflicts of interest that are not addressed. High RoB cohort studies have a clear, high RoB that would affect findings.

Certainty of Evidence Assessment: Overall Certainty of Evidence

We assigned each outcome a summary judgment for the overall certainty of evidence based on the system developed by the Grading of Recommendations, Assessment, Development, and Evaluation Working Group (GRADE).[128,129] Two independent experienced researchers assigned ratings, with disagreements resolved by a third rater. The GRADE system defines the overall certainty of a body of evidence for an outcome in the following manner:

- **High:** Raters are very confident that the estimate of the effect of the intervention on the outcome lies close to the true effect. Typical sets of studies are RCTs with few or no limitations, and the estimate of effect is likely stable.
- **Moderate:** Raters are moderately confident in the estimate of the effect of the intervention on the outcome. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is different. Typical sets of studies are RCTs with some limitations or well-performed nonrandomized studies with additional strengths that guard against potential bias and have large estimates of effects.
- **Low:** Raters have little confidence in the estimate of the effect of the intervention on the outcome. The true effect may be substantially different from the estimate of the effect. Typical sets of studies are RCTs with serious limitations or nonrandomized studies without special strengths.

- **Very low:** Raters have no confidence in the estimate of the effect of the intervention on the outcome. The true effect is likely to be substantially different from the estimate of effect. Typical sets of studies are nonrandomized studies with serious limitations or inconsistent results across studies.
- **Not applicable:** Researchers did not identify any eligible articles.

Appendix B. Full Evidence Tables

Table B1. Evidence Table RCTs (Study and Population Characteristics)

Authors, Year Country Trial Name Trial Number Risk of Bias	Population	Age Gender Race/Ethnicity	Other Population Characteristics	Funding
Brown et al., 2018[42] 35 sites in the United Kingdom SWITCH NR High	Adults with RA ≥ 24 weeks with inadequate response to TNF-α inhibitors treatment	Age, mean (SD): 57 (12); range 24–81 Alternative TNF-α inhibitors: 54 (10) Abatacept 125 mg: 58 (14) Rituximab 1 g: 58 (12) Female, n (%): 102 (84) Alternative TNF-α inhibitors: 33 (81) Abatacept 125 mg: 39 (95) Rituximab 1 g: 30 (75) Race/ethnicity, n (%): NR	Concomitant medication: • MTX, NSAIDs, corticosteroids (oral prednisolone not exceeding 10 mg daily) Inclusion: • Patients 18 years of age or older with persistent RA for 24 weeks or more, attending hospital-based rheumatology outpatient departments failed csDMARD therapy (at least 2 csDMARDs including MTX) treated with a current initial TNF-α inhibitors agent for at least 12 weeks, were MTX and NSAIDs and/or corticosteroids dose stable for 4 weeks prior to the screening visit provided written informed consent prior to any trial-specific procedures Exclusion: • Major surgery (including joint surgery) within 8 weeks prior to the screening visit or planned major surgery within 52 weeks following randomization • Inflammatory joint disease of different origin, mixed connective tissue disease, Reiter's syndrome, psoriatic arthritis, systemic lupus erythematosus, or any arthritis with onset prior to 16 years of age; other comorbidities including acute, severe infections, uncontrolled diabetes, uncontrolled or severe CVDs, active gastrointestinal diseases, recent stroke; untreated active current or latent TB or active current hepatitis B and/or C infection • Prednisolone of > 10 mg/day within the 4 weeks	National Institute for Health Research

Authors, Year Country Trial Name Trial Number Risk of Bias	Population	Age Gender Race/Ethnicity	Other Population Characteristics	Funding
			• Patients with active current infection or any major episode of infection requiring hospitalization or treatment with intravenous antibiotics within 12 weeks of start of the treatment protocol or oral antibiotics within 4 weeks of start of the protocol treatment; patients at significant risk of infection • Patients with primary or secondary immunodeficiency unrelated to primary disease	
Burmester et al., 2016[48] Strand et al., 2018[79] 86 centers in Europe, Israel, Russia, South Africa, South America, South Korea, and the US MONARCH NCT02332590 Moderate	Patients with active RA intolerant of, or inadequate responders to, MTX, with disease duration ≥ 3 months	Age, mean (SD): 52.2 (12.3) Sarilumab 200 mg: 50.9 (12.6) Adalimumab 40 mg: 53.6 (11.9) Female, n (%): 307 (83) Sarilumab 200 mg: 157 (85.3) Adalimumab 40 mg: 150 (81.1) Race/ethnicity: White, n (%) Adalimumab 40 mg: 164 (88.6) Sarilumab 200 mg: 171 (92.9)	Concomitant medication: • Concomitant oral corticosteroids Inclusion: • ≥ 18 years at baseline • Fulfilled the 2010 ACR/EULAR Classification Criteria for RA and ACR class I–III functional status, based on the 1991 revised criteria • Active RA, defined as ≥ 6 of 66 swollen and ≥8 of 68 tender joints and high-sensitivity CRP ≥8 mg/L or ESR ≥ 28 mm/hours and DAS28-ESR > 5.1 • With disease duration ≥ 3 months • If patients were, per investigator judgment, either intolerant of or considered inappropriate candidates for continued treatment with MTX, or inadequate responders if treated with an adequate MTX dose (10–25 mg/week or 6–25 mg/week for patients within Asia-Pacific region) for ≥ 12 weeks Exclusion: • Patients with prior bDMARD experience	Sanofi and Regeneron Pharmaceuticals, Inc.
Elmedany et al., 2019[32] 1 site in Saudi Arabia	Adult females with active RA with moderate-to-severe disease activity	Age, mean (SD): Tocilizumab 8 mg/kg: 51 (16) Abatacept 500/750/1000 mg: 48 (15)	Concomitant medication: • Oral MTX as 15 mg once weekly • Full doses of NSAIDs and/or low-dose oral steroids (< 10 mg/day of prednisone) Inclusion:	None

Authors, Year Country Trial Name Trial Number Risk of Bias	Population	Age Gender Race/Ethnicity	Other Population Characteristics	Funding
NR NR High	who failed to respond to at least 1 anti-TNF drug	Female, n (%): 132 (100) Tocilizumab 8 mg/kg: 68 (100) Abatacept 500/750/1,000 mg: 64 (100) Race/ethnicity, n (%): NR	• 18 years of age or older female patients with moderate-to-severe disease activity (based on the DAS28 ≥ 3.2) • Patients were free from other comorbidities, and had failed to improve or achieve remission with at least 1 anti-TNF drug Exclusion: • Patients with other comorbidities such as diabetes mellitus, hypertension, hyperlipidemia, ischemic heart disease, end-stage renal failure, or any other autoimmune diseases as systemic lupus erythematosus • Patients with evidence or history of significant infection within the previous 6 months (hepatitis B or C virus, HIV; ruled out by clinical examination and serological markers) • Patients with evident or suspected latent TB (ruled out by tuberculin purified protein derivative skin testing) • History of gastrointestinal bleeding or malignancy • Altered laboratory investigations such as elevated liver aminotransferases (AST and/or ALT), 1.5 times ULN, decreased Hb < 10.0 g/dL, a total leukocytic cell count < 3.0 × 103/mm3, an absolute neutropenia < 1200 cells/mL, or lymphopenia < 750 cells/mL, and GFR < 40 mL/min • Male patients	
Emery et al., 2018[36] US, South America, Western Europe, Eastern	Adults with RA for ≥ 3 months	Age, mean (SD): 52 (NR) Sarilumab 150 mg: 55 (12) Sarilumab 200 mg: 52 (13) Tocilizumab 4 mg/kg: 50 (13) Female, n (%): > 80%	Concomitant medication: • In both studies, all patients received concomitant csDMARDs. Inclusion: • ≥ 18 years of age • With an RA diagnosis for ≥ 3 months as determined by the 2010 revised ACR criteria as well as functional	Sanofi Genzyme and Regeneron Pharmaceuticals, Inc.

Authors, Year Country Trial Name Trial Number Risk of Bias	Population	Age Gender Race/Ethnicity	Other Population Characteristics	Funding
Europe, and Russia ASCERTAIN NR High		Sarilumab 150 mg: 41 (84) Sarilumab 200 mg: 39 (77) Tocilizumab 4 mg/kg: 82 (80) Race/ethnicity: Nonwhite, n (%): Sarilumab 150 mg: 2 (4) Sarilumab 200 mg: 54 (10) Tocilizumab 4 mg/kg: 5 (8)	class I–III as categorized by the 1991 revised ACR criteria • Continuous treatment with 1 or a combination of csDMARDs for 512 consecutive weeks before screening and were on a stable dose for 56 consecutive weeks Exclusion: • Patients with a history of severe systemic RA (e.g., vasculitis, pulmonary fibrosis); juvenile idiopathic arthritis or onset of arthritis before age 16 • Patients with past or current autoimmune, inflammatory systemic or localized joint disease other than RA	
Fleischmann et al., 2012[51] 63 centers in the US, Europe, Latin America, and the Republic of Korea NR NCT00550446 Moderate	Patients aged 18 or older with a diagnosis of RA for > 6 months meeting the ACR criteria and active disease, defined as 6 or more tender/painful joints (TJC68) and 6 or more swollen joints (SJC66) and either an ESR above the ULN or a CRP level > 7 mg/L	Age, mean (SD): Tofacitinib 1 mg: 55 (13.3) Tofacitinib 3 mg: 53 (12.2) Tofacitinib 5 mg: 54 (13.5) Tofacitinib 10 mg: 52 (10.9) Tofacitinib 15 mg: 53 (13.0) Adalimumab 40 mg: 54 (11.9) Placebo: 53 (13.7) Female, n (%): Tofacitinib 1 mg: 46 (85.2) Tofacitinib 3 mg: 44 (86.3) Tofacitinib 5 mg: 43 (87.8) Tofacitinib 10 mg: 53 (86.9) Tofacitinib 15 mg: 50 (87.7) Adalimumab 40 mg: 45 (84.9) Placebo: 52 (88.1) Race/ethnicity: White, n (%): Tofacitinib 1 mg: 44 (81.5)	Key inclusion criteria: • Failure of at least 1 DMARD due to lack of efficacy or toxicity, and washout of all DMARDs except antimalarial agents at stable doses. Key exclusion criteria: • Discontinuation of a previous TNF-α inhibitor due to lack of efficacy or AEs; previous adalimumab therapy; evidence of hematopoietic disorders at screening or within 3 months prior to the first dose of the study drug (Hb level < 9.0 g/dL, hematocrit < 30%, white blood cell count < 3.0 x 109/L, absolute neutrophil count < 1.2 x 109/L, or platelet count < 100 x 109/L); estimated glomerular filtration rate < 50 mL/min; total bilirubin, AST, or ALT levels < 2 x ULN; untreated infection with mycobacterium TB or and a history of malignancy, with the exception of adequately treated nonmetastatic basal cell or squamous cell cancer of the skin or cervical carcinoma in situ.	Pfizer, Abbott, Actelion, Mundipharma

Authors, Year Country Trial Name Trial Number Risk of Bias	Population	Age Gender Race/Ethnicity	Other Population Characteristics	Funding
		Tofacitinib 3 mg: 38 (74.5) Tofacitinib 5 mg: 36 (73.5) Tofacitinib 10 mg: 44 (72.1) Tofacitinib 15 mg: 46 (80.7) Adalimumab 40 mg: 43 (81.1) Placebo: 43 (72.9)		
Fleischmann et al., 2017[52] Strand et al., 2019[78] 194 centers in 25 countries ORAL – Strategy NCT02187055 Moderate	Individuals aged 18 years or older who met the 2010 ACR and EULAR classification criteria for RA 20, with active RA defined as having 4 or more tender or painful joints on motion and 4 or more swollen joints (DAS28) at baseline despite treatment with MTX 15–25 mg per week, high-sensitivity CRP of 3 mg/L or more	Age, mean (SD): NR Tofacitinib 5 mg: 49.7 (12.2) Tofacitinib 5 mg + MTX: 50 (13.4) Adalimumab 40 mg + MTX: 50.7 (13.4) Female, n (%): Tofacitinib 5 mg: 319 (83) Tofacitinib 5 mg + MTX: 311 (83) Adalimumab 40 mg + MTX: 320 (83) Race/ethnicity: White, n (%): Tofacitinib 5 mg: 296 (77) Tofacitinib 5 mg + MTX: 286 (76) Adalimumab 40 mg + MTX: 293 (76)	Concomitant medication: • Patients were required to discontinue all conventional synthetic DMARDs, other than MTX, for at least 4 weeks before baseline, but could continue to receive stable NSAIDs, analgesics, or oral corticosteroids (≤ 10 mg prednisone or equivalent per day), or a combination, throughout the trial. Patients who had responded inadequately or had an AE secondary to treatment with a biological DMARD could be included but had to have discontinued the biological DMARD for a minimum period of time before randomization. Patients were excluded if they had contraindications for any study treatment; a history of infections requiring treatment within 2 weeks, or any admission to hospital within the 6 months before randomization; had exclusionary morbidities, HIV, hepatitis B or C, inadequately treated or undocumented treatment of TB; had more than 1 episode of herpes zoster, 1 episode of disseminated herpes zoster or herpes simplex; any clinically significant laboratory abnormalities; or were pregnant. Patients who had absence of efficacy or biological DMARD-related AEs with previous treatment with a TNF-α inhibitor, or who had previously received tofacitinib, adalimumab, or glucocorticoids (equivalent to > 10 mg per day prednisone within the previous 4 weeks	Pfizer

Authors, Year Country Trial Name Trial Number Risk of Bias	Population	Age Gender Race/Ethnicity	Other Population Characteristics	Funding
Fleischmann et al., 2019[30] Strand et al., 2021[77] 286 sites in 41 countries in Europe, South and Central America, North America, Europe, Asia SELECT-COMPARE NCT02629159 Moderate	Adults with active RA for ≥ 3 months that fulfilled the 2010 ACR/ EULAR classification criteria with inadequate response to MTX	Age, mean (SD): Upadacitinib 15 mg: 54 (12) Adalimumab 40 mg: 54 (12) Placebo: 54 (12) Female, n (%): Upadacitinib 15 mg: 259 (79) Adalimumab 40 mg: 521 (80) Placebo: 512 (79) Race/ethnicity, n (%): NR	Concomitant medication: • Patients continued to receive oral or parenteral MTX at a stable dosage (15–25 mg/week, or ≥10 mg/week in patients who could not tolerate MTX at ≥ 12.5 mg/week) for at least 4 weeks before the study start, with dose reductions permitted for safety reasons only. Patients also continued to receive stable doses of NSAIDs, acetaminophen or oral steroids (dose of ≤ 10 mg prednisone or equivalent per day) Inclusion: • Age ≥ 18 years • Diagnosis of RA for ≥ 3 months that fulfilled the 2010 ACR/EULAR classification criteria • Active RA, defined as ≥ 6 swollen joints (SJC66), ≥ 6 tender joints (TJC68), an hsCRP level of ≥ 5 mg/L (ULN, 2.87 mg/L), and at least 1 of the following features at screening: ≥ 3 erosions on radiographs of the hands and feet or ≥ 1 erosion and positivity for either RF or anticyclic CCP antibodies • Received MTX for ≥ 3 months at a stable dosage of 15–25 mg/week for ≥ 4 weeks prior to the first dose of study drug (or ≥ 10 mg/week if intolerant to 15 mg), which was maintained for the duration of the trial • Patients exposed to, at most, 1 bDMARD (except for adalimumab) could be included if they had < 3 months' exposure or had discontinued the bDMARD due to intolerance Exclusion: • Patients with an inadequate response to a prior bDMARD or prior exposure to a JAK inhibitor	AbbVie, Inc
Gabay et al., 2013[49]	Adults with RA for ≥ 6 months	Age, mean (SD): NR	• Patients previously treated with a biological DMARDs were excluded. Patients had to stop taking all synthetic	LA Roche

Authors, Year Country Trial Name Trial Number Risk of Bias	Population	Age Gender Race/Ethnicity	Other Population Characteristics	Funding
76 centers in 15 countries in North and South America, Australasia, and Europe ADACTA NCT01119859 Moderate	who were intolerant to MTX or for whom continuation of MTX was deemed inappropriate	Tocilizumab 8 mg/kg: 54.4 (13.0) Adalimumab 40 mg: 53.3 (12.4) Female, n (%): NR Tocilizumab 8 mg: 129 (79) Adalimumab 40 mg: 133 (82) Race/ethnicity: White, n (%): NR Tocilizumab 8 mg/kg: 145 (89) Adalimumab 40 mg: 133 (82)	DMARDs except leflunomide 2 weeks or more before baseline; leflunomide had to be withdrawn 12 weeks or more before baseline or after standard washout	
Genovese et al., 2017[27] 41 sites in 6 countries (US [20 sites], Poland [6 sites], Hungary [5 sites], Czech Republic [4 sites], Mexico [4 sites], and Bulgaria [3 sites]) NR NR Moderate	Adults with moderate-to-severe RA and an inadequate response or intolerance to a previous csDMARD	Age, mean (SD): Peficitinib 25 mg: 52.6 (10.2) Peficitinib 50mg: 54.8 (10.0) Peficitinib 100 mg: 54.9 (11.3) Peficitinib 150 mg: 54.4 (12.5) Placebo: 52.7 (12.2) Female, n (%): Peficitinib 25 mg: 46 (78.0) Peficitinib 50mg: 48 (84.2) Peficitinib 100 mg: 51 (87.9) Peficitinib 150 mg: 50 (78.1) Placebo: 42 (82.4) Race/ethnicity, n (%): NR	Concomitant medication: • NSAIDs, csDMARDs (400 mg or less of hydroxychloroquine per day, 250 mg or less of chloroquine per day, and 3 gm or less of sulfasalazine per day), and/or oral corticosteroids (10 mg or less of prednisone or equivalent per day) Inclusion: • 18 years of age or older and moderate-to-severe RA ≥ 6 months prior to screening • Inadequate response or intolerance to a previous csDMARD • Active disease Exclusion: • Previous csDMARD therapy, biologic agents approved for the treatment of RA, intraarticular or parenteral corticosteroids, more than10 mg oral prednisone (or	Astellas Pharma Global Development

Authors, Year Country Trial Name Trial Number Risk of Bias	Population	Age Gender Race/Ethnicity	Other Population Characteristics	Funding
			equivalent) per day, treatment with another investigational drug, and medications that are CYP3A substrates with a narrow therapeutic range • Abnormal findings on a chest radiograph within 90 days of screening or at screening, virus vaccination within 30 days prior to the first dose of study drug, hepatitis B/C or HIV, any other autoimmune rheumatic disease other than Sjogren's syndrome, clinically significant infections, and any malignancy except for successfully treated basal or squamous cell carcinoma of the skin or in situ carcinoma of the cervix • Patients with TB who were not taking guideline antimicrobial therapy	
Giardina et al., 2010[25] Italy NR NR High	Adults with ankylosing spondylitis and inadequate response to oral NSAIDs	Age, mean (SD): Overall: 32.2 (8) Etanercept: 32.6 (6.8) Infliximab: 31.9 (9.2) Female, n (%): Overall: 21% Etanercept: 5 (20) Infliximab: 6 (24) Race/ethnicity, n (%): NR	Concomitant medication: • NR Inclusion: • Patients with ankylosing spondylitis • Active disease for at least 3 months, a BASDAI > 4 and a VAS for spinal pain score > 4 • Nonresponders to oral NSAIDs and naïve for DMARDs or other TNF blocking agents Exclusion: • Complete ankylosis (fusion) of the spine	NR
Giles et al., 2019[31] NR ENTRACTE NR Moderate	Patients were seropositive for RF or anti-CCP, ≥ 8 swollen joints (SJC66) and 8 tender joints (TJC68) at screening, and	Age, mean (SD): Tocilizumab 8 mg/kg: 61 (7) Etanercept 50 mg: 61 (8) Female, n (%): Tocilizumab 8 mg/kg: 1193 (78) Etanercept 50 mg: 1202 (78)	Concomitant medication: • Concomitant RA therapies: MTX, antimalarials, sulfasalazine, leflunomide, corticosteroids, NSAIDs Inclusion: • 50 years of age or older and active RA • Inadequate response to a previous csDMARD or anti-TNF treatment • Seropositivity for RF or anti-CCP	F. Hoffmann-La Roche Ltd.

Authors, Year Country Trial Name Trial Number Risk of Bias	Population	Age Gender Race/Ethnicity	Other Population Characteristics	Funding
	CRP > 0.3 mg/dL.	Race/ethnicity: Nonwhite population, n (%): Tocilizumab 8 mg/kg: 378 (25) Etanercept 50 mg: 355 (23)	• ≥ 8 swollen joints (SJC66) and 8 tender joints (TJC68) at screening, and CRP > 0.3 mg/dL • ≥ 1 traditional CVD risk factors, extra-articular RA manifestations or history of a CVD event. Exclusion: • Moderate or severe heart failure • Previous treatment with a non-TNF-biologic or etanercept • History of diverticulitis, diverticulosis requiring antibiotic treatment or chronic ulcerative lower gastrointestinal disease such as Crohn 's disease, ulcerative colitis or other symptomatic lower gastrointestinal conditions that might predispose to perforations • Patients who previously received treatment with non-etanercept TNF-α inhibitors was restricted to 20%	
Glatt et al., 2019[39] NR NR NCT02430909 Moderate	Adults with moderate-to-severe RA of ≥6 months' duration	Age, median (range): Certolizumab pegol plus bimekizumab: 53 (26–69) Certolizumab pegol plus placebo: 57 (30–67) Female, n (%): Certolizumab pegol plus bimekizumab: 45 (87) Certolizumab pegol plus placebo: 23 (85.2) Race/ethnicity: Nonwhite population, n (%): 0	Concomitant medication: • Certolizumab pegol Inclusion: • Adults (18–69 years) with moderate-to-severe RA for at least 6 months • Body mass index 18–35 kg/m2, with a body weight of ≥ 50 kg (men) or 45 kg (women); ≥ 6 tender joints (TJC68), ≥ 6 swollen joints (SJC66) and ≥ 10 mg/L CRP; and IR to ≥ 1 csDMARD, • Nonresponders to certolizumab pegol Exclusion: • Previous exposure to anti-TNFs, IL-17 inhibitors or bimekizumab • Receipt of any investigational drug or experimental procedure within 90 days prior to baseline; and receipt of prohibited medications	The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors

Authors, Year Country Trial Name Trial Number Risk of Bias	Population	Age Gender Race/Ethnicity	Other Population Characteristics	Funding
			• Active/high risk of infection, active or latent TB, known central nervous system demyelinating disorder or neoplastic disease within 5 years of study entry	
Gottenberg et al., 2016[57] 47 clinical centers in France NR NCT01000441 Moderate	Adults with a diagnosis of RA according to the 1987 ACR criteria, presence of erosions and a disease activity score in DAS28-ESR of ≥ 3.2; insufficient response to anti-TNF according to the physician was needed. In the study, a new medication (either non-TNF biological or another anti-TNF drug) was added to the regimen of an already prescribed anti-TNF drug.	Age, mean (SD): 57.1 (12.2) Non-TNF-biologic: 58.2 (11.1) Second anti-TNF drug: 55.9 (13.1) Female, n (%): 243 (83.2) Non-TNF-biologic: 120 (82) Second anti-TNF drug: 123 (84) Race/ethnicity, n (%): NR	Inclusion: • Patients > 18 years were included, if they had) a diagnosis of RA according to the 1987 ACR criteria, presence of erosions and a disease activity score in DAS28-ESR of 3.2 or more. Furthermore, insufficient response to anti-TNF according to the physician was needed. In the study, a new medication (either non-TNF biological or another anti-TNF drug) was added to the regimen of an already prescribed anti-TNF drug. • Stable dose of oral corticosteroids of 15 mg/day or less of equivalent prednisone within 4 weeks before enrollment and a stable dose of synthetic DMARDs within 4 weeks of enrollment. Exclusion: • Discontinuation of the first anti-TNF agent due to an AE only; previous treatment with 2 or more anti-TNF agents; previous treatment with abatacept, rituximab, or tocilizumab; contraindication to all anti-TNF agents and other biologics, as well as pregnancy and breast-feeding.	French Ministry of Health (Programme Hospitalier de Recherche Clinique National
Hetland et al., 2020[18]	Adults with early (less than	Age, mean (SD): 54.3 (NR)	Concomitant medication:	Public sources

Authors, Year Country Trial Name Trial Number Risk of Bias	Population	Age Gender Race/Ethnicity	Other Population Characteristics	Funding
29 sites in Sweden, Denmark, Norway, Finland, the Netherlands, and Iceland NORD-STAR NCT01491815 Low	24 months) moderate to severe RA	Active conventional treatment: 54.6 (14.5) Certolizumab pegol + MTX: 55.3 (15.3) Abatacept + MTX: 54.7 (14.4) Tocilizumab + MTX: 52.4 (14.5) Female, n (%): 559 (68.8) Active conventional treatment: 139 (69.5) Certolizumab pegol + MTX: 139 (68.5) Abatacept + MTX: 140 (68.6) Tocilizumab + MTX: 129 (68.6) Race/ethnicity, n (%): NR	• All patients started methotrexate on day 1 (escalated within 4 weeks to 25 mg every week) with folic acid supplementation (minimum 5 mg every week). Inclusion: • Adults with RA and symptom duration less than 24 months, moderate to severe disease activity Exclusion: • Previous treatment with DMARDs	
Humby et al., 2021[17] 19 sites, 5 European countries: the UK, Belgium, Italy, Portugal, and Spain R4RA ISRCTN97443826 High	Adults with RA and inadequate response to anti-TNF therapy	Age, mean (range): 55.5 (47.4–65.3) Rituximab 1,000 mg: 55.7 (47.7–65.5) Tocilizumab 8 mg/kg: 55.5 (47.3–65.1) Female, n (%): 128 (80) Rituximab 1,000 mg: 62 (76) Tocilizumab 8 mg/kg: 66 (84) Race/ethnicity, n (%): NR	Concomitant medication: • NR Inclusion: • 18 years of age or older and RA who have failed anti-TNF therapy • Eligible for rituximab therapy according to UK NICE guidelines • Patients should be receiving a stable dose of methotrexate for at least 4 weeks prior to biopsy visit. Exclusion: • History of or current primary inflammatory joint disease or primary rheumatological autoimmune disease other than RA (if secondary to RA, then the patient is still eligible), prior exposure to rituximab or tocilizumab	National Institute for Health Research

Authors, Year Country Trial Name Trial Number Risk of Bias	Population	Age Gender Race/Ethnicity	Other Population Characteristics	Funding
			for the treatment of RA, active infection, septic arthritis within a native joint within the last 12 months, sepsis of a prosthetic joint within 12 months or indefinitely if the joint remains in situ • Known HIV or active hepatitis B/C infection. hepatitis B screening test must be performed at or in the preceding 3 months of screening visit, latent TB infection unless they have completed adequate antibiotic prophylaxis, malignancy (other than basal cell carcinoma) within the last 10 years, NYHA grade 3 or 4 congestive cardiac failure, demyelinating disease, latex allergy or allergy to any excipients of rituximab or tocilizumab • Treatment with any investigational agent ≤ 4 weeks prior to baseline (or < 5 half-lives of the investigational drug, whichever is the longer), intra-articular or parenteral corticosteroids ≤ 4 weeks prior to biopsy visit • Presence of a transplanted organ (with the exception of a corneal transplant >3 months prior to screening) • Other severe acute or chronic medical or psychiatric condition	
Jobanputra et al., 2012[46] England RED SEA NR High	Adults with active RA despite treatment with 2 DMARDs including MTX	Age, mean (SD): 54.1 (12.9) Adalimumab 40 mg: 55.0 (12.5) Etanercept 50 mg: 53.2 (13.4) Female, n (%): 87 (72.5%) Adalimumab 40 mg: 45 (75) Etanercept 50 mg: 42 (70) Race/ethnicity, n (%): NR	Concomitant medication: • MTX • Other DMARDs (azathioprine, hydroxychloroquine, leflunomide, penicillamine, sulfasalazine) • Oral steroids Inclusion: • Patients ≥ 18 years of age, who met the ACR 1987 criteria for RA • Lack of response to at least 2 DMARDs including MTX Exclusion:	Queen Elizabeth Hospital Birmingham Charity

Authors, Year Country Trial Name Trial Number Risk of Bias	Population	Age Gender Race/Ethnicity	Other Population Characteristics	Funding
			• Patients treated previously with any licensed or experimental biological TNF-α inhibitor • Noncompliant or unsuitable patients for TNF-α inhibitors treatment	
Kivitz et al., 2017[28] 43 sites in 8 countries (the US, Poland, Colombia Mexico, Bulgaria, Czech Republic, Hungary, and Belgium) NR NR Moderate	Adults with moderate-to-severe RA with an inadequate response to MTX	Age, mean (SD): Ranged from 52.3 to 54.5 years Peficitinib 25 mg: 52.8 (11.9) Peficitinib 50 mg: 52.3 (12.6) Peficitinib 100 mg: 54.5 (12.8) Peficitinib 150 mg: 54.2 (12.5) Placebo: 52.6 (12.2) Female, n (%): 83% Peficitinib 25 mg: 55 (83.3) Peficitinib 50 mg: 65 (83.3) Peficitinib 100 mg: 68 (81.0) Peficitinib 150 mg: 64 (82.1) Placebo: 63 (87.5) Race/ethnicity: Non-Hispanic/Non-Latino, n (%): NR (66–77) Peficitinib 25 mg: 45(68) Peficitinib 50 mg: 52(67) Peficitinib 100 mg: 56 (67) Peficitinib 150 mg: 60 (77) Placebo: 52 (72)	Concomitant medication: • The only permitted concomitant medications for RA other than MTX were NSAIDs, hydroxychloroquine (400 mg/day or less), chloroquine (250 mg/day or less), sulfasalazine (3 gm/day or less), and/or oral corticosteroids (prednisone or equivalent [10 mg/day or less]) Inclusion: • 18 years of age or older and active (moderate-to-severe) RA for at least 6 months, treated with oral MTX for 90 days or more at a stable dosage of 15–25 mg/week for 28 days or more prior to first dose Exclusion: • Previous DMARDs or biologic agents, non–anti-TNF-biologic DMARD, or intolerance to JAK inhibitors • Patients with Mycobacterium TB infection, abnormal chest radiograph, virus vaccination within 30 days prior to the first dose of study drug, hepatitis B, hepatitis C, HIV, any other autoimmune rheumatic disease other than Sjogren's syndrome, clinically significant infections, or any malignancy except successfully treated basal or squamous cell carcinoma or in situ carcinoma of the cervix	Astellas Pharma Global Development
Kume et al., 2011[47]	Patients with active RA with no prior	Age, mean (SD): NR Tocilizumab 8 mg/kg: 62 (16)	All patients with worsening disease activity (measured by DAS28-ESR at week 12, defined by change of DAS28-ESR from a baseline value of > 1.2, or DAS28-ESR > 5.1,	NR

Authors, Year Country Trial Name Trial Number Risk of Bias	Population	Age Gender Race/Ethnicity	Other Population Characteristics	Funding
Japan NR NR Moderate	treatment with MTX, steroids or biologics and stable dosage of all DMARDs for at least 8 weeks prior to enrollment	Etanercept 25 mg: 61 (15) Adalimumab 40 mg: 63 (17) Female, n (%): NR Tocilizumab 8 mg/kg: 19 (86) Etanercept 25 mg: 18 (86) Adalimumab 40 mg: 18 (86) Race/ethnicity, n (%): NR	were allowed to leave the group (by clinician's judgment). Only patients who completed the study at 24 weeks were analyzed	
Manders et al., 2015[56] Multicenter trial in the Netherlands NR NR High	Patients with treatment failure with their first TNF-α inhibitors, moderate-to-high disease activity and no previous treatment with abatacept or rituximab	Age, mean (SD): 56.34 (11.24) Abatacept 500–1,000 mg IV: 56.16 (9.95) Rituximab 1,000 mg IV: 57.09 (11.08) TNF-α inhibitors: 55.81 (12.53) Female, n (%): 104 (74.8) Abatacept 500–1,000 mg IV: 38 (88.4) Rituximab 1,000 mg IV: 29 (63.0) TNF-α inhibitors: 37 (74.0) Race/ethnicity, n (%): NR	Inclusion criteria: • Patients with treatment failure with their first TNF-α inhibitors, moderate-to-high disease activity DAS28 > 3.2) and no previous treatment with abatacept or rituximab were included in this study. Patients were randomized in 3 groups: abatacept, rituximab and TNF-α inhibitors, with each medication mentioned in "Interventions" not being either rituximab or abatacept being a TNF-α inhibitor. Type of TNF-α inhibitors was individually chosen by the treating physician and the patient Exclusion criteria: • Patients were excluded if they had a contraindication for treatment (for example, pregnancy, the presence of a serious infection) based on the rheumatologist's judgment of if they had a strong preference or dislike for 1 of the treatment agents or did not want to be randomized	Netherlands Organisation for Health Research and Development
Rubbert-Roth et al., 2020[19] 120 sites in 28 countries, Europe,	Adults having a moderate-to-severe active RA for at least 3 months and	Age, mean (SD): NR Upadacitinib 15 mg: 55.3 (11.4)	Concomitant medication: • csDMARDs, NSDAI, acetaminophen, or oral or inhaled glucocorticoids Inclusion:	AbbVie

Authors, Year Country Trial Name Trial Number Risk of Bias	Population	Age Gender Race/Ethnicity	Other Population Characteristics	Funding
Asia, North and South America SELECT-CHOICE NCT03086343 Low	inadequate response to bDMARDS.	Abatacept 500–1,000 mg: 55.8 (11.9) Female, n (%): NR Upadacitinib 15 mg: 249 (82.2) Abatacept 500–1,000 mg: 253 (81.9) Race/ethnicity: Black, n (%): NR Upadacitinib 15 mg: 7 (2.3) Abatacept 500–1,000 mg: 14 (4.5) American Indian or Alaska Native, n (%): NR Upadacitinib 15 mg: 1 (0.3) Abatacept 500–1,000 mg: 2 (0.6) Asian, n (%): NR Upadacitinib 15 mg: 5 (1.7) Abatacept 500–1,000 mg: 6 (1.9)	• 18 years of age or older with a diagnosis of mild-severe RA for at least 3 months with at least 1 biologic DMARD or had unacceptable side effects from at least 1 biologic DMARD and taking a stable dose of up to 2 conventional synthetic DMARDs for at least 4 weeks before entry Exclusion: • Previous exposure to a JAK inhibitor or abatacept or had a history of inflammatory joint disease other than RA	
Ruscitti et al., 2019[21] Italy TRACK	Adults with moderate to severe RA and type 2 diabetes mellitus and with inadequate	Age, mean (SD): 62.7 (10) Anakinra 100 mg: 62.9 (9.7) TNF inhibitors: 62.5 (10.6) Female, n (%): 29 (74.4) Anakinra 100 mg: 17 (77.2)	Concomitant medication: • Concomitant stable doses of corticosteroids (not more than 7.5 mg of prednisone or the equivalent per day) Inclusion: • 18 years of age or older and moderate to severe RA • Inadequate response to previous treatment with MTX characterized by DAS28 > 3.2	None

Authors, Year Country Trial Name Trial Number Risk of Bias	Population	Age Gender Race/Ethnicity	Other Population Characteristics	Funding
NCT02236481 High	response to MTX	TNF inhibitors: 12 (70.6) Race/ethnicity, n (%): NR	• Type 2 diabetes classified according to American Diabetes Association (ADA) criteria and of at least 6 months' duration; and with percentage of glycated hemoglobin (HbA1c%) > 7% and < 10% and a body mass index (BMI) < 35 Exclusion: • Type 2 diabetes diagnosed more than 10 years prior to the study • Ongoing acute or chronic infection • Previous ischemic attack or myocardial infarction; heart failure of NYHA class III or IV; hepatic or progressive liver disease • Presence of known malignancy	
Schiff et al., 2007[44] 86 sites in 14 countries in North, South, and Central America, Europe, and Africa ATTEST NCT00095147 Moderate	Patients with RA who had the disease for at least 1 year and had an inadequate response to MTX	Age, mean (SD): Abatacept: 49.0 (12.5) Infliximab 3 mg/kg: 49.1 (12.0) Placebo: 49.4 (11.5) Female, n (%): NR Abatacept: 130 (83.3) Infliximab 3 mg/kg: 136 (82.4) Placebo: 96 (87.3) Race/ethnicity: Caucasian, n (%): NR Abatacept: 126 (80.8) Infliximab 3 mg/kg: 133 (80.6) Placebo: 84 (76.4)	Concomitant medications • Permitted between days 1–197: oral corticosteroids (10 mg of prednisone or equivalent daily (stable for > 25 out of 28 days prior to randomization)), and/or stable NSAIDs including ASS and analgesics not containing ASS or NSAIDs. No MTX dose adjustments were permitted except in the occurrence of AEs. Between days 198–365, dose modification was permitted for MTX (25 mg/week) and oral corticosteroids (10 mg prednisone or equivalent daily) Inclusion: • Patients of at least 18 years of age who met the ACR criteria for RA, who had the disease for at least 1 year and had an inadequate response to MTX, as demonstrated by ongoing active disease (at randomization > 10 swollen joints, > 12 tender joints, and CRP levels > 1 mg/dL). All patients had received MTX > 15 mg/week for > 3 months prior to randomization (stable	Bristol-Myers Squibb, Princeton, New Jersey, USA

Authors, Year Country Trial Name Trial Number Risk of Bias	Population	Age Gender Race/Ethnicity	Other Population Characteristics	Funding
			for at least 28 days and washed out all DMARDs > 28 days prior except for MTX Exclusion: • No prior experience of abatacept or anti-TNF therapy was permitted	
Smolen et al., 2016[45] 151 centers in Europe, Australia, and North America EXXELERATE NCT01500278 Moderate	Adults with active RA, prognostic factors for severe disease progression and inadequate response to MTX	Age, mean (SD): Certolizumab pegol 200 mg: 53.5 (12.3) Adalimumab 40 mg: 52.9 (12.8) Female n (%): Certolizumab pegol 200 mg: 360 (79) Adalimumab 40 mg: 362 (79) Race/ethnicity, n (%): NR	Concomitant medication: • Stable doses of NSAIDs and oral glucocorticoids (≤ 10 mg/day prednisolone equivalent) were allowed, if the regimen was stable for the 7 and 28 days prior to baseline, respectively Inclusion criteria: • Patients were aged 18 years or older with a diagnosis of RA at screening, as defined by the 2010 ACR/EULAR criteria, and had prognostic factors for severe disease progression, including a positive rheumatoid factor, or anti-CCP antibody result, or both. Patients had active RA, defined as: DAS28-ESR higher than 3.2, ≥ 4 swollen joints (DAS28), and increased acute phase reactants (hsCRP ≥ 10 mg/L, or ESR ≥ 28 mm/hour, or both) at screening and baseline. Patients were bDMARD-naive and with active disease despite a minimum 12-week course of MTX therapy prior to the screening visit, including a minimum of at least 28 days of stable dose MTX (15–25 mg per week orally or subcutaneously) before baseline Exclusion criteria: • Serious infections within 12 months prior to baseline, active or ongoing TB infection, any history of congestive heart failure, demyelinating disorders, active malignancy or a history of cancer (≤ 2 episodes of basal cell carcinoma, or cervical carcinoma in situ that occurred > 5 years prior to baseline were allowed)	UCB Pharma

Authors, Year Country Trial Name Trial Number Risk of Bias	Population	Age Gender Race/Ethnicity	Other Population Characteristics	Funding
Takeuchi et al., 2015[26] 43 sites in Japan NR NCT01649999 Moderate	Adult with active RA at least 6 months prior to screening.	Age, mean (SD): Peficitinib 25 mg: 52.9(9.5) Peficitinib 50 mg: 54.2(11.6) Peficitinib 100 mg: 52.1(12.1) Peficitinib 150 mg: 51.6(12.1) Placebo: 54.2(12.1) Female, n (%): Peficitinib 25 mg: 46(83.6) Peficitinib 50 mg: 46 (80.7) Peficitinib 100 mg: 42 (76.4) Peficitinib 150 mg: 51 (87.9) Placebo: 43 (76.8) Race/ethnicity, n (%): NR	Concomitant medication: • Concomitant stable dose of NSAIDs, oral morphine (≤ 30 mg/day or an equivalent amount of opioid analgesics), acetaminophen or an oral corticosteroid (≤ 10 mg/day of a prednisolone equivalent) were permitted Inclusion: • 20 to 75 years of age at the time of informed consent and active RA for at least 6 months prior to screening Exclusion: • Patients were excluded if they had taken biologic or nonbiologic DMARDs within the following period prior to the first dose of study drug: within 28 days (etanercept and nonbiologic DMARDs including MTX), 60 days (adalimumab, golimumab, infliximab and tocilizumab), 90 days (abatacept) and 180 days (rituximab)	Astellas Pharma Inc.
Takeuchi et al., 2019[41] 161 centers in Japan NR Moderate	Adults with active RA for < 10 years and an inadequate response to MTX	Age, mean (SD): 56.7 (11.6) Placebo: 55.3 (12.1) Peficitinib 100 mg: 58.5 (10.8) Peficitinib 150 mg: 56.2 (11.6) Female, n (%): 364 (70.3) Placebo: 121 (71.2) Peficitinib 100 mg: 118 (67.8) Peficitinib 150 mg: 125 (71.8) Race/ethnicity, n (%): NR	Concomitant medication: • MTX Inclusion: • 20 years of age or older and active RA • RA for less than 10 years • Inadequate response to MTX 8 mg/week or more for at least 28 days Exclusion: • Previous biological DMARDs or other JAK inhibitors, infections or laboratory abnormalities, or a history of or concurrent malignant tumor	Astellas Pharma, Inc
Tanaka et al. 2019[40] 165 sites in 3 countries (Japan,	Adults with active RA and inadequate response to, or intolerance of,	Age, mean (SD): 55.3 Placebo: 56.3 (11.7) Peficitinib 100 mg: 54.1 (12.2)	Concomitant medication: • DMARDs Inclusion: • 20 years of age or older and active RA	Astellas Pharma, Inc.

Authors, Year Country Trial Name Trial Number Risk of Bias	Population	Age Gender Race/Ethnicity	Other Population Characteristics	Funding
Korea, and Taiwan) NR NR Moderate	at least 1 DMARD	Peficitinib 150 mg: 55.0 (12.8) Etanercept: 55.5 (11.6) Female, n (%): 366 (72.2) Placebo: 73 (72.3) Peficitinib 100 mg: 77 (74.0) Peficitinib 150 mg: 78 (76.5) Etanercept: 138 (69.0) Race/ethnicity, n (%): NR	• Inadequate response to, or intolerance of, at least 1 DMARD administered for 90 days or more prior to screening Exclusion: • Inadequate response to ≥ 3 biological DMARDs • Diagnosis of inflammatory arthritis other than RA and laboratory abnormalities	
Taylor et al., 2017[29] 281 centers in 26 countries in North and South America, Europe, and Asia RA-BEAM NR Moderate	Adults with active RA and inadequate response to MTX	Age, mean (SD): Baricitinib 4 mg: 54 (2) Adalimumab 40 mg: 53 (12) Placebo: 53 (2) Female, n (%): 1008 (77) Baricitinib 4 mg: 375 (77) Adalimumab 40 mg: 251 (76) Placebo: 382 (78) Race/ethnicity, n (%): NR	Concomitant medication: • Concomitant stable doses of conventional synthetic DMARDs, NSAIDs, analgesics, or glucocorticoids (≤ 10 mg of prednisone or the equivalent per day) were permitted Inclusion: • 18 years of age or older and active RA • Inadequate response to MTX, having received 12 weeks or more of therapy before trial entry, including 8 weeks or more at stable doses of 15 to 25 mg per week, unless lower doses were clinically indicated Exclusion: • Previous biologic DMARD therapy, selected laboratory abnormalities, and recent clinically serious infection • Patients with evidence of latent TB could enroll if appropriate treatment had commenced 4 weeks or more before randomization	Eli Lilly and Incyte
van der Heijde et al., 2020[20]	Adults with active ankylosing spondylitis for 3 months or more	Age, mean (SD): 42.2 (11.8) Bimekizumab 16 mg: 43.3 (12.6)	Concomitant medication: • NR Inclusion:	UCB Pharma

Authors, Year Country Trial Name Trial Number Risk of Bias	Population	Age Gender Race/Ethnicity	Other Population Characteristics	Funding
74 sites, 10 countries, Europe and the US BE AGILE NCT02963506 Low		Bimekizumab 64 mg: 40.4 (10.9) Bimekizumab 160 mg: 42.4 (13.1) Bimekizumab 320 mg: 45.0 (11.4) Placebo: 39.7 (10.3) Female, n (%): 47 (15.5) Bimekizumab 16 mg: 8 (13.1) Bimekizumab 64 mg: 9 (14.8) Bimekizumab 160 mg: 8 (13.3) Bimekizumab 320 mg: 11 (18.0) Placebo: 11 (18.3) Race/ethnicity: Non-Caucasian, n (%): 5 (1.7) Bimekizumab 16 mg: 3 (4.9) Bimekizumab 64 mg: 1 (1.6) Bimekizumab 160 mg: 1 (1.7) Bimekizumab 320 mg: 0 (0) Placebo: 0 (0)	• 18 years of age or older and active ankylosing spondylitis with symptom duration of ≥3 months, age at onset of <45 • At least 1 of the following: inadequate response to NSAIDs, intolerance to ≥1 NSAID or contraindication(s) to NSAIDs Exclusion: • Patients with active/symptomatic Crohn's disease or ulcerative colitis • Total ankylosis of the spine; a concurrent or history of malignancy during the past 5 years; a diagnosis of other inflammatory conditions, active infection, or infection requiring antibiotics within 2 weeks of baseline; a history of chronic or recurrent infections or a serious/life-threatening infection within 6 months of baseline; presence of significant, uncontrolled neuropsychiatric disorder; active suicidal ideation; or positive suicide behavior within the past 6 months	
Vollenhofen et al., 2013[50] 115 centers worldwide ORAL Standard	Patients were eligible for enrollment if they were 18 years of age or older and had received a diagnosis of	Age, mean (SD): Tofacitinib 5 mg: 53.0 (11.9) Tofacitinib 10 mg: 52.9 (11.8) Adalimumab 40 mg: 52.5 (11.7) Placebo + tofacitinib 5 mg: 55.5 (13.7)	Concomitant medication: • All patients were taking background MTX. Inclusion criteria: • Active disease was defined as the presence of 6 or more tender or painful joints (of 68 joints examined) and 6 or more swollen joints (of 66 joints examined) and either an ESR > 28 mm/hour or a CRP level > 7 mg/L. Patients were receiving 7.5 to 25 mg of MTX	Pfizer

Authors, Year Country Trial Name Trial Number Risk of Bias	Population	Age Gender Race/Ethnicity	Other Population Characteristics	Funding
NCT00853385 Moderate	active RA, as defined according to the ACR 1987 Revised Criteria.	Placebo + tofacitinib 10 mg: 51.9 (13.7) Female, n (%): Tofacitinib 5 mg: 174 (85.3) Tofacitinib 10 mg: 168 (83.6) Adalimumab 40 mg: 162 (79.4) Placebo + tofacitinib 5 mg: 43 (76.8) Placebo + tofacitinib 10 mg: 39 (75.0) Race/ethnicity: White, n (%): Tofacitinib 5 mg: 151 (74.0) Tofacitinib 10 mg: 143 (71.1) Adalimumab 40 mg: 148 (72.5) Placebo + tofacitinib 5 mg: 40 (71.4) Placebo + tofacitinib 10 mg: 35 (67.3)	weekly and had an incomplete response (defined as sufficient residual disease activity to meet entry criteria) Key exclusion criteria: • Current treatment with other antirheumatic agents, including biologic agents; prior treatment with adalimumab; lack of response to prior anti-TNF-biologic treatment; and current infection or evidence of active or inadequately treated infection with Mycobacterium TB	
Weinblatt et al., 2013[43] Schiff et al., 2013[89] 120 sites in North and South America AMPLE	Adults with confirmed diagnosis of RA for less than 5 years, inadequate response to MTX, and nor previous bDMARD therapy	Age, mean (SD): Abatacept 125 mg SC: 51.4 (12.6) Adalimumab 40 mg SC: 51.0 (12.8) Female, n (%): Abatacept 125 mg SC: 259 (81.4) Adalimumab 40 mg SC: 270 (82.3) Race/ethnicity:	Concomitant medication: • Patients were concomitantly treated with a stable dosage of MTX (between 15 mg/week and 25 mg/week, or at least 7.5 mg/week in patients with documented intolerance to higher doses). In addition, patients were allowed to receive either hydroxychloroquine or sulfasalazine; other DMARDs were not allowed during the study. Stable, low-dose oral corticosteroids (10 mg/day prednisone equivalent) were permitted. Up to 2 courses of high-dose corticosteroids (such as a short [defined as a maximum of 2 weeks] oral course of high-dose corticosteroids, a single intramuscular dose of	Bristol-Myers Squibb and Abbott

Authors, Year Country Trial Name Trial Number Risk of Bias	Population	Age Gender Race/Ethnicity	Other Population Characteristics	Funding
NCT00929864 Moderate		White, n (%): Abatacept 125 mg SC: 257 (80.8) Adalimumab 40 mg SC: 256 (78.0)	corticosteroid, or a single intraarticular injection of cortico-steroid) were permitted, except within 42 days of day 365. Use of NSAIDs, including aspirin, was permitted, provided that the dosage was stable; additional NSAIDs were not allowed within 12 hours before a clinical assessment. Inclusion: • Patients met the ACR 1987 classification criteria for RA, were at least 18 years of age, had a confirmed diagnosis of RA for less than 5 years, had an inadequate response to MTX, and had not received previous bDMARD therapy. At randomization, patients were required to have active disease, defined as a score of > 3.2 on the DAS28-CRP, as well as a history of 1 or both of the following features: 1) seropositivity for anticyclic citrullinated peptide antibodies or rheumatoid factor, and/or 2) an elevated ESR or CRP level.	

Abbreviations. ACR20/50/70: American College of Rheumatology, numbers refer to percentage improvement; ADA: American Diabetes Association; AE: adverse event; ALT: alanine transaminase; ASS: acetylsalicylic acid; AST: aspartate transaminase; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; bDMARD: biologic disease-modifying antirheumatic drug; BMI: body mass index; CCP: cyclic citrullinated peptide; CRP: C-reactive protein; csDMARD: conventional synthetic disease-modifying antirheumatic drug; CVD: cardiovascular disease; DAS28: 28-joint Disease Activity Score; DAS28-CRP: 28-joint Disease Activity Score using C-reactive protein; DAS28-ESR: 28-joint Disease Activity Score using erythrocyte sedimentation rate; dL: deciliter; DMARD: disease-modifying antirheumatic drug; ESR: erythrocyte sedimentation rate; EULAR: European League Against Rheumatism; g: gram; GFR: glomerular filtration rate; Hb: hemoglobin; HIV: human immunodeficiency virus; hsCRP: high-sensitivity C-reactive protein; IL: interleukin; IR: incidence rate; IV: intravenous; JAK: Janus kinase; kg: kilogram; L: liter; m: meter; mg: milligram; min: minute; mL: milliliter; mm: millimeter; m/s: meters per second; MTX: methotrexate; N: number; NA: not applicable; NCT: US National Clinical Trial Identifier; NR: not reported; NSAID: nonsteroidal anti-inflammatory drug; NYHA: New York Heart Association; RA: rheumatoid arthritis; RCT: randomized controlled trial; RF: rheumatoid factor; SC: subcutaneous; SD: standard deviation; SJC28/66: swollen joint count, numbers refer to joints assessed; TB: tuberculosis; TJC28/68: tender joint count, numbers refer to joints assessed; TNF-α: tumor necrosis factor-alpha; ULN: upper limit of laboratory normal; VAS: Visual Analogue Scale.

Table B2. Evidence Table RCTs of Previous Reports (Study and Population Characteristics)

Authors, Year Country Trial Name Trial Number Risk of Bias	Population	Age Gender Race/Ethnicity	Other Population Characteristics	Funding
Genovese et al., 2004[54] 41 sites, US NR Moderate	Adults with active RA for more than 6 months, despite MTX therapy	Age, mean (SD): Etanercept 25 mg + placebo: 54 (14) Etanercept 25 mg + anakinra 100 mg: 54 (12) Etanercept 25 mg + anakinra 100 mg: 56 (13) Female, n (%): Etanercept 25 mg + placebo: 66 (83) Etanercept 25 mg + anakinra 100 mg daily: 58 (72) Etanercept 25 mg + anakinra 100 mg: 63 (78) Race/ethnicity: Non-white race, n (%): Etanercept 25 mg + placebo: 11 (14) Etanercept 25 mg + anakinra 100 mg: 18 (22) Etanercept 25 mg + anakinra 100 mg: 20 (25)	Concomitant medication: • Patients continued to receive stable doses of MTX and other medications (e.g., corticosteroids and NSAID) throughout the study. Inclusion: • Patients at least 18 years old and more than 6-month history of RA, as diagnosed by the ACR classification criteria • Patients had at least 6 swollen joints and 9 tender/painful joints and at least 2 of the following: morning stiffness lasting at least 45 minutes, a serum CRP level of at least 1.5 mg/dl, or an ESR of at least 28 mm/hour. • Patients had received MTX for at least 16 weeks, with the dosage stable at 10–25 mg/week for at least 8 weeks. Exclusion: • Received any DMARD other than MTX within the past 4 weeks • Had been treated with anakinra or any protein-based TNF inhibitor (e.g., etanercept, infliximab) • Received any intraarticular or systemic corticosteroid injections within the past 4 weeks, or had a recent history of significant infection or other important concurrent illness	Amgen Inc.
De Filippis et al. 2006[53] Italy	Adults with RA and incomplete response to DMARDs	Age, mean (SD): Etanercept 25 mg: 45 (14) Infliximab 3 mg: 47 (11) Female, n (%):	Concomitant medication: • COX2 inhibitors, NSAIDs, corticosteroids Inclusion: • Patients with active rheumatoid arthritis, aged 20 to 60 years	NR

Authors, Year Country Trial Name Trial Number Risk of Bias	Population	Age Gender Race/Ethnicity	Other Population Characteristics	Funding
NR Moderate		NR <u>Race/Ethnicity, n (%):</u> NR	• Symptom's duration > 2 years • Not responding to DMARDs for > 6 months, including a stable dose of methotrexate (between 10-15 mg/ week) in the 3 months before entering the study Exclusion: • Early onset disease (< 2 years) • Hospitalization in the previous 6 months for important medical problems or infections, renal or hepatic failure • Positivity for ANA, heart failure (class III-IV NYHA) • Corticosteroid therapy > 10mg of prednisolone or equivalent	
Weinblatt et al., 2006[58] NR ASSURE NR Moderate	Adults with active RA despite TIMs and/or DMARDs treatment for at least 3 months	<u>Age, mean (SD):</u> Abatacept 10 mg + Other TIMs (anakinra, etanercept, infliximab, and adalimumab): 54.6 (11) Other TIMs Alone (anakinra, etanercept, infliximab, and adalimumab): 52.8 (11) <u>Female, n (%):</u> Abatacept 10 mg/kg + Other TIMs (anakinra, etanercept, infliximab, and adalimumab): 78 (76) Other TIM Alone (anakinra, etanercept, infliximab, and adalimumab): 48 (75) <u>Race/ethnicity:</u>	Concomitant medication: • TIMs, NSAIDs Inclusion: • Age ≥ 18 years • Diagnosis of active RA that fulfilled the 1987 ACR classification criteria and the 1991 ACR criteria for RA functional classes I, II, III, or IV • ≥ 1 biologic and/or nonbiologic DMARD approved for RA for at least 3 months, and at a stable dose for at least 28 days prior to day 1 of the trial Exclusion: • Unstable or uncontrolled renal, endocrine, hepatic, hematologic, gastrointestinal, pulmonary, cardiac, or neurologic diseases, or any autoimmune disorder other than RA as the main diagnosis • Active or chronic recurrent bacterial infections unless treated and resolved, active herpes zoster infection within the previous 2 months, hepatitis B or	Bristol-Myers Squibb

Authors, Year Country Trial Name Trial Number Risk of Bias	Population	Age Gender Race/Ethnicity	Other Population Characteristics	Funding
		Non-white population, n (%): Abatacept 10 mg + Other TIMs (anakinra, etanercept, infliximab, and adalimumab): 3 (3) Other TIMs Alone (anakinra, etanercept, infliximab, and adalimumab): 5 (8)	hepatitis C virus infection, and active or latent tuberculosis unless appropriately treated • Pregnant or nursing women	
Weinblatt et al., 2007[55] US NR Moderate	Adults with active RA for 1 yeardespite TIM (etanercept) treatment (at least 3 months)	Age, mean (range): Abatacept 10 mg + Etanercept 25 mg: 48.9 (23–73) Etanercept 25 mg + Placebo: 54.3 (28–71) Female, n (%): Abatacept 10 mg + Etanercept 25 mg: 66 (78) Etanercept 25 mg + placebo: 26 (72) Race/ethnicity: Non-white population, n (%): Abatacept 10 mg/kg + Etanercept 25 mg: 5 (6) Etanercept 25 mg+ Placebo: 0 (0)	Concomitant medication: • NR Inclusion: • Patients >18 years of age with RA, in functional class I, II or III • Patients who received at least one infusion of study drug (one or more) • Patients must have received etanercept 25 mg twice weekly for ≥ 3 months and have ≥ 8 swollen joints (66-joint count) and ≥ 10 tender joints (68-joint count) Exclusion: • Active or latent infection, recent opportunist infection, tuberculosis requiring treatment within the previous 3 years, history of cancer within the previous 5 years or history of drug or alcohol misuse	Bristol-Myers Squibb
Greenwald et al., 2011[59] US NR	Adults with active RA for 6 months or more despite MTX and TNF-α inhibitors treatment (at	Age, mean (range): TNF-α inhibitors + MTX + placebo: 50 (29–63) TNF-α inhibitors + Rituximab 500 mg + MTX: 50 (19–65)	Concomitant medication: • Corticosteroid stable dose of 10 mg/day or less (prednisone or equivalent) for 4 weeks or more prior to infusion Inclusion: • Adults (18 – 65 years) with RA for 6 months or more	Biogen Idec, Genentech, and Roche

Authors, Year Country Trial Name Trial Number Risk of Bias	Population	Age Gender Race/Ethnicity	Other Population Characteristics	Funding
Moderate	least 12 weeks).	Female, n (%): TNF-α inhibitors + MTX + placebo: 17 (94) TNF-α inhibitors + Rituximab 500 mg + MTX: 28 (85) Race/ethnicity, n (%): Non-white population: TNF-α inhibitors + MTX + placebo: 1 (6) TNF-α inhibitors + Rituximab 500 mg + MTX: 2 (6)	• SJC of at least 5 (of 66 joints assessed) and TJC of at least 5 (of 68 joints assessed) • Patients must have been treated with etanercept at 50 mg/week (25 mg twice per week or 50 mg once per week) or adalimumab at 40 mg every other week for at least 12 weeks immediately prior to randomization • Use of MTX for at least 12 weeks, at a stable dose of 10–25 mg/week for 4 weeks prior to treatment Exclusion: • Patients with a rheumatic autoimmune disease (other than RA) or significant systemic involvement secondary to RA (e.g., vasculitis, pulmonary fibrosis, or Felty's syndrome) • Patients with congestive heart failure, uncontrolled concomitant disease, • Cancer, or serious or opportunistic infections within 2 years of screening.	

Abbreviations. ACR20/50/70: American College of Rheumatology, numbers refer to percentage improvement; ANA: antinuclear antibody; CRP: C-reactive protein; COX2 inhibitor: cyclooxygenase-2 inhibitors; DAS: joint Disease Activity Score; dL: deciliter; DMARD: disease-modifying antirheumatic drug; ESR: erythrocyte sedimentation rate; IR: incidence rate; IV: intravenous; JAK: Janus kinase; kg: kilogram; L: liter; m: meter; mg: milligram; mm: millimeter; MTX: methotrexate; N: number; NA: not applicable; NR: not reported; NSAID: nonsteroidal anti-inflammatory drug; NYHA: New York Heart Association; RA: rheumatoid arthritis; RCT: randomized controlled trial; SC: subcutaneous; SD: standard deviation; SJC: swollen joint count; TB: tuberculosis; TIM: Targeted Immune Modulators; TJC: tender joint count; TNF-α: tumor necrosis factor-alpha; US: United States.

Table B3. Evidence Table RCTs (Intervention and Results)

Authors, Year Country Trial Name Trial Number Risk of Bias	Interventions	N	Efficacy/Effectiveness Outcomes	AEs (General)	AEs (Specific)
Brown et al., 2018[42] 35 sites in the United Kingdom SWITCH NR High	• Abatacept 125 mg SC weekly (minimum 24 weeks) • Rituximab 1 g IV at days 0 (week 0) and 15 (week 2) • Alternative TNF-α inhibitors: etanercept (50 mg SC weekly for a minimum of 24 weeks), Adalimumab (40 mg SC every 2 weeks for a minimum of 24 weeks), Infliximab (3 mg/kg IV, administered on a day-case unit or equivalent at weeks 0, 2, and 6 and then every 8 weeks thereafter for a minimum of 24 weeks), certolizumab pegol (400 mg SC at weeks 0, 2, and 4 and then 200 mg every 2 weeks thereafter for a minimum of 24 weeks), golimumab (50 mg SC every 4 weeks for a minimum of 24 weeks)	Total N = 122 Alternative TNF-α inhibitors = 41 Abatacept 125 mg = 41 Rituximab 1 g = 40	Week 24: DAS28, adjusted mean reduction from baseline Rituximab 1 g: 1.17 (0.56 to 1.77) Abatacept 125 mg: 1.20 (0.62 to 1.78) Difference in mean reductions Abatacept vs. rituximab: -0.4 units (95% CI, -0.72 to 0.79; P = .93). DAS28, adjusted mean reduction from baseline: Abatacept 125 mg: -1.20 Alternative TNF-α inhibitors: -1.47 *P* value NR Week 48 DAS28: Adjusted mean: Rituximab 1 g: 4.79 (4.28 to 5.29) Abatacept 125 mg: 4.84 (4.38 to 5.31) Difference in mean DAS28 reductions	Week 48: Any AE: Rituximab 1 g: 31 of 40 (77.5%) Abatacept 125 mg: 31 of 41 (75.6%) SAEs: Rituximab 1 g: 4 of 40 (10%) Abatacept 125 mg: 4 of 41 (9.8%) Withdrawal because of AEs: Rituximab 1 g: 4 of 40 (10%) Abatacept 125 mg: 2 of 41 (4.9%)	Week 48: Death: Rituximab 1 g: 1 of 40 (2.5%*) Abatacept 125 mg: 1 of 41 (2.4%*) Melanoma skin cancer: Rituximab 1 g: 1 of 40 (2.5%*) Abatacept 125 mg: 0 of 41 (0%*) Pneumonia: Rituximab 1 g: 1 of 40 (2.5%*) Abatacept 125 mg: 1 of 41 (2.4%*) Injection site reactions (angioedema): Rituximab 1 g: 0 of 40 (0%*) Abatacept 125 mg: 1 of 41 (2.4%*)

Authors, Year Country Trial Name Trial Number Risk of Bias	Interventions	N	Efficacy/Effectiveness Outcomes	AEs (General)	AEs (Specific)
	• A patient who lost an initial 6-month (week 24) response, as per NICE's guidance, could receive a further cycle of rituximab after a minimum of 6 months following the first dose. The second cycle of rituximab was, again, given at a dose of 1 g; 2 intravenous infusions administered at a 2-week interval. Prior to receiving rituximab, 100 mg of IV methylprednisolone was given as a premedication.		Abatacept vs. rituximab: 0.06 (−0.59 to 0.71) P = .86 Reduction in DAS28 ≥ 1.2 units: Rituximab 1 g: 1.15 (0.49 to 2.71) Abatacept 125 mg: 1.05 (0.50 to 2.19) Abatacept vs. rituximab OR 0.91 (0.30 to 2.73) P = .87 Week 24: ACR20 (aOR): Abatacept vs. rituximab 1.19 (0.44 to 3.21) P = .74 Week 48: DAS28 low disease activity: Rituximab 1 g: 1 of 40 (2.5%) Abatacept 125 mg: 1 of 41 (2.4%) ACR20: Rituximab 1 g: 12 of 28 (42.9%) Abatacept 125 mg: 11 of 31 (35.5%) ACR50: Rituximab 1 g: 6 of 29 (20.7%)		* self-calculated

Authors, Year Country Trial Name Trial Number Risk of Bias	Interventions	N	Efficacy/Effectiveness Outcomes	AEs (General)	AEs (Specific)
			Abatacept 125 mg: 6 of 32 (18.8%) ACR70: Rituximab 1 g: 3 of 30 (10.0%) Abatacept 125 mg: 3 of 32 (9.4%) DAS28 remission: Rituximab 1 g: 2 of 40 (5.0%) Abatacept 125 mg: 2 of 41 (4.9%) EULAR good response: Rituximab 1 g: 2 of 40 (5.0%) Abatacept 125 mg: 2 of 41 (4.9%) CDAI (median (quartiles)): Rituximab 1 g: 20.3 (5.3, 32.3) Abatacept 125 mg: 14.1 (5.9, 29.2) SDAI improvement (median (quartiles)): Rituximab 1 g: 20.1 (5.3, 34.0) Abatacept 125 mg: 13.7 (6.3, 31.2) HAQ-DI improvement (median (quartiles)): Rituximab 1 g: 1.7 (1.1, 2.1) Abatacept 125 mg: 1.6 (1.0, 2.1)		

Authors, Year Country Trial Name Trial Number Risk of Bias	Interventions	N	Efficacy/Effectiveness Outcomes	AEs (General)	AEs (Specific)
Burmester et al., 2016[48] Strand et al., 2018[79] 86 centers in Europe, Israel, Russia, South Africa, South America, South Korea and the US MONARCH NCT02332590 Moderate	• Sarilumab 200 mg SC every 2 weeks plus placebo SC • Adalimumab 40 mg SC every 2 weeks plus placebo	Total n = 369 Sarilumab 200 mg = 184 Adalimumab 40 mg = 185	Primary outcome: Week 24 DAS28-ESR: mean change from baseline (SE) Adalimumab 40 mg: −2.20 (0.106) Sarilumab 200 mg: −3.28 (0.105) P < .0001 Secondary outcome: Week 24 DAS28-ESR < 2.6: Adalimumab 40 mg: 13 of 185 (7.0%) Sarilumab 200 mg: 49 of 184 (26.6%) P < .0001 HAQ-DI mean change from baseline, (SE) Adalimumab 40 mg: −0.43 (0.05) Sarilumab 200 mg: −0.61 (0.05) P = .004 ACR20 response Adalimumab 40 mg: 108 of 185 (58.4%) Sarilumab 200 mg: 132 of 184 (71.7%) P = .007	AEs: Adalimumab 40 mg: 117 of 184 (63.6%) Sarilumab 200 mg: 118 of 184 (64.1%) SAEs: Adalimumab 40 mg: 12 of 184 (6.5%) Sarilumab 200 mg: 9 of 184 (4.9%) Withdrawal because of AEs: Adalimumab 40 mg: 13 of 184 (7.1%) Sarilumab 200 mg: 11 of 184 (6.0%)	Infections: Adalimumab 40 mg: 51 of 184 (27.7%) Sarilumab 200 mg: 53 of 184 (28.8%) Injection site erythema: Adalimumab 40 mg: 6 of 184 (3.3%) Sarilumab 200 mg: 14 of 184 (7.6%) Serious infections: Adalimumab 40 mg: 2 of 184 (1.1%) Sarilumab 200 mg: 2 of 184 (1.1%)

Authors, Year Country Trial Name Trial Number Risk of Bias	Interventions	N	Efficacy/Effectiveness Outcomes	AEs (General)	AEs (Specific)
			ACR50 response Adalimumab 40 mg: 55 of 185 (29.7%) Sarilumab 200 mg: 84 of 184 (45.7%) P = .002 ACR70 response Adalimumab 40 mg: 22 of 185 (11.9%) Sarilumab 200 mg: 43 of 184 (23.4%) P = .004		
Elmedany et al., 2019[32] 1 site in Saudi Arabia NR NR High	• Tocilizumab IV 8 mg/kg every 4 weeks • Abatacept IV 500 mg for patients less than 60 kg body weight, 750 mg for 60–100 kg, and 1,000 mg for patients more than 100 kg body weight on days 1, 15, and 29 and then every 4 weeks	Total N = 132 Tocilizumab 8 mg/kg = 68 Abatacept 500/750/1,000 mg = 64	Week 24: DAS28-ESR: mean change from baseline: Tocilizumab 8 mg/kg: -3.3 Abatacept 500/750/1,000 mg: -2.6 P = .049 DAS28-ESR mean (SD): Tocilizumab 8 mg/kg: 2.4 (0.84) Abatacept 500/750/1,000 mg: 2.8 (0.78) P = .055 HAQ (VAS) mean (SD): Tocilizumab 8 mg/kg: 15.95 (7.86)	Week 24: Any AE: Tocilizumab 8 mg/kg: 40 of 68 (60.3%) Abatacept 500/750/1,000 mg: 18 of 64 (28.1%) Withdrawal because of AEs: Tocilizumab 8 mg/kg: 10 of 68 (14.7%) Abatacept	Injection site reaction: Tocilizumab 8 mg/kg: 12 of 68 (17.6%) Abatacept 500/750/1,000 mg: 10 of 64 (15.6%) Herpes zoster: Tocilizumab 8 mg/kg: 0 of 68 (0%) Abatacept 500/750/1,000 mg: 0 of 64 (0%) New cancer incidence:

Authors, Year Country Trial Name Trial Number Risk of Bias	Interventions	N	Efficacy/Effectiveness Outcomes	AEs (General)	AEs (Specific)
			Abatacept 500/750/1,000 mg: 20.74 (8.82) P = .001 HAQ-DI mean (SD): Tocilizumab 8 mg/kg: 0.89 (1.12) Abatacept 500/750/1,000 mg: 1.01 (1.24) P = .56	500/750/1,000 mg: 4 of 64 (6.3%) SAEs: Tocilizumab 8 mg/kg: 10 of 68 (14.7%) Abatacept 500/750/1,000 mg: 4 of 64 (6.3%)	Tocilizumab 8 mg/kg: 0 of 68 (0%) Abatacept 500/750/1,000 mg: 0 of 64 (0%) Major adverse cardiovascular events: Tocilizumab 8 mg/kg: 0 of 68 (0%) Abatacept 500/750/1,000 mg: 0 of 64 (0%) Gastrointestinal perforation: Tocilizumab 8 mg/kg: 0 of 68 (0%) Abatacept 500/750/1,000 mg: 0 of 64 (0%)
Emery et al., 2018[36] US, South America, Western Europe, Eastern Europe and Russia	• Sarilumab 150 mg or 200 mg every 2 weeks (for 24 weeks) • Tocilizumab 4 mg/kg body weight to 8 mg/kg body weight IV every 4 weeks	Total N = 202 Sarilumab 150 mg = 49 Sarilumab 200 mg = 51 Tocilizumab 4 mg/kg = 102	NR	Week 24: Any AE: Sarilumab 150 mg:33 of 49 (67%) Sarilumab 200 mg: 36 of 51 (71%) Tocilizumab 4 mg/kg: 68 of 102	Week 24 Infection: Sarilumab 150 mg: 20 of 49 (40.8%) Sarilumab 200 mg: 11 of 51 (21.6%) Tocilizumab 4 mg/kg: 32 of 102 (31.4%)

Authors, Year Country Trial Name Trial Number Risk of Bias	Interventions	N	Efficacy/Effectiveness Outcomes	AEs (General)	AEs (Specific)
ASCERTAIN NR High				(67%) Withdrawal because of AEs: Sarilumab 150 mg: 6 of 49 (12%) Sarilumab 200 mg: 8 of 51 (16%) Tocilizumab 4 mg/kg: 4 of 102 (4%) SAEs: Sarilumab 150 mg: 1 of 49 (2%) Sarilumab 200 mg: 3 of 51 (6%) Tocilizumab 4 mg/kg: 7 of 102 (7%)	Serious infection Sarilumab 150 mg: 0 of 49 (0%) Sarilumab 200 mg: 1 of 51 (2.0%) Tocilizumab 4 mg/kg: 2 of 102 (2.0%) Death Sarilumab 150 mg: 0 of 49 (0%) Sarilumab 200 mg: 0 of 51 (0%) Tocilizumab 4 mg/kg: 1 of 102 (1.0%)
Fleischmann et al., 2012[51] 63 centers in the US, Europe, Latin America, and the Republic of Korea NR	• Tofacitinib 1 mg twice a day • Tofacitinib 3 mg twice a day • Tofacitinib 5 mg twice a day, • Tofacitinib 10 mg twice a day, • Tofacitinib 15 mg twice a day	Total n = 384 Tofacitinib 1 mg = 54, Tofacitinib 3 mg = 51, Tofacitinib 5 mg = 49, Tofacitinib 10 mg = 61,	Primary outcome: 12 weeks ACR20 response: P-value vs. placebo Tofacitinib 1 mg: 17 of 54 (31.5%) Tofacitinib 3 mg: 20 of 51 (39.2%) (P < .05) Tofacitinib 5 mg: 29 of 49 (59.2%) (P < .0001)	AEs: Tofacitinib 1 mg: 19 of 37 (51.4%) Tofacitinib 1 mg reassigned*: 5 of 17 (29.4%) Tofacitinib 3 mg: 18 of 34 (52.9%) Tofacitinib 3 mg	Infections: Tofacitinib 1 mg: 11 of 37 (29.7%) Tofacitinib 1 mg reassigned*: 2 of 17 (11.8%) Tofacitinib 3 mg: 7 of 34 (20.6%) Tofacitinib 3 mg

Authors, Year Country Trial Name Trial Number Risk of Bias	Interventions	N	Efficacy/Effectiveness Outcomes	AEs (General)	AEs (Specific)
NCT00550446 Moderate	• Adalimumab 40 mg SC every 2 weeks • Placebo	Tofacitinib 15 mg = 57, Adalimumab 40 mg = 53 Placebo = 59	Tofacitinib 10 mg: 43 of 61 (70.5%) (P < .0001) Tofacitinib 15 mg: 41 of 57 (71.9%) (P < .0001) Adalimumab 40 mg: 19 of 53 (35.9%) Placebo: 13 of 59 (22%) 24 weeks ACR20 response: P -value vs. placebo Tofacitinib 1 mg: 13 of 54 (24.1%) Tofacitinib 3 mg: 19 of 51 (37.3%) Tofacitinib 5 mg: 25 of 49 (51.0%) (P < .05) Tofacitinib 10 mg: 40 of 61 (65.6%) (P < .0001) Tofacitinib 15 mg: 38 of 57 (66.7%) (P < .0001) Adalimumab 40 mg: NR Placebo: 15 of 59 (25.4%) Secondary outcomes: 12 weeks ACR50 response: P-value vs. placebo Tofacitinib 1 mg: 6 of 54 (11.1%) Tofacitinib 3 mg: 12 of 51 (23.5%) Tofacitinib 5 mg: 18 of 49 (36.7%) (P < .001)	reassigned*: 6 of 17 (35.3%) Tofacitinib 5 mg: 27 of 49 (55.1%) Tofacitinib 10 mg: 36 of 61 (59.0%) Tofacitinib 15 mg: 35 of 57 (61.4%) Adalimumab 40 mg at week 12: 27 of 53 (50.9%) Adalimumab 40 mg reassigned*: 28 of 44 (63.6%) Placebo: 16 of 34 (47.1%) Placebo reassigned*: 13 of 25 (52.0%) SAEs: Tofacitinib 1 mg: 2 of 37 (5.4%) Tofacitinib 1 mg reassigned*: 0 of 17 (0%) Tofacitinib 3 mg: 1 of 34 (2.9%) Tofacitinib 3 mg reassigned*: 0 of	reassigned*: 3 of 17 (17.6%) Tofacitinib 5 mg: 17 of 49 (34.7%) Tofacitinib 10 mg: 21 of 61 (34.4%) Tofacitinib 15 mg: 19 of 57 (33.3) Adalimumab 40 mg: 10 of 53 (18.9%) Adalimumab 40 mg reassigned*: 11 of 44 (25.0%) Placebo: 6 of 34 (17.6%) Placebo reassigned*: 6 of 25 (24.0%) Serious Infections: Tofacitinib 1 mg: 2 of 37 (5.4%) Tofacitinib 1 mg reassigned*: 0 of 17 (0%) Tofacitinib 3 mg: 0 of 34 (0%) Tofacitinib 3 mg reassigned*: 0 of 17 (0%) Tofacitinib 5 mg: 0 of

Authors, Year Country Trial Name Trial Number Risk of Bias	Interventions	N	Efficacy/Effectiveness Outcomes	AEs (General)	AEs (Specific)
			Tofacitinib 10 mg: 27 of 61 (44.3%) (P < .0001) Tofacitinib 15 mg: 29 of 57 (50.9%) (P < .0001) Adalimumab 40 mg: 10 of 53 (18.9%) Placebo: 6 of 59 (10.2%) ACR70 response: P-value vs. placebo Tofacitinib 1 mg: 3 of 54 (5.6%) Tofacitinib 3 mg: 6 of 51 (11.8%) Tofacitinib 5 mg: 6 of 49 (12.2%) Tofacitinib 10 mg: 15 of 61 (24.6%) (P < .001) Tofacitinib 15 mg: 15 of 57 (26.3%) (P < .001) Adalimumab 40 mg: 2 of 53 (3.8%) Placebo: of 59 (3.4%) 24 weeks ACR50 response: P -value vs. placebo Tofacitinib 1 mg: 4 of 54 (7.4%) Tofacitinib 3 mg: 14 of 51 (27.5%) (P < .05) Tofacitinib 5 mg: 17 of 49 (34.7%) (P < .05) Tofacitinib 10 mg: 27 of 61	17 (0%) Tofacitinib 5 mg: 0 of 49 (0%) Tofacitinib 10 mg: 1 of 61 (1.6%) Tofacitinib 15 mg: 4 of 57 (7.0%) Adalimumab 40 mg: 1 of 53 (1.9%) Adalimumab 40 mg reassigned*: 4 of 44 (9.1%) Placebo: 2 of 34 (5.9%) Placebo reassigned*: 0 of 25 (0%) Withdrawal because of AEs: Tofacitinib 1 mg: 4 of 37 (10.8%) Tofacitinib 1 mg reassigned*: 0 of 17 (0%) Tofacitinib 3 mg: 3 of 34 (8.8%) Tofacitinib 3 mg reassigned*: 0 of 17 (0%)	49 (2%) Tofacitinib 10 mg: 0 of 61 (1.6%) Tofacitinib 15 mg: 1 of 57 (1.8) Adalimumab 40 mg: 0 of 53 (0.0%) Adalimumab 40 mg reassigned*: 1 of 44 (2.3%) Placebo: 1 of 34 (2.9%) Placebo reassigned*: 0 of 25 (0.0%) Deaths: Tofacitinib 15 mg: 1 of 57 (1.8%) No deaths have been reported in the other groups. * After 12 weeks, patients were reassigned to receive 5 mg tofacitinib twice a day from week 12 to week 24

Authors, Year Country Trial Name Trial Number Risk of Bias	Interventions	N	Efficacy/Effectiveness Outcomes	AEs (General)	AEs (Specific)
			(44.3%) (P < .0001) Tofacitinib 15 mg: 31 of 57 (54.4%) (P < .0001) Placebo: 6 of 59 (10.2%) ACR70 response: P -value vs. placebo Tofacitinib 1 mg: 3 of 54 (5.6%) Tofacitinib 3 mg: 7 of 51 (13.7%) Tofacitinib 5 mg: 10 of 49 (20.4%) (P < .05) Tofacitinib 10 mg: 23 of 61 (37.7%) (P < .0001) Tofacitinib 15 mg: 19 of 57 (33.3%) (P < .001) Placebo: 4 of 59 (6.8%)	Tofacitinib 5 mg: 1 of 49 (2%) Tofacitinib 10 mg: 1 of 61 (1.6%) Tofacitinib 15 mg: 3 of 57 (5.3) Adalimumab 40 mg: 4 of 53 (7.5%) Adalimumab 40 mg reassigned*: 3 of 44 (6.8%) Placebo: 1 of 34 (2.9%) Placebo reassigned*: 0 of 25 (0%) * After 12 weeks, patients were reassigned to receive 5 mg tofacitinib twice a day from week 12 to week 24	
Fleischmann et al., 2017[52] Strand et al., 2019[78]	• Tofacitinib 5 mg twice daily • Tofacitinib 5 mg twice daily + background MTX	Total n = 1146 Tofacitinib 5 mg = 384 Tofacitinib 5 mg + MTX = 376	Primary outcome: 6 months ACR50 response Tofacitinib 5 mg: 147 of 384 (38%)	AEs: Tofacitinib 5 mg: 226 of 384 (59%) Tofacitinib 5 mg + MTX: 231 of 376	Serious infections: Tofacitinib 5 mg: 6 of 384 (1.6%) Tofacitinib 5 mg + MTX: 10 of 376

Authors, Year Country Trial Name Trial Number Risk of Bias	Interventions	N	Efficacy/Effectiveness Outcomes	AEs (General)	AEs (Specific)
194 centers in 25 countries. ORAL – Strategy NCT02187055 Moderate	• Adalimumab 40 mg every 2 weeks + background MTX	Adalimumab 40 mg + MTX = 386	Tofacitinib 5 mg + MTX: 173 of 376 (46%) Adalimumab 40 mg + MTX: 169 of 386 (44%) Secondary outcomes: 6 months ACR20 response: Tofacitinib 5 mg: 249 of 384 (65%) Tofacitinib 5 mg + MTX: 275 of 376 (73%) Adalimumab 40 mg + MTX: 274 of 386 (71%) ACR70 response: Tofacitinib 5 mg: 70 of 384 (18%) Tofacitinib 5 mg + MTX: 94 of 376 (25%) Adalimumab 40 mg + MTX: 80 of 386 (21%) DAS28 < 3.2: Tofacitinib 5 mg: 79 of 384 (21%) Tofacitinib 5 mg + MTX: 100 of 376 (27%) Adalimumab 40 mg + MTX: 106 of 386 (27%) DAS28-ESR < 2.6:	(61%) Adalimumab 40 mg + MTX: 253 of 386 (66%) SAEs: Tofacitinib 5 mg: 35 of 384 (9%) Tofacitinib 5 mg + MTX: 27 of 376 (7%) Adalimumab 40 mg + MTX: 24 of 386 (6%) Withdrawal because of AEs: Tofacitinib 5 mg: 23 of 384 (6%) Tofacitinib 5 mg + MTX: 26 of 376 (7%) Adalimumab 40 mg + MTX: 37 of 386 (10%)	(2.7%) Adalimumab 40 mg + MTX: 6 of 386 (1.6%) Herpes zoster: Tofacitinib 5 mg: 4 of 384 (1%) Tofacitinib 5 mg + MTX: 8 of 376 (2.1%) Adalimumab 40 mg + MTX: 6 of 386 (1.6%) Opportunistic infections: Tofacitinib 5 mg: 2 of 384 (1%) Tofacitinib 5 mg + MTX: 1 of 376 (0.3%) Adalimumab 40 mg + MTX: 2 of 386 (0.5%) Malignancies: Tofacitinib 5 mg: 1 of 384 (< 1%) Tofacitinib 5 mg + MTX: 0 of 376 (0.0%) Adalimumab 40 mg + MTX: 0 of 386 (0.0%) Deaths:

Authors, Year Country Trial Name Trial Number Risk of Bias	Interventions	N	Efficacy/Effectiveness Outcomes	AEs (General)	AEs (Specific)
			Tofacitinib 5 mg: 40 of 384 (10%) Tofacitinib 5 mg + MTX: 45 of 376 (12%) Adalimumab 40 mg + MTX: 48 of 386 (12%) PtGA: LSM changes from baseline (±SE): Tofacitinib 5 mg: −35.7 (0.98) Tofacitinib 5 mg + MTX: −38.4 (0.99) Adalimumab 40 mg + MTX: −38.8 (0.98) P < .05 for ADA + MTX vs. tofacitinib Pain: LSM changes from baseline (SE): Tofacitinib 5 mg: −26.6 (1.26) Tofacitinib 5 mg + MTX: −30.7 (1.26) Adalimumab 40 mg + MTX: −28.1 (1.26) P < .05 for tofacitinib + MTX vs. tofacitinib HAQ-DI: LSM changes from baseline (±SE): Tofacitinib 5 mg: −0.52 (0.03) Tofacitinib 5 mg + MTX: −0.58		Tofacitinib 5 mg: 2/384 (0.5%) Tofacitinib 5 mg + MTX: 0 of 376 (0.0%) Adalimumab 40 mg + MTX: 0 of 386 (0.0%)

Authors, Year Country Trial Name Trial Number Risk of Bias	Interventions	N	Efficacy/Effectiveness Outcomes	AEs (General)	AEs (Specific)
			(0.03) Adalimumab 40 mg + MTX: −0.54 (0.03) FACIT-F: LSM changes from baseline (±SE): Tofacitinib 5 mg: 7.14 (0.50) Tofacitinib 5 mg + MTX: 7.59 (0.50) Adalimumab 40 mg + MTX: 6.07 (0.50) P < .05 for tofacitinib + MTX vs. ADA+MTX SF-36 PCS: LSM changes from baseline (±SE): Tofacitinib 5 mg: 6.7 (0.44) Tofacitinib 5 mg + MTX: 7.9 (0.43) Adalimumab 40 mg + MTX: 7.8 (0.43) SF-36 MCS: LSM changes from baseline (±SE): Tofacitinib 5 mg: 5.2 (0.52) Tofacitinib 5 mg + MTX: 5.7 (0.51) Adalimumab 40 mg + MTX: 4.4 (0.51)		
Fleischmann et al., 2019[30]	• Upadacitinib 15 mg once daily + MTX	Total N = 1629 Upadacitinib 15	Primary outcomes: Week 12:	Week 26: Any AE:	Week 26: Infection:

Authors, Year Country Trial Name Trial Number Risk of Bias	Interventions	N	Efficacy/Effectiveness Outcomes	AEs (General)	AEs (Specific)
Strand et al., 2021[77] 286 sites in 41 countries in Europe, North, South and Central America, Europe, Asia SELECT-COMPARE NCT02629159 Moderate	• Adalimumab 40 mg SC every 2 weeks + MTX • Placebo	mg = 651 Adalimumab 40 mg = 327 Placebo = 651	ACR20 response: Upadacitinib 15 mg: 462 of 650* (71%) Adalimumab 40 mg: 206 of 327 (63%) P ≤ .05 DAS28-CRP score of < 2.6: Upadacitinib 15 mg: 189 of 650* (29%) Adalimumab 40 mg: 59 of 327 (18%) P ≤ .001 Secondary outcomes: Week 12: ACR50 response: Upadacitinib 15 mg: 293 of 650* (45%) Adalimumab 40 mg: 95 of 327 (29%) P ≤ .001 DAS28-CRP score of ≤ 3.2: Upadacitinib 15 mg: 293 of 650* (45%) Adalimumab 40 mg: 95 of 327 (29%) P ≤ .001	Upadacitinib 15 mg: 417 of 650* (64.2%) Adalimumab 40 mg: 197 of 327 (60.2%) Withdrawal because of AEs: Upadacitinib 15 mg: 23 of 650* (3.5%) Adalimumab 40 mg: 20 of 327 (6.1%) SAEs: Upadacitinib 15 mg: 24 of 650* (3.7%) Adalimumab 40 mg: 14 of 327 (4.3%) *One patient who was randomized to receive upadacitinib received only placebo injection,	Upadacitinib 15 mg: 226 of 650* (34.8%) Adalimumab 40 mg: 95 of 327 (29.1%) Serious infection: Upadacitinib 15 mg: 12 of 650* (1.8%) Adalimumab 40 mg: 5 of 327 (1.5%) Opportunistic infection: Upadacitinib 15 mg: 4 of 650* (0.6%) Adalimumab 40 mg: 1 of 327 (0.3%) Herpes zoster: Upadacitinib 15 mg: 5 of 650* (0.8%) Adalimumab 40 mg: 1 of 327 (0.3%)

Authors, Year Country Trial Name Trial Number Risk of Bias	Interventions	N	Efficacy/Effectiveness Outcomes	AEs (General)	AEs (Specific)
			HAQ-DI: mean change from baseline Upadacitinib 15 mg: -0.60 Adalimumab 40 mg: -0.49 P ≤ .01 PtGA: LSM mean change Upadacitinib 15 mg: −30.39 (95% CI, −32.62 to −28.16) Adalimumab 40 mg: −23.55 (95% CI, −26.43 to −20.67) Pain VAS: LSM mean change Upadacitinib 15 mg: −31.76 (95% CI, −33.96 to −29.56) Adalimumab 40 mg: −25.31 (95% CI, −28.16 to −22.47) AM stiffness severity LSM mean change Upadacitinib 15 mg: −3.37 (95% CI, −3.59 to −3.15) Adalimumab 40 mg: −2.86 (95% CI, −3.14 to −2.57) FACIT-F LSM mean change Upadacitinib 15 mg: 8.95 (95% CI,	along with background MTX, before discontinuing the treatment; this patient was included in the placebo group for safety assessments	

Authors, Year Country Trial Name Trial Number Risk of Bias	Interventions	N	Efficacy/Effectiveness Outcomes	AEs (General)	AEs (Specific)
			7.98 to- 9.93) Adalimumab 40 mg: 7.44 (95% CI, 6.25 to 8.64) RA-WIS LSM mean change Upadacitinib 15 mg: −5.16 (95% CI, −6.10 -to −4.23) Adalimumab 40 mg: −4.45 (95% CI, −5.61 to- −3.28) SF-36 - Role-physical: LSM mean change Upadacitinib 15 mg: 6.85 (95% CI, 6.06 to 7.65) Adalimumab 40 mg: 5.16 (95% CI, 4.19 to 6.14) SF-36 - Bodily pain: Upadacitinib 15 mg: 9.85 (95% CI, (9.02-10.68) Adalimumab 40 mg: 8.03 (95% CI, 7.02 to 9.05) SF-36 - Vitality: Upadacitinib 15 mg: 8.24 (95% CI, (7.38-9.10) Adalimumab 40 mg: 6.79 (95% CI, (5.74 to 7.84)		

Authors, Year Country Trial Name Trial Number Risk of Bias	Interventions	N	Efficacy/Effectiveness Outcomes	AEs (General)	AEs (Specific)
			SF-36 - Social functioning: Upadacitinib 15 mg: 7.19 (95% CI, (6.32-8.06) Adalimumab 40 mg: 5.75 (95% CI, (4.69 to 6.82) SF-36 - Role-emotional: Upadacitinib 15 mg: 6.24 (95% CI, 5.31 to 7.18) Adalimumab 40 mg: 5.21 (95% CI, (4.05 to 6.36) SF-36 - Mental health: Upadacitinib 15 mg: 6.99 (95% CI, (6.11 to 7.87) Adalimumab 40 mg: 5.91 (95% CI, (4.83 to 6.99) SF-36—Physical functioning: LSM mean change Upadacitinib 15 mg: 7.31 (95% CI, 6.45 to 8.18) Adalimumab 40 mg: 6.18 (95% CI, 5.12 to 7.25) SF-36—General health: Upadacitinib 15 mg: 7.27 (95% CI, 6.49 to 8.05) Adalimumab 40 mg: 5.67 (95% CI, 4.72 to 6.63)		

Authors, Year Country Trial Name Trial Number Risk of Bias	Interventions	N	Efficacy/Effectiveness Outcomes	AEs (General)	AEs (Specific)
Gabay et al., 2013[49] 76 centers in 15 countries in North and South America, Australia and Europe ADACTA NCT01119859 Moderate	• Tocilizumab 8 mg/kg IV every 4 weeks + placebo SC every 2 weeks • Adalimumab 40 mg SC every 2 weeks + placebo IV every 4 weeks	Total N = 325 Tocilizumab 8 mg/kg = 163 Adalimumab 40 mg = 162	Primary outcome: Week 24: DAS28 score: mean change from baseline Tocilizumab 8 mg/kg: −3.3 Adalimumab 40 mg: −1.8 Difference: −1.5 P < .0001 Secondary outcomes: Week 24: DAS28 score of < 2.6: Tocilizumab 8 mg/kg: 65 of 163 (39.9%) Adalimumab 40 mg: 17 of 162 (10.5%) P < .0001 DAS28 score of ≤ 3.2: Tocilizumab 8 mg/kg: 84 of 163 (51.5%) Adalimumab 40 mg: 32 of 162 (19.8%) P < .0001 EULAR response good or moderate: Tocilizumab 8 mg/kg: 127 of 163 (77.9%) Adalimumab 40 mg: 89 of 162	Week 24: AEs: Tocilizumab 8 mg/kg: 430 Adalimumab 40 mg: 443 Patients with at least 1 AE: Tocilizumab 8 mg/kg: 133 of 162 (82.1%) Adalimumab 40 mg: 134 of 162 (82.7%) SAEs: Tocilizumab 8 mg/kg: 23 of 162 (14.2%) Adalimumab 40 mg: 21 of 162 (13.0%)	Week 24: Infection: Tocilizumab 8 mg/kg: 113 of 162 (69.8%) Adalimumab 40 mg: 106 of 162 (65.4%) At least 1 infection: Tocilizumab 8 mg/kg: 77 of 162 (47.5%) Adalimumab 40 mg: 68 of 162 (42.0%) At least 1 serious infection: Tocilizumab 8 mg/kg: 5 of 162 (3.1%) Adalimumab 40 mg: 5 of 162 (3.1%) Cancers: Tocilizumab 8 mg/kg: 1 of 162 (0.6%) Adalimumab 40 mg: 1 of 162 (0.6%) Deaths: Tocilizumab 8 mg/kg: 2 of 162 (1.2%) Adalimumab 40 mg: 0

Authors, Year Country Trial Name Trial Number Risk of Bias	Interventions	N	Efficacy/Effectiveness Outcomes	AEs (General)	AEs (Specific)
			(54.9%) P < .0001 EULAR response good: Tocilizumab 8 mg/kg: 84 of 163 (51.5%) Adalimumab 40 mg: 32 of 162 (19.8%) P < .0001 ACR20 response: Tocilizumab 8 mg/kg: 106 of 163 (65.0%) Adalimumab 40 mg: 80 of 162 (49.4%) P = .0038 ACR50 response: Tocilizumab 8 mg/kg: 77 of 163 (47.2%) Adalimumab 40 mg: 45 of 162 (27.8%) P = .0002 ACR70 response: Tocilizumab 8 mg/kg: 53 of 163 (32.5%) Adalimumab 40 mg: 29 of 162 (17.9%) P = .0023		of 162 (0.0%)

Authors, Year Country Trial Name Trial Number Risk of Bias	Interventions	N	Efficacy/Effectiveness Outcomes	AEs (General)	AEs (Specific)
Genovese et al., 2017[27] 41 sites in 6 countries (the US, Poland, Hungary, Czech Republic, Mexico, and Bulgaria NR NR Moderate	• Peficitinib 25 mg, 50 mg, 100 mg, 150 mg once a day for 12 weeks • Placebo	Total N = 289 Peficitinib 25 mg = 59 Peficitinib 50 mg = 57 Peficitinib 100 mg = 58 Peficitinib 150 mg = 64 Placebo = 51	Week 12: ACR20 response: Peficitinib 25 mg: 13 of 59 (22.0%) Peficitinib 50 mg: 21 of 57 (36.8%) Peficitinib 100 mg: 28 of 58 (48.3%), P < .05 Peficitinib 150 mg: 36 of 64 (56.3%), P < .01 Placebo: 15 of 51 (29.4%) ACR50 response: Peficitinib 25 mg: 9 of 59 (15.3%), Peficitinib 50 mg: 14 of 57 (24.6%), P < .05 Peficitinib 100 mg: 16 of 58 (27.6%), P < .05 Peficitinib 150 mg: 18 of 68 (28.1%), P < .01 Placebo: 5 of 51 (9.8%) ACR70 response: Peficitinib 25 mg: 4 of 59 (6.8%), Peficitinib 50 mg: 9 of 57 (15.8%), Peficitinib 100 mg: 11 of 58 (19.0%), Peficitinib 150 mg: 7 of 64 (10.9%), Placebo: 4 of 51 (7.8%)	Week 12: Any AE: Peficitinib 25 mg: 22 of 59 (37.3%) Peficitinib 50 mg: 19 of 57 (33.3%) Peficitinib 100 mg: 30 of 58 (51.7%) Peficitinib 150 mg: 28 of 64 (43.8%) Placebo: 22 of 51 (43.1%) Withdrawal because of AEs: Peficitinib 25 mg: 4 of 59 (6.8%) Peficitinib 50 mg: 2 of 57 (3.5%) Peficitinib 100 mg: 1 of 58 (1.7%) Peficitinib 150 mg: 2 of 64 (3.1%) Placebo: 0 of 51 (0%) SAEs: Peficitinib 25 mg: 2 of 59 (3.4%) Peficitinib 50 mg: 2	Week 12: Deaths: Peficitinib 25 mg: 0 of 59 (0.0%) Peficitinib 50 mg: 0 of 57 (0.0%) Peficitinib 100 mg: 0 of 58 (0.0%) Peficitinib 150 mg: 0 of 64 (0.0%) Placebo: 0 of 51 (0.0%) Serious infections: Peficitinib 25 mg: 1 of 59 (1.7%) Peficitinib 50 mg: 0 of 57 (0.0%) Peficitinib 100 mg: 0 of 58 (0.0%) Peficitinib 150 mg: 0 of 64 (0.0%) Placebo: 0 of 51 (0.0%)

Authors, Year Country Trial Name Trial Number Risk of Bias	Interventions	N	Efficacy/Effectiveness Outcomes	AEs (General)	AEs (Specific)
			P > .05 DAS28-CRP < 2.6 Peficitinib 25 mg: 4 of 58 (6.8%) Peficitinib 50 mg: 7 of 56 (12.5%) Peficitinib 100 mg: 13 of 57 (22.8%) Peficitinib 150 mg: 13 of 60 (20.3%) Placebo: 5 of 51 (9.8%)	of 57 (3.5%) Peficitinib 100 mg: 4 of 58 (6.9%) Peficitinib 150 mg: 2 of 64 (3.1%) Placebo: 2 of 51 (3.9%)	
Giardina et al., 2010[25] Italy NR NR High	• Etanercept vs. inflixi-mab	Total N = 50 Etanercept = 25 Infliximab = 25	12 weeks: ASAS 20: Etanercept = 15 of 25 (60.0%) Infliximab = 19 of 25 (76.0%) ASAS 40: Etanercept = 11 of 25 (44.0%) Infliximab = 14 of 25 (56.0%) BASFI: Etanercept = 5 Infliximab = 3.5 P < .005 BASDAI: Etanercept = 5.6 Infliximab = 3.5 P < .005	Week 104: Overall AEs: NR Discontinuation due to AEs: Etanercept: 0 of 25 (0.0%) Infliximab: 0 of 25 (0.0%) SAEs: NR	Week 104: Injection site reactions: Etanercept: 5 of 25 (20%) Infliximab: 1 of 25 (4.0%) P < .005 Severe infections: Etanercept: 1 of 25 (4.0%) Infliximab: 2 of 25 (8.0%) P = NS

Authors, Year Country Trial Name Trial Number Risk of Bias	Interventions	N	Efficacy/Effectiveness Outcomes	AEs (General)	AEs (Specific)
Giles et al., 2019[31] NR ENTRACTE NR Moderate	• Tocilizumab 8 mg/kg intravenous every 4 weeks • Etanercept 50 mg sub-cutaneous weekly	Total N = 3,080 Tocilizumab 8 mg/kg = 1,538 Etanercept 50 mg = 1,542	NR	Overall AEs: NR SAEs: Tocilizumab 8 mg/kg: 421 of 1,538 (27.4%), 666 events, IR per 100 pys 15.7 Etanercept 50 mg: 356 of 1,542 (23.1%), 631 events, IR per 100 pys 14.4 Tocilizumab vs. etanercept HR, 1.10 (95% CI, 0.94 to 1.28) Withdrawal because of AEs: Tocilizumab 8 mg/kg: 120 of 1,538 (5%), 120 events, IR per 100 pys 2.8 Etanercept 50 mg: 105 of 1,542 (7%), 105 events, IR per 100 pys 2.4	MACE, including undetermined cause of death: Tocilizumab 8 mg/kg: 83 of 1,538 (5.4%), events/100 pys 1.82 (95% CI, 1.46 to 2.24) Etanercept 50 mg: 78 of 1,542 (5.1%), events/100 pys 1.70 (95% CI, 1.35 to 2.10) Tocilizumab vs. etanercept HR, 1.05 (95% CI, 0.77 to 1.43) Nonfatal and fatal MI: Tocilizumab 8 mg/kg: 2 of /1,538 (2%), events/100 pys 0.61 (95% CI, 0.41 to 0.87) Etanercept 50 mg: 32 of 1,542 (2%), events/100 pys 0.67 (95% CI, 0.46 to 0.95) Tocilizumab vs. Etanercept HR, 0.90 (95% CI, 0.54 to 1.48)

Authors, Year Country Trial Name Trial Number Risk of Bias	Interventions	N	Efficacy/Effectiveness Outcomes	AEs (General)	AEs (Specific)
				Tocilizumab vs. etanercept HR, 1.15 (95% CI, 0.89 to 1.49)	Nonfatal and fatal stroke, all types: Tocilizumab 8 mg/kg: 26 of 1,538 (2%), events/100 pys 0.53 (95% CI, 0.35 to 0.78) Etanercept 50 mg: 16 of 1,542 (1%), events/100 pys 0.35 (95% CI, 0.2 to 0.56) Tocilizumab vs. etanercept HR, 1.55 (95% CI, 0.83 to 2.9) Death from any cause: Tocilizumab 8 mg/kg: 64 of 1,538 (4%), events/100 pys 1.31 (95% CI, 1.01 to 1.67) Etanercept 50 mg: 64 of 1,542 (4%), events/100 pys 1.31 (95% CI, 1.01 to 1.67) Tocilizumab vs. etanercept HR, 0.99 (95% CI, 0.70 to 1.41)

Authors, Year Country Trial Name Trial Number Risk of Bias	Interventions	N	Efficacy/Effectiveness Outcomes	AEs (General)	AEs (Specific)
					* self-calculated
Glatt et al., 2019[39] NR NR NCT02430909 Moderate	• Combination therapy (certolizumab pegol plus bimekizumab vs. certolizumab pegol plus placebo)	Total N = 79 Certolizumab pegol plus bimekizumab = 52 Certolizumab pegol plus placebo = 27	12 weeks: DAS28-CRP < 3.2, n (%): Certolizumab pegol plus bimekizumab = 21 of 52 (46%) Certolizumab pegol plus placebo: 7 of 27 (29%) ACR20, n (%): Certolizumab pegol plus bimekizumab = 26 of 52 (61%) Certolizumab pegol plus placebo: 13 of 27 (54%) DAS28-CRP < 2.6 Certolizumab pegol plus bimekizumab: 12 of 52 (26%) Certolizumab pegol plus placebo: 2 of 27 (8%)	Any treatment-emergent AE: Certolizumab pegol plus bimekizumab: 41 of 52 (78.8%) Certolizumab pegol plus placebo: 16 of 27 (59.3%) Serious treatment-emergent AEs: Certolizumab pegol plus bimekizumab: 2 of 52 (3.8%) Certolizumab pegol plus placebo: 3 of 27 (11.1%) Discontinuation due to AEs: Certolizumab pegol plus bimekizumab: 4 of 52 (7.7%) Certolizumab pegol plus placebo: 3 of 27 (11.1%)	Death: Certolizumab pegol plus bimekizumab: 0 of 52 (0.0%) Certolizumab pegol plus placebo: 1 of 27 (3.7%) Infections: Certolizumab pegol plus bimekizumab: 26 of 52 (50.0%) Certolizumab pegol plus placebo: 6 of 27 (22.2%)
Gottenberg et al., 2016[57]	Non-TNF biologics: • Abatacept: 500–1,000 mg IV in weeks 0, 2, and 4 and once	Total n = 292 Non-TNF-biologic = 146	Primary outcome: Week 24: EULAR response good or	AEs: NR	Deaths: Non-TNF-biologic: 1 of 146 0.7(%)

Authors, Year Country Trial Name Trial Number Risk of Bias	Interventions	N	Efficacy/Effectiveness Outcomes	AEs (General)	AEs (Specific)
47 clinical centers in France NR NCT01000441 Moderate	monthly from week 4 on. • Rituximab: 1,000 mg IV in weeks 0 and 2 • Tocilizumab: 8 mg/kg IV every month • TNF agents: • Adalimumab: 40 mg SC every 2 weeks • Certolizumab: 400 mg SC in weeks 0, 2, and 4, followed by 200 mg SC every 2 weeks • Etanercept: 50 mg SC once a week • Infliximab: 3 mg/kg IV in weeks 2 and 6, and every 2 months there-after	Second anti-TNF drug = 146	moderate: Non-TNF-biologic: 101 of 146 (69%) Second anti-TNF drug: 76 of 146 (52%) P = .004 Secondary outcomes: Week 12: EULAR response good or moderate: Non-TNF-biologic: 88 of 137 (64%) Second anti-TNF drug: 65 of 136 (48%) P = .005 DAS28-ESR < 3.2: Non-TNF-biologic: 42 of 137 (31%) Second anti-TNF drug: 31 of 134 (23%) P = .16 DAS28-ESR < 2.6: Non-TNF-biologic: 28 of 137 (20%) Second anti-TNF drug: 13 of 135 (10%) P = .02	SAEs: Non-TNF-biologic: 16 of 146 (11.0%) Second anti-TNF drug: 8 of 146 (5.5%) Withdrawal because of AEs: Non-TNF-biologic: 1 of 146 (0.7%) Second anti-TNF drug: 1 of 146 (0.7%)	Second anti-TNF drug: 0 of 146 (0.0%) Cancer: Non-TNF-biologic: 1 of 146 (0.7%) Second anti-TNF drug: 0 of 146 (0.0%) Serious infections: Non-TNF-biologic: 7 of 146 (4.79%) Second anti-TNF drug: 10 of 146 (6.85%) Cutaneous infections: Non-TNF-biologic: 3 of 146 (2.05%) Second anti-TNF drug: 0 of 146 (0.0%) Tuberculosis Non-TNF-biologic: 0 of 146 (0%) Second anti-TNF drug: 1 of 146 (0.7%) Cardiovascular events:

Authors, Year Country Trial Name Trial Number Risk of Bias	Interventions	N	Efficacy/Effectiveness Outcomes	AEs (General)	AEs (Specific)
			Week 24: DAS28-ESR < 3.2: Non-TNF-biologic: 62 of 139 (45%) Second anti-TNF drug: 39 of 140 (28%) DAS28-ESR < 2.6: Non-TNF-biologic: 38 of 139 (27%) Second anti-TNF drug: 26 of 140 (19%) Week 52: EULAR response good or moderate: Non-TNF-biologic: 78 of 131 (60%) Second anti-TNF drug: 57 of 134 (43%) DAS28-ESR < 3.2: Non-TNF-biologic: 53 of 130 (41%) Second anti-TNF drug: 31 of 133 (23%) DAS28-ESR < 2.6: Non-TNF-biologic: 35 of 130 (27%)		Non-TNF-biologic: 6 of 146 (4.11%) Second anti-TNF drug: 1 of 146 (0.7%)

Authors, Year Country Trial Name Trial Number Risk of Bias	Interventions	N	Efficacy/Effectiveness Outcomes	AEs (General)	AEs (Specific)
			Second anti-TNF drug: 18 of 133 (14%)		
Hetland et al., 2020[18] 29 sites in Sweden, Denmark, Norway, Finland, the Netherlands, and Iceland NR NCT01491815 Low	• Abatacept 125 mg SC weekly + MTX • Certolizumab pegol 200 mg SC every 2 weeks (loading dose 400 mg at week 0, 2, and 4) + MTX • Tocilizumab 8 mg/kg IV every 4 weeks or 162 mg SC weekly + MTX • Active conventional treatment: oral predni-solone (tapered from 20 to 5 mg/day in 9 weeks); or sulfasala-zine (2 g/day) +hy-droxy-chloroquine (35 mg/kg every week or 200 mg/day) and in-tra-articular triamcino-lone hexacetonide in-jection (or equivalent) in all swollen joints at each visit	Total N = 812 Abatacept + MTX = 204 Certolizumab pegol + MTX = 203 Tocilizumab + MTX = 188 Active conventional treatment = 200	Primary endpoint: Week 24: CDAI remission: Abatacept 125 mg + MTX: 107 of 193 (55.4%) Certolizumab pegol 200 mg + MTX: 97 of 180 (53.9%) Tocilizumab 8 mg/kg + MTX: 77 of 165 (46.7%) Active conventional treatment: 84 of 178 (47.2%) Secondary endpoints: Week 24: DAS28 remission: Abatacept 125 mg + MTX: 142 of 192 (74.0%) Certolizumab pegol 200 mg + MTX: 139 of 180 (77.2%) Tocilizumab 8 mg/kg + MTX: 119 of 163 (73.0%) Active conventional treatment: 127 of 178 (71.3%) SDAI remission: Abatacept 125 mg + MTX: 105 of 192 (54.7%)	Week 24: Any AEs: Abatacept 125 mg + MTX: 163 of 204 (79.9%) Certolizumab pegol 200 mg + MTX: 167 of 202 (82.7%) Tocilizumab 8 mg/kg + MTX: 175 of 184 (95.1%) Active conventional treatment: 170 of 197 (86.3%) Withdrawal because of AEs: Abatacept 125 mg + MTX: 4 of 204 (2.0%) Certolizumab pegol 200 mg + MTX: 9 of 202 (4.5%) Tocilizumab 8 mg/kg + MTX: 10 of 184 (5.4%)	Death: Abatacept 125 mg + MTX: 0 of 204 (0.0%) Certolizumab pegol 200 mg+ MTX: 1 of 202 (0.5%) Tocilizumab + MTX: 0 of 184 (0.0%) Active conventional treatment: 0 of 197 (0.0%) Infections: Abatacept 125 mg + MTX: 70 of 204 (34.3%) Certolizumab pegol 200 mg + MTX: 74 of 202 (36.6%) Tocilizumab 8 mg/kg + MTX: 84 of 184 (45.7%) Active conventional treatment: 68 of 197 (34.5%) Cardiovascular

Authors, Year Country Trial Name Trial Number Risk of Bias	Interventions	N	Efficacy/Effectiveness Outcomes	AEs (General)	AEs (Specific)
			Certolizumab pegol 200 mg + MTX: 101 of 180 (56.1%) Tocilizumab 8 mg/kg + MTX: 80 of 163 (49.1%) Active conventional treatment: 83 of 177 (46.9%) EULAR good response: Abatacept 125 mg + MTX: 163 of 192 (84.9%) Certolizumab pegol 200 mg + MTX: 156 of 180 (86.7%) Tocilizumab 8 mg/kg + MTX: 134 of 163 (82.2%) Active conventional treatment: 143 of 178 (80.3%)	Active conventional treatment: 0 of 197 (0%) SAEs: Abatacept 125 mg + MTX: 10 of 204 (4.9%) Certolizumab pegol 200 mg + MTX: 17 of 202 (8.4%) Tocilizumab 8 mg/kg + MTX: 9 of 184 (4.9%) Active conventional treatment: 11 of 197 (5.6%)	disease: Abatacept 125 mg + MTX: 9 of 204 (4.4%) Certolizumab pegol 200 mg + MTX: 7 of 202 (3.5%) Tocilizumab 8 mg/kg + MTX: 6 of 184 (3.3%) Active conventional treatment: 3 of 197 (1.5%) Herpes zoster: Abatacept 125 mg+ MTX: 0 of 204 (0.0%) Certolizumab pegol 200 mg + MTX: 1 of 202 (0.5%) Tocilizumab 8 mg/kg + MTX: 0 of 184 (0.0%) Active conventional treatment: 3 of 197 (1.5%) Malignancy: Abatacept 125 mg + MTX: 2 of 204 (1.0%)

Authors, Year Country Trial Name Trial Number Risk of Bias	Interventions	N	Efficacy/Effectiveness Outcomes	AEs (General)	AEs (Specific)
					Certolizumab pegol200 mg+ MTX: 1 of 202 (0.5%) Tocilizumab 8 mg/kg + MTX: 3 of 184 (1.6%) Active conventional treatment: 0 of 197 (0.0%)
Humby et al., 2021[17] 19 sites, 5 European countries: the UK, Belgium, Italy, Portugal, and Spain R4RA ISRCTN97443826 High	• Rituximab 1,000 mg IV every 2 weeks • Tocilizumab 8 mg/kg IV every month	Total N = 164 Rituximab 1,000 mg = 82 Tocilizumab 8 mg/kg = 79	Week 16: CDAI ≥50% improvement Rituximab 1000 mg: 37 of 82 (45.1%) Tocilizumab 8 mg/kg: 44 of 79 (55.7%) P = NR	NR	NR
Jobanputra et al., 2012[46] England	• Adalimumab 40 mg SC every other week • Etanercept 50 mg IV weekly	Total N = 125 Adalimumab 40 mg = 63 (60 received treatment)	Primary endpoint: Week 52: Retention in treatment: Adalimumab 40 mg: 39 of 60 (65.0%)	Any AE*: Adalimumab 40 mg: NR Etanercept 50 mg: NR	Injection site reaction: Adalimumab 40 mg: 9 of 60 (15.0%) Etanercept 50 mg: 19 of 60 (31.7%)

Authors, Year Country Trial Name Trial Number Risk of Bias	Interventions	N	Efficacy/Effectiveness Outcomes	AEs (General)	AEs (Specific)
RED SEA NR High		Etanercept 50 mg = 62 (60 received treatment)	Etanercept 50 mg: 34 of 60 (56.7%) Adalimumab was not inferior to etanercept at the 15% margin Secondary endpoints: Week 104: Retention in treatment: Adalimumab 40 mg: 35 of 60 (58.3%) Etanercept 50 mg: 26 of 60 (43.3%) Week 24: Retention in treatment: Adalimumab 40 mg: 43 of 60 (71.7%) Etanercept 50 mg: 43 of 60 (71.7%) Week 52 DAS28 (CRP4): Good: Adalimumab 40 mg: 16 of 60 (26.3%) Etanercept 50 mg: 10 of 60 (16.7%) Moderate: Adalimumab 40 mg: 20 of 60	Withdrawal because of AEs: Baricitinib 4 mg: NR Adalimumab 40 mg: NR SAEs: Adalimumab 40 mg: NR Etanercept 50 mg: NR *Number of participants with at least 1 AE not reported. Overall number of AEs reported.	Cardiovascular events: Adalimumab 40 mg: 5 of 60 (8.3%) Etanercept 50 mg: 6 of 60 (10.0%) Death: Adalimumab 40 mg: 2 of 60 (3.3%) Etanercept 50 mg: 0 of 60 (0%) Malignancy Adalimumab 40 mg: 1 of 60 (1.7%) Etanercept 50 mg: 1 of 60 (1.7%)

Authors, Year Country Trial Name Trial Number Risk of Bias	Interventions	N	Efficacy/Effectiveness Outcomes	AEs (General)	AEs (Specific)
			(33.3%) Etanercept 50 mg: 19 of 60 (31.7%) Nonresponders: Adalimumab 40 mg: 24 of 60 (40.4%) Etanercept 50 mg: 31 of 60 (51.7%) P = .158 DAS28 -CRP4*, median (IQR) Adalimumab 40 mg: 4.4 (3.1–5.4) Etanercept 50 mg: 4.6 (3.5–5.6) EQ-5D Utility Score*, median (IQR) Adalimumab 40 mg: 0.59 (0.52–0.69) Etanercept 50 mg: 0.59 (0.24–0.53) Patient global assessment*, median (IQR) Adalimumab 40 mg: 49 (20–65) Etanercept 50 mg: 50 (27–71) *Data for the modified intention-to-treat population with baseline values carried forward for those who discontinued therapy within		

Authors, Year Country Trial Name Trial Number Risk of Bias	Interventions	N	Efficacy/Effectiveness Outcomes	AEs (General)	AEs (Specific)
			1 year		
Kivitz et al., 2017[28] 43 sites in 8 countries (US [16 locations], Poland [7 locations], Colombia [5 locations], Mexico [4 locations], Bulgaria [3 locations], Czech Republic [3 locations], Hungary [3 locations], and Belgium [2 locations]) NR NR Moderate	• Peficitinib 25 mg, 50 mg, 100 mg, or 150 mg • Placebo	Total N = 378 Peficitinib 25 mg = 66 Peficitinib 50 mg = 78 Peficitinib 100 mg = 84 Peficitinib 150 mg = 78 Placebo = 72	Week 12: ACR20 response: Peficitinib 25 mg: 29 of 66 (43.9%) Peficitinib 50 mg: 48 of 78 (61.5%), P < .05 Peficitinib 100 mg: 39 of 84 (46.4%) Peficitinib 150 mg: 45 of 78 (57.7%) Placebo: 32 of 72 (44.4%) ACR50 response: Peficitinib 25 mg: 12 of 66 (18.2%) Peficitinib 50 mg: 26 of 78 (33.3%) Peficitinib 100 mg: 28 of 84 (33.3%) Peficitinib 150 mg: 29 of 78 (37.2%) Placebo: 19 of 72 (26.4%) P > .05	Week 12: Any AE: Peficitinib 25 mg: 28 of 66 (42.4%) Peficitinib 50 mg: 39 of 78 (50.0%) Peficitinib 100 mg: 40 of 84 (47.6%) Peficitinib 150 mg: 39 of 78 (50.0%) Placebo: 34 of 72 (47.2%) Withdrawal because of AEs: Peficitinib 25 mg: 0 of 66 (0%) Peficitinib 50 mg: 0 of 78 (0%) Peficitinib 100 mg: 3 of 84 (3.6%) Peficitinib 150 mg: 4 of 78 (5.1%) Placebo = 1 of 72 (1.4%) SAEs: Peficitinib 25 mg: 0	Week 12: Serious infections: Peficitinib 25 mg: 0 of 66 (0%) Peficitinib 50 mg: 0 of 78 (0.0%) Peficitinib 100 mg: 1 of 84 (1.2%) Peficitinib 150 mg: 1 of 78 (1.3%) Placebo: 0 of 72 (0.0%). Death: Peficitinib 25 mg: 0 of 66 (0.0%) Peficitinib 50 mg: 0 of 78 (0.0%) Peficitinib 100 mg: 0 of 84 (0.0%) Peficitinib 150 mg: 0 of 78 (0.0%) Placebo: 0 of 72 (0.0%)

Authors, Year Country Trial Name Trial Number Risk of Bias	Interventions	N	Efficacy/Effectiveness Outcomes	AEs (General)	AEs (Specific)
				of 66 (0%) Peficitinib 50 mg: 0 of 78 (0%) Peficitinib 100 mg: 2 of 84 (2.4%) Peficitinib 150 mg: 1 of 78 (1.3%) Placebo: 0 of 72 (0.0%)	
Kume et al., 2011[47] Japan NR NR Moderate	• Tocilizumab 8 mg/kg SC every 4 weeks • Etanercept 25 mg SC twice a week • Adalimumab 40 mg SC every 2 weeks	Total N = 64 Tocilizumab 8 mg/kg = 22 Etanercept 25 mg = 21 Adalimumab 40 mg = 21	Week 24: Arterial stiffness (CAVI): Mean change from baseline in m/s (SD) Tocilizumab 8 mg/kg: 0.85 (0.15) Etanercept 25 mg: 0.81 (0.18) Adalimumab 40 mg = 0.90 (0.21) P > .05 HAQ score: Mean change from baseline (SD) Tocilizumab 8 mg/kg: 0.70 (0.08) Etanercept 25 mg: 0.68 (0.09) Adalimumab 40 mg: 0.69 (0.11) P > .05 DAS28-ESR score: Mean change from baseline (SD) Tocilizumab 8 mg/kg: −2.10 (0.35) Etanercept 25 mg: −2.84 (0.42)	NR	NR

Authors, Year Country Trial Name Trial Number Risk of Bias	Interventions	N	Efficacy/Effectiveness Outcomes	AEs (General)	AEs (Specific)
			Adalimumab 40 mg: −2.12 (0.38) P > .05 CIMT, mean change from baseline in mm (SD) Tocilizumab 8 mg/kg: 0.00 (0.13) m/s Etanercept 25 mg: 0.00 (0.22) Adalimumab 40 mg: −0.01 (0.13) P > .05 Ankle-brachial index: Mean change from baseline (SD) Tocilizumab 8 mg/kg: 0.03 (0.01) Etanercept 25 mg: 0.09 (0.02) Adalimumab 40 mg: −0.03 (0.02) P > .05		
Manders et al., 2015[56] Multicenter trial in the Netherlands NR NR High	• Adalimumab 40 mg SC every 2 weeks • Etanercept 50 mg once a week or 25 mg twice a week • Infliximab 3 mg/kg every 8 weeks after loading doses given at 0, 2, and 6 weeks • Golimumab 50 mg every 4 weeks	Total n = 139 Abatacept 500-100 mg IV = 43 Rituximab 1,000 mg IV = 46 TNF-α inhibitors = 50	Primary outcome: 12 months DAS28 score: mean (SD) Abatacept 500−1,000 mg IV: 3.8 (1.2) Rituximab 1,000 mg IV: 3.4 (1.2) TNF-α inhibitors: 3.5 (1.5)	Total AEs: Abatacept 500−1,000 mg IV: 16 of 43 (37.21%) Rituximab 1,000 mg IV: 15 of 46 (32.61%) TNF-α inhibitors: 20 of 50 (40%)	Infections: Abatacept 500−1,000 mg IV: 6 of 43 (13.95%) Rituximab 1,000 mg IV: 4 of 46 (8.70%) TNF-α inhibitors: 7 of 50 (14.00%) Malignancies: Abatacept 500−1,000 mg IV: 0 of 43 (0%)

Authors, Year Country Trial Name Trial Number Risk of Bias	Interventions	N	Efficacy/Effectiveness Outcomes	AEs (General)	AEs (Specific)
	• Certolizumab 200 mg every 2 weeks with initial 400 mg loading doses in weeks 0, 2, and 4 • Abatacept dosage dependent on bodyweight: < 60 kg = 500 mg; 60 - 100 kg = 750 mg; > 100 kg = 1000 mg; IV every 4 weeks • Rituximab 1,000 mg IV at weeks 0 and 2 with a second course after 6 months in responders				Rituximab 1000 mg IV: 3 of 46 (6.52%) TNF-α inhibitors: 0 of 50 (0%)
Rubbert-Roth et al., 2020[19] 120 sites in 28 countries, Europe, Asia, North and South America SELECT-CHOICE NCT03086343 Low	• Upadacitinib 15 mg once daily • Abatacept intravenous 500 mg in patients with a body weight of <60 kg, 750 mg in those with a weight of 60 to 100 kg, and 1,000 mg in those with a weight of >100 kg	Total N = 612 Upadacitinib 15 mg = 303 Abatacept 500–1,000 mg = 309	Primary outcome Week 12: DAS28-CRP Mean change from baseline: Upadacitinib 15 mg: −2.52 Abatacept 500-1,000 mg: −2.00 Difference -0.52, 95% CI −0.69 to −0.35 P < .001 Secondary outcome: Week 12: DAS28-CRP remission (< 2.6) Upadacitinib 15 mg: 86 of 303 (28.4%)	Week 24 Any AEs: Upadacitinib 15 mg: 209 of 303 (69.0%) Abatacept 500–1,000 mg: 189 of 309 (61.2%) Withdrawal because of AEs Upadacitinib 15 mg: 14 of 303 (4.6%) Abatacept	Week 24: Death: Upadacitinib 15 mg: 2 of 303 (0.7%) Abatacept 500–1,000 mg: 1 of 309 (0.3%) Serious infection: Upadacitinib 15 mg: 3 of 303 (1.0%) Abatacept 500–1,000 mg: 1 of 309 (0.3%) Opportunistic infection

Authors, Year Country Trial Name Trial Number Risk of Bias	Interventions	N	Efficacy/Effectiveness Outcomes	AEs (General)	AEs (Specific)
			Abatacept 500–1,000 mg: 38 of 309 (12.3%)	500–1,000 mg: 9 of 309 (2.9%) SAEs: Upadacitinib 15 mg: 10 of 303 (3.3%) Abatacept 500–1,000 mg: 5 of 309 (1.6%)	Upadacitinib 15 mg: 4 of 303 (1.3%) Abatacept 500–1,000 mg: 1 of 309 (0.3%) Herpes zoster infection: Upadacitinib 15 mg: 4 of 303 (1.3%) Abatacept 500–1,000 mg: 4 of 309 (1.3%) Gastrointestinal perforation: Upadacitinib 15 mg: 0 of 303 (0.0%) Abatacept 500–1,000 mg: 0 of 309 (0.0%) Cancer: Upadacitinib 15 mg: 0 of 303 (0.0%) Abatacept 500–1,000 mg: 0 of 309 (0.0%) Major adverse cardiovascular event: Upadacitinib 15 mg: 1 of 303 (0.3%) Abatacept 500–1,000

Authors, Year Country Trial Name Trial Number Risk of Bias	Interventions	N	Efficacy/Effectiveness Outcomes	AEs (General)	AEs (Specific)
					mg: 0 of 309 (0.0%) Venous thromboembolic event: Upadacitinib 15 mg: 2 of 303 (0.7%) Abatacept 500–1,000 mg: 0 of 309 (0.0%)
Ruscitti et al., 2019[21] Italy TRACK NCT02236481 High	• Anakinra 100 mg SC once daily • TNF inhibitors (adalimumab, certolizumab pegol, etanercept, infliximab, or golimumab)	Total N = 39 Anakinra 100 mg = 22 TNF inhibitors = 17	DAS28, mean (SD): Baseline: Anakinra 100 mg: 5.42 (1.18) TNF inhibitors: 5.70 (0.80) Week 24: Anakinra 100 mg: 2.70 (1.16) TNF inhibitors: 3.58 (1.45) EULAR good response: Anakinra 100 mg: 19 of 20 (95.0%) TNF inhibitors: 10 of 16 (62.5%) EULAR remission: Anakinra 100 mg: 10 of 20 (50.0%) TNF inhibitors: 4 of 16 (25.0%) SDAI , mean (SD): Baseline:	Week 24: Any AEs: NR Withdrawal because of AEs: Anakinra 100 mg: 4 of 22 (18.2%) TNF inhibitor: 0 of 17 (0.0%) SAEs: Anakinra 100 mg: 0 of 22 (0.0%) TNF inhibitor: 0 of 17 (0.0%)	Death: Week 24: Anakinra 100 mg: 0 of 22 (0.0%) TNF inhibitor: 0 of 17 (0.0%)

Authors, Year Country Trial Name Trial Number Risk of Bias	Interventions	N	Efficacy/Effectiveness Outcomes	AEs (General)	AEs (Specific)
			Anakinra 100 mg: 34.98 (25.18) TNF inhibitors: 35.86 (3.47) Week 24: Anakinra 100 mg: 7.89 (9.23) TNF inhibitors: 14.93 (9.92) PGA, mean (SD): Baseline: Anakinra 100 mg: 61.90 (19.17) TNF inhibitors: 62.00 (17.81) Week 24: Anakinra 100 mg: 18.53 (23.53) TNF inhibitors: 25.97 (19.99)		
Schiff et al., 2007[44] 86 sites in 14 countries in North, South, and Central America, Europe, and Africa ATTEST NCT00095147 Moderate	• Abatacept: Dosage according to body weight: < 60 kg receive 500 mg; 60 kg to 100 kg receive 750 mg; > 100 kg receive 1,000 mg IV on days 1, 15, 29, and every 28 days thereafter + Placebo IV simultaneously and at the remaining visits • Infliximab 3 mg/kg IV on days 1, 15, 43, and 85 and every 56 days thereafter + Placebo	Total N = 431 Abatacept = 156 Infliximab 3 mg/kg = 165 Placebo = 110	Primary outcome: Day 197 DAS28 score: Mean change from baseline Abatacept: −2.53 Infliximab 3 mg/kg: −2.25 P > .05 Day 365 DAS28 score: Mean change from baseline Abatacept: −2.88 Infliximab 3 mg/kg: −2.25 P < .05 Secondary outcomes:	Day 197: AEs: Abatacept: 129 of 156 (82.7%) Infliximab 3 mg/kg: 140 of 165 (84.8%) SAEs: Abatacept: 8 of 156 (5.1%) Infliximab 3 mg/kg: 19 of 165 (11.5%) Withdrawal because of AEs: Abatacept: 2 of	Day 197: Deaths: Abatacept: 1 of 156 (0.6%) Infliximab 3 mg/kg: 1 of 165 (0.6%) Serious infections Abatacept: 2 of 156 (1.3%) Infliximab 3 mg/kg: 7 of 165 (4.2%) Malignant symptoms and disorders: Abatacept: 1 of 156

Authors, Year Country Trial Name Trial Number Risk of Bias	Interventions	N	Efficacy/Effectiveness Outcomes	AEs (General)	AEs (Specific)
	IV simultaneously and at the remaining visits • Placebo		Day 365 EULAR response good Abatacept: 50 of 156 (32.0%) Infliximab 3 mg/kg: 31 of 165 (18.5%) P < .05 DAS28 defined remission Abatacept: 29 of 156 (18.7%) Infliximab 3 mg/kg: 20 of 165 (12.2%) PCS & MCS: mean difference from baseline Abatacept vs. Infliximab: 1.93 P < .05	156 (1.3%) Infliximab 3 mg/kg: 4 of 165 (2.4%)	(0.6%) Infliximab 3 mg/kg: 2 of 165 (1.2%)
Smolen et al., 2016[45] 151 centers in Europe, Australia, and North America EXXELERATE NCT01500278	• Certolizumab pegol SC 400 mg in weeks 0, 2, and 4 followed by 200 mg every 2 weeks + MTX • Adalimumab 40 mg SC every 2 weeks + MTX	Total n = 908 Certolizumab pegol 200 mg = 454 Adalimumab 40 mg = 454	Primary outcomes: Week 12: ACR20 response: Certolizumab pegol 200 mg: 314 of 454 (69.2%) Adalimumab 40 mg: 324 of 454 (71.4%) 95% CI (0.67 to 1.20) Week 104: DAS28-ESR < 3.2: Certolizumab pegol 200 mg: 161	Treatment-emergent AEs: Certolizumab pegol 200 mg: 389 of 516 (75.4%) Adalimumab 40 mg: 386 of 523 (73.8%) Serious treatment-emergent AEs: Certolizumab pegol	Serious infections: Certolizumab pegol 200 mg: 17 of 516 (3.3%) Adalimumab 40 mg: 16 of 523 (3.1%) Serious cardiac disorders: Certolizumab pegol 200 mg: 8 of 516 (1.6%)

Authors, Year Country Trial Name Trial Number Risk of Bias	Interventions	N	Efficacy/Effectiveness Outcomes	AEs (General)	AEs (Specific)
Moderate			of 454 (35.5%) Adalimumab 40 mg: 152 of 454 (33.5%) P = .532 Secondary outcomes: Week 104: HAQ-DI: Mean change from baseline Certolizumab pegol 200 mg: -0.72 Adalimumab 40 mg: -0.62 ACR20 response of primary responders: Certolizumab pegol 200 mg: 229 of 353 (65%) Adalimumab 40 mg: 241 of 361 (67%) ACR50 response of primary responders: Certolizumab pegol 200 mg: 188 of 353 (53%) Adalimumab 40 mg: 205 of 361 (57%) ACR70 response of primary responders: Certolizumab pegol 200 mg: 140 of 353 (40%)	200 mg: 67 of 516 (13.0%) Adalimumab 40 mg: 58 of 523 (11.1%) Discontinuation due to AEs: Certolizumab pegol 200 mg: 65 of 516 (12.6%) Adalimumab 40 mg: 63 of 523 (12.0%)	Adalimumab 40 mg: 9 of 523 (1.7%) Malignancies: Certolizumab pegol 200 mg: 8 of 516 (1.6%) Adalimumab 40 mg: 7 of 523 (1.3%) Opportunistic infections excluding tuberculosis: Certolizumab pegol 200 mg: 3 of 516 (0.6%) Adalimumab 40 mg: 3 of 523 (0.6%) Tuberculosis Certolizumab pegol 200 mg: 0 of 516 (0%) Adalimumab 40 mg: 1 of 523 (0.2%) Deaths: Certolizumab pegol 200 mg: 3 of 516 (0.6%) Adalimumab 40 mg: 3

Authors, Year Country Trial Name Trial Number Risk of Bias	Interventions	N	Efficacy/Effectiveness Outcomes	AEs (General)	AEs (Specific)
			Adalimumab 40 mg: 149 of 361 (41%)		of 523 (0.6%)
Takeuchi et al., 2015[26] 43 sites in Japan NR NCT01649999 Moderate	• Peficitinib 25, 50, 100, 150 mg orally administered once daily after breakfast • Placebo	Total N = 281 Peficitinib 25 mg = 55 Peficitinib 50 mg = 57 Peficitinib 100 mg = 55 Peficitinib 150 mg = 58 Placebo = 56	Week 12: ACR20 response: Peficitinib 25 mg: 13 of 55 (23.6%) Peficitinib 50 mg: 18 of 57 (31.6%), P = .021 Peficitinib 100 mg: 30 of 55 (54.5%), P < .001 Peficitinib 150 mg: 38 of 58 (65.5%), P < .001 Placebo: 6 of 56 (10.7%) ACR50 response: Peficitinib 25 mg: 4 of 55 (7.3%) Peficitinib 50 mg: 5 of 57 (8.8%), Peficitinib 100 mg: 17 of 55 (30.9%), P < .001 Peficitinib 150 mg: 17 of 58 (29.3%), P = .001 Placebo: 3 of 56 (5.4%) ACR70 response: Peficitinib 25 mg: 0 of 45 (0%) Peficitinib 50 mg: 1 of 57 (1.8%), Peficitinib 100 mg: 9 of 55 (16.4%), P = .008 Peficitinib 150 mg: 7 of 58	Week 12: Any AE: Peficitinib 25 mg: 39 of 55 (70.9%) Peficitinib 50 mg: 37 of 57 (64.9%) Peficitinib 100 mg: 29 of 55 (52.7%) Peficitinib 150 mg: 39 of 58 (67.2%) Placebo: 36 of 56 (64.3%) Withdrawal because of AEs: Peficitinib 25 mg: 7 of 55 (12.7%) Peficitinib 50 mg: 5 of 57 (8.8%) Peficitinib 100 mg: 6 of 55 (10.9%) Peficitinib 150 mg: 4 of 58 (6.9%) Placebo: 10 of 56 (17.9%) SAEs:	Week 12: Infection: Peficitinib 25 mg: 18 of 55 (32.7%) Peficitinib 50 mg: 14 of 57 (24.6%) Peficitinib 100 mg: 7 of 55 (12.7%) Peficitinib 150 mg: 17 of 58 (29.3%) Placebo: 12 of 56 (21.4%)

Authors, Year Country Trial Name Trial Number Risk of Bias	Interventions	N	Efficacy/Effectiveness Outcomes	AEs (General)	AEs (Specific)
			(12.1%), Placebo: 1 of 56 (1.8%) DAS28-CRP < 2.6: Peficitinib 25 mg: 0 of 45 (0%) Peficitinib 50 mg: 4 of 57 (7.0%) Peficitinib 100 mg: 15 of 55 (27.3%), P < .01 Peficitinib 150 mg: 12 of 58 (20.7%) P < .05 Placebo: 3 of 56 (5.4%)	Peficitinib 25 mg: 1 of 55 (1.8%) Peficitinib 50 mg: 2 of 57 (3.5%) Peficitinib 100 mg: 3 of 55 (5.5%) Peficitinib 150mg: 0 of 58 (0%) Placebo: 1 of 56 (1.8%)	
Takeuchi et al., 2019[41] 161 centers in Japan NR Moderate	• Peficitinib 100 mg or 150 mg once daily, orally • Placebo	Total N = 518 Placebo N = 170 Peficitinib 100 mg N = 174 Peficitinib 150 mg N = 174	Week 12: ACR20 response: Placebo: 37 of 170 (21.8%) Peficitinib 100 mg: 102 of 174 (58.6%) Peficitinib 150 mg: 112 of 174 (64.4%) P < .001 mTSS - mean change from baseline: Placebo: 3.37 Peficitinib 100 mg: 1.62 Peficitinib 150 mg: 1.03 P < .001 DAS28-CRP < 2.6: Placebo: 13 of 169 (7.7%)	Week 12: Any AE: Placebo: 84 of 170 (49.4%) Peficitinib 100 mg: 89 of 174 (51.1%) Peficitinib 150 mg: 104 of 174 (59.8%) Withdrawal because of AEs: Placebo: 7 of 170 (4.1%) Peficitinib 100 mg: 5 of 174 (2.9%) Peficitinib 150 mg: 5 of 174 (2.9%)	Week 12: Death: Placebo: 0 of 170 (0.0%) Peficitinib 100 mg: 0 of 174 (0.0%) Peficitinib 150 mg: 0 of 174 (0.0%)

Authors, Year Country Trial Name Trial Number Risk of Bias	Interventions	N	Efficacy/Effectiveness Outcomes	AEs (General)	AEs (Specific)
			Peficitinib 100 mg: 54 of 172 (31.4%) Peficitinib 150 mg: 60 of 171 (35.1%) P < .001	SAEs: Placebo: 4 of 170 (2.4%) Peficitinib 100 mg: 5 of 174 (2.9%) Peficitinib 150 mg: 3 of 174 (1.7%) Week 52: Any AE: Peficitinib 100 mg: 154 of 174 (88.5%) Peficitinib 150 mg: 153 of 174 (87.9%) Withdrawal because of AEs: Peficitinib 100 mg: 13 of 174 (7.5%) Peficitinib 150 mg: 12 of 174 (6.9%) SAEs: Peficitinib 100 mg: 19 of 174 (2109%) Peficitinib 150 mg: 13 of 174 (7.5%)	
Tanaka et al., 2019[40]	• Peficitinib 100 mg or 150 mg orally once daily	Total N = 507 placebo = 101 peficitinib 100	Week 12: ACR20 response: Placebo: 31 of 101 (30.7%)	Week 12: Any AE: Placebo: 54 of 101	Infection: Placebo: 0 of 101 (0%)

Authors, Year Country Trial Name Trial Number Risk of Bias	Interventions	N	Efficacy/Effectiveness Outcomes	AEs (General)	AEs (Specific)
165 sites, 3 countries, Japan, Korea and Taiwan NR NR Moderate	• Etanercept 50 mg SC once weekly • Placebo	mg = 104 peficitinib 150 mg = 102 etanercept = 200	Peficitinib 100 mg: 60 of 104 (57.7%), P < .001 vs. placebo Peficitinib 150 mg: 76 of 102 (74.5%), P < .001 vs. placebo Etanercept: 167 of 200 (83.5%) DAS28-ESR < 2.6 Placebo: 1 of 100 (1.0%) Peficitinib 100 mg: 12 of 103 (11.7%) Peficitinib 150 mg: 18 of 101 (17.8%), P = .003 vs. placebo Etanercept: 63 of 199 (31.7%) DAS28-CRP < 2.6 Placebo: 5 of 100 (5.0%) Peficitinib 100 mg: 25 of 102 (24.5%) P < .001 vs. placebo Peficitinib 150 mg: 35 of 101 (34.7%), P < .001 vs. placebo Etanercept: 91 of 200 (45.5%)	(53.5%) Peficitinib 100 mg: 59 of 104 (56.7%) Peficitinib 150 mg: 55 of 102 (53.95%) Etanercept: 119 of 200 (59.5%) Withdrawal because of AEs: Placebo: 4 of 101 (4%) Peficitinib 100 mg: 6 of 104 (5.8%) Peficitinib 150 mg: 3 of 102 (2.9%) Etanercept: 5 of 200 (2.5%) SAEs: Placebo: 4 of 101 (4%) Peficitinib 100 mg: 3 of 104 (2.9%) Peficitinib 150 mg: 2 of 102 (2.0%) Etanercept: 4 of 200 (2.0%) Week 52:	Peficitinib 100 mg: 1 of 104 (1.0%) Peficitinib 150 mg: 2 of 102 (2.0%) Etanercept: 4 of 200 (2.0%) Herpes zoster: Placebo: 0 of 101 (0%) Peficitinib 100 mg: 5 of 104 (4.8%) Peficitinib 150 mg: 4 of 102 (3.9%) Etanercept: 5 of 200 (2.5%)

Authors, Year Country Trial Name Trial Number Risk of Bias	Interventions	N	Efficacy/Effectiveness Outcomes	AEs (General)	AEs (Specific)
				Any AE: Peficitinib 100 mg: 92 of 104 (88.5%) Peficitinib 150 mg: 89 of 102 (87.3%) Etanercept: 178 of 200 (89.0%) Withdrawal because of AEs: Peficitinib 100 mg: 13 of 104 (12.5%) Peficitinib 150 mg: 6 of 102 (5.9%) Etanercept: 13 of 200 (6.5%) SAEs: Peficitinib 100 mg: 7 of 104 (6.7%) Peficitinib 150 mg: 8 of 102 (7.8%) Etanercept: 18 of 200 (9.0%)	
Taylor et al., 2017[29] 281 centers in 26 countries in North	• Baricitinib 4 mg once daily Adalimumab 40 mg SC every 2 weeks • Placebo	Total N = 1305 Baricitinib 4 mg = 487 Adalimumab 40 mg = 330	Week 12: ACR20 response: Baricitinib 4 mg: 341 of 487 (70%) Adalimumab 40 mg: 201 of 330 (61%)	Week 52: Any AE: Baricitinib 4 mg: 384 of 487 (78.9%) Adalimumab 40	Week 52: Infection: Baricitinib 4 mg: 233 of 487 (47.8%) Adalimumab 40 mg:

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and South America, Europe, and Asia RA-BEAM NR Moderate	• Baricitinib 2 mg if estimated glomerular filtration rate of 40 to less than 60 mL/min/1.73 m2 (approximately 4%) received 2 mg of baricitinib if assigned to baricitinib treatment	Placebo = 488	P = .014 DAS28-CRP: Mean change from baseline: Baricitinib 4 mg: −2.24 Adalimumab 40 mg: −1.95 P < .0011 DAS28-ESR ≤ 3.2: Baricitinib 4 mg: 117 of 487 (24.0%) Adalimumab 40 mg: 70 of 330 (21.2%) P > .05 SDAI ≤ 3.3: Baricitinib 4 mg: 41 of 487 (8%) Adalimumab 40 mg: 24 of 330 (7%) *P* value NR SDAI ≤ 11: Baricitinib 4 mg: 205 of 487 (42.1%) Adalimumab 40 mg: 115 of 330 (34.8%) P ≤ .05 CDAI ≤ 10: Baricitinib 4 mg: 196 of 487	mg: 253 of 330 (76.7%) Withdrawal because of AEs: Baricitinib 4 mg: 36 of 487 (7.4%) Adalimumab 40 mg: 13 of 330 (3.9%) SAEs: Baricitinib 4 mg: 38 of 487 (7.8%) Adalimumab 40 mg: 13 of 330 (3.9%)	145 of 330 (43.9%) Herpes zoster: Baricitinib 4 mg: 11 of 487 (2.3%) Adalimumab 40 mg: 5 of 330 (1.5%) Tuberculosis: Baricitinib 4 mg: 0 of 487 (0.0%) Adalimumab 40 mg: 1 of 330 (0.3%) Serious infection: Baricitinib 4 mg: 10 of 487 (2.1%) Adalimumab 40 mg: 5 of 330 (1.5%) Cancer: Baricitinib 4 mg: 3 of 487 (0.6%) Adalimumab 40 mg: 0 of 330 (0.0%) Non-melanoma skin cancer: Baricitinib 4 mg: 0 of 487 (0.0%)

Authors, Year Country Trial Name Trial Number Risk of Bias	Interventions	N	Efficacy/Effectiveness Outcomes	AEs (General)	AEs (Specific)
			(40.2%) Adalimumab 40 mg: 108 of 330 (32.7%) P ≤ .05 HAQ-DI ≥0.22: Baricitinib 4 mg: 363 of 487 (74.5%) Adalimumab 40 mg: 234 of 330 (70.9%) Week 52: HAQ-DI ≥0.22: Baricitinib 4 mg: 329 of 487 (67.6%) Adalimumab 40 mg: 192 of 330 (58.2%) mTSS: LSM change from baseline: Baricitinib 4 mg: 0.71 Adalimumab 40 mg: 0.60 P > .05 Pain, 0-100 VAS: Baricitinib 4 mg: -37 Adalimumab 40 mg: -30 P ≤ .001 SJC:		Adalimumab 40 mg: 0 of 330 (0.0%) Major adverse cardiovascular event: Baricitinib 4 mg: 2 of 487 (0.4%) Adalimumab 40 mg: 1 of 330 (0.3%) Gastrointestinal perforation: Baricitinib 4 mg: 0 of 487 (0.0%) Adalimumab 40 mg: 0 of 330 (0.0%)

Authors, Year Country Trial Name Trial Number Risk of Bias	Interventions	N	Efficacy/Effectiveness Outcomes	AEs (General)	AEs (Specific)
			Baricitinib 4 mg: -9 Adalimumab 40 mg: -10 P ≤ .05		
van der Heijde et al., 2020[20] 74 sites, 10 countries, Europe and the USA BE AGILE NCT02963506 Low	• Bimekizumab 16 mg SC every 4 weeks • Bimekizumab 64 mg SC every 4 weeks • Bimekizumab 160 mg SC every 4 weeks • Bimekizumab 320 mg SC every 4 weeks • Placebo	Total N = 303 Bimekizumab 16 mg = 61 Bimekizumab 64 mg = 61 Bimekizumab 160 mg = 60 Bimekizumab 320 mg = 61 Placebo = 60	Primary outcome at week 12: ASAS40 response: Bimekizumab 16 mg: 18 of 61 (29.5%) Bimekizumab 64 mg: 26 of 61 (42.6%) Bimekizumab 160 mg: 28 of 60 (46.7%) Bimekizumab 320 mg: 28 of 61 (45.9%) Placebo: 8 of 60 (13.3%) Bimekizumab 16 mg vs. placebo: OR 2.6 (95% CI: 1.0 to 6.5); Bimekizumab 64 mg vs. placebo: OR 4.5 (95% CI: 1.8 to 10.9); Bimekizumab 160 mg vs. placebo: OR 5.5 (95% CI: 2.3 to 13.5); Bimekizumab 320 mg vs. placebo: OR 5.3 (95% CI: 2.2 to 12.9) Secondary outcomes at week 12: ASAS20 response: Bimekizumab 16 mg: 25 of 61 (41.0%) Bimekizumab 64 mg: 38 of 61 (62.3%)	Week 12: Any AEs: Bimekizumab 16 mg: 26 of 61 (42.6%) Bimekizumab 64 mg: 17 of 58 (29.3%) Bimekizumab 160 mg: 20 of 63 (31.7%) Bimekizumab 320 mg: 29 of 61 (47.5%) Placebo: 26 of 60 (43.3%) Withdrawal because of AEs: Bimekizumab 16 mg: 2 of 61 (3.3%) Bimekizumab 64 mg: 1 of 58 (1.7%) Bimekizumab 160 mg: 1 of 63 (1.6%) Bimekizumab 320	Week 12: Mortality: Bimekizumab 16 mg: 0 of 61 (0.0%) Bimekizumab 64 mg: 0 of 58 (0.0%) Bimekizumab 160 mg: 1 of 63 (1.6%) Bimekizumab 320 mg: 0 of 61 (0.0%) Placebo: 0 of 60 (0.0%) Opportunistic infection Bimekizumab 16 mg: 1 of 61 (1.6%) Bimekizumab 64 mg: 0 of 58 (0.0%) Bimekizumab 160 mg: 0 of 63 (0.0%) Bimekizumab 320 mg: 0 of 61 (0.0%) Placebo: 0 of 60 (0.0%)

Authors, Year Country Trial Name Trial Number Risk of Bias	Interventions	N	Efficacy/Effectiveness Outcomes	AEs (General)	AEs (Specific)
			Bimekizumab 160 mg: 35 of 60 (58.3%) Bimekizumab 320 mg: 44 of 61 (72.1%) Placebo: 17 of 60 (28.3%) ASAS5/6 response: Bimekizumab 16 mg: 18 of 60 (29.5%) Bimekizumab 64 mg: 30 of 61 (49.2%) Bimekizumab 160 mg: 32 of 60 (53.3%) Bimekizumab 320 mg: 33 of 61 (54.1%) Placebo: 4 of 60 (6.7%) BASDAI change from baseline (mean(SD)): Bimekizumab 16 mg: −1.7 (2.3) Bimekizumab 64 mg: −2.7 (2.2) Bimekizumab 160 mg: −2.5 (1.8) Bimekizumab 320 mg: −2.9 (2.2) Placebo: −1.0 (1.7) BASFI change from baseline (mean(SD)): Bimekizumab 16 mg: −1.4 (2.2) Bimekizumab 64 mg: −1.9 (2.4) Bimekizumab 160 mg: −1.7 (1.8)	mg: 2 of 61 (3.3%) Placebo: 1 of 60 (1.7) SAEs: Bimekizumab 16 mg: 0 of 61 (0%) Bimekizumab 64 mg: 2 of 58 (3.4%) Bimekizumab 160 mg: 1 of 63 (1.6%) Bimekizumab 320 mg: 0 of 61 (0.0%) Placebo: 2 of 60 (3.3%)	Malignancies Bimekizumab 16 mg: 0 of 61 (0.0%) Bimekizumab 64 mg: 0 of 58 (0.0%) Bimekizumab 160 mg: 0 of 63 (0.0%) Bimekizumab 320 mg: 0 of 61 (0.0%) Placebo: 0 of 60 (0.0%) Major cardiovascular events Bimekizumab 16 mg: 0 of 61 (0.0%) Bimekizumab 64 mg: 0 of 58 (0.0%) Bimekizumab 160 mg: 1 of 63 (1.6%) Bimekizumab 320 mg: 0 of 61 (0.0%) Placebo: 0 of 60 (0.0%)

Authors, Year Country Trial Name Trial Number Risk of Bias	Interventions	N	Efficacy/Effectiveness Outcomes	AEs (General)	AEs (Specific)
			Bimekizumab 320 mg: −2.2 (2.0) Placebo: −0.6 (1.9) ASDAS change from baseline (mean(SD)): Bimekizumab 16 mg: −0.9 (1.0) Bimekizumab 64 mg: −1.7 (1.1) Bimekizumab 160 mg: −1.4 (0.9) Bimekizumab 320 mg: −1.5 (0.9) Placebo: −0.4 (0.7)		
Vollenhofen et al., 2012[50] 115 centers worldwide ORAL Standard NCT00853385 Moderate	• Tofacitinib 5 mg twice daily • Tofacitinib 10 mg twice daily • Adalimumab 40 mg every 2 weeks • Placebo followed by tofacitinib 5 mg twice daily • Placebo followed by tofacitinib 10 mg	Total n = 717 Tofacitinib 5 mg = 204 Tofacitinib 10 mg = 201 Adalimumab 40 mg = 204 Placebo + Tofacitinib 5 mg = 56 Placebo + Tofacitinib 10 mg = 52	Primary outcomes: 6 months ACR20 response: Tofacitinib 5 mg: 51.5% Tofacitinib 10 mg: 52.6% Adalimumab 40 mg: 47.2% Placebo: 28.3% P < .001 for all comparisons with the Placebo group DAS28-4(ESR) < 2.6: Tofacitinib 5 mg: 6.2% Tofacitinib 10 mg: 12.5% Adalimumab 40 mg: 6.7% Placebo: 1.1% 3 months HAQ-DI Mean change from baseline:	3 months: AEs: Tofacitinib 5 mg: 106 of 204 (52.0%) Tofacitinib 10 mg: 94 of 201 (46.8%) Adalimumab 40 mg: 105 of 204 (51.5%) Placebo: 51 of 108 (47.2%) Withdrawal because of AEs: Tofacitinib 5 mg: 14 of 204 (6.9%) Tofacitinib 10 mg: 10 of 201 (5.0%) Adalimumab 40	

Authors, Year Country Trial Name Trial Number Risk of Bias	Interventions	N	Efficacy/Effectiveness Outcomes	AEs (General)	AEs (Specific)
			Tofacitinib 5 mg: -0.55 Tofacitinib 10 mg: -0.661 Adalimumab 40 mg: -0.49 Placebo: -0.24	mg: 10 of 204 (4.9%) Placebo: 3 of 108 (2.8%) SAEs: Tofacitinib 5 mg: 12 of 204 (5.9%) Tofacitinib 10 mg: 10 of 201 (5.0%) Adalimumab 40 mg: 50 of 204 (2.5%) Placebo: 2 of 108 (1.9%)	
Weinblatt et al., 2013[43] Schiff et al., 2013[89] 120 sites, North and South America AMPLE NCT00929864 Moderate	• Abatacept 125 mg SC every week • Adalimumab 40 mg SC every 2 week • Both treatments were given in combination with background MTX	Total n = 646 Abatacept 125 mg SC = 318 Adalimumab 40 mg SC = 328	Primary outcome: 365 days ACR20 response: Abatacept 125 mg SC: 64.8% Adalimumab 40 mg SC: 63.4% Secondary outcomes: 365 days ACR50 response: Abatacept 125 mg SC: 46.2% Adalimumab 40 mg SC: 46.0% ACR70 response: Abatacept 125 mg SC: 29.2% Adalimumab 40 mg SC: 26.2%	365 days AEs: Abatacept 125 mg SC: 280 of 318 (88.1%) Adalimumab 40 mg SC: 283 of 328 (86.3%) Withdrawal because of AEs: Abatacept 125 mg SC: 11 of 318 (3.5%) Adalimumab 40 mg	365 days Serious infections: Abatacept 125 mg SC: 7 of 318 (2.2%) Adalimumab 40 mg SC: 9 of 328 (2.7%) Malignancies: Abatacept 125 mg SC: 5 of 318 (1.6%) Adalimumab 40 mg SC: 4 of 328 (1.2%) Deaths: Abatacept 125 mg SC:

Authors, Year Country Trial Name Trial Number Risk of Bias	Interventions	N	Efficacy/Effectiveness Outcomes	AEs (General)	AEs (Specific)
			ACR90 response: Abatacept 125 mg SC: 10.4% Adalimumab 40 mg SC: 6.4% DAS28-CRP score < 2.6: Abatacept 125 mg SC: 43.3% Adalimumab 40 mg SC: 41.9% DAS28-CRP score < 3.2: Abatacept 125 mg SC: 59.3% Adalimumab 40 mg SC: 61.4% HAQ-DI response: Abatacept 125 mg SC: 60.4% Adalimumab 40 mg SC: 57.0% Schiff et al. Primary outcome: 2 years ACR20 response: Abatacept 125 mg SC: 59.7% Adalimumab 40 mg SC: 60.1% Secondary outcomes: 2 years ACR50 response: Abatacept 125 mg SC: 44.7% Adalimumab 40 mg SC: 46.6%	SC: 20 of 328 (6.1%) SAEs: Abatacept 125 mg SC: 32 of 318 (10.1%) Adalimumab 40 mg SC: 30 of 328 (9.1%) Withdrawal because of SAEs: Abatacept 125 mg SC: 4 of 318 (1.3%) Adalimumab 40 mg SC: 10 of 328 (3.0%) Schiff et al. 2 years AEs: Abatacept 125 mg SC: 295 of 318 (92.8%) Adalimumab 40 mg SC: 300 of 328 (91.5%)	1 of 318 (0.3%) Adalimumab 40 mg SC: 0 of 328 (0%) Local injection site reactions: Abatacept 125 mg SC: 12 of 318 (3.8%) Adalimumab 40 mg SC: 30 of 328 (9.1%) Herpes zoster infections: Abatacept 125 mg SC: 4 of 318 (1.2%) Adalimumab 40 mg SC: 3 of 328 (0.9%) Opportunistic infections: Abatacept 125 mg SC: 1 of 318 (0.3%) Adalimumab 40 mg SC: 1 of 328 (0.3%) Schiff et al. 2 years Serious infections: Abatacept 125 mg SC:

Authors, Year Country Trial Name Trial Number Risk of Bias	Interventions	N	Efficacy/Effectiveness Outcomes	AEs (General)	AEs (Specific)
			ACR70 response: Abatacept 125 mg SC: 31.1% Adalimumab 40 mg SC: 29.3% ACR90 response: Abatacept 125 mg SC: 14.5% Adalimumab 40 mg SC: 8.2% DAS-CRP score < 2.6: Abatacept 125 mg SC: 50.6% Adalimumab 40 mg SC: 53.3% DAS-CRP score < 3.2 Abatacept 125 mg SC: 65.3% Adalimumab 40 mg SC: 68.0% HAQ-DI response: Abatacept 125 mg SC: 54.1% Adalimumab 40 mg SC: 48.8%	Withdrawal because of AEs: Abatacept 125 mg SC: 12 of 318 (3.8%) Adalimumab 40 mg SC: 31 of 328 (9.5%) SAEs: Abatacept 125 mg SC: 44 of 318 (13.8%) Adalimumab 40 mg SC: 54 of 328 (16.5%) Withdrawal because of SAEs: Abatacept 125 mg SC: 5 of 318 (1.6%) Adalimumab 40 mg SC: 16 of 328 (4.9%)	12 of 318 (3.8%) Adalimumab 40 mg SC: 19 of 328 (5.8%) Malignancies: Abatacept 125 mg SC: 7 of 318 (2.2%) Adalimumab 40 mg SC: 7 of 328 (2.1%) Deaths: Abatacept 125 mg SC: 1 of 318 (0.3%) Adalimumab 40 mg SC: 1 of 328 (0.3%) Herpes zoster infections: Abatacept 125 mg SC: 9 of 318 (2.8%%) Adalimumab 40 mg SC: 6 of 328 (1.8%) Opportunistic infections: Abatacept 125 mg SC: 4 of 318 (1.3%) Adalimumab 40 mg SC: 4 of 328 (1.2%)

Abbreviations. aOR: adjusted Odds Ratio; ACR 20/50/70/90: American College of Rheumatology, numbers refer to percentage Improvement; AE: adverse event; ASAS20/40: assessment in ankylosing spondylitis, numbers refer to percentage improvement; ASDAS: Ankylosing Spondylitis Disease Activity Score; ASQoL: Ankylosing Spondylitis Quality Of Life Score; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; AM: morning; BASMI: Bath Ankylosing Spondylitis Metrology Index; CAVI: Cardio-Ankle Vascular Index; CDAI: Clinical Disease Activity Index; CI: Confidence Interval; CIMT: Carotid Intima Media Thickness; CRP: C-reactive protein; DAS28, 28-joint Disease Activity Score; DAS28-CRP: 28-joint Disease Activity Score based on C-reactive protein; DAS28-ESR: 28-joint Disease Activity Score based on erythrocyte sedimentation rate; EQ-5D: European Quality of Life 5 Dimension Health Questionnaire; ESR: erythrocyte sedimentation rate; EULAR: European League Against Rheumatism; FACIT-F: Functional Assessment of Chronic Illness Therapy–Fatigue; HAQ: Health Assessment Questionnaire; HAQ-DI: Health Assessment Questionnaire-Disability Index; HR: hazard ratio; IQR: interquartile range; IR: incidence rate; IV: intravenous; kg: kilogram; L: liter; LDA: Low Disease Activity; LSM: least square mean; MACE: major adverse cardiovascular events; MCS: mental component score; mg: milligram; MI: myocardial infarction; min: minute; mL: milliliter; mm: millimeter; m/s: meters per second; mTSS: modified total Sharp score; MTX: methotrexate; N: number; NA: Not Applicable; NCT: US National Clinical Trial Identifier; NICE: National Institute For Health And Care Excellence; NR: not reported; OR: Odds Ratio; P: *probability value; PCS: physical component score; PGA: Physician's Global Assessment of disease activity; pys: person-years; RA: rheumatoid arthritis; RA-WIS: Work Instability Scale for RA; RCT: randomized controlled trial; SAE: serious adverse event; SC: subcutaneous; SD: standard deviation; SDAI: Simple Disease Activity Index; SE: standard error; SEM: standard error of the mean; SF-36: Short Form 36-item Health Survey; SJC28/66: Swollen Joint Count, numbers refer to joints assessed; TJC28/68: Tender Joint Count, numbers refer to joints assessed; TNF-α: tumor necrosis factor alpha; VAS: Visual Analogue Scale; vs.: versus.*

Table B4. Evidence Tables of RCTs of Previous Reports (Intervention and Results)

Authors, Year Country Trial Name Trial Number Risk of Bias	Interventions	N	Efficacy/Effectiveness Outcomes	AEs (General)	AEs (Specific)
Genovese et al., 2004[54] 41 sites, US NR Moderate	• Etanercept 25 mg SC twice weekly + placebo SC • Etanercept 25 mg SC weekly + anakinra 100 mg SC daily • Etanercept 25 mg SC twice weekly + anakinra 100 mg SC daily	Total N = 242 Etanercept 25 mg + placebo = 80 Etanercept 25 mg + anakinra 100 mg = 81 Etanercept 25 mg + anakinra 100 mg =81	Primary endpoint: Week 24: ACR50: Etanercept 25 mg + placebo: 33 of 80 (41%) Etanercept 25 mg + anakinra 100 mg: 32 of 81 (39%) Etanercept 25 mg + anakinra 100 mg: 25 of 81 (31%) Secondary endpoints: ACR20: Etanercept 25 mg + placebo: 54f 80 (68%) Etanercept 25 mg + anakinra 100 mg: 41of 81 (51%) Etanercept 25 mg + anakinra 100 mg: 50 of 81 (62%) ACR70: Etanercept 25 mg + placebo: 17 of 80 (21%) Etanercept 25 mg + anakinra 100 mg: 19 of 81 (24%) Etanercept 25 mg + anakinra 100 mg: 11 of 81 (14%) Modified Disease Activity Score (DAS):	Any adverse event: Etanercept 25 mg + placebo: 72 of 80 (90.0%) Etanercept 25 mg + anakinra 100 mg: 77 of 81 (95.1%) Etanercept 25 mg + anakinra 100 mg: 76 of 81 (93.8%) Withdrawal because of adverse event: Etanercept 25 mg + placebo: 0 of 80 (0.0%) Etanercept 25 mg + anakinra 100 mg: 7 of 81 (8.6%) Etanercept 25 mg + anakinra 100 mg: 6 of 81 (7.4%) Serious adverse event: Etanercept 25 mg + placebo: 2 of 80 (2.5%) Etanercept 25 mg + anakinra 100 mg: 4 of 81 (4.9%) Etanercept 25 mg + anakinra 100 mg: 12 of 81 (14.8)	Injection-site reaction: Etanercept 25 mg + placebo: 32 of 80 (40.0%) Etanercept 25 mg + anakinra 100 mg: 55 of 81 (67.9%) Etanercept 25 mg + anakinra 100 mg: 57 of 81 (70.4%) Any infection: Etanercept 25 mg + placebo: 32 of 80 (40.0%) Etanercept 25 mg + anakinra 100 mg: 30 of 81 (37.0%) Etanercept 25 mg + anakinra 100 mg: 38 of 81 (46.9%) Serious infection: Etanercept 25 mg + placebo: 0 of 80 Etanercept 25 mg + anakinra 100 mg: 3 of 81 (3.7%) Etanercept 25 mg + anakinra 100 mg: 6 of 81 (7.4%) Herpes zoster:

Authors, Year Country Trial Name Trial Number Risk of Bias	Interventions	N	Efficacy/Effectiveness Outcomes	AEs (General)	AEs (Specific)
			Etanercept 25 mg + placebo: 17 of 80 (21%) Etanercept 25 mg + anakinra 100 mg: 19 of 81 (24%) Etanercept 25 mg + anakinra 100 mg: 11 of 81 (14%) European League Against Rheumatism (EULAR) response: Etanercept 25 mg + placebo: 17 of 80 (21%) Etanercept 25 mg + anakinra 100 mg: 19 of 81 (24%) Etanercept 25 mg + anakinra 100 mg: 11 of 81 (14%)		Etanercept 25 mg + placebo: 0 of 80 (0.0%) Etanercept 25 mg + anakinra 100 mg: 0 of 81 (0.0%) Etanercept 25 mg + anakinra 100 mg: 1 of 81 (1.2%) Malignant Lymphoma: Etanercept 25 mg + placebo: 0 of 80 (0.0%) Etanercept 25 mg + anakinra 100 mg: 0 of 81 (0.0%) Etanercept 25 mg + anakinra 100 mg: 1 of 81 (1.2%)
De Filippis et al., 2006[53] Italy NR Moderate	• Etanercept 25 mg SC twice weekly + MTX • Infliximab 3 mg/kg at 0, 2, 6 weeks and then, every 2 months + MTX	Total N = 32 Etanercept 25 mg = 16 Infliximab 3 mg/kg = 16	54 weeks: ACR responders: Etanercept 25 mg: 11 of 15 (74.4%) Infliximab 3 mg: 9 of 15 (60%) P = NR Tender joint count (TJC): Etanercept 25 mg: -61.3% Infliximab 3 mg/kg: -24.33% P = .02 Swollen joint count (SJC):	NR	NR

Authors, Year Country Trial Name Trial Number Risk of Bias	Interventions	N	Efficacy/Effectiveness Outcomes	AEs (General)	AEs (Specific)
			Etanercept 25 mg: -49.5% Infliximab 3 mg/kg: -45.3% P = NS Health Assessment Questionnaire (HAQ): Etanercept 25 mg: -32.3% Infliximab 3 mg/kg: -21.6% P = NS VAS Pain Perception: Etanercept: -43.06% Infliximab 3 mg/kg: -21.1% P = .01 VAS Patient's Global Assessment: Etanercept 25 mg: -50.6% Infliximab 3 mg/kg: -22.2% P ≤ .01 VAS Physician's Global Assessment: Etanercept 25 mg: -41.8% Infliximab 3 mg/kg: -43.6% P = NS		
Weinblatt et al., 2006[58] NR ASSURE	• Abatacept 10 mg/kg IV days 1, 15, and 29, and every 4 weeks thereafter +	Total N = 167 Abatacept 10 mg + other TIMs = 103 Other TIM alone = 64	Week 52: HAQ-DI: mean change from baseline (SD): Abatacept 10 mg + other TIMs: -0.33 (NR) Other TIM alone: -0.23 (NR)	Week 52: Any AE: Abatacept 10 mg + other TIMs: 98 of 103 (95.1%) Other TIM alone: 57 of 64 (89.1%)	Week 52: Death: Abatacept 10 mg + other TIMs: 0 of 103 (0.0%) Other TIM alone: 0 of 64 (0.0%)

Authors, Year Country Trial Name Trial Number Risk of Bias	Interventions	N	Efficacy/Effectiveness Outcomes	AEs (General)	AEs (Specific)
NR Moderate	Other TIMs (anakinra, etanercept, infliximab, and adalimumab) • Other TIM alone (anakinra, etanercept, infliximab, and adalimumab)			Withdrawal because of AEs: Abatacept 10 mg + other TIMs: 9 of 103 (8.7%) Other TIM alone: 2 of 64 (3.1%) SAEs: Abatacept 10 mg + other TIMs: 23 of 103 (22.3%) Other TIM alone: 8 of 64 (12.5%)	Malignancies: Abatacept 10 mg + other TIMs: 7 of 103 (6.8%) Other TIM alone: 1 of 64 (1.6%) Serious infections: Abatacept 10 mg + other TIMs: 6 of 103 (5.8%) Other TIM alone: 1 of 64 (1.6%)
Weinblatt et al., 2007[55] USA NR Moderate	• Abatacept 2 mg days 1, 15, and 30 and then every 4 weeks IV + etanercept 25 mg SC BIW • Etanercept 25 mg SC BIW + placebo	Total N = 121 Abatacept 2 mg + Etanercept 25 mg = 85 Etanercept 25 mg + placebo = 36	Week 52: ACR20: Abatacept 2 mg + Etanercept 25 mg: 41 of 85 (48.2%) Etanercept 25 mg + Placebo: 11 of 36 (30.6%) ACR50: Abatacept 2 mg + Etanercept 25 mg: 24 of 85 (28.2%) Etanercept 25 mg + placebo: 6 of 36 (16.7%) ACR 70: Abatacept 2 mg + Etanercept 25 mg: 8 of 85 (9.4%) Etanercept 25 mg + placebo: 2 of 36 (5.6%)	Week 52: Any AE: Abatacept 2 mg + Etanercept 25 mg: 79 of 85 (92.9%) Etanercept 25 mg + placebo: 32 of 36 (88.9%) Withdrawal because of AEs: Abatacept 2 mg + Etanercept 25 mg: 10 of 85 (11.8%) Etanercept 25 mg+ placebo: 1 of 36 (2.8%) SAEs:	Week 52: Death: Abatacept 2 mg + Etanercept 25 mg: 0 of 85 (0.0%) Etanercept 25 mg+ placebo: 0 of 36 (0.0%) Malignancies: Abatacept 2 mg + Etanercept 25 mg: 0 of 85 (0.0%) Etanercept 25 mg + placebo: 0 of 36 (0.0%) Serious infections: Abatacept 2 mg + Etanercept 25 mg: 3 of 85 (3.5%)

Authors, Year Country Trial Name Trial Number Risk of Bias	Interventions	N	Efficacy/Effectiveness Outcomes	AEs (General)	AEs (Specific)
			Tender joints: mean change from baseline (SD) Abatacept 2 mg + Etanercept 25 mg: -11.6 (13.9) Etanercept 25 mg + placebo: -8.8 (13.7) Swollen joints: mean (SD) Abatacept 2 mg + Etanercept 25 mg: -7.8 (9.5) Etanercept 25 mg + placebo: -4.4 (9.2) Patient assessment of pain: mean change from baseline (SD) Abatacept 2 mg + Etanercept 25 mg: -22 (29) Etanercept 25 mg + placebo: -6.1 (23.2) Patient assessment of function: mean change from baseline (SD) Abatacept 2 mg + Etanercept 25 mg: -0.3 (0.5) Etanercept 25 mg + placebo: -0.2 (0.4) Patient assessment of disease activity: mean change from baseline (SD)	Abatacept 2 mg + Etanercept 25 mg: 14 of 85 (16.5%) Etanercept 25 mg + placebo: 1 of 36 (2.8%)	Etanercept 25 mg + placebo: 0 of 36 (0.0%)

Authors, Year Country Trial Name Trial Number Risk of Bias	Interventions	N	Efficacy/Effectiveness Outcomes	AEs (General)	AEs (Specific)
			Abatacept 2 mg + Etanercept 25 mg: -18.2 (29.1), p<0.001 Etanercept 25 mg + placebo: -7.1 (21.3) Physician assessment of disease activity: mean change from baseline (SD) Abatacept 2 mg + Etanercept 25 mg: -25.7 (27) Etanercept 25 mg + placebo: -18.2 (20.4)		
Greenwald et al., 2011[59] USA NR Moderate	• Rituximab 500 mg IV 2 weeks apart+ ada-limumab 40 mg every 2 weeks or etanercept 50 mg once per week or 25 mg twice peer week SC + MTX • Adalimumab 40 mg every two weeks SC or etanercept 50 mg once per week or 25 mg twice per week SC + MTX	Total N = 51 Rituximab 500 mg + adalimumab 40 mg or etanercept 50 mg + MTX: 33 Adalimumab 40 mg or etanercept 50 mg + MTX = 18	Week 24: ACR 50: Rituximab 500 mg + adalimumab 40 mg or etanercept 50 mg + MTX: 4 of 33 (12%) Adalimumab 40 mg or etanercept 50 mg + MTX: 1 of 18 (6%) DAS28-ESR < 2.6: Rituximab 500 mg + adalimumab 40 mg or etanercept 50 mg + MTX: 6 of 33 (18%) Adalimumab 40 mg or etanercept 50 mg + MTX: 1 of 18 (6%)	Week 24: Any AE: Rituximab 500 mg + adalimumab 40 mg or etanercept 50 mg + MTX: 31 of 33 (93.9%) Adalimumab 40 mg or etanercept 50 mg + MTX: 15 of 18 (83.3%) Withdrawal because of AEs: Rituximab 500 mg + adalimumab 40 mg or etanercept 50 mg + MTX: 2 of 33 (6.1%) Adalimumab 40 mg or etanercept 50 mg + MTX: 0 of 18 (0.0%)	24 weeks: Death: Rituximab 500 mg + adalimumab 40 mg or etanercept 50 mg + MTX: 0 of 33 (0.0%) Adalimumab 40 mg or etanercept 50 mg + MTX: 0 of 18 (0.0%) Acute infusion reactions: Rituximab 500 mg + adalimumab 40 mg or etanercept 50 mg + MTX: 4 of 33 (12.1%) Adalimumab 40 mg or etanercept 50 mg + MTX: 6 of 18 (33.3%) Serious infections:

Authors, Year Country Trial Name Trial Number Risk of Bias	Interventions	N	Efficacy/Effectiveness Outcomes	AEs (General)	AEs (Specific)
				SAEs: Rituximab 500 mg + adalimumab 40 mg or etanercept 50 mg + MTX: 2 of 33 (6.1%) Adalimumab 40 mg or etanercept 50 mg + MTX: 15 of 18 (0%)	Rituximab 500 mg + adalimumab 40 mg or etanercept 50 mg + MTX: 1 of 33 (3.0%) Adalimumab 40 mg or etanercept 50 mg + MTX: 0 of 18 (0.0%) All Infections Rituximab 500 mg + adalimumab 40 mg or etanercept 50 mg + MTX: 18 of 33 (54.5%) Adalimumab 40 mg or etanercept 50 mg + MTX: 11 of 18 (61.1%)

Abbreviations. ACR 20/50/70/90: American College of Rheumatology, numbers refer to percentage Improvement; AE: adverse event; ASAS20/40: assessment in ankylosing spondylitis, numbers refer to percentage improvement; DAS, Disease Activity Score; EULAR: European League Against Rheumatism; HAQ: Health Assessment Questionnaire; HAQ-DI: Health Assessment Questionnaire-Disability Index; HR: hazard ratio; IQR: interquartile range; IR: incidence rate; IV: intravenous; kg: kilogram; L: liter; mg: milligram; MTX: methotrexate; N: number; NA: Not Applicable; NR: not reported; NS. Not significant; OR: odds ratio; P: *probability value; pys: person-years; RA: rheumatoid arthritis; SAE: serious adverse event; SC: subcutaneous; SD: standard deviation; SJC28/66: Swollen Joint Count, numbers refer to joints assessed; TIM: Targeted Immune Modulators; TJC28/68: Tender Joint Count, numbers refer to joints assessed; TNF-α: tumor necrosis factor alpha; US: United States; VAS: Visual Analogue Scale; vs.: versus.*

Table B5. Evidence Tables of Cohort Studies of Previous Report

Authors, Year Country Risk of Bias	Drug(s)	Sample Time Frame, Data Source	N	Population Characteristics	Harms	Funder
Chen et al., 2020[24] US Moderate	• Abatacept • TNF-α inhibitors (adalimumab, certolizumab, etanercept, golimumab or infliximab) • Rituximab • Tocilizumab • Tofacitinib	IBM MarketScan Research Database (2005–2016)	Total = 10,019 Abatacept = 1,785 TNF-α inhibitors = 5,953 Rituximab = 888 Tocilizumab = 759 Tofacitinib = 634	Adults with RA and diabetes mellitus type 1 or 2 and use of at least 1 antidiabetic drug at baseline	Herpes zoster infection: Abatacept: 1,785 patients, 24 events, 1,399.1 pys, IR per 100 pys: 17.2 (95% CI, 11.5 to 25.6) TNF-α inhibitors: 5,953 patients, 93 events, 5,316.9 pys, IR per 100 pys: 17.5 (95% CI, 14.3 to 21.4) Rituximab: 888 patients, 23 events, 691.2 pys, IR per 100 pys: 33.3 (95% CI, 22.1 to 50.1) Tocilizumab: 759 patients, 19 events, 557.1 pys, IR per 100 pys: 34.1 (95% CI, 21.8 to 53.5) Tofacitinib: 634 patients, 15 events, 408.2 pys, IR per 100 pys: 36.8 (95% CI, 22.2 to 61.0) TNF-α inhibitors vs. abatacept: aHR, 1.48 (95% CI, 0.88 to 2.49) Rituximab vs. abatacept: aHR, 1.82 (95% CI, 1.02 to 3.24) Tocilizumab vs. abatacept: aHR, 1.98 (95% CI, 1.06 to 3.68) Tofacitinib vs. abatacept: aHR 2.16 (95% CI, 1.09 to 4.28)	Bristol-Myer-Squibb

Authors, Year Country Risk of Bias	Drug(s)	Sample Time Frame, Data Source	N	Population Characteristics	Harms	Funder
Desai et al., 2021[22] US Moderate	• Tofacitinib • TNF inhibitors (adalimumab, certolizumab, etanercept, golimumab or infliximab)	MarketScan (2012–2018) Medicare (2012–2017) Optum Clinformatics (2012–2019)	Total N = 87,653 MarketScan: Tofacitinib = 2,992 TNF inhibitors = 39,209 Medicare: Tofacitinib = 1,795 TNF inhibitors = 23,283 Optum: Tofacitinib = 1,987 TNF inhibitors = 18,387	Adults with RA	Venous thromboembolism (pooled data from the 3 databases): Tofacitinib: 29 events, 6,774 patients, 5,301 pys, 0.55 (95% CI, 0.37 to 0.79) IR per 100 pys TNF inhibitors: 365 events, 80,879 patients, 75,824 pys, 0.48 (95% CI, 0.43 to 0.53) IR per 100 pys Tofacitinib vs. TNF inhibitors: aHR, 1.13 (95% CI, 0.77 to 1.65) Deep vein thrombosis (pooled data from the 3 databases): Tofacitinib vs. TNF inhibitors: aHR, 1.00 (95% CI, 0.79 to 1.26) Pulmonary embolism: Tofacitinib vs. TNF inhibitors: aHR 1.02 (95% CI, 0.60 to 1.73) Outcome definition: Composite endpoint of incident venous thromboembolism including pulmonary embolism or deep vein thrombosis.	Internal sources of the Division of Pharmacoepidemiology & Pharmacoeconomics, Brigham & Women's Hospital, Harvard Medical School
Kim et al., 2018[33] US Moderate	• Tocilizumab • Abatacept	Three large US insurance claims databases: Medicare Parts A/B/D (2010–2013)	Total N = 20,922 Tocilizumab = 6,237 Abatacept = 14,685 N after propensity score matching with 1:3 variable ratio.	Adults with RA who newly started tocilizumab or abatacept	Composite of hospitalization for myocardial infarction or stroke (primary endpoint): Combined data from 3 databases: Tocilizumab: 6237 patients, 32 events, 4,596 pys, IR per 100 pys: 0.70 (95%, CI 0.49 to 0.97)	Genentech

Authors, Year Country Risk of Bias	Drug(s)	Sample Time Frame, Data Source	N	Population Characteristics	Harms	Funder
		IMS PharMetrics Plus (2011–2014) Truven MarketScan (2011—June 2015)			Abatacept: 14,685 patients, 112 events, 11,684 pys, IR per 100 pys: 0.96 (95% CI, 0.79 to 1.15) Tocilizumab vs. abatacept: aHR, 0.82 (95% CI, 0.55 to 1.22) Outcome definition: Myocardial infarction was identified with a hospital discharge diagnosis code of acute myocardial infarction (ICD-9 code 410.x excluding 410.x2). Stroke was based on a hospital discharge diagnosis code of ischemic or hemorrhagic stroke (ICD-9-CM430,431,433.x1,434.x1, and 436)	
Kim et al., 2019[34] US Moderate	• Tocilizumab • Abatacept	Three large US insurance claims databases: Medicare Parts A/B/D (2010- 2015) IMS PharMetrics Plus (2011-2015) Truven MarketScan' (2011- 2015)	Total N = 16,930 Tocilizumab: 8,465 Abatacept: 8,465 N patients are from the secondary comparison cohort after propensity score matching with 1:1 variable ratio	Adults with RA previously treated with 1 or more other biologic DMARD than tocilizumab, abatacept or tofacitinib	Any new malignancies excluding non-melanoma skin cancer (primary outcome) As-treated analysis: Combined data from 3 databases: Tocilizumab: 8,465 patients, 101 events, 7,155 pys, IR per 1,000 pys: 14.12 (95% CI, 11.36 to 16.87) Abatacept: 8,465 patients, 111 events, 77,336 pys, IR per 1,000 pys: 15.13 (95% CI, 12.32 to 17.95) Tocilizumab vs. abatacept: aHR, 0.97 (95% CI, 0.74 to 1.27) Intention-to-treat analysis up to 365	Roche

Authors, Year Country Risk of Bias	Drug(s)	Sample Time Frame, Data Source	N	Population Characteristics	Harms	Funder
					days: Combined data from 3 databases: Tocilizumab: 8,465 patients, 107 events, 7,069 pys, IR per 1,000 pys: 15.14 (95% CI, 12.27 to 18.00) Abatacept: 8,465 patients, 119 events, 7,003 pys, IR per 1,000 pys: 16.99 (95% CI, 13.94 to 20.05) Tocilizumab vs. abatacept: aHR, 0.89 (95% CI, 0.69 to 1.16) Most common cancers (secondary outcomes) Non-Hodgkin lymphoma Tocilizumab vs. abatacept: aHR, 1.31 (95% CI, 0.35 to 4.92) Melanoma Tocilizumab vs. abatacept: aHR, 0.88 (95% CI, 0.39 to 2.02) aHR, for other types of cancer also reported Outcome definition: The primary outcome was development of any new malignancies excluding non-melanoma skin cancer defined by a validated claims-based algorithm using 2 inpatient or outpatient ICD-9 or ICD-10 diagnosis codes of the same type of malignancy within 60 days. Secondary outcomes	

Authors, Year Country Risk of Bias	Drug(s)	Sample Time Frame, Data Source	N	Population Characteristics	Harms	Funder
					were the individual endpoints of the top 10 most common cancers (i.e., breast, prostate, lung, colorectal, uterine, melanoma, kidney, bladder, and thyroid cancer, and non-Hodgkin lymphoma), HPV-related cancers (i.e., anal, cervical, penile, oropharyngeal, vaginal, vulvar), and leukemia. All carcinomas in situ were excluded.	
Patel et al., 2021[16] US Moderate	• Abatacept • TNF-α inhibitors (adalimumab, certolizumab pegol, etanercept, golimumab, and infliximab) • Other non-TNF-α inhibitors (anakinra, sarilumab, tocilizumab, baricitinib, rituximab, and tofacitinib)	Medicare (2009–2017)	Total N tDMARD naïve patient cohort = 30,439 Abatacept = 6,303 TNF-α inhibitors (adalimumab, certolizumab pegol, etanercept, golimumab, and infliximab) = 18,032 Other non- TNF-α inhibitors (anakinra, sarilumab, tocilizumab, baricitinib, rituximab, and tofacitinib) = 6,104 Total N TNF-experienced cohort = 16,647 switched to abatacept = 6,343; switched to another	Adults 65 years or older with RA	Risk of infection-related hospitalization: tDMARD-naïve cohort: TNF-α inhibitors vs. abatacept: aHR, 1.59 (95% CI, 1.43 to 1.77) Other TNF-α inhibitors vs. abatacept: aHR, 1.63 (95% CI, 1.44 to 1.83) TNF-α-experienced cohort: TNF-α inhibitors vs. abatacept: aHR, 1.48 (95% CI, 1.26 to 1.75) Other TNF-α inhibitors vs. abatacept: aHR, 1.46 (95% CI, 1.28 to 1.66)	Bristol Myers Squibb

Authors, Year Country Risk of Bias	Drug(s)	Sample Time Frame, Data Source	N	Population Characteristics	Harms	Funder
			TNF-α inhibitor = 5,054, switched to other non- TNF-α inhibitor = 5,250			
Pawar et al., 2019[38] US Moderate	• Tocilizumab • Abatacept	Three large US insurance claims databases: Medicare (2010-2015) IMS "PharMetrics" Plus (2011-2015) Truven "MarketScan" 2011-2015	Total N = 20,828 Tocilizumab: 10,414 Abatacept: 10,414	Adults with RA	As-treated analysis: Combine data from 3 databases: Serious infections: Tocilizumab: 10,414 patients, 388 events, 8,599 pys, IR per 100 pys: 4.51 (95% CI, 4.06 to 4.96) Abatacept: 10,414 patients, 295 events, 9,094 pys, IR per 100 pys: 3.24 (95% CI, 2.87 to 3.61) Tocilizumab vs. abatacept: aHR, 1.40 (95% CI, 1.20 to 1.63) Rate difference: 1.27 (95% CI, 0.69 to 1.85) Serious bacterial infections: Tocilizumab: 10,414 patients, 331 events, 8,619 pys, IR per 100 pys: 3.84 (95% CI, 3.43 to 4.25) Abatacept: 10,414 patients, 234 events, 9,121 pys, IR per 100 pys: 2.57 (95% CI, 2.24 to 2.89) Tocilizumab vs. abatacept: aHR, 1.50 (95% CI, 1.27 to 1.78) Rate difference: 1.27 (95% CI, 0.74 to 1.8) Herpes zoster: Tocilizumab: 10,414 patients, 13	Roche

Authors, Year Country Risk of Bias	Drug(s)	Sample Time Frame, Data Source	N	Population Characteristics	Harms	Funder
					events, 8,743 pys, IR per 100 pys: 0.15 (95% CI, 0.07 to 0.23) Abatacept: 10,414 patients, NR events, 9,199 pys, IR per 100 pys: 0.09 (95% CI, 0.03 to 0.15) Tocilizumab vs. abatacept: aHR, 1.77 (95% CI, 0.73 to 4.28) Rate difference:- Opportunistic infections: Tocilizumab: 10414 patients, 14 events, 8,745 pys, IR per 100 pys: 0.16 (95% CI, 0.08 to 0.24) Abatacept: 10414 patients, NR events, 9,202 pys, IR per 100 pys: 0.07 (95% CI, 0.01 to 0.12) Tocilizumab vs. abatacept: aHR, 2.42 (95% CI, 0.92 to 6.39) Rate difference:- Skin and soft tissue infection: Tocilizumab: 10,414 patients, 21 events, 8,745 pys, IR per 100 pys: 0.24 (95% CI, 0.14 to 0.34) Abatacept: 10,414 patients, NR events, 9,200 pys, IR per 100 pys: 0.05 (95% CI, 0.01 to 0.10) Tocilizumab vs. abatacept: aHR, 2.82 (95% CI, 1.00 to 7.95) Rate difference:- Intention-to-treat analysis up to 180 days:	

Authors, Year Country Risk of Bias	Drug(s)	Sample Time Frame, Data Source	N	Population Characteristics	Harms	Funder
					Tocilizumab: 10,414 patients, 252 events, 46,61 pys, IR per 100 pys: 5.41 (95% CI, 4.74 to 6.07) Abatacept: 10,414 patients, 188 events, 4,693 pys, IR per 100 pys: 4.01 (95% CI, 3.43 to 4.58) Tocilizumab vs. abatacept: aHR, 1.34 (95% CI, 1.11 to 1.63) Rate difference: 1.40 (95% CI, 0.52 to 2.28)	
Pawar et al., 2020[23] USA Low	• Tofacitinib • Abatacept • Adalimumab • Certolizumab • Etanercept • Golimumab • Infliximab • Tocilizumab	Three large US databases: Medicare (2012–2015) Optum (2012–2018), IBM MarketScan (2012–2017)	Total N (Optum + MarketScan + Medicare) = 130,718 Tofacitinib = 1,705 + 2,090 + 1204 Abatacept = 2,831 + 5,463 + 5,934 Adalimumab = 10,205 + 20,752 + 5,320 Certolizumab = 2,137 + 2,277 + 3,852 Etanercept = 8,128 + 20,826 + 7,007 Golimumab = 911 + 2,508 + 2,089 Infliximab = 597 + 6,029 + 8,897 Tocilizumab = 1,079 + 1,904 + 1,859	Adults with RA	Combined data from 3 databases: Composite endpoint of admission to hospital for serious infection including bacterial, viral, or opportunistic infection (primary outcome): Abatacept vs. tofacitinib: aHR, 1.20 (95% CI, 0.97 to 1.49) Adalimumab vs. tofacitinib: aHR, 1.06 (95% CI, 0.87 to 1.30) Certolizumab vs. tofacitinib: aHR, 1.02 (95% CI, 0.80 to 1.29) Etanercept vs. tofacitinib: aHR, 1.41 (95% CI, 1.15 to 1.73) Golimumab vs. tofacitinib: aHR, 1.23 (95% CI, 0.94 to 1.62) Infliximab vs. tofacitinib: aHR, 0.81 (95% CI, 0.65 to 1.00)	Division of Pharmacoepidemiology and Pharmacoeconomics, Brigham and Women's Hospital, Harvard Medical School

Authors, Year Country Risk of Bias	Drug(s)	Sample Time Frame, Data Source	N	Population Characteristics	Harms	Funder
					Tocilizumab vs. tofacitinib: aHR, 1.17 (95% CI, 0.89 to 1.53) Specific types of serious infection (secondary outcomes): Herpes zoster Abatacept vs. tofacitinib: aHR, 1.94 (95% CI, 1.53 to 2.44) Adalimumab vs. tofacitinib: aHR, 1.99 (95% CI, 1.63 to 2.43) Certolizumab pegol vs. tofacitinib: aHR, 2.24 (95% CI, 1.68 to 2.99) Etanercept vs. tofacitinib: aHR, 2.12 (95% CI, 1.73 to 2.58) Golimumab vs. tofacitinib: aHR, 1.84 (95% CI, 1.35 to 2.50) Infliximab vs. tofacitinib: aHR, 1.94 (95% CI, 1.51 to 2.50) Tocilizumab vs. tofacitinib: aHR, 2.14 (95% CI, 1.53 to 2.99)	
Rutherford et al., 2018[35] NR	• Rituximab • Tocilizumab • Anti-TNF pooled data	-	Total N = 19,282 Anti-TNF = 16,742 Rituximab = 5,072 Tocilizumab = 2,171	-	Opportunistic infections excluding tuberculosis Rituximab: 25 events, 5072, patients, 146 (95% CI, 98 to 217) IR per 100 000 pys Tocilizumab: 3 events, 2171 patients,	-

Authors, Year Country Risk of Bias	Drug(s)	Sample Time Frame, Data Source	N	Population Characteristics	Harms	Funder
Moderate					78 (95% CI, 25 to 241) IR per 100 000 pys Tuberculosis Rituximab: 2 events, 5072 patients, 12 (95% CI, 3 to 46) IR per 100 000 pys Tocilizumab: 1 event, 2171 patients, 26 (95% CI, 4 to 183) IR per 100 000 pys Etanercept vs. rituximab aHR, 4.63 (95% CI, 1.06 to 20.2) Outcome definition and assessment: Any serious opportunistic infection as defined by Winthrop et al. All opportunistic infections were validated independently by 2 clinicians who were blinded to the treatment exposure. Differences in coding were resolved by discussion or, if consensus could not be reached, by a third clinician.	
Rutherford et al., 2018[37] United Kingdom Moderate	• Etanercept • Infliximab • Adalimumab • Rituximab • Tocilizumab • Certolizumab	British Society for Rheumatology Biologics Register for RA (BSRBR-RA) since 2001	Total N = 19,282 Etanercept = 8,630 Infliximab = 4,908 Adalimumab = 7,818 Rituximab = 5,101 Tocilizumab = 2,174 Certolizumab = 1,446	Patients with RA starting a new biologic treatment	Serious infections Etanercept: 852 events, 8603 patients, 15,314 years follow-up time, 5.56 (95% CI, 5.20 to 5.95) IR per 100 pys Infliximab: 472 events, 4,908 patients, 8,829 years follow-up time, 5.35 (95% CI, 4.89 to 5.85) IR per 100 pys Adalimumab: 709 events, 7,818 patients, 13071 years follow-up time,	NIHR Biomedical Research Centre at Guy's and St Thomas' NHS Foundation Trust and King's College London, Abbvie, Celltrion, Hospira, Pfizer, UCB and Roche, and in the past Swedish Orphan

Authors, Year Country Risk of Bias	Drug(s)	Sample Time Frame, Data Source	N	Population Characteristics	Harms	Funder
					5.42 (95% CI, 5.04 to 5.84) IR per 100 pys Rituximab: 372 events, 5,101 patients, 5,910 years follow-up time, 6.29 (95% CI, 5.69 to 6.97) IR per 100 pys Tocilizumab: 137 events, 2,174 patients, 1,963 years follow-up time, 6.98 (95% CI, 5.90 to 8.25) IR per 100 pys Certolizumab: 64 events, 1,446 patients, 1,685 years follow-up time, 3.80 (95% CI, 2.97 to 4.85) IR per 100 pys aHR, Infliximab vs. etanercept: 0.89 (95% CI, 0.79 to 1.00) Adalimumab vs. etanercept: 1.00 (95% CI, 0.90 to 1.10) Rituximab vs. etanercept: 0.91 (95% CI, 0.80 to 1.03) Tocilizumab vs. etanercept: 1.21 (95% CI, 1.01 to 1.46) Certolizumab vs. etanercept: 0.75 (95% CI, 0.58 to 0.97)	Biovitrum and Merck

Abbreviations. bDMARD: biologic DMARD; CI: confidence interval; DMARD: Disease-Modifying Antirheumatic Drug; HPV: human papillomavirus; aHR: adjusted hazard ratio; ICD: International Classification of Disease; (a)IR: (adjusted) incidence rate; N: number; NR: not reported; P: *probability value; pys: patient-years; RA: rheumatoid arthritis; aRR: adjusted risk ratio; TIM: targeted immune modulator; TNF: tumor necrosis factor.*

Table B6. Evidence Table of Previous Reports for Cohort Studies of TIMs in Rheumatoid Arthritis

Authors, Year Country Risk of Bias	Drug(s)	Sample Time Frame, Data Source	N	Population Characteristics	Harms	Funder
Arkema et al., 2015[60] Sweden Moderate	• Adalimumab • Infliximab • Etanercept • Golimumab • Rituximab • Abatacept • Anakinra • Tocilizumab Certolizumab pegol	NPR (inpatient care 1969–2011 and outpatient, nonprimary care 2001–2011) and the Swedish Rheumatology Quality Register (SRQ; 1997–2011)	Total = 10,800	Adults with RA (≥2 visits with an International Classification of Diseases (ICD) code for RA in the NPR, with ≥1 visit to a rheumatology or internal medicine department and ≥1 in outpatient care).	TB (ever exposed participants): Etanercept vs. adalimumab: aHR 2.3 (95% CI, 0.8 to 7.2) Etanercept vs. infliximab: aHR 2.0 (95% CI, 0.6 to 5.9) Etanercept vs. rituximab aHR 0.7 (95% CI, 0.1 to 7.5) TB (most recent exposure): Etanercept vs. adalimumab 3.1 (95% CI, 0.8 to 12.5) Etanercept vs. infliximab 2.7 (95% CI, 0.7 to 10.9) Etanercept vs. rituximab 0.6 (95% CI, 0.1 to 7.0)	Swedish Society for Rheumatology, Swedish Foundation for Strategic Research, Swedish public–private COMBINE research consortium
Baddley et al., 2014[61] USA Moderate	• TNF-α inhibitors (including Infliximab, Adalimumab and Etanercept [not included for IBD]); • nbDMARD regimens.	1998 - 2007 Four large US data systems (National Medicaid (MAX) and dual Medicaid-Medicare databases; TennCare; The New Jersey's Pharmaceutical Assistance to the Aged and Disabled (PAAD) and the	N = 33,324	New users of TNF-α inhibitors among cohorts of RA, IBD, and psoriasis-psoriatic arthritis-ankylosing spondylitis (PsO-PsA-AS) patients during 1998–2007	Opportunistic infections: Infliximab vs. etanercept: aHR 2.9, (95% CI: 1.5 to 5.4)	FDA, US DHHS and AHRQ

Authors, Year Country Risk of Bias	Drug(s)	Sample Time Frame, Data Source	N	Population Characteristics	Harms	Funder
		Pennsylvania's Pharmaceutical Assistance Contract for the Elderly (PACE) programs linked to Medicare data; and Kaiser Permanente Northern California (KPNC)).				
Curtis, 2012[63] USA Moderate	• Infliximab • Etanercept • Adalimumab	Medicare and Medicaid between 2000 and 2006 (the governmentally insured population) or commercially insured RA patients enrolled in Aetna between 2005 and 2010.	Government insurance: DMARDs = 14,693 Anti-TNF = 6,560 Commercial insurance: DMARDs = 8,823 Anti-TNF = 5,097	RA patients based on the International Classification of Disease, Ninth Revision (ICD-9)–coded physician diagnoses, who filled a new prescription for MTX or other nbDMARDs or an anti-TNF agent (infliximab, etanercept, or adalimumab)	Infections (commercially insured RA participants): Infliximab vs. etanercept: aHR 1.52 (95% CI 1.08 to 2.12) Infliximab vs. adalimumab: aHR 1.49 (95% CI 1.05to 2.10) Infliximab vs. etanercept (first 90 days): aHR 1.56 (95% CI 1.17 to −2.10) Infliximab vs. etanercept: aHR 1.10 (95% CI 0.91to 1.35) beyond 90 days. Infliximab vs. adalimumab: aHR 1.87 (95% CI 1.37to 2.58) within 90 days Infliximab vs. adalimumab: aHR 0.91 (95% CI 0.75 to 1.10) beyond 90 days.	AHRQ and the Doris Duke Charitable Foundation. Dr. Curtis's work was supported by the NIH. Dr. Saag's work was supported by the NIH.
Curtis et al., 2016[62]	• Abatacept • Rituximab	Medicare (2006-2013) Marketscan	Abatacept = 12,305 Rituximab = 5,078 TNF-α inhibitors=	RA adults initiating tofacitinib or other TIMs with no	Herpes zoster and herpes simplex: Adalimumab vs. abatacept: aHR:	

Authors, Year Country Risk of Bias	Drug(s)	Sample Time Frame, Data Source	N	Population Characteristics	Harms	Funder
USA Moderate	• TNF-α inhibitors • Tocilizumab • Tofacitinib	(2010-2014)	42,850 Tocilizumab = 6,967 Tofacitinib = 2,526	history of herpes zoster and herpes simplex virus	0.89 (95% CI, 0.77 to 1.03) Certolizumab vs. abatacept:aHR: 1.00 (95% CI, 0.83to1.19) Etanercept vs. abatacept: aHR: 0.86 (0.74 - 1.00) Golimumab vs. abatacept: aHR: 1.01 (95% CI, 0.80 to 1.27) Infliximab vs. abatacept: aHR: 1.06 (95% CI, 0.93 to 1.21) Rituximab vs. abatacept:aHR: 0.98 (95% CI, 0.83 to 1.15) Tocilizumab vs. abatacept: aHR: 1.15 (95% CI, 0.99 to 1.34) Tofacitinib vs. abatacept: aHR: 1.40 (95% CI, 1.09 to 1.81)	
Dixon et al., 2010[64] UK Moderate	• Adalimumab or infliximab • Etanercept	BSRBR (2001-2008)	Total = 10,712 Adalimumab = 3,504 Infliximab = 3,295 Etanercept = 3,913	Adults with active RA	Tuberculosis: Adalimumab vs. Etanercept: aIRR, 4.2 (95% CI, 1.4 to 12.4) Infliximab vs. etanercept: aIRR, 3.1 (95% CI, 1.0 to 9.5)	BSR
Galloway et al., 2011[66] UK Moderate	• Etanercept • Infliximab • Adalimumab	From 2001 to 31 December 2009. Recruitment targets of 4000 patients for the ETN cohort were met in 2005, for INF in 2007 and for ADA in 2008.	N = 15,554 nbDMARD = 3,673 Etanercept = 4,139 Infliximab = 3,475 Adalimumab = 4,267	Adults with RA	Septic arthritis: Etanercept vs. nbDMARDS: aHR 2.5 (95% CI 1.3 to 4.9) Infliximab vs. nbDMARDS: aHR 2.4 (95% CI, 1.0 to 5.8) Adalimumab vs. nbDMARDS: aHR 1.9 (95% CI, 0.9 to 4.0) There were no differences between the monoclonal antibody class and etanercept that achieved statistical significance (results not shown).	The BSR which received restricted income from UK pharmaceutical companies, presently Abbott Laboratories, Amgen, Schering

Authors, Year Country Risk of Bias	Drug(s)	Sample Time Frame, Data Source	N	Population Characteristics	Harms	Funder
						Plough (now MSD) and Wyeth Pharmaceuticals (now Pfizer).
Galloway et al., 2011[65] UK Low	• Adalimumab • Etanercept • Infliximab	BSRBR, 2003-2008	Total N = 11,798 Adalimumab = 4,202 Etanercept = 4,129 Infliximab = 3,467	Adults with RA	Serious infections: In the adjusted analysis, there was no significant difference in serious infections rates between the three TNF-α agents (results not shown).	BSRBR
Galloway, 2013[67] UK Moderate	• Etanercept • Infliximab • Adalimumab	BSRBR	N = 11,881	Adults with RA	Shingles: Infliximab vs. adalimumab: HR 1.5; 95% CI 1.1 to 2.0). The aHR using propensity modeling for each agent vs. nbDMARDs were: adalimumab 1.5 (95% CI, 0.9 - 2.4); etanercept 1.7 (95% CI, 1.0 - 2.7); infliximab 2.2 (95% CI, 1.4 - 3.4) Adalimumab vs. nbDMARD: aHR 1.1, 95% CI 0.6 to 2.1; Etanercept vs. nbDMARD: aHR 0.5, 95% CI 0.9 to 2.5; Infliximab vs. nbDMARD: aHR 1.5, 95% CI 0.9 to 2.5. No significant difference was apparent when comparing the rates of shingles with etanercept with the monoclonal antibodies combined.	BSR
Grijalva, 2011[68]	• TNF-α inhibitors (including	National US Medicaid and Medicare	N = 10,484 Etanercept= 4,496 Infliximab= 3,911	RA adults initiating study regimens.	Serious infections: Infliximab vs. etanercept: aHR, 1.26 (95% CI, 1.07 to 1.47)	FDA, US Department of Health and

Authors, Year Country Risk of Bias	Drug(s)	Sample Time Frame, Data Source	N	Population Characteristics	Harms	Funder
USA Moderate	infliximab, adalimumab, and etanercept)	databases, excluding Tennessee (Medicaid Analytic eXtract, 2000-2005; Medicare, 2000-2006; and Medicare Part D, 2006); Tennessee Medicaid (TennCare, 1998-2005); New Jersey's Pharmaceutical Assistance to the Aged and Disabled and Pennsylvania's Pharmaceutical Assistance Contract for the Elderly (PAAD/PACE,1998-2006); and Kaiser Permanente Northern California (KPNC, 1998-2007).	Adalimumab= 2,077		Infliximab vs. adalimumab: aHR 1.23 (95% CI, 1.02 to 1.48) Adalimumab vs. etanercept: aHR 1.05 (95% CI, 0.87 to 1.25)	Human Services, AHRQ, NIH, National Institute of Arthritis and Musculoskeletal and Skin Diseases

Authors, Year Country Risk of Bias	Drug(s)	Sample Time Frame, Data Source	N	Population Characteristics	Harms	Funder
Mercer et al., 2012[130] UK Moderate	• Etanercept • Infliximab • Adalimumab	Follow-up was censored at the date of the most recently received hospital follow-up form before 31 December 2008 or death, if this came first. BSRBR	N = 11,881 Etanercept = 4,139 Infliximab = 3,475 Adalimumab = 4,267	Patients with RA who received a TNF-α inhibitor as their first biological therapy and who registered with the BSRBR within 6 months of starting treatment.	No significant different between the rates for the individual agents: adalimumab HR, 0.68 (95% CI, 0.33 to 1.38); etanercept HR, 0.69 (95% CI, 0.37 to 1.29); and infliximab HR, 1.15 (95% CI, 0.60 to 2.21). Analysis stratified by anti-TNF drug found a higher risk for infliximab than for the other two anti-TNF, although this was not statistically significant.	BSR
Monemi et al., 2016[70] USA Moderate	• TNF-α inhibitors (data presented for Etanercept, Adalimumab, Infliximab) • Abatacept • Tocilizumab	MarketScan 2010-2014	Total =27,255 Etanercept = 3,675 Adalimumab = 5,765 Infliximab = 2,339 Abatacept = 6,320 Tocilizumab = 3,602	Adult patients with RA who had evidence of a prescription for or administration of a biologic agent	All GIPs: aIRRs (95% CI) tocilizumab vs. TNF-α inhibitors 2.2 (95% CI, 0.7 to 6.6) specific definition; 2.2 (95% CI, 0.9 to 5.4) sensitive definition Lower GIPs: aIRRs (95% CI) Tocilizumab vs. TNF-α inhibitors 4.0 (95% CI, 1.1 to 14.1) specific definition; 3.1 (95% CI, 1.1 to 8.4) sensitive definition	Sponsorship and article processing charges for this study were funded by Roche
Winthrop et al., 2013[71] USA Moderate	• Etanercept • Adalimumab • Infliximab	Kaiser Permanente Northern California (KPNC) (2000 – 2008)	N = 36,212 Etanercept = 10,138 Adalimumab = 6,711 Infliximab = 8,087 nbDMARD = 11,828	Patients with ≥ 1 clinical visit and ≥ 1 outpatient prescription for etanercept or adalimumab, or ≥ 1 infusion of infliximab.	Herpes zoster: Etanercept vs. Infliximab: aHR 1.09 (95% CI, 0.82 to 1.45) Adalimumab vs. Infliximab: aHR 0.82 (95% CI, 0.55 to 1.22)	This work was funded by a grant from UCB pharmaceuticals. KL Winthrop's work on this manuscript

Authors, Year Country Risk of Bias	Drug(s)	Sample Time Frame, Data Source	N	Population Characteristics	Harms	Funder
						was funded by AHRQ grant
Wolfe et al., 2004[72] USA High	• Etanercept • Infliximab • Non-TNF-α Inhibitors	National Databank for Rheumatic Diseases	Total = 13,171 Etanercept = 1,525 Infliximab = 4,152 Non-TNF-α Inhibitors = 7,339	Adults with RA	Heart failure (all participants): Infliximab vs. Non-TNF-α Inhibitors: aIR −1.4% (95% CI, −2.2% to −0.6%) Etanercept vs. Non-TNF-α Inhibitors: aIR −0.5% (−1.5% to 0.4%) Heart failure (n persons without any history of cardiovascular disease): Infliximab vs. Non-TNF-α Inhibitors: aIR -0.1% (95% CI, -0.1% to -0.0%) Etanercept vs. Non-TNF-α Inhibitors: aIR 0% (-0.0% to 0.1%)	NR
Xie et al., 2016[73] Canada Moderate	• Any TNF-α inhibitors (data presented for adalimumab, Etanercept, Infliximab) • Abatacept • Rituximab • Tocilizumab • Tofacitinib	Medicare (2006–2013) MarketScan (2010–2014)	Total = 167,113 Adalimumab = 34,787 Etanercept = 35,076 Infliximab = 28,722 Abatacept = 31,214 Rituximab = 4,392 Tocilizumab = 11,705 Tofacitinib = 4,755 Leftover: other TNF inhibitors, not reported separately	Adults with >=2 physician billing diagnoses for RA (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] 714.0, 714.2, 714.81).	Gastrointestinal perforation: - Reference Abatacept vs. any TNF-α inhibitors: aHR 1.44 (95% CI, 0.92 to 2.26) Rituximab vs. any TNF-α inhibitors: aHR 0.93 (95% CI, 0.22 to 4.00) Tocilizumab vs. any TNF-α inhibitors: 2.51 (95% CI, 1.31 to 4.80) Tofacitinib vs. any TNF-α inhibitors: aHR 1.94 (95% CI, 0.49 to 7.65)	NR

Authors, Year Country Risk of Bias	Drug(s)	Sample Time Frame, Data Source	N	Population Characteristics	Harms	Funder
Yun et al., 2016[75] USA Low	• Abatacept • Adalimumab • Certolizumab • Pegol • Etanercept • Golimumab • Infliximab • Rituximab • Tocilizumab	2006-2011 Medicare data	n = 189,326 final eligible cohort: 31,801 new biologic episodes among 23,784 unique RA patients	Female: more than 80% Age: 60.4 to 66.8 years	Infections requiring hospitalization: Adalimumab vs. abatacept: aHR 1.08 (95% CI, 0.93 to 1.25) Certolizumab pegol vs. abatacept: aHR 1.07 (95% CI, 0.86 to 1.32) Etanercept vs abatacept: aHR 1.24 (95% CI, 1.07 to 1.45) Golimumab vs. abatacept: aHR 1.14 (95% CI, 0.90 to 1.44) Infliximab vs. abatacept: aHR 1.39 (95% CI, 1.21 to 1.60) Rituximab vs. abatacept: aHR 1.36 (95% CI, 1.21 to 1.53) Tocilizumab vs. abatacept: 1.10 (95% CI, 0.89 to 1.34).	AHRQ Research grants and/or consulting for unrelated work with Amgen, Abbott, BMA, Celgene, Centocor, CORRONA, Crescendo, Genentech, Janssen, Pfizer, Roche, UCB, Shire, Takeda, AstraZeneca, Immune Pharmaceuticals, AbbVie, Prometheus, Nestel, Lilly, Roche, Astellas, Merck, Novartis
Yun et al., 2015[74] USA Low	• Abatacept • Adalimumab • Etanercept • Infliximab • Rituximab	2006-2010 Medicare data	N = 10,183 patients with 10,794 index hospitalization episodes	Patients with RA and an 'index hospitalization' with an infection while receiving an anti-TNF therapy.	Infections requiring hospitalization Abatacept vs. Infliximab: aIR 0.80 (95% CI, 0.64 to 0.99); *P* = .048 Abatacept vs. Adalimumab: aIR 0.88 (95% CI, 0.68 to 1.12); *P* > .05 Abatacept vs. Etanercept: aIR 0.97 (95% CI, 0.76 to 1.23); *P* > .05	AHRQ; R01 HS018517

Authors, Year Country Risk of Bias	Drug(s)	Sample Time Frame, Data Source	N	Population Characteristics	Harms	Funder
					Abatacept vs. Rituximab: aIR 0.93 (95% CI, 0.64 to 1.36); *P* > .05 Rituximab vs. Infliximab: aIR 0.87 (95% CI, 0.63 to 1.20); *P* > .05 Rituximab vs. Adalimumab: aIR 0.94 (95% CI, 0.67 to 1.32); *P* > .05 Rituximab vs. Etanercept: aIR 1.04 (95% CI, 0.74 to 1.46); *P* > .05 Etanercept vs. Infliximab: aIR 0.83 (95% CI, 0.72 to 0.97); *P* = .013 Etanercept vs. Adalimumab: aIR 0.91 (95% CI, 0.76 to 1.08); P > .05 Adalimumab vs. Infliximab: aIR 0.92 (95% CI, 0.79 to 1.09); *P* > .05	
Zhang et al., 2016[76] USA Moderate	• Etanercept • Infliximab • Abatacept • Tocilizumab • Rituximab • Golimumab • Certolizumab • Adalimumab	January 2006 to December 2012	N = 47,193	Age: 64 (SD, 13) Gender: 85% women	Acute myocardial infarction: Tocilizumab vs abatacept: aHR: 0.87, (95% CI, 0.51 to 1.49) Rituximab vs abatacept: aHR: 1.06 (95% CI, 0.80 to 1.42) Infliximab vs abatacept: aHR: 1.30 (95% CI, 1.03 to 1.64) Golimumab vs abatacept: aHR: 1.08 (95% CI, 0.55 to 2.12) Etanercept vs abatacept: aHR: 1.33 (95% CI, 1.01 to 1.76) Certolizumab vs abatacept: aHR: 1.21 (9% CI, 0.75 to 1.97) Adalimumab vs abatacept: aHR: 1.23 (95% CI, 0.92 to 1.65) Composite coronary heart disease outcome (AMI, percutaneous coronary intervention or coronary artery bypass grafting):	NR

Authors, Year Country Risk of Bias	Drug(s)	Sample Time Frame, Data Source	N	Population Characteristics	Harms	Funder
					Tocilizumab vs abatacept: aHR: 0.64 (95% CI, 0.40 to 1.01) Rituximab vs abatacept: aHR: 0.94 (95% CI, 0.75 to 1.17) Infliximab vs abatacept: aHR: 1.07 (95% CI, 0.90 to 1.28) Golimumab vs abatacept: aHR: 0.77 (95% CI, 0.43 to 1.38) Etanercept vs abatacept: aHR: 1.04 (95% CI, 0.83 to 1.29) Certolizumab vs abatacept: aHR: 0.79 (95% CI, 0.52 to 1.22) Adalimumab vs abatacept: aHR: 1.00 (95% CI, 0.80 to 1.26) Composite coronary heart disease outcome (AMI, percutaneous coronary intervention or coronary artery bypass grafting) Etanercept: 140 events; crude IR per 1,000 pys, 12.09 (95% CI 10.24 to 14.26) Infliximab: 280 events; crude IR per 1,000 pys,14.46 (95% CI, 12.86 to 16.26)	

Abbreviations. AHRQ: Agency for Healthcare Research and Quality; AMI: acute myocardial infarction; BSRB: British Society for Rheumatology Biologics Register; CI: confidence interval; DMARD: Disease-Modifying Antirheumatic Drug; FDA: Food and Drug Administration; HPV: human papillomavirus; aHR: adjusted hazard ratio; ICD: International Classification of Disease; (a)IR: (adjusted) incidence rate; N: number; NPR: National Patient Register; NR: not reported; P: *probability value; pys: patient-years; RA: rheumatoid arthritis; aRR: risk ratio; TIM: targeted immune modulator; TNF: tumor necrosis factor.*

Appendix C. Evidence Grade Profiles

Table C1. Evidence Profile of Comparisons of TIMs for Treatment of Rheumatoid Arthritis: First-line Treatments

Number of Studies / Number of Participants	Design	Risk of Bias	Consistency	Directness	Precision	Magnitude of Effect	Certainty of Evidence
Abatacept vs. adalimumab							
Clinical improvement (ACR50 response at 48 weeks)							
1 study[43] / 646	Open-label RCT	Moderate	NA	Direct	Imprecise	Similar between groups (46% vs. 46%)	Low[a,c]
Disease remission (ACR70 response at 48 weeks)							
1 study[43] / 646	Open-label RCT	Moderate	NA	Direct	Imprecise	Similar between groups (29% vs. 26%)	Low[a,c]
Overall AEs (at 48 weeks)							
1 study[43] / 646	Open-label RCT	Moderate	NA	Direct	Imprecise	Similar between groups (88% vs. 86%)	Low[a,c]
SAEs (at 48 weeks)							
1 study[43] / 646	Open-label RCT	Moderate	NA	Direct	Imprecise	Similar between groups (10% vs. 9%)	Very low[b,c]
Abatacept vs. certolizumab pegol							
Clinical improvement (EULAR response at 24 weeks)							
1 study[18] / 407	Open-label RCT	Low	NA	Direct	Imprecise	Similar between groups (85% vs. 87%)	Moderate[a]
Disease remission (CDAI at 24 weeks)							
1 study[18] / 407	Open-label RCT	Low	NA	Direct	Imprecise	Similar between groups (56% vs. 53%)	Moderate[a]
Overall AEs (at 24 weeks)							
1 study[18] / 407	Open-label RCT	Low	NA	Direct	Imprecise	Similar between groups (80 vs. 83%; *P* value NR)	Moderate[a]
SAEs (at 24 weeks)							
1 study[18] / 407	Open-label RCT	Low	NA	Direct	Imprecise	Similar between groups (5% vs. 8%; *P* value NR)	Low[b]
Abatacept vs. infliximab							
Clinical improvement (ACR50 response at 24 weeks)							
1 study[44] / 321 (431 including placebo)	RCT	Moderate	NA	Direct	Imprecise	Similar between groups (40% vs. 37%)	Low[b]
Disease remission (ACR70 response at 24 weeks)							
1 study[44] / 321	RCT	Moderate	NA	Direct	Imprecise	Similar between groups (21% vs. 24%)	Low[b]

Number of Studies / Number of Participants	Design	Risk of Bias	Consistency	Directness	Precision	Magnitude of Effect	Certainty of Evidence
(431 including placebo)							
Overall AEs (at 24 weeks)							
1 study[44] / 321 (431 including placebo)	RCT	Moderate	NA	Direct	Imprecise	Similar between groups (83% vs. 85%)	Moderate[a]
SAEs (at 24 weeks)							
1 study[44] / 321 (431 including placebo)	RCT	Moderate	NA	Direct	Imprecise	Lower proportion of SAEs with abatacept than infliximab (5% vs. 12%)	Low[b]
Abatacept vs. tocilizumab							
Clinical improvement (EULAR response at 24 weeks)							
1 study[18] / 392	Pragmatic open-label RCT	Low	NA	Direct	Imprecise	Similar between groups (85% vs. 82%)	Moderate[a]
Disease remission (CDAI at 24 weeks)							
1 study[18] / 392	Pragmatic open-label RCT	Low	NA	Direct	Imprecise	Similar between groups (56% vs. 49%)	Moderate[a]
Overall AEs (at 24 weeks)							
1 study[18] / 392	Pragmatic open-label RCT	Low	Consistent	Direct	Imprecise	Lower proportion of overall AE for abatacept than tocilizumab (80% vs. 95%; *P* value NR)	Moderate[a]
SAEs (at 24 weeks)							
1 study[18] / 392	Pragmatic open-label RCT	Low	Consistent	Direct	Imprecise	Similar between groups (5% vs. 5%)	Low[b]
Adalimumab vs. baricitinib							
Clinical improvement (ACR20 response at 12 weeks)							
1 study[29] / 817 (1,307 including placebo)	RCT	Moderate	NA	Direct	Precise	Lower proportion of response with adalimumab than baricitinib (61% vs. 70%)	High
Disease remission (SDAI < 3.3 at 12 weeks)							
1 study[29] / 817 (1,307 including placebo)	RCT	Moderate	NA	Direct	Imprecise	Similar between groups (8% vs. 7%)	Low[b]

Number of Studies / Number of Participants	Design	Risk of Bias	Consistency	Directness	Precision	Magnitude of Effect	Certainty of Evidence
Overall AEs (at 52 weeks)							
1 study[29] / 817 (1,307 including placebo)	RCT	Moderate	NA	Direct	Precise	Similar between groups (77% vs. 79%)	High
SAEs (at 52 weeks)							
1 study[29] / 817 (1,307 including placebo)	RCT	Moderate	NA	Direct	Imprecise	Lower proportion of SAEs events with adalimumab than baricitinib (4% vs. 8%)	Low[b]
Adalimumab vs. certolizumab pegol							
Clinical improvement (ACR20 response at 12 weeks)							
1 study[45] / 915	RCT	Moderate	NA	Direct	Precise	Similar between groups (71% vs. 69%)	High
Disease remission							
1 study[45] / 915	RCT	Moderate				Similar but data not reported	NA
Overall AEs (at 12 weeks)							
1 study[45] / 915	RCT	Moderate	NA	Direct	Precise	Similar between groups (74% vs. 75%)	High
SAEs (at 12 weeks)							
1 study[45] / 915	RCT	Moderate	NA	Direct	Imprecise	Similar between groups (11% vs. 13%)	Low[b]
Adalimumab vs. etanercept							
Clinical improvement (improvements on the DAS28-ESR at 24 weeks)							
2 studies[46,47] / 190	Open-label RCT	High	Consistent	Direct	Imprecise	Similar between groups (-2.12 vs. -2.84)	Very low[b,c]
SAEs (at 48 weeks)							
1 study[46] / 125	Open-label RCT	High	NA	Direct	Imprecise	Similar between groups (10% vs. 12%)	Very low[b,c]
Adalimumab vs. sarilumab							
Quality of life (SF-36 at 24 weeks)							
1 study[48] / 369	RCT	Moderate	NA	Direct	Imprecise	Smaller improvements for adalimumab than sarilumab (6.09 vs. 8.75)	Moderate[a]
Clinical improvement (ACR50 at 24 weeks)							
1 study[48] / 369	RCT	Moderate	NA	Direct	Imprecise	Lower proportion of response with adalimumab than sarilumab (30% vs. 46%)	Moderate[a]

Number of Studies / Number of Participants	Design	Risk of Bias	Consistency	Directness	Precision	Magnitude of Effect	Certainty of Evidence
Disease remission (CDAI at 24 weeks)							
1 study[48] / 369	RCT	Moderate	NA	Direct	Imprecise	Lower proportion of remission with adalimumab than sarilumab (3% vs. 7%)	Low[b]
Overall AEs (at 24 weeks)							
1 study[48] / 369	RCT	Moderate	NA	Direct	Imprecise	Similar between groups (64% vs. 64%)	Moderate[a]
SAEs (at 24 weeks)							
1 study[48] / 369	RCT	Moderate	NA	Direct	Imprecise	Similar between groups (7% vs. 5%)	Low[b]
Adalimumab vs. tocilizumab							
Quality of life (SF-36 at 24 weeks)							
1 study [49] / 326	RCT	Moderate	NA	Indirect	Imprecise	Similar between groups (7.6 vs. 9.2)	Low[a,d]
Clinical improvement (ACR50 at 24 weeks)							
2 studies[47,49] / 369	Open-label RCT / RCT	Moderate	Consistent	Indirect	Imprecise	Lower proportion of response with adalimumab than tocilizumab (28% vs. 47%)	Low[a,d]
Disease remission (ACR70 at 24 weeks)							
2 studies[47,49] / 369	Open-label RCT / RCT	Moderate	Consistent	Indirect	Imprecise	Lower proportion of remission with adalimumab than tocilizumab (18% vs. 33%)	Low[a,d]
Overall AEs (at 24 weeks)							
1 study[49] / 326	RCT	Moderate	NA	Indirect	Imprecise	Similar between groups (83% vs. 82%)	Low[a,d]
SAEs (at 24 weeks)							
1 study[49] / 326	RCT	Moderate	NA	Indirect	Imprecise	Similar between groups (10% vs. 12%)	Low[a,d]
Adalimumab vs. tofacitinib							
Clinical improvement (ACR50 at 24 weeks)							
3 studies[50-52] / 2,247	RCT	Moderate	Consistent	Direct	Precise	Similar between groups (44% vs. 46%)	High
Disease remission (ACR70 at 24 weeks)							
2 studies[50,52] / 1,863	RCT	Moderate	Consistent	Direct	Precise	Similar between groups (28% vs. 31%)	High

Number of Studies / Number of Participants	Design	Risk of Bias	Consistency	Directness	Precision	Magnitude of Effect	Certainty of Evidence
Functional capacity (HAQ-DI change from baseline at 24 weeks)							
1 study[78] / 1,146	RCT	Moderate	NA	Direct	Precise	Similar between groups (HAQ-DI −0.54 vs. −0.58)	High
Overall AEs (at 12, 24 and 48 weeks)							
3 studies[50-52] / 2,247	RCT	Moderate	NA	Direct	Precise	Similar between groups (60% vs. 58%)	High
SAEs (at 12, 24, and 48 weeks)							
3 studies[50-52] / 2,247	RCT	Moderate	NA	Direct	Imprecise	Similar between groups (5% vs. 6%)	Moderate[a]
Adalimumab vs. upadacitinib							
Quality of life and functional capacity (SF-36, HAQ-DI)							
1 study[30,77] / 978 (1,629 with placebo)	RCT	Moderate	NA	Direct	Precise	Less improvement with adalimumab than upadacitinib (HAQ-DI −0.51 vs. −0.61)	High
Clinical improvement (ACR50 response at 12 weeks)							
1 study[30] / 978 (1,629 with placebo)	RCT	Moderate	NA	Direct	Precise	Lower proportion of response with adalimumab than upadacitinib (29% vs. 45%)	High
Disease remission (DAS28 < 2.6 at 12 weeks)							
1 study[30] / 978 (1,629 with placebo)	RCT	Moderate	NA	Direct	Precise	Lower proportion of remission with adalimumab than upadacitinib (18% vs. 29%)	High
Overall AEs (at 12 weeks)							
1 study[30] / 978 (1,629 with placebo)	RCT	Moderate	NA	Direct	Precise	Similar between groups (60% vs. 64%)	High
SAEs (at 12 weeks)							
1 study[30] / 978 (1,629 with placebo)	RCT	Moderate	NA	Direct	Imprecise	Similar between groups (4% vs. 4%)	Low[b]
Anakinra vs. TNF-α inhibitors							
Clinical improvement (EULAR response at 24 weeks)							
1 study[21] / 39	Open-label RCT	High	NA	Direct	Imprecise	Higher proportion of clinical improvement with anakinra than TNF-α inhibitors (95% vs. 63%; *P* value NR)	Very low[b,c]

Number of Studies / Number of Participants	Design	Risk of Bias	Consistency	Directness	Precision	Magnitude of Effect	Certainty of Evidence
Disease remission (EULAR remission at 24 weeks)							
1 study[21] / 39	Open-label RCT	High	NA	Direct	Imprecise	Higher proportion of remission with anakinra than TNF-α Inhibitors (50% vs. 25%; *P* value NR)	Very low[b,c]
SAEs (at 24 weeks)							
1 study[21] / 39	Open-label RCT	High	NA	Direct	Imprecise	Similar between groups (0% vs. 0%)	Very low[b,c]
Certolizumab pegol vs. tocilizumab							
Clinical improvement (EULAR response at 24 weeks)							
1 study[18] / 391	Pragmatic open-label RCT	Low	NA	Direct	Imprecise	Similar between groups (86% vs. 82%; *P* value NR)	Moderate[a]
Disease remission (CDAI at 24 weeks)							
1 study[18] / 391	Pragmatic open-label RCT	Low	NA	Direct	Imprecise	Similar between groups (53% vs. 49%; *P* value NR)	Moderate[a]
Overall AEs at 24 weeks							
1 study[18] / 391	Pragmatic open-label RCT	Low	NA	Direct	Imprecise	Lower proportion of overall AEs for certolizumab pegol than tocilizumab (83% vs. 95%; *P* value NR)	Moderate[a]
SAEs at 24 weeks							
1 study[18] / 391	Pragmatic open-label RCT	Low	NA	Direct	Imprecise	Similar between groups (8% vs. 5%; *P* value NR)	Low[b]
Etanercept vs. infliximab							
Clinical improvement (ACR20 response at 54 weeks)							
1 study[53] / 32	Open-label RCT	High	NA	Indirect	Imprecise	Higher proportion of response for etanercept than infliximab (74% vs. 60%; *P* value NR)	Very low[b,c,e]
Etanercept vs. tocilizumab							
Clinical improvement (DAS28-ESR at 24 weeks)							
1 study[47] / 43	Open-label RCT	High	NA	Direct	Imprecise	Similar between groups (−2.84 vs. −2.10)	Very low[b,c]

Number of Studies / Number of Participants	Design	Risk of Bias	Consistency	Directness	Precision	Magnitude of Effect	Certainty of Evidence
SAEs at 24 weeks							
1 study[31] / 3,080	Open-label RCT	Moderate	NA	Direct	Imprecise	Similar between groups (23% vs. 27%)	Moderate[c]
Combination therapies (etanercept + abatacept vs. etanercept; etanercept + anakinra vs. etanercept)							
Clinical improvement (ACR50 response at 24 and 52 weeks)							
2 studies[54,55] / 365	RCT	Moderate	Consistent	Direct	Imprecise	No additional clinical benefit of combination therapy vs. monotherapy	Moderate[a]
Overall AEs at 24 and 52 weeks							
2 studies[54,55] / 365	RCT	Moderate	Consistent	Direct	Imprecise	Similar between groups (94% vs. 90%)	Moderate[a]
SAEs at 24 and 52 weeks							
2 studies[54,55] / 365	RCT	Moderate	Consistent	Direct	Imprecise	Higher proportion of SAEs for combination of etanercept and abatacept or anakinra than etanercept alone (11% vs. 3%)	Low[b]

Notes. [a] downgraded 1 level for imprecision; [b] Downgraded 2 levels for very serious imprecision; [c] Downgraded 1 level for RoB; [d] Downgraded for indirectness because dosage of tocilizumab was higher than FDA-approved; [e] Downgraded for indirectness because no dose adjustments were allowed for infliximab.
Abbreviations. ACR20/50/70: American College of Radiology, number refers to percentage improvement; AE: adverse event; CDAI: Clinical Disease Activity Index; DAS28: 28-joint Disease Activity Score; DAS28-ESR: 28-joint Disease Activity Score using erythrocyte sedimentation rate; EULAR: European League Against Rheumatism; FDA: US Food and Drug Administration; HAQ-DI: Health Assessment Questionnaire – Disability Index; NA: not applicable; RCT: randomized controlled trial; SAE: serious adverse event; SDAI: Simplified Disease Activity Index; SF-36: 36-item Short Form Health Survey; TIM: targeted immune modulator; vs.: versus.

Table C2. Evidence Profile of Comparisons of TIMs for Treatment of Rheumatoid Arthritis: Second-line Treatments

Number of Studies / Number of Participants	Design	Risk of Bias	Consistency	Directness	Precision	Magnitude of Effect	Quality of Evidence
Abatacept vs. TNF-α inhibitors							
Quality of life (SF-36 at 52 weeks)							
1 study[56] / 93	Open-label RCT	High	NA	Direct	Imprecise	Similar between groups (data NR)	Very low[a,b]
Clinical improvement (DAS28 at 52 weeks)							
2 studies[42,56] / 176	Open-label RCT	High	NA	Direct	Imprecise	Similar between groups (difference -0.27 units)	Low[a,b]
Abatacept vs. rituximab							
Quality of life (SF-36 at 52 weeks)							
1 study[56] / 93	RCT	High	NA	Direct	Imprecise	Similar between groups (data NR)	Very low[a,b]
Clinical improvement (DAS28 at 24 weeks)							
2 studies[42,56] / 174	RCT	High	NA	Direct	Imprecise	Similar between groups (difference -0.40 units)[c]	Low[a,d]
Overall AEs (at 48 and 52 weeks)							
2 studies[42,56] / 174	RCT	Moderate	NA	Direct	Imprecise	Similar between groups (56% vs. 54%)	Low[a,d]
SAEs (at 48 weeks)							
1 study[42] / 81	Open-label RCT	High	NA	Direct	Imprecise	Similar between groups (10% vs. 10%)	Very low[a,b]
Abatacept vs. tocilizumab							
Clinical improvement (DAS28-ESR at 24 weeks)							
1 study[32] / 132	Open-label RCT	High	NA	Direct	Imprecise	Similar between groups (2.8 vs. 2.5; P = .06)	Low[a,d]
Functional capacity (HAQ-DI score at 24 weeks)							
1 study[32] / 132	Open-label RCT	High	NA	Direct	Imprecise	Similar between groups (1.01 vs. 0.89; P = .56)	Low[a,d]
Overall AEs (at 24 weeks)							
1 study[32] / 132	Open-label RCT	High	NA	Direct	Imprecise	Lower proportion of overall AEs for abatacept than tocilizumab (28% vs.	Low[a,d]

Number of Studies / Number of Participants	Design	Risk of Bias	Consistency	Directness	Precision	Magnitude of Effect	Quality of Evidence
						60%; *P* value NR)	
SAEs (at 24 weeks)							
1 study[32] / 132	Open-label RCT	High	NA	Direct	Imprecise	Similar between groups (6% vs. 15%; *P* value NR)	Very low[a,b]
Abatacept vs. upadacitinib							
Clinical improvement (DAS28-CRP at 24 weeks)							
1 study[19] / 612	RCT	Low	NA	Direct	Precise	Greater clinical improvement with upadacitinib than abatacept (mean difference −0.52, 95% CI, −0.69 to −0.35)	High
Disease remission (DAS28-CRP remission at 24 weeks)							
1 study[19] / 612	RCT	Low	NA	Direct	Imprecise	Higher proportion of remission with upadacitinib than abatacept (12% vs. 28%; *P* value NR)	Moderate[d]
Overall AEs (at 24 weeks)							
1 study[19] / 612	RCT	Low	NA	Direct	Imprecise	Similar between groups (61% vs. 69%; *P* value NR)	Moderate[d]
SAEs (at 24 weeks)							
1 study[19] / 612	RCT	Low	NA	Direct	Imprecise	Similar between groups (2% vs. 3%; *P* value NR)	Low[b]
Rituximab vs. tocilizumab							
Clinical improvement (CDAI 50% improvement at 16 weeks)							
1 study[17] / 164	Open-label RCT	High	NA	Direct	Imprecise	Similar between groups (56% vs. 45%; *P* value NR)	Very low[a,b]
Tocilizumab vs. sarilumab							
Overall AEs (at 24 weeks)							
1 study[36] / 153	RCT	High	NA	Direct	Imprecise	Similar between groups (67% vs. 71%; *P* value NR)	Low[a,d]

Number of Studies / Number of Participants	Design	Risk of Bias	Consistency	Directness	Precision	Magnitude of Effect	Quality of Evidence
SAEs (at 24 weeks)							
1 study[36] / 153	RCT	High	NA	Direct	Imprecise	Similar between groups (7% vs. 6%; *P* value NR)	Very low[a,b]
TNF-α inhibitors (adalimumab, certolizumab pegol, etanercept, infliximab, golimumab) vs. other TIMs (abatacept, rituximab, tocilizumab)							
Clinical improvement (EULAR response at 24 weeks)							
1 study[57] / 300	Open-label RCT	Moderate	NA	Direct	Imprecise	Higher proportion of response with non-TNF-α inhibitors than TNF-α inhibitors (OR, 2.06; 95% CI, 1.27 to 3.37)	Low[a,d]
Disease remission (DAS28-ESR < 2.6 at 52 weeks)							
1 study[57] / 300	RCT	Moderate	NA	Direct	Imprecise	Higher proportion of remission with non-TNF- α inhibitors than TNF-α inhibitors (27% vs. 14%, P < .01)	Low[a,d]
Combination therapies (rituximab + adalimumab or etanercept)							
Clinical improvement (ACR50 response at 24 weeks)							
1 study[59] / 54	RCT	Moderate	NA	Direct	Imprecise	Higher proportion of response for combination of rituximab with TNF-α inhibitors than TNF-α inhibitor maintenance (12% vs. 6%, *P* value NR)	Low[b]
Disease remission (DAS28-ESR < 2.6 at 24 weeks)							
1 study[59] / 54	RCT	Moderate	NA	Direct	Imprecise	Higher proportion of remission for combination of rituximab with TNF-α inhibitors than TNF-α inhibitor maintenance (18% vs. 6%, *P* value NR)	Low[b]
Overall AEs (at 24 weeks)							
1 study[59] / 54	RCT	Moderate	NA	Direct	Imprecise	Similar between groups (94% vs. 83%; *P* value NR)	Low[b]
SAEs (at 24 weeks)							
1 study[59] / 54	RCT	Moderate	NA	Direct	Imprecise	Higher proportion of SAEs for combination of rituximab with TNF-α inhibitors than TNF-α inhibitor	Low[b]

Number of Studies / Number of Participants	Design	Risk of Bias	Consistency	Directness	Precision	Magnitude of Effect	Quality of Evidence
						maintenance (6% vs. 0%; *P* value NR)	
Combination therapies (abatacept + other TIM [adalimumab, anakinra, etanercept, or infliximab] vs. another TIM alone)							
Functional capacity (HAQ-DI change from baseline at 52 weeks)							
1 study[58] / 167	RCT	Moderate	NA	Direct	Imprecise	Similar between groups (-0.33 vs.-0.23; *P* value NR)	Low[b]
Overall AEs (at 52 weeks)							
1 study[58] / 167	RCT	Moderate	NA	Direct	Imprecise	Similar between groups (95% vs.89%; *P* value NR)	Low[b]
SAEs (at 52 weeks)							
1 study[58] / 167	RCT	Moderate	NA	Direct	Imprecise	Similar between groups (22% vs. 13%; *P* value NR)	Low[b]

Notes. [a] Downgraded 1 level for RoB; [b] Downgraded 2 levels for very serious imprecision; [c] Numbers based on Moderate-quality trial; [d] Downgraded 1 level for imprecision. Abbreviations. ACR20/50/70: American College of Radiology, number refers to percentage improvement; AE: adverse event; CI: confidence interval; DAS28: 28-joint Disease Activity Score; DAS28-ESR: 28-joint Disease Activity Score using erythrocyte sedimentation rate; EULAR: European League Against Rheumatism; mg: milligram; NA: not applicable; NR: not reported; OR: odds ratio; P: probability value; RCT: randomized controlled trial; SAE: serious adverse event; SF-36: 36-item Short Form Health Survey; TIM: targeted immune modulator; TNF-α: tumor necrosis factor alpha; vs.: versus.

Table C3. Evidence Profile for Pipeline TIMs for Treatment of Rheumatoid Arthritis

Number of Studies / Number of Participants	Design	Risk of Bias	Consistency	Directness	Precision	Magnitude of Effect	Certainty of Evidence
Peficitinib vs. placebo							
Clinical improvement (ACR20 response at 12 weeks)							
5 studies[26-28,40,41] / 1,977	RCT	Moderate	Consistent	Direct	Precise	Higher proportion of response for peficitinib than placebo (peficitinib 100 mg: 59% and 58%; peficitinib 150 mg: 64% and 75%; placebo: 22% and 31%; P < .001 for all comparisons with placebo)[a]	High
Disease remission (DAS28-CRP < 2.6)							
4 studies[26,27,40,41] / 1,598	RCT	Moderate	Consistent	Direct	Precise	Higher proportion of remission with peficitinib than placebo (peficitinib 100 mg: 25% and 31%; peficitinib 150 mg: 35% and 35%; placebo: 8% and 5%, P < .001 for all comparisons with placebo)b	High
Overall AEs (at 12 weeks)							
5 studies[26-28,40,41] / 1,977	RCT	Moderate	Consistent	Direct	Imprecise	No difference between groups (peficitinib 100 mg: 51% and 57%; peficitinib 150 mg: 60% and 54%; placebo: 49% and 54%; *P* value NR)b.	Moderate[b]
SAEs (at 12 weeks)							
5 studies[26-28,40,41] / 1,977	RCT	Moderate	Consistent	Direct	Imprecise	No difference between groups (peficitinib 100 mg: 3% in both studies; peficitinib 150 mg: 2% in both studies; placebo: 2% and 4%; *P* value NR)b.	Moderate[b]
Peficitinib vs. etanercept							
Clinical improvement (ACR20 response at 12 weeks)							
1 study[40] / 509	RCT	Moderate	Consistent	Direct	Precise	Lower proportion of response with peficitinib than etanercept (peficitinib 100 mg: 58%; peficitinib 150 mg: 75%; etanercept: 84%, *P* value NR)	Moderate[d]
Disease remission (DAS28-CRP < 2.6)							
1 study[40] /509	RCT	Moderate	Consistent	Direct	Precise	Lower proportion of remission with peficitinib than etanercept (peficitinib 100 mg: 25%; peficitinib 150 mg: 35%; etanercept: 46%, *P* value NR).	Moderate[d]

Number of Studies / Number of Participants	Design	Risk of Bias	Consistency	Directness	Precision	Magnitude of Effect	Certainty of Evidence
Overall AEs							
1 study[40] / 509	RCT	Moderate	Consistent	Direct	Imprecise	No difference between groups (peficitinib 100 mg: 57%; peficitinib 150 mg: 54%; etanercept: 60% (*P* value NR).	Low[b,d]
SAEs							
1 study[40] / 509	RCT	Moderate	Consistent	Direct	Imprecise	No difference between groups (peficitinib 100 mg: 7%; peficitinib 150 mg: 8%; etanercept: 9%; *P* value NR).	Low[b,d]
Combination therapy (certolizumab pegol + bimekizumab vs. certolizumab pegol)							
Clinical improvement (DAS28-CRP < 3.2 at 12 weeks)							
1 study[39] / 79	RCT	Moderate	NA	Direct	Imprecise	Higher proportion of response for combination therapy than TNF-α inhibitor maintenance therapy (46% vs. 29%, *P* value NR)	Low[c]
Disease remission (DAS28-CRP < 2.6)							
1 study[39] / 79	RCT	Moderate	NA	Direct	Imprecise	Higher proportion of remission with combination therapy than TNF-α inhibitor maintenance therapy (26% vs. 8%, *P* value NR)	Low[c]
Overall AEs							
1 study[39] / 79	RCT	Moderate	NA	Direct	Imprecise	Higher proportion of overall AEs for combination therapy than TNF-α inhibitor maintenance therapy (79% vs. 59%, *P* value NR)	Low[c]
SAEs							
1 study[39] / 79	RCT	Moderate	NA	Direct	Imprecise	Lower proportion of SAEs for combination therapy than TNF-α inhibitor maintenance therapy (4% vs. 11%, *P* value NR)	Low[c]

Notes.;[a] Data based on phase III studies; [b] Downgraded 1 level for imprecision; [c] Downgraded 2 levels for very serious imprecision; [d] Downgraded 1 level for RoB. Abbreviations. ACR20/50/70: American College of Radiology, number refers to percentage improvement; AE: adverse event; DAS28: 28-joint Disease Activity Score; DAS28-CRP: 28-joint Disease Activity Score using C-reactive protein; mg: milligram; NA: not applicable; NR: not reported; P: probability value; RCT: randomized controlled trial; SAE: serious adverse event; SF-36: 36-item Short Form Health Survey; TIM: targeted immune modulator; TNF-α: tumor necrosis factor alpha; vs.: versus.

Table C4: Evidence Profile of Comparisons of TIMs for Treatment of Ankylosing Spondylitis

Number of Studies / Number of Participants	Design	Risk of Bias	Consistency	Directness	Precision	Magnitude of Effect	Certainty of Evidence
Etanercept vs. infliximab							
Clinical improvement (BASDAI at 12 weeks)							
1 RCT[25] / 50	RCT	High	NA	Direct	Imprecise	Smaller improvements for etanercept than infliximab (4.8 vs. 5.9; *P* < .005)	Very low[a,b]

Notes. [a] *Downgraded 1 level for RoB;* [b] *Downgraded 2 levels for very serious imprecision.*
Abbreviations. BASDAI: Bath Ankylosing Spondylitis Activity Index; NA: not applicable; P: *probability value; RCT: randomized controlled trial; TIM: targeted immune modulator; vs.: versus.*

Table C5: Evidence Profile of Comparisons of TIMs for Treatment of Ankylosing Spondylitis (Pipeline Drugs)

Number of Studies / Number of Participants	Design	Risk of Bias	Consistency	Directness	Precision	Magnitude of Effect	Certainty of Evidence
Bimekizumab vs. placebo							
Functional ability (BASFI at 12 weeks)							
1 RCT[20] / 303	RCT	Low	NA	Direct	Imprecise	Greater improvement with bimekizumab than placebo (bimekizumab 16 mg: −1.4; bimekizumab 64 mg: −1.9; bimekizumab 160 mg: −1.7; bimekizumab 320 mg: −2.2; placebo: −0.6; *P* value NR)	Moderate[a]
Clinical improvement (BASDAI at 12 weeks)							
1 RCT[20] / 303	RCT	Low	NA	Direct	Imprecise	Greater improvements with bimekizumab than placebo (bimekizumab 16 mg: −1.7; bimekizumab 64 mg: −2.7; bimekizumab 160 mg: −2.5; bimekizumab 320 mg: −2.9; placebo: −1.0; *P* value NR)	Moderate[a]
Overall AEs							
1 RCT[20] / 303	RCT	Low	NA	Direct	Imprecise	Similar between groups (bimekizumab 16 mg: 43%; placebo: 43%; *P* value NR) Lower proportion of overall AE for bimekizumab 64 mg and bimekizumab 160 mg than placebo; (29% vs. 32% vs. 43%; *P* value NR) Higher proportion of overall AE for bimekizumab 320 mg than placebo (48% vs. 43%; *P* value NR)	Low[b]
SAEs							
1 RCT[20] / 116	RCT	Low	NA	Direct	Imprecise	Similar between groups (bimekizumab 64 mg: 3%; placebo: 3%; *P* value NR) Lower proportion of overall AE for bimekizumab 16 mg, bimekizumab 160 mg, and bimekizumab 320 mg than placebo; (0% vs. 2% vs. 0% vs. 3%; *P* value NR)	Low[b]

Notes. [a] *Downgraded 1 level for imprecision;* [b] *Downgraded 2 levels for very serious imprecision.*
Abbreviations. AE: adverse event; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; mg: milligram; NA: not applicable; NR: not reported; P: *probability value; RCT: randomized controlled trial; SAE: serious adverse event; SF-36: 36-item Short Form Health Survey; TIM: targeted immune modulator; vs: versus.*

Appendix D. Instruments Used to Measure Outcomes in Trials of TIMs

Table D1. Instruments Used to Measure Outcomes in Trials of TIMs for RA and Ankylosing Spondylitis

Abbreviation	Name	Condition(s) Used in	General Description	Range and Direction
ACR 20/50/70	American College of Rheumatology, numbers refer to percentage improvement	RA	Improvement is defined by ≥ 20%/50%/70% improvement in TJC and in SJC, and at least 20%/50%/70% improvement in 3 of the 5 measures: ESR or CRP; PGA of disease activity; PtGA of disease activity; patient assessment of pain; disability.	0 to 10, higher is worse
ASAS 20/40/50/70	Assessment in Ankylosing Spondylitis, numbers refer to percentage improvement	AS	Improvement of ≥ 20%/40%/50%/70% and absolute improvement of 10 units (on a scale of 0-100) in 3 of the following 4 domains: PtGA; pain; function; inflammation; absence of deterioration in the potential remaining domain, where deterioration is defined as a change for the worse of 20% and net worsening of 10 units (on a scale of 0-100).	0 to 100, higher is better
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index	AS	Six 10-cm horizontal visual analog scales to measure severity of fatigue, spinal and peripheral joint pain, localized tenderness and morning stiffness (both qualitative and quantitative).	0 to 10, lower is better
BASFI	Bath Ankylosing Spondylitis Functional Index	AS	Defining and monitoring functional ability in patients with AS.	0 to 10, lower is better
CDAI	Clinical Disease Activity Index	RA	A clinical composite index (tender and swollen joint counts and patient's and physician's global assessments of disease activity), without an acute-phase reactant, for assessing disease activity	0 to 76, lower is better
EQ-5D	European Quality of Life-5 Dimensions	RA, AS	Descriptive system of health-related quality of life states consisting of 5 dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) each of which can take 1 of 3 responses. The responses record 3 levels of severity (no problems/some or moderate problems/extreme problems) within a particular dimension.	0 to 1, higher is better
ESR	Erythrocyte sedimentation rate	RA, AS	Rate at which red blood cells precipitate in a period of 1 hour.	Ranges from 10 to 25 or more, lower is better

Abbreviation	Name	Condition(s) Used in	General Description	Range and Direction
EULAR response	European League Against Rheumatism	RA	A good response is defined as reaching a DAS of 2.4 or a DAS28 of 3.2 ("low" disease activity) in combination with an improvement > 1.2 (twice the measurement error) in DAS or DAS28. A nonresponse is defined as an improvement of 0.6, and also as an improvement of 1.2 with a DAS > 3.7 or DAS28 > 5.1 ("high" disease activity). All other possibilities are defined as a moderate response.	Lower is better
HAQ	Health Assessment Questionnaire	RA, AS	Five generic patient-centered health dimensions: (1) to avoid disability; (2) to be free of pain and discomfort; (3) to avoid adverse treatment effects; (4) to keep dollar costs of treatment low; and (5) to postpone death.	0 to 60, higher is worse
HAQ-DI	Disability Index of the Health Assessment Questionnaire	RA, AS	Patient's level of functional ability, includes questions of fine movements of the upper extremity, locomotor activities of the lower extremity, and activities that involve both upper and lower extremities. There are 20 questions in 8 categories of functioning which represent a comprehensive set of functional activities: dressing, rising, eating, walking, hygiene, reach, grip, and usual activities.	For DI, 0 to 3, lower is better
SDAI	Simple Disease Activity Index	RA	A sum of five outcome parameters (tender and swollen joint count, patient and physician global assessment of disease activity and level of C-reactive protein) used to monitor the disease activity	0 to 86, lower is better
SF−36	Medical Outcomes Study Short Form 36-item Health Survey	RA, AS	Measures the general level of wellbeing, consists of 8 domains reflecting 8 dimensions of life: • PF, Physical Functioning; • RP, Role Physical; • BP, Bodily Pain; • GH, General Health; • VT, Vitality; • SF, Social Functioning; • RE, Role Emotional; • MH, Mental Health.	0 to 100, higher is better

Abbreviations. AS: ankylosing spondylitis; cm: centimeter; CRP: C-reactive protein; DAS: Disease Activity Score; DAS28: 28-joint Disease Activity Score; ESR: erythrocyte sedimentation rate; PGA: Physician Global Assessment of Disease Activity; PtGA: Patient Global Assessment of Disease Activity; RA: rheumatoid arthritis; SJC: swollen joint count; TIM: targeted immune modulator; TJC: tender joint count.

Appendix E. Detailed Results from Network Meta-Analyses

Table E1. Indirect Comparison Results from Network Meta-analysis for Rheumatoid Arthritis[120-125]

	ABA	ADA	ANA	BAR	CTZ	ETN	GLM	IFX	RTX	SAR	TCZ	TFB	UPA
Clinical Response (ACR50)													
ABA						0.94 (0.49 to 1.77)	0.89 (0.41 to 1.88)						
ADA							1.08 (0.52 to 2.25)	1.26 (0.64 to 2.46)					
ANA	1.64 (0.68 to 3.98)	1.69 (0.73 to 4.24)											
BAR	0.83 (0.43 to 1.51)		0.50 (0.18 to 1.32)										
CTZ			0.36 (0.14 to 0.89)	0.70 (0.36 to 1.44)		1.42 (0.73 to 2.72)	1.34 (0.61 to 2.86)	1.54 (0.75 to 3.16)					
ETN			0.13 (0.01 to 1.25)	0.27 (0.03 to 2.36)			0.93 (0.49 to 1.82)						
GLM			0.62 (0.20 to 2.04)	1.24 (0.48 to 3.47)				1.16 (0.57 to 2.39)			0.82 (0.41 to 1.7)		
IFX			0.62 (0.24 to 1.52)	1.22 (0.62 to 2.47)							0.7 (0.3 to 1.38)		

	ABA	ADA	ANA	BAR	CTZ	ETN	GLM	IFX	RTX	SAR	TCZ	TFB	UPA
RTX													
SAR											1.6 (1.01 to 2.62)		
TCZ			0.44 (0.17 to 1.09)	0.86 (0.42 to 1.76)									
TFB	0.74 (0.39 to 1.37)		0.45 (0.17 to 1.18)	0.89 (0.43 to 1.91)	1.26 (0.63 to 2.50)	3.39 (0.38 to 28.1)	0.72 (0.26 to 1.87)	0.73 (0.37 to 1.46)			1.03 (0.52 to 2.15)		
UPA													
Clinical Remission													
ABA						1.19 (0.18 to 7.61)	0.71 (0.12 to 4.06)						
ADA						1.32 (0.08 to 20.5)	0.8 (0.05 to 11.3)	1.2 (0.09 to 16.4)					
ANA													
BAR													

	ABA	ADA	ANA	BAR	CTZ	ETN	GLM	IFX	RTX	SAR	TCZ	TFB	UPA
CTZ													
ETN							0.61 (0.11 to 3.06)	0.9 (0.13 to 5.87)			0.13 (0.02 to 0.65)		
GLM								1.48 (0.25 to 9.3)			0.22 (0.05 to 0.98)		
IFX											0.15 (0.02 to 0.86)		
RTX													
SAR													
TCZ													
TFB													
UPA													

	ABA	ADA	ANA	BAR	CTZ	ETN	GLM	IFX	RTX	SAR	TCZ	TFB	UPA
Overall AEs													
ABA													
ADA													
ANA													
BAR													
CTZ													
ETN	1.05 (0.68 to 1.63)	1.00 (0.64 to 1.54)			1.00 (0.68 to 1.52)								
GLM	1.00 (0.63 to 1.62)	0.96 (0.59 to 1.51)			0.96 (0.63 to 1.51)	0.96 (0.66 to 1.4)							
IFX		0.9 (0.54 to 1.39)			0.90 (0.57 to 1.4)	0.90 (0.59 to 1.31)	0.93 (0.59 to 1.40)						
RTX													

	ABA	ADA	ANA	BAR	CTZ	ETN	GLM	IFX	RTX	SAR	TCZ	TFB	UPA
SAR													
TCZ					0.85 (0.58 to 1.31)		0.90 (0.60 to 1.32)	0.95 (0.64 to 1.46)					
TFB													
UPA													
SAEs													
ABA						0.62 (0.32 to 1.07)	0.35 (0.14 to 0.78)						
ADA							0.44 (0.17 to 1.06)	0.91 (0.48 to 1.77)					
ANA													
BAR													
CTZ							1.22 (0.59 to 2.46)	0.7 (0.27 to 1.75)	1.45 (0.71 to 3)				

	ABA	ADA	ANA	BAR	CTZ	ETN	GLM	IFX	RTX	SAR	TCZ	TFB	UPA
ETN								0.57 (0.23 to 1.32)	1.19 (0.66 to 2.20)				
GLM								2.08 (0.93 to 4.95)			1.63 (0.7 to 3.86)		
IFX											0.78 (0.43 to 1.45)		
RTX													
SAR													
TCZ													
TFB				0.7 (0.3 to 1.72)									
UPA												0.84 (0.18 to 2.67)	
Discontinuation due to AEs													
ABA													

	ABA	ADA	ANA	BAR	CTZ	ETN	GLM	IFX	RTX	SAR	TCZ	TFB	UPA
ADA							1.38 (0.56 to 3.27)	0.78 (0.36 to 1.64)	0.44 (0.12 to 1.34)				
ANA													
BAR 4 mg	1.56 (0.73 to 3.30)				0.80 (0.38 to1.66)	1.25 (0.51 to 3.04)	1.29 (0.47 to 3.45)	0.73 (0.30 to 1.76)	0.43 (0.11 to 1.40)		0.96 (0.44 to 1.95)	0.86 (0.37 to 1.86)	
CTZ									0.52 (0.14 to 1.66)				
ETN	1.25 (0.55 to 2.86)				0.65 (0.28 to 1.43)		1.04 (0.35 to 2.94)	0.59 (0.22 to 1.49)	0.33 (0.08 to 1.17)				
GLM	1.21 (0.48 to 3.09)				0.62 (0.25 to 1.56)				0.32 (0.08 to 1.23)		0.74 (0.30 to 1.82)		
IFX					1.10 (0.48 to 2.50)		1.78 (0.62 to 5.05)		0.57 (0.14 to 2.02)		1.31 (0.57 to 2.90)		
RTX													
SAR													

	ABA	ADA	ANA	BAR	CTZ	ETN	GLM	IFX	RTX	SAR	TCZ	TFB	UPA
TCZ									0.44 (0.12 to 1.42)				
TFB 10 mg		1.11 (0.61 to 2.02)			0.94 (0.47 to 1.92)	1.46 (0.62 to 3.56)	1.52 (0.57 to 3.94)	0.85 (0.37 to 2.05)	0.49 (0.13 to 1.64)		1.12 (0.55 to 2.25)		1.46 (0.63 to 3.36)
UPA 15 mg					0.65 (0.30 to 1.40)	1.00 (0.41 to 2.58)	1.04 (0.37 to 2.88)	0.59 (0.24 to 1.49)	0.34 (0.09 to 1.17)		0.77 (0.36 to 1.66)		

*Notes. Row drug is vs. column drug; for OR (95% CI) or (95% CrI), ORs > 1.0 favor the row drug for efficacy measures, and ORs < 1.0 favor the row drug for safety outcomes. Values in **bold** are 95% CI values that do not include the neutral value and indicate the superiority of 1 of the alternatives. Gray cells denote no comparison needed (same drug). Green cells denote that a direct comparison is available.*

Abbreviations. ABA: abatacept; ACR50: ≥ 50% improvement in American College of Rheumatology measure; ADA: adalimumab; AE: adverse event; ANA: anakinra; BAR: baricitinib; CI: confidence interval; CrI: credible interval; CTZ: certolizumab pegol; ETN: etanercept; GLM: golimumab; IFX: infliximab; OR: odds ratio; RA: rheumatoid arthritis; RTX: rituximab; SAE: serious adverse event; SAR: sarilumab; TCZ: tocilizumab; TFB: tofacitinib; UPA: upadacitinib.

Table E2. Indirect Comparison Results From Network Meta-analysis for Ankylosing Spondylitis[126]

	ABA	ADA	ANA	BAR	CTZ	ETN	GLM	IFX	IFX-dyyb
Clinical Response (BASDAI)									
ABA									
ADA					0.08 (−1.3 to 1.5)	0.2 (−1.5 to 1.9)	−0.3 (−1.7 to 1.1)	0.5 (−1.3 to 1.7)	1.1 (−1.2 to 2.8)
ANA									
BAR									
CTZ						0.1 (−1.6 to 1.8)	−0.3 (−1.8 to 1)	0.4 (−1.4 to 1,7)	1.2 (−0.6 to 2.6)
ETN							−0.4 (−2.2 to 1.2)	0.3 (−1.7 to 1.8)	1.3 (−-0.1 to 2.6)
GLM								0.7 (−1.0 to 2)	1.6 (−0.1 to 3)
IFX									
IFX-dyyb									
Clinical Response (BASFI)									
ABA									
ADA					−0.3 (−2.1 to 1.6)	−0.3 (−2.4 to 2)	−0.4 (−1.9 to 1.3)	−0.2 (−2 to 1.6)	0.2 (−2.3 to 2.8)
ANA									

	ABA	ADA	ANA	BAR	CTZ	ETN	GLM	IFX	IFX-dyyb
BAR									
CTZ						0.01 (−2.2 to 2.2)	−0.1 −1.6 to 1.5)	0.05 (−1.8 to 1.9)	0.6 (−1.7 to 2.8)
ETN							-0.1 (−2.1 to 1.9)	0.03 (−2.2 to 2.2)	0.7 (−1.3 to 2.7)
GLM								0.1 (−1.5 to 1.7)	0.6 (−1.5 to 2.7)
IFX									
IFX-dyyb									

Notes. Table presents mean difference with 95% CrI; The columns represent the reference medication for each comparison, and the rows represent the comparators; a negative value means greater improvement by the comparator, indicating the comparator is more efficacious than the reference drug; a positive value means less improvement by the comparator, indicating the reference medication is more efficacious than the comparator. Gray cells denote no comparison needed (same drug), or no direct comparison found.
Abbreviations. BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; ABA: abatacept; ADA: adalimumab; ANA: anakinra; BAR: baricitinib; CrI: credible interval; CTZ: certolizumab; ETN: etanercept; GLM: golimumab; IFX: infliximab; IFN-dyyb: infliximab biosimilar.

Appendix F. Bibliography of Included Studies

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Appendix G. Bibliography of Excluded Studies

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Ineligible Outcome (11 studies)

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Ineligible Publication Type (7 studies)

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- Lee IP, Boey HB, Lin SH, Chang YS. Severe systemic lupus erythematosus flare after abatacept treatment. *Lupus.* 2020;29(12):1650-1651. doi: 10.1177/0961203320948963
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- Mortimer I, Bissell LA, Hensor EMA, et al. Improvement in cardiovascular biomarkers sustained at 4 years following an initial treat-to-target strategy in early rheumatoid arthritis. *Rheumatology*. 2019;58(9):1684-1686. doi: 10.1093/rheumatology/kez114
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conventional synthetic DMARDs and/or biological DMARDs: data from a local registry. *Clin Rheumatol*. 2020;19:19. doi: 10.1016/j.reuma.2020.04.011
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Ineligible Research Question (4 studies)

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- Courvoisier DS, Chatzidionysiou K, Mongin D, et al. The impact of seropositivity on the effectiveness of biologic anti-rheumatic agents: results from a collaboration of 16 registries. *Rheumatology*. 2021;60(2):820-828. doi: 10.1093/rheumatology/keaa393
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Ineligible Study Design (9 studies)

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- Pavelka K, Szekanecz Z, Damjanov N, et al. Upadacitinib versus placebo or adalimumab with background methotrexate in patients with rheumatoid arthritis and an inadequate response

to methotrexate: a subgroup analysis of a phase III randomized controlled trial in Central and Eastern European patients. *Drugs Context*. 2020;9. doi: 10.7573/dic.2020-7-5
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- Takeuchi T, Matsubara T, Atsumi T, et al. Efficacy and safety of filgotinib in Japanese patients with refractory rheumatoid arthritis: subgroup analyses of a global phase 3 study (FINCH 2). *Mod Rheumatol*. 2021:1-16. doi: 10.1080/14397595.2020.1859675
- Wei JC, Tsou HK, Leong PY, Chen CY, Huang JX. Head-to-head comparison of etanercept vs. adalimumab in the treatment of ankylosing spondylitis: an open-label randomized controlled crossover clinical trial. *Front Med (Lausanne)*. 2020;7:566160. doi: 10.3389/fmed.2020.566160

Observational Without Direct Comparison (7 studies)

- Chao WC, Wang CY, Hsu BC, et al. Factors associated with sepsis risk in immune-mediated inflammatory diseases receiving tumor necrosis factor inhibitors: a nationwide study. *Ther Adv Musculoskelet Dis*. 2020;12. doi: 10.1177/1759720X20929208
- Chatzidionysiou K, Delcoigne B, Frisell T, et al. How do we use biologics in rheumatoid arthritis patients with a history of malignancy? an assessment of treatment patterns using Scandinavian registers. *RMD Open*. 2020;6(2):09. doi: 10.1136/rmdopen-2020-001363
- Gomides APM, de Albuquerque CP, Santos ABV, et al. Real-life data of survival and reasons for discontinuation of biological disease-modifying drugs 'in' rheumatoid arthritis. *Int J Clin Pharm*. 2021;43(3):737-742. doi: 10.1007/s11096-020-01171-5
- Komel Pimenta PR, Ribeiro da Silva MR, Ribeiro Dos Santos JB, Kakehasi AM, Assis Acurcio F, Alvares-Teodoro J. Effectiveness and safety of anti-TNF therapy for ankylosing spondylitis: a real-world study. *J Comp Eff Res*. 2021;10(6):509-517. doi: 10.2217/cer-2020-0275
- Kostev K, Jacob L. Persistence and treatment-free interval in patients being prescribed biological drugs in rheumatology practices in Germany. *Eur J Clin Pharmacol*. 2019;75(5):717-722. doi: 10.1007/s00228-019-02627-y
- Paul SK, Montvida O, Best JH, Gale S, Petho-Schramm A, Sarsour K. Association of biological antirheumatic therapy with risk for type 2 diabetes: a retrospective cohort study in incident rheumatoid arthritis. *BMJ Open*. 2021;11(6):e042246. doi: 10.1136/bmjopen-2020-042246
- Rahman P, Baer P, Keystone E, et al. Long-term effectiveness and safety of infliximab, golimumab and golimumab-IV in rheumatoid arthritis patients from a Canadian prospective observational registry. *BMC Rheumatol*. 2020;4:46. doi: 10.1186/s41927-020-00145-4

Sample Size < 10,000 for Observational (9 studies)

- Barbieri MA, Cicala G, Cutroneo PM, et al. Safety Profile of Biologics Used in Rheumatology: An Italian Prospective Pharmacovigilance Study. *J Clin Med*. 2020;9(4):24. doi: 10.3390/jcm9041227 **(N = 531 participants)**
- Freitas R, Godinho F, Madeira N, et al. Safety and effectiveness of biologic disease-modifying antirheumatic drugs in older patients with rheumatoid arthritis: a prospective cohort study. *Drugs Aging*. 2020;37(12):899-907. doi: 10.1007/s40266-020-00801-x **(N = 2,401 participants)**

- Gron KL, Glintborg B, Norgaard M, et al. Overall infection risk in rheumatoid arthritis during treatment with abatacept, rituximab and tocilizumab; an observational cohort study. *Rheumatology*. 2020;59(8):1949-1956. doi: 10.1093/rheumatology/kez530 **(N = 2,716 participants)**
- Hsieh MJ, Lee CH, Tsai ML, et al. Biologic agents reduce cardiovascular events in rheumatoid arthritis not responsive to tumour necrosis factor inhibitors: a national cohort study. *Can J Cardiol*. 2020;36(11):1739-1746. doi: 10.1016/j.cjca.2020.01.003 **(N = 1,584 participants)**
- Koo BS, Lim YC, Lee MY, et al. The risk factors and incidence of major infectious diseases in patients with ankylosing spondylitis receiving tumor necrosis factor inhibitors. *Mod Rheumatol*. 2021;31(6):1192-1201. doi: 10.1080/14397595.2021.1878985 **(N = 2,515 participants)**
- Rempenault C, Lukas C, Combe B, et al. Risk of diverticulitis and gastrointestinal perforation in rheumatoid arthritis treated with tocilizumab compared to rituximab or abatacept. *Rheumatology*. 2021;16:16. doi: 10.1093/rheumatology/keab438 **(N = 4,501 participants)**
- Rotar Z, Svetina P, Tomsic M, Hocevar A, Prapotnik S. Tuberculosis among patients treated with TNF inhibitors for rheumatoid arthritis, ankylosing spondylitis and psoriatic arthritis in Slovenia: a cohort study. *BMJ Open*. 2020;10(2):e034356. doi: 10.1136/bmjopen-2019-034356 **(N = 1,355 participants)**
- Sanchez-Piedra C, Hernandez Miguel MV, Manero J, et al. Objectives and methodology of BIOBADASER phase iii. *Reumatol Clin (Engl Ed)*. 2019;15(4):229-236. doi: 10.1016/j.reuma.2017.08.001 **(N = 2,664 participants)**
- Shin A, Park EH, Dong YH, et al. Comparative risk of osteoporotic fracture among patients with rheumatoid arthritis receiving TNF inhibitors versus other biologics: a cohort study. *Osteoporos Int*. 2020;31(11):2131-2139. doi: 10.1007/s00198-020-05488-9 **(N = 3,102 participants)**

Appendix H. Excluded Observational Studies from Previous Report

Table H1. Excluded Observational Studies (N = 19 studies) From Previous Report due to Sample Size[a] or Lack of Adjusted Analysis

Studies are presented by specific serious adverse event outcomes (some studies reported more than 1 outcome of interest)

Authors, Year Registry Name, Country	Number of Participants	Follow-up	Comparison	Population	Outcome	Results	Risk of Bias
Mortality							
Listing et al., 2015[131] RABBIT, Germany	8,908	31,378 pys 42.4 months	Adalimumab or infliximab vs. etanercept	RA	Mortality	No significant differences	Low
Simard et al., 2012[132] ARTIS, Sweden	5,212	19,118 pys	Adalimumab or infliximab vs. etanercept	RA	Mortality	No significant differences	Moderate
Serious infections							
Gron et al., 2019[133] ARTIS, Sweden and DANBIO, Denmark	6,648	24 months	Abatacept vs. tocilizumab vs. rituximab	RA	Serious infections	No significant differences	High
Mori et al., 2017[134] SARABA, Japan	1,596 new treatment episodes	1,239 pys	Adalimumab, abatacept, infliximab, or tocilizumab vs. etanercept	RA	Serious infections	No significant differences	High
Aaltonen et al., 2015[135] ROB-FIN, Finland	3,532	7,875 pys	Pooled TNF-α inhibitors (adalimumab, etanercept, infliximab) vs. rituximab	RA	Serious infections	No significant differences	Low
Chiang et al., 2014[136] NHIRD, Taiwan	2,144	12 months	Adalimumab vs. etanercept	RA	Infections	Significantly higher for etanercept vs. adalimumab (aHR, 2.04; 95% CI, 1.13 to 3.61)	Low

Authors, Year Registry Name, Country	Number of Participants	Follow-up	Comparison	Population	Outcome	Results	Risk of Bias
Curtis et al., 2014[93] VHA, US	3,152	1 year	Abatacept, adalimumab, infliximab, or rituximab vs. etanercept	RA	Hospitalized bacterial infections	Significantly higher for infliximab vs. etanercept (aHR, 2.3; 95% CI, 1.3 to 4.0)	Low
Flouri et al., 2014[137] Hellenic Registry of Biologic Therapies, Greece	1,208	Median follow-up 2.9 to 3 years	Adalimumab vs. etanercept vs. infliximab	RA	Serious infections	Significantly higher for infliximab vs. adalimumab and etanercept (IR, 4.0 vs. 2.7 vs. 2.1 per 100 pys; P < .001)	Low
Chiu et al., 2014[138] NHIRD, Taiwan	2,238	NR	Adalimumab vs. etanercept	RA	Serious bacterial infections	Significantly higher for adalimumab vs. etanercept (IRR, 1.83; 95% CI, 1.19 to 2.77)	Low
Van Dartel et al., 2013[139] DREAM, Netherlands	2,356	4,832 pys	Adalimumab vs. etanercept vs. infliximab	RA	Serious infections	Significantly lower for etanercept vs. adalimumab (aHR, 1.83; 95% CI, 1.49 to 2.26) and infliximab (aHR, 2.04; 95% CI, 1.62 to 2.58)	Moderate
Johnston et al., 2013[140] SABER, US	4,332	Abatacept: 1,005 pys; adalimumab: 1,772 pys; etanercept: 1,392 pys; infliximab: 7,89 pys; rituximab: 463 pys	Abatacept vs. adalimumab vs. etanercept vs. infliximab vs. rituximab	RA	Severe infections	Significantly higher for infliximab vs. rituximab (aHR, 1.62; 95% CI, 1.03 to 2.55)	Low

Authors, Year Registry Name, Country	Number of Participants	Follow-up	Comparison	Population	Outcome	Results	Risk of Bias
Atzeni et al., 2012[141] GISEA, Italy	2,769	NR	Adalimumab vs. etanercept vs. infliximab	RA	Serious infections	Significantly higher for adalimumab vs. etanercept (aHR, 2.22; 95% CI, 1.12 to 4.42) Significantly higher for infliximab vs. etanercept (aHR, 4.92; 95% CI, 2.71 to 8.91)	Moderate
Curtis et al., 2011[142] Aetna, US	4,916	Median 8.4 months, 4,611 pys	Abatacept, adalimumab, etanercept, or rituximab vs. infliximab	RA	Serious infections	Significantly lower for abatacept (aHR 0.68; 95% CI 0.48 to 0.96), adalimumab (aHR 0.52; 95% CI 0.39 to 0.71), etanercept (aHR 0.64; 95% CI 0.49 to 0.84) vs. infliximab	Fair
Favalli, et al., 2009[143] LOHREN (Lombardy Rheumatology Network), Italy	1,064	24 months	Adalimumab vs. infliximab vs. etanercept	RA	Serious infections	No significant differences	Fair
Tuberculosis							
Chiu et al., 2014[138] NHIRD, Taiwan	2,238	NR	Adalimumab vs. etanercept	RA	Tuberculosis	Significantly higher for adalimumab vs. etanercept (IRR, 2.35; 95% CI, 1.29 to 4.15)	Low

Authors, Year Registry Name, Country	Number of Participants	Follow-up	Comparison	Population	Outcome	Results	Risk of Bias
Malignancies							
Harigai et al., 2016[144] SECURE, Japan	14,440	5 years	Adalimumab, etanercept, or tocilizumab vs. infliximab	RA	Malignant lymphoma; Nonhematopoietic malignancy	Significantly higher for infliximab vs. etanercept (IR 2.32 per 1,000 pys vs. IR 0.70 per 1,000 pys; *P* < .001; on drug analysis) Significantly higher for infliximab vs. etanercept (IR 3.38 per 1,000 pys vs. IR 1.30 per 1,000 pys; *P* < .001; ever-exposed analysis) No significant differences	High
Aaltonen et al., 2015[135] ROB-FIN, Finland	3,532	7,875 pys	Pooled TNF-α inhibitors (adalimumab, etanercept, infliximab) vs. rituximab	RA	Malignancies	No significant differences	Low
Askling et al., 2009[145] SWEDSIH, Sweden	6,366	25,693 pys	Adalimumab vs. etanercept vs. infliximab	RA	Malignancy	No significant differences	Low
Wolfe et al., 2007[145] National Databank for Rheumatic Diseases, US	6,282	49,000 pys	Adalimumab vs. etanercept vs. infliximab vs. anakinra	RA	Malignancy (excluding non-melanoma skin cancer), Lymphoma	No significant differences	Low

Authors, Year Registry Name, Country	Number of Participants	Follow-up	Comparison	Population	Outcome	Results	Risk of Bias
Nonmelanoma and melanoma skin cancer							
Amari et al., 2011[146] Veterans Affairs, (Austin Information Technology Center), US	4,088	11,084 pys	Adalimumab or infliximab vs. etanercept	RA	Nonmelanoma skin cancers	Significantly higher for adalimumab vs. etanercept (IR, 0.036 per pys vs. 0.021 per pys; *P* < .001)	Moderate
Wolfe et al., 2007[147] National Databank for Rheumatic Diseases, US	6,282	49,000 pys	Adalimumab vs. etanercept vs. infliximab vs. anakinra	RA	Nonmelanoma skin cancers; Melanoma	No significant differences	Low
Cardiovascular events and congestive heart failure							
Iannone et al., 2017[148] GISEA, Italy	7,539	2 years	Pooled TNF-α inhibitors (adalimumab, etanercept, infliximab) vs. tocilizumab or abatacept	RA	Cardiovascular events	No significant differences	High

Note. [a] *Sample size < 10,000.*

Abbreviations. aHR, adjusted hazard ratio; ARTIS: antirheumatic therapy in Sweden biologics registry; BSRBR: British Society for Rheumatology biologics register; CI: confidence interval; DANBIO: nationwide registry of biological therapies in Denmark; GISEA: Italian Group for the Study of Early Arthritis; IR: unadjusted incidence rate; IRR: incidence rate ratio; NHIRD: National Health Insurance Research Database Taiwan; NR: not reported; pys: patient-years; RA: rheumatoid arthritis; RABBIT: rheumatoid arthritis – observation of biologic therapy register; ROB-FIN: National Register for Biologic Treatment in Finland; SABER: Safety Assessment of Biologic Therapy; SARABA: SAfety profile of RA patients receiving Biological Agents study; SECURE: SafEty of biologics in Clinical Use in Japanese patients with RhEumatoid arthritis; SWEDISH: Swedish Inpatient Register, the Swedish Outpatient Register, the Swedish Early RA Register, the Swedish National Population Registers, Swedish Tuberculosis Register, and the Swedish Biologics; TNF-α: tumor necrosis factor-alpha; UK: United Kingdom; VHA: Veterans Health Administration; vs.: versus.

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