Targeted Immune Modulators for Rheumatoid Arthritis and Ankylosing Spondylitis: Update

Systematic Review

April 2020

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Executive Summary

Background

Targeted immune modulators (TIMs) are a category of medications used to treat certain types of immunologic 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 U.S. 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), tocilizumab (Actemra)
- Janus kinase (JAK) inhibitors: baracitinib (Olumiant), tofacitinib (Xeljanz/Xeljanz XR), 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] filgotinib, and peficitinib[6] are pipeline drugs under investigation but not yet approved for the treatment of RA or ankylosing spondylitis. ABBV-3373 is a TNF-α inhibitor, bimekizumab an interleukin 17 receptor inhibitor, and filgotinib and peficitinib are JAK inhibitors. Janus kinase 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 (DMARDs).[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 that evaluated 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 evaluated the effectiveness and harms (compared to placebo) of selected pipeline TIM agents.

This review addresses 4 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, we searched Ovid MEDLINE, Cochrane Library, ClinicalTrials.gov, International Standard Randomised Controlled Trials Number (ISRCTN) registry from January 1, 2017 up to September 5, 2019, and several other websites to identify eligible studies. We rated the methodological quality 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 interval (CI) based on data provided in the study when not reported by authors. We rated the quality of the body of evidence 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 23 new studies[16-38] and carried forward 52 studies[39-91] from the previous report for a total of 75 eligible studies in this update. All RCTs (except 1)[16] and all cohort studies (except 2)[61,84] evaluated TIM agents among participants with RA. One RCT[16] evaluated TIMs agents for ankylosing spondylitis; 2 cohort studies[61,84] assessed TIMs in a mixed population that included participants with RA and ankylosing spondylitis.

Of the 75 eligible studies, 34 were RCTs[16-26,29,31,35-55] and 41 were cohort studies.[27,28,30,32-34,56-91] Among the 34 RCTs, we rated 6 studies[16,26,31,38,42,52] as of poor methodological quality; we rated the others as of fair methodological quality. Among the 41 cohort studies, we rated 5 studies[33,75,76,81,85] as of poor methodological quality, 11 studies[56,59,62,63,66,70,71,77,78,86,88,89] as of good methodological quality, and the rest as of fair methodological quality. Outcomes selected for GRADE ratings ranged from very low to high quality of evidence (QoE); the majority was very low. Generally, outcomes were downgraded for study limitations and imprecision (i.e., wide CI because of small sample size).

Rheumatoid Arthritis

- For comparative effectiveness (Key Question 1) of TIMs as first-line treatments, we identified 15 RCTs[21,24,39-51] that provided evidence for 11 different head-to-head comparisons and 2 comparisons of combination treatments with monotherapy.
    - *Abatacept vs. adalimumab* (1 RCT[39]): 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 QoE for response; low QoE for remission).

- *Abatacept vs. infliximab* (1 RCT[40]): No significant differences in response (ACR50), remission (ACR70), or improvements in functional capacity (HAQ-DI) at 24 weeks (low QoE for response and remission).
- *Adalimumab vs. baracitinib* (1 RCT[21]): Adalimumab significantly less effective than baracitinib 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 < 3.3; high QoE for response; low QoE for remission).
- *Adalimumab vs. certolizumab pegol* (1 RCT[41]): No significant differences in response (ACR20) and remission (ACR70) at 12 weeks (high QoE for response; data not reported [NR] for remission).
- *Adalimumab vs. etanercept* (2 RCTs[42,43]): No significant differences in disease activity and improvements in functional capacity (HAQ-DI, Disease Activity Score28 [DAS28], Patient Global Assessment) at 24 weeks (very low QoE).
- *Adalimumab vs. sarilumab* (1 RCT[44,92]): Adalimumab was significantly less effective than sarilumab for achieving response (ACR50, 30% vs. 46%), remission (Clinical Disease Activity Index: 3% vs. 7%), improvements in functional capacity (HAQ-DI, −0.43 vs. −0.61), and quality of life (Short Form 36-item Health Survey [SF-36], 6.09 vs. 8.75) at 24 weeks (moderate QoE for QoL and response; low QoE for remission).
- *Adalimumab vs. tocilizumab* (2 RCTs[43,45]): 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 QoE for all three). Tocilizumab was used at a higher dose than FDA-approved.
- *Adalimumab vs. tofacitinib* (3 RCTs[46-48]*):* No significant difference in response (ACR50), remission (ACR70), and improvements in functional capacity (HAQ-DI) at 24 weeks (high QoE for response and remission).
- *Adalimumab vs. upadacitinib* (1 RCT[24]): Adalimumab was significantly less effective than upadactinib 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 QoE for response and remission).
- *Etanercept vs. infliximab* (1 RCT[49]): 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 QoE for response).
- *Etanercept vs. tocilizumab* (1 RCT[43])*:* No significant differences in clinical improvement (DAS-28) and improvement in functional capacity (HAQ-DI) at 24 weeks (very low QoE for clinical improvement).
- *Combination strategies* (2 RCTs[50,51]): No additional benefits (response, remission) from the combination of etanercept with abatacept or anakinra, compared to etanercept monotherapy (moderate QoE).

- For comparative effectiveness (Key Question 1) of TIMs as second-line treatments for RA, we identified 5 RCTs[26,38,52,53,55] that provided evidence for 4 different head-to-head

comparisons of TIM agents and 1 comparison of TIM combination treatment with TIM monotherapy.

- *Abatacept vs. TNF-α inhibitors* (2 RCTs[38,52]): No significant differences in clinical improvement (DAS28) and QoL (SF-36) at 52 weeks (very low QoE for QoL; low QoE for clinical improvement).
- *Abatacept vs. rituximab* (2 RCTs[38,52]): No significant differences in clinical improvement (DAS28) and QoL (SF-36) at 52 weeks (very low QoE for QoL; low QoE for clinical improvement).
- *Abatacept vs. tocilizumab* (1 RCT[26]): No significant differences in clinical improvement (DAS28) and functional capacity (HAQ-DI) at 24 weeks (low QoE for clinical improvement).
- *TNF-α Inhibitors vs. other TIMs* (1 RCT[53]): Non-TNF-α inhibitors were significantly more effective than TNF drugs 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 QoE for both).
- *Combination therapies* (1 RCT[55]): Combination treatment was significantly more effective than TNF-α inhibitor maintenance treatment for achieving response (ACR50, 12% vs. 6%; *P* value NR) and remission (DAS28 < 2.6, 18% vs. 6%) at 24 weeks (low QoE for both).

- For efficacy and safety of pipeline drugs, we included 8 placebo-controlled RCTs that assessed the efficacy of filgotinib or peficitinib compared to placebo for the treatment of RA[17-20,22,23,36,37]; 1 RCT compared also peficitinib with etanercept.[36] In addition, we included 1 comparison of combination treatments with monotherapy.[35]
  - *Filgotinib vs. placebo* (3 RCTs[19,22,23]*):* Filgotinib was significantly more effective than placebo for achieving response (ACR20, 66% vs. 31%), remission (DAS28-erythrocyte sedimentation rate (ESR), 31% vs. 12%), and improvement of QoL (SF-36: 7.6 vs. 3.6) at 12 weeks (high QoE for all).
  - *Peficitinib vs. placebo* (5 RCTs[17,18,20,36,37]): peficitinib was significantly more efficacious than placebo for achieving response (ACR20, 64% vs. 22%) and remission (DAS28-ESR < 2.6, 35% vs. 8%) at 12 weeks. No significant difference in overall AE and SAE (high QoE for response and remission; moderate QoE for AE and SAE).
  - *Peficitinib vs. etanercept* (1 RCT[36]): Peficitinib was less effective than etanercept in achieving response (ACR20, 75% vs. 84%) at 52 weeks. No significant difference in overall AE and SAE (moderate QoE for response; low QoE for AE and SAE).
  - *Combination therapies* (1 RCT[35]): Combination treatment was more effective than monotherapy for achieving response (DAS28-C-reactive protein (CRP) < 3.2, 46% vs. 29%) and remission (DAS28-CRP < 2.6, 26% vs. 8%). Significantly higher incidence of overall AE (79% vs. 59%), but fewer SAEs with combination treatment than monotherapy (low QoE for all outcomes).

- For comparative harms (Key Question 2), we identified 20 RCTs[21,24-26,31,38-42,44-48,50-52,54,55] providing evidence for 17 different head-to-head comparisons; in addition, we identified 41 cohort studies.[27,28,30,32-34,56-90] Overall, we observed few differences in harms in head-to-head RCT comparisons of TIM agents. In the following key points, we focus on statistically significant differences observed in included studies.

- *Abatacept vs. infliximab* (1 RCT[40]): Significantly fewer SAEs with abatacept than infliximab (5% vs. 12%; *P* value NR) at 24 weeks. No significant differences in overall AEs (low QoE for SAEs and moderate QoE for overall AEs).
- *Abatacept vs. tocilizumab* (1 RCT[26]): Significantly lower incidence of overall AEs (28% vs. 60%; *P* value NR) and SAEs (6% vs. 15%; *P* value NR) for abatacept than tocilizumab (low QoE for overall AEs and very low QoE for SAEs).
- *Adalimumab vs. baracitinib* (1 RCT[21]): Significantly fewer SAEs with adalimumab than baracitinib (4% vs. 8%) at 52 weeks. No significant differences in overall AEs (low QoE for SAEs and high QoE for overall AEs).

- *Combination therapies* (4 RCTs[50,51,54,55]): Combination of etanercept with abatacept or anakinra resulted in more SAEs (11% vs. 3%) compared to etanercept monotherapy, but no significant difference (moderate QoE). Abatacept plus other TIM (adalimumab, anakinra, etanercept, or infliximab) resulted in more SAEs (22% vs. 13%) compared to other TIM alone but no significant difference (low QoE). Higher proportion of overall AEs (94% vs. 83%; *P* value NR) for combination of rituximab with TNF-α inhibitors compared to TNF-α inhibitor maintenance therapy (low QoE for SAEs and overall AEs). We did not identify any studies for differences in effectiveness and harms in subgroups (Key Question 3).

Ankylosing Spondylitis

- For comparative effectiveness (Key Question 1), we identified 1 head-to-head trial.[16]
  - *Etanercept vs. infliximab* (1 RCT[16]): Etanercept was significantly less effective for clinical improvement than infliximab (Bath Ankylosing Spondylitis Activity Index, 5.9 vs. 4.8) at 12 weeks. No significant differences on weeks 54 and 104 (very low QoE).
- For comparative harms (Key Question 2), we identified 1 head-to-head trial[16] reporting on discontinuation due to AEs, but it did not provide the overall number of patients with at least one AE or SAE.
- For differences in effectiveness and harms in subgroups (Key Question 3), we did not identify any studies.
- For efficacy and safety of pipeline drugs, we included 1 placebo-controlled trial[29] that assessed the efficacy of filgotinib compared to placebo for the treatment of ankylosing spondylitis. [29]
  - *Filgotinib vs. placebo* (1 RCT[29]): Filgotinib was significantly more effective than placebo for achieving clinical improvement (ankylosing spondylitis disease activity score [ASDAS], −1.47 vs. −0.57) and improvement of QoL (SF-36, 8.4 vs. 3.8) at 12 weeks (moderate QoE). Similar incidence of AEs and SAEs (low QoE).

Ongoing Studies

- For RA, we identified 16 ongoing comparative effectiveness trials of TIM agents and 2 ongoing placebo-controlled trials of filgotinib.
- For ankylosing spondylitis, we identified 4 ongoing comparative effectiveness trials of TIM agents and 1 ongoing placebo-controlled trial of filgotinib.

Conclusions

The evidence for the comparative effectiveness and harms for TIM agents provides data on 12 comparisons of TIMs as first-line treatments and 6 comparisons as second-line treatments for RA. Most comparisons are limited to single trials. Consequently, the QoE for many outcomes is very low or low, precluding definitive conclusions. Evidence rated as moderate or high quality indicates that baricitinib, sarilumab, and upadacitinib are more effective than adalimumab as first-line treatments for RA. High and moderate QoE indicates no differences in the incidence of overall AEs and SAEs. Significant differences for the incidence of AEs or SAEs of some comparisons are rated as very low or low QoE and need to be interpreted with caution.

The evidence on ankylosing spondylitis is sparse. We identified only 1 poor-methodological-quality 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 filgotinib for the treatment of ankylosing spondylitis. Twenty-four studies of head-to-head comparisons of TIM agents for the treatment of RA and ankylosing spondylitis are currently in progress; 10 will be completed before 2021.

List of Brand Names and Generics

Table 1. Included Drugs and Biosimilars

Generic Name	Trade Name	Mechanism	Route	Approved Population[a]
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-atto	Amjevita	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
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

Generic Name	Trade Name	Mechanism	Route	Approved Population[a]
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 Drugs				
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
Filgotinib[b]	NA	JAK inhibitor	PO	Under investigation for RA or ankylosing spondylitis
Peficitinib[c]	NA	JAK inhibitor	PO	

Notes. [a] Details of approved indications for each drug can be found in the full prescribing information; [b] Approved in Japan for the treatment of rheumatoid arthritis; [c] submitted for FDA approval. Abbreviations. IL: interleukin; IV: intravenous; JAK: Janus kinase; NA: not applicable; PO: per os (orally); 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's disease, ulcerative colitis, and plaque psoriasis.[1] The U.S. Food and Drug Administration (FDA) approved the first TIM, infliximab, in 1998 and numerous additional agents including biosimilar TIM agents since then.[2] Table 1 summarizes currently available TIMs approved in the U.S. 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 pro-inflammatory 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 pro-inflammatory 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 that consists of the extracellular domain of human cytotoxic T lymphocyte-associated antigen (CTLA-4) and the modified Fc portion of IgG1.[2]

Rituximab, a chimeric murine/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.[93] 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 pro-inflammatory cytokine produced by a variety of cell types including T- and B-cells, lymphocytes, monocytes, and fibroblasts.[2]

Baricitinib, tofacitinib, and upadacitinib are orally administered TIMs that act as Janus kinase (JAK) inhibitors.[2,94] 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 4 pipeline drugs in this update. Bimekizumab is an IL-17 receptor inhibitor currently under investigation for the treatment of ankylosing spondylitis.[5] Filgotinib and peficitinib are orally administered JAK inhibitors. Filgotinib is currently under investigation for RA and ankylosing spondylitis and selectively targets JAK 1.[6] Peficitinib has been approved for the treatment of RA in Japan (but not in the U.S.) and targets primarily JAK subtype 3.[95] ABBVIE-3373 is a TNF-α inhibitor under investigation for RA.[4]

Rheumatoid Arthritis

RA is an autoimmune disease that affects about 1% of the population worldwide.[96] The exact etiology of RA is not completely understood, but genetic susceptibility factors have been described in certain populations.[96] The hallmarks of the disease are inflammation of the synovial tissues with progressive erosion of bone leading to malalignment of the joint and, in most cases, disability.[97] TNF-α plays a central role in the pathobiology of RA.[97,98]

The diagnosis of RA is primarily clinical.[97] Constitutional symptoms, such as fatigue and low-grade fevers, are common before the onset of joint swelling and pain.[97] Joint stiffness is almost always present and is frequently most severe after periods of prolonged rest.[97] 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.[97] Severe disease may be complicated by involvement of the eyes, lungs, nerves, and the cardiovascular system.[97]

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.[99] Peripheral joint disease can occur and may be destructive in some cases.[99] The sacroiliac joints are usually the first joints involved, and the disease is characterized by progressive involvement of the spine.[99] Enthesitis, inflammation of the insertion of ligaments and tendons on bones, is one of the hallmarks of the disease.[99]

Existing diagnostic criteria are relatively insensitive and have limited utility in clinical practice.[100] Radiographs of the sacroiliac joints, when abnormal, can be useful in assessing the presence of ankylosing spondylitis; however, they are frequently normal in early disease.[100] Over time, patients with ankylosing spondylitis develop progressive fusion of the spine with resultant deformity and disability.[99] Because TNF has been implicated in the pathophysiology of ankylosing spondylitis, biologic agents targeting TNF-α are now recommended as part of the standard treatment approach.[8,101]

PICOS

Population

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

Interventions

- TIMs and respective biosimilars that have FDA approval for the treatment of RA or ankylosing spondylitis, and select pipeline drugs likely to be approved soon (Table 1)

Comparators

- 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
- Harms
  - Overall adverse events (AEs)
  - Withdrawals due to AEs
  - Serious adverse events (SAEs)
  - Specific AEs (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 outcomes on harms
  - > 12-week study duration
  - Minimum total sample size of 1,000

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, we searched Ovid MEDLINE, Cochrane Library, ClinicalTrials.gov, International Standard Randomised Controlled Trials Number (ISRCTN) registry from January 1, 2017 up to September 5, 2019, and several other websites to identify eligible studies. We rated the methodological quality of eligible studies using

standard instruments adapted from national and international quality. We rated the methodological quality 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) and risk ratio (RR), and associated 95% confidence interval (CI) based on data provided in the study when not reported by authors. We rated the quality of the body of evidence 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 Drug Effectiveness Review Project (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.

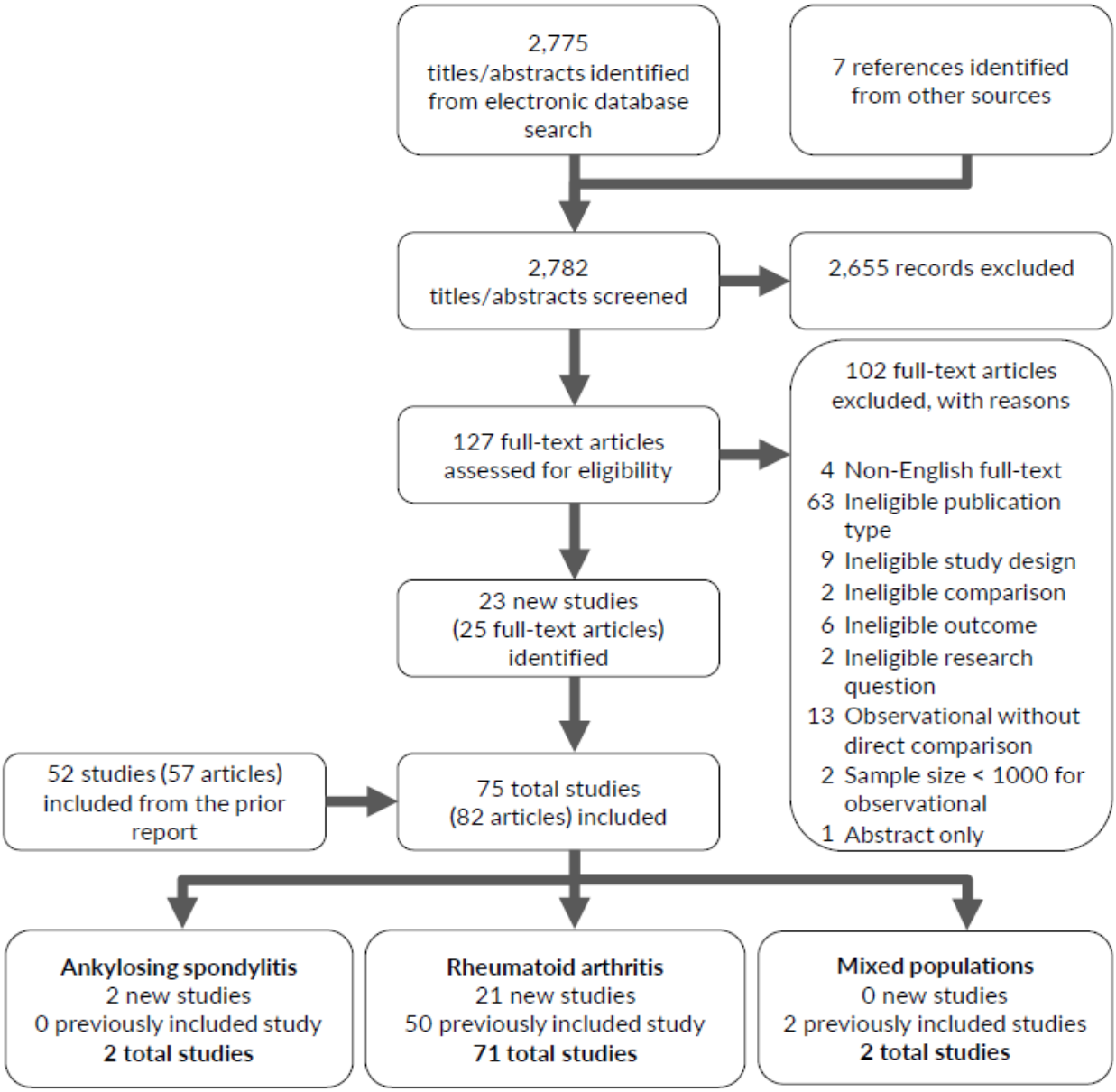
Findings

For this update we included 7 new head-to-head RCTs (in 7 publications[16,21,24-26,31,38]) on the comparative effectiveness and harms of TIM agents that are approved for the treatment of RA or ankylosing spondylitis. We carried forward 17 RCTs[39-55] from the prior report for a total of 24 RCTs in this update.

In addition, we included 9 placebo-controlled trials[17-20,22,23,29,36,37] (in 10 publications) on filgotinib and peficitinb. One of these studies also compared peficitinb to etanercept.[36] In addition, we identified 1 head-to head trial on bimekizumab in combination with certolizumab pegol compared to certolizumab pegol alone,[35] TIMs that the FDA have not yet approved for the treatment of RA or ankylosing spondylitis. Overall, this update includes 34 RCTs and 41 observational studies (Figure 1), providing evidence for 21 head-to-head comparisons for the treatment of RA, and 1 head-to-head comparison[16] for the treatment of ankylosing spondylitis. We rated 6 RCTs as of poor methodological quality[16,26,31,38,42,52]; we rated the others as of fair methodological quality, primarily because of extensive manufacturer involvement in study design, execution, and reporting.

We did not identify any studies that addressed differences in effectiveness or harms by subgroup (Key Question 3). Appendix G provides the bibliography of studies identified in the update search but that we excluded at 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 one 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 (Key Question 1)

We identified 15 RCTs evaluating the comparative effectiveness of TIMs as first-line treatment.[21,24,39-51] These studies provided evidence on 11 head-to-head comparisons of TIM agents and 2 comparison of combination TIM treatment with TIM monotherapy. Appendix B, Table B1 and Table B2 provide detailed study characteristics and results from the included RCTs. The Summary of Findings (GRADE) for these comparisons are in Table 2 with detailed evidence profiles in Appendix C presents a summary of efficacy outcomes. The rest of this section describes each of the comparisons. 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	Quality of Evidence	Relationship	Rationale
Abatacept Compared to Adalimumab			
Clinical improvement or response (1 RCT[39])	Low ●●○○	No difference between groups	Downgraded 1 level for study limitations and 1 level for imprecision
Disease remission (1 RCT[39])	Low ●●○○	No difference between groups	Downgraded 1 level for study limitations and 1 level for imprecision
Abatacept Compared to Infliximab			
Clinical improvement or response (1 RCT[40]	Low ●●○○	No difference between groups	Downgraded 2 levels for very serious imprecision
Disease remission (1 RCT[40])	Low ●●○○	No difference between groups	Downgraded 2 levels for very serious imprecision
Adalimumab Compared to Baracitinib			
Clinical improvement or response (1 RCT[21])	High ●●●●	Lower proportion improved with adalimumab than baracitinib	Not downgraded
Disease remission (1 RCT[21])	Low ●●○○	No difference between groups	Downgraded 2 levels for very serious imprecision
Adalimumab Compared to Certolizumab pegol			
Clinical improvement or response (1 RCTs[41])	High ●●●●	No difference between groups	Not downgraded
Adalimumab Compared to Etanercept			
Clinical improvement or response (2 RCTs[42,43])	Very low ●○○○	No difference between groups	Downgraded 1 level for study limitations and 2 levels for very serious imprecision

Outcome	Quality of Evidence	Relationship	Rationale
Adalimumab Compared to Sarilumab			
Quality of life (1 RCT[44])	Moderate ●●●○	Smaller improvements for adalimumab than sarilumab	Downgraded 1 level for imprecision
Clinical improvement or response (1 RCT[44])	Moderate ●●●○	Lower proportion improved with adalimumab than sarilumab	Downgraded 1 level for imprecision
Disease remission (1 RCT[44])	Low ●●○○	Lower proportion with remission with adalimumab than sarilumab	Downgraded 2 levels for very serious imprecision
Adalimumab Compared to Tocilizumab			
Quality of life (1 RCT[45])	Low ●●○○	Similar between groups	Downgraded 1 level for indirectness and 1 level for imprecision
Clinical improvement or response (2 RCTs[43,45])	Low ●●○○	Lower proportion improved with adalimumab than tocilizumab	Downgraded 1 level for indirectness and 1 level for imprecision
Disease remission (2 RCTs[43,45])	Low ●●○○	Lower proportion with remission with adalimumab than tocilizumab	Downgraded 1 level for indirectness and 1 level for imprecision
Adalimumab Compared to Tofacitinib			
Clinical improvement or response (3 RCTs[46-48])	High ●●●●	No difference between groups	Not downgraded
Disease remission (2 RCTs[46,48])	High ●●●●	No difference between groups	Not downgraded
Adalimumab Compared to Upadacitinib			
Clinical improvement or response (1 RCT[24])	High ●●●●	Lower proportion improved with adalimumab than upadacitinib	Not downgraded
Disease remission (1 RCT[24])	High ●●●●	Lower proportion with remission for adalimumab than upadacitinib	Not downgraded
Etanercept Compared to Infliximab			
Clinical improvement or response (1 RCT[49])	Very low ●○○○	Relationship cannot be determined	Downgraded 1 level for study limitations and 2 levels for very serious imprecision,
Etanercept Compared to Tocilizumab			
Clinical improvement or response (1 RCT[43])	Very low ●○○○	No difference between groups	Downgraded 1 level for study limitations and 2 levels for very serious imprecision
TIM Combination Therapies Compared to TIM Monotherapy			
Clinical improvement or response (2 RCTs[50,51])	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; TIM: targeted immune modulator.

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	Duration	Comparisons	Primary Outcome	Secondary Outcomes	Population	Results	Study Quality
Abatacept Compared to Adalimumab								
Weinblatt et al., 2013[39] Schiff et al., 2014[102] Fleischmann et al., 2015[103] 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	Fair
Abatacept Compared to Infliximab								
Schiff et al., 2008[40] 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 dose adjustment allowed for infliximab)	Fair
Adalimumab Compared to Baracitinib								
Taylor et al., 2017[21] RA-BEAM	RCT 1,305	52 weeks	Adalimumab 40 mg Q2W SC + MTX • Baracitinib 4 mg QD PO + MTX • Placebo +MTX	ACR20 after 12 weeks	ACR 50/70, DAS28-CRP, HAQ-DI, SDAI, CDAI	Active RA with inadequate response to MTX; mean disease duration, 10 years	Adalimumab less effective than baracitinib	Fair

Authors, Year Trial Name	Study Design Number of Participants	Duration	Comparisons	Primary Outcome	Secondary Outcomes	Population	Results	Study Quality
Adalimumab Compared to Certolizumab pegol								
Smolen et al., 2016[41] 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	ACR 50/70, DAS28-ESR, HAQ-DI	Active RA with inadequate response to MTX; prognostic factors for severe disease progression; mean disease duration, 5.8 to 6.0 years	No difference in efficacy for adalimumab and certolizumab pegol	Fair
Adalimumab Compared to Etanercept								
Jobanputra et al., 2012[42] NR	Pragmatic, open-label RCT 125	52 weeks	• Adalimumab 40 mg Q2W SC + MTX[a] • 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	Poor
Kume et al., 2011[43] NR	Open-label RCT 42	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	Fair

Authors, Year Trial Name	Study Design Number of Participants	Duration	Comparisons	Primary Outcome	Secondary Outcomes	Population	Results	Study Quality
Adalimumab Compared to Sarilumab								
Burmester et al., 2017[44,92] 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	Fair
Adalimumab Compared to Tocilizumab								
Gabay et al., 2013[45] ADACTA	RCT 326	26 weeks	• Adalimumab 40 mg Q2W SC • Tocilizumab 8mg/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)	Fair
Kume et al., 2011[43] NR	Open-label RCT 43	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	Fair

Authors, Year Trial Name	Study Design Number of Participants	Duration	Comparisons	Primary Outcome	Secondary Outcomes	Population	Results	Study Quality
Adalimumab Compared to Tofacitinib								
van Vollenhoven et al., 2012[46,104] 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	ACR 50/70, 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	Fair
Fleischmann et al., 2012[47] 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	ACR 50/70, 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	Fair
Fleischmann et al., 2017[48] ORAL Strategy	RCT 1,146	48 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	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	Fair

Authors, Year Trial Name	Study Design Number of Participants	Duration	Comparisons	Primary Outcome	Secondary Outcomes	Population	Results	Study Quality
Adalimumab Compared to Upadacitinib								
Fleischmann et al., 2019[24] 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, VAS, HAQ-DI	Active RA with an inadequate response to MTX treatment; mean disease duration, 8 years	Adalimumab less effective than upadacitinib	Fair
Etanercept vs. Infliximab								
De Filippis et al., 2006[49] 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	ACR 50/70, 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)	Fair
Etanercept Compared to Tocilizumab								
Kume et al., 2011[43] NR	Open-label RCT 43	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	Fair

Authors, Year Trial Name	Study Design Number of Participants	Duration	Comparisons	Primary Outcome	Secondary Outcomes	Population	Results	Study Quality
Combination Strategies								
Genovese et al., 2004[50] 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 compared to etanercept monotherapy	Fair
Weinblatt et al., 2007[51] 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	ACR 50/70, HAQ-DI	Chronic RA; on etanercept for at least 3 months; mean disease duration, 12.9 years	Limited additional benefit from abatacept + etanercept compared to etanercept monotherapy	Fair

Note. [a] *As 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; 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: Functional Assessment of Chronic Illness Therapy; FDA: U.S. Food and Drug Administration; HAQ: Health Assessment Questionnaire; HAQ-DI: Health Assessment Questionnaire-Disability Index; IV: intravenous administration; kg: kilogram; mg: milligram; MTX: methotrexate; PtGA: Patient Global Assessment; PO: per os (oral administration); QD: dose delivered daily; QM: dose delivered monthly; Q2M: dose delivered every two month; QW: dose delivered weekly; Q2W: dose delivered every 2 weeks; RA: rheumatoid arthritis; RCT: randomized controlled trial; SC: subcutaneous administration; SDAI: Simple Disease Activity Index; SF-36: Short Form 36-item Health Survey; TIM: targeted immune modulator; VAS: Visual Analogue Scale.*

Abatacept Compared to Adalimumab

We did not identify any new RCTs for this update. The previous review included 1 fair-methodological-quality, open-label, noninferiority, RCT (AMPLE [Abatacept versus Adalimumab Comparison in Biologic-Naïve RA Subjects with Background Methotrexate], N = 646) that compared abatacept (125 mg weekly) and adalimumab (40 mg every other week) in combination with methotrexate.[39] The study was funded by the manufacturer of abatacept.[39] The primary outcome measure was the American College of Rheumatology (ACR) 20 response at 12 months.[39] At study endpoint, ACR20 response rates were similar between participants treated with abatacept and adalimumab (65% vs. 63%; *P* value not reported [NR]).[39]

Other efficacy outcomes were also similar for participants in the 2 treatment groups. At 1 year, participants in both groups had similar ACR50 (46% vs. 46%; *P* value NR) and ACR70 (29% vs. 26%; *P* value NR) responses.[39] Likewise, participants treated with abatacept had similar improvements on Disease Activity Score 28 (DAS-28, −2.30 vs. −2.27) and the Health Assessment Questionnaire-Disability Index (HAQ-DI, −0.60 vs. 0.58) compared to participants on adalimumab.[39]

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.[102] Disease activity (assessed with DAS-28, 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.[102,103]

Abatacept Compared to Infliximab

We did not identify any new RCTs for this update. The ATTEST (Abatacept or infliximab compared to placebo, a Trial for Tolerability, Efficacy, and Safety in Treating RA) study, was a fair-methodological-quality RCT that allocated 431 participants to abatacept (10 mg/kg every 4 weeks), infliximab (3 mg/kg every 8 weeks), or placebo.[40] All participants were on methotrexate background therapy.[40] 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).[40] 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.[40] Likewise, improvements in physical functioning between participants treated with abatacept or adalimumab were not significantly different.[40]

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 greater 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).[40] 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.[40] 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.

Adalimumab Compared to Baracitinib

We identified 1 new, fair-methodological-quality 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), baracitinib (4 mg once daily), or placebo.[21] All participants received background therapy with methotrexate. The study was funded by the manufacturer of baracitinib and lasted 52 weeks.[21] The primary endpoint was the ACR20 response at week 12.[21] Significantly fewer participants in the adalimumab than baracitinib treatment group achieved a response (61% vs. 70%; *P* = .01) at endpoint.[21] Likewise, participants treated with adalimumab had significantly lower changes from baseline in DAS28–CRP than participants in the baracitinib group (−1.95 vs. −2.24; *P* < .001).[21] Additionally, significantly fewer achieved HAQ-DI score improvements of > 0.22 (58% vs. 68%; *P* < .01).[21] Remission rates (Simplified Disease Activity Index [SDAI] ≤ 3.3) at 12 weeks were not different between the 2 treatment groups (8% vs. 7%; *P* value NR).[21] The statistically significant differences between treatment groups were maintained through week 52.[21]

Adalimumab Compared to 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).[41] All participants remained on methotrexate background treatment.[41] The study, sponsored by the manufacturer of certolizumab pegol, was rated as of fair-methodological quality.[41] 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.[41] The study did not report any outcomes data for functional capacity at 12 weeks.[41]After 12 weeks, nonresponders in each treatment arm were switched to the opposite treatment[41] (see section on effectiveness of TIMs as second-line treatments).

Adalimumab Compared to Etanercept

We did not identify any new RCTs for this update. The previous reviews included 2 open-label RCTs, one of fair-[43] and the other of poor-methodological quality[42] that compared adalimumab with etanercept.

The fair-methodological-quality study was a small (N = 64), open-label, RCT that compared 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.[43] As secondary outcomes, this study assessed changes on the HAQ-DI and the DAS28-ESR (erythrocyte sedimentation rate) after 24 weeks of treatment.[43] The statistical analysis was performed as a "completers analysis" only; however, only few participants dropped out of the study (2 persons in the adalimumab group and 1 person in the etanercept group).[43] 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).[43] The study did not report response or remission rates.[43]

The second trial (N = 125) was a pragmatic, open-label RCT that we rated as poor-methodological quality because of a high loss to follow-up.[42] After 52 week, participants in the adalimumab and etanercept groups had similar improvements in the Patient Global Assessment (PtGA) and DAS28-CRP.[42]

Adalimumab Compared to Sarilumab

We did not identify any new RCTs for this update, but an additional publication described patient-reported outcomes of the MONARCH trial.[92] MONARCH was a fair-methodological quality, 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.[44] We rated the study as fair-methodological quality because of extensive manufacturer involvement in study design, execution, and reporting.[44] Participants were randomized to adalimumab monotherapy (40 mg once every 2 weeks) or sarilumab monotherapy (200 mg once every 2 weeks).[44] Participants did not receive methotrexate background therapy. The manufacturer of sarilumab funded the study.[44] 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; $P < .001$).[44] 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.[44]

This study also assessed differences for several patient-reported outcomes that measure functional capacity or QoL.[92] Adalimumab monotherapy resulted in smaller improvements for most patient-reported outcomes than sarilumab monotherapy.[92] 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.[92]

Adalimumab Compared to Tocilizumab

We did not identify any new RCTs for this update. The previous report included 2 fair-methodological-quality trials, a double-blinded RCT[45] and a small, open-label RCT[43]; 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.[45] The primary endpoint was the change in DAS28-ESR from baseline to week 24.[45] 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; $P < .001$).[45] 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.[45] 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.[45] We note that in this trial tocilizumab was used at a higher dosage than the FDA has approved.[45] 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.[43] 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).[43] The statistical analysis was a completers analysis only; however, only a few participants dropped out of the study (2 persons in the adalimumab group and 1 person in the tocilizumab group).[43]

Adalimumab Compared to Tofacitinib

We did not identify any new RCTs for this update. The previous report included 3 fair-methodological quality, double-blinded, RCTs[46-48] 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.[47] We rated the studies as of fair-methodological quality because of extensive manufacturer involvement in study design, execution, and reporting.[47]

The largest of the 3 RCTs (ORAL [Oral Rheumatoid Arthritis Trial] Strategy trial) was a noninferiority, double-blinded RCT that enrolled 1,146 participants with active RA despite treatment with conventional DMARDs.[48] 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).[48] The primary outcome was the ACR50 response after 6 months.[48] 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).[48] The combination treatment of tofacitinib and methotrexate reached formal noninferiority compared to adalimumab and methotrexate combination treatment (noninferiority boundary: −13 percentage points).[48] Tofacitinib monotherapy did not achieve noninferiority (i.e., no combination with methotrexate).[48] At 12 months, 46% of participants in the adalimumab and 48% in the tofacitinib combined with methotrexate groups had an ACR50 response.[48] 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).[48]

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.[46,104] Tofacitinib 10 mg twice daily is not an FDA-approved dosage. All treatment groups received methotrexate background therapy. 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%). ACR50 and ACR70 responses and HAQ-DI changes were also similar among the 3 treatment groups.[46]

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).[47]

Adalimumab Compared to Upadacitinib

We identified 1 new, fair-methodological-quality RCT for this update. The SELECT-COMPARE trial was a global, phase 3, double-blinded RCT that enrolled 1,629 patients with active RA despite treatment with methotrexate.[24] The study randomized participants to adalimumab (40 mg every other week), upadacitinib (15 mg once daily), or placebo.[24] All participants received methotrexate background therapy. The manufacturer of updacitinib funded the study, which lasted 52 weeks.[24] 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.[24] 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).[24] 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.[24]

Etanercept Compared to Infliximab

We did not identify any new RCTs for this update. The previous report included a fair-methodological-quality, small (N = 32), open-label RCT that compared etanercept (25 mg twice weekly) with infliximab (3 mg/kg, weeks 0, 2, 6, and every 2 months).[49] 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.[49] 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).[49] The trial did not report data on ACR50 or ACR70 response rates.[49] 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 Compared to Tocilizumab

We did not identify any new RCTs for this update. The previous report included a small (N = 64), fair-methodological-quality, open-label RCT that compared 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.[43] As secondary outcomes, this trial also assessed changes on the HAQ-DI and the DAS28-ESR after 24 weeks of treatment.[43] 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).[43] 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).[43]

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 2-TIM combination therapies; overall, they provide data on 363 participants.[50,51] The larger study, a fair-methodological-quality 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 to monotherapy

etanercept (25 mg twice per week).[50] 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).[50]

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 to abatacept monotherapy (2 mg/kg), reached similar conclusions.[51] The combination was associated with increased SAEs but only limited additional clinical benefit (ACR50, 26% vs. 19%; *P* value NR).[51]

Comparative Efficacy as Second-line Treatments (Key Question 1)

We identified 5 RCTs evaluating the comparative effectiveness of TIMs as second-line treatment.[26,38,52,53,55] These studies provided evidence on 4 head-to-head comparisons of TIM agents and 1 comparison of TIM combination treatment with 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 B2 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	Quality of Evidence	Relationship	Rationale
Abatacept Compared to TNF-α Inhibitors			
Quality of life (1 RCT[52])	Very low ●○○○	No difference between groups	Downgraded 1 level for study limitations and 2 levels for very serious imprecision
Clinical improvement (2 RCTs[38,52])	Low ●●○○	No difference between groups	Downgraded 2 levels for very serious imprecision
Abatacept Compared to Rituximab			
Quality of life (1 RCT[52])	Very low ●○○○	No difference between groups	Downgraded 1 level for study limitations and 2 levels for very serious imprecision
Clinical improvement (2 RCTs[38,52])	Low ●●○○	No difference between groups	Downgraded 1 level for study limitations and 1 level for imprecision
Abatacept Compared to Tocilizumab			
Clinical improvement (1 RCT[26])	Low ●●○○	No difference between groups	Downgraded 1 level for study limitations and 1 level for imprecision
TNF-α inhibitors Compared to Other TIMs			
Clinical improvement (1 RCT[53])	Low ●●○○	Higher proportion with improvement with non-TNF-α inhibitors than TNF-α inhibitors	Downgraded 1 level for study limitations and 1 level for imprecision
Remission (1 RCT[53])	Low ●●○○	Higher proportion of remission with non-TNF-α inhibitors than TNF-α inhibitors	Downgraded 1 level for study limitations and 1 level for imprecision

Outcome	Quality of Evidence	Relationship	Rationale
Combination Therapies			
Clinical improvement (1 RCT[55])	Low ●●○○	Higher proportion of response with combination therapy than TNF-α inhibitor maintenance therapy	Downgraded 2 levels for very serious imprecision
Remission (1 RCT[55])	Low ●●○○	Higher proportion of remission with combination therapy than TNF-α inhibitor maintenance therapy	Downgraded 2 levels for very serious imprecision

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

Abatacept Compared to TNF-α inhibitors

We included 1 new, poor-methodological-quality RCT for this update.[38] The previous review included a poor-methodological-quality open-label, pragmatic trial conducted in the Netherlands, in patients who had failed TNF-α inhibitor treatment and which compared abatacept, rituximab, and TNF-α inhibitors as second-line treatments.[52] This trial enrolled 144 patients who had moderate-to-high disease activity despite previous treatment with different TNF-α inhibitors.[52] The only exclusion reason in this effectiveness trial was a contraindication for treatment (e.g., pregnancy, presence of a serious infection).[52] Patients were randomly assigned to intravenous abatacept (N = 43) every 4 weeks (dosage based on body weight: patients under 60 kg received 500 mg, patients between 60 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).[52] The primary outcome for effectiveness was the DAS28-ESR over time.[52] We rated the study as of poor methodological quality because outcomes 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.[52]

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

The second trial, SWITCH, is described in more detail below (abatacept compared to rituximab).[38] 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. Changes in DAS28-ESR scores; however, were similar between abatacept and TNF-α inhibitors (−1.20 vs. −1.47; *P* value NR).[38]

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	Study Quality
Abatacept Compared to TNF-α Inhibitors and Rituximab								
Manders et al., 2015[52] 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 weeks 0 and 2 IV • 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	Poor
Brown et al., 2018[38] NR	Open-label RCT 81	24 weeks	• Abatacept 125 mg SC QW vs. 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	Poor

Authors, Year Trial Name	Study Design Number of Participants	Duration	Comparisons	Primary Outcome	Secondary Outcomes	Population	Results	Study Quality
Abatacept Compared to Tocilizumab								
Elmedany et al., 2019[26] NR	Open-label RCT 132	24 weeks	• Abatacept 500 – 1000 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	Poor
TNF-α inhibitors Compared to Other TIMs								
Gottenberg et al., 2016[53] 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	Fair

Authors, Year Trial Name	Study Design Number of Participants	Duration	Comparisons	Primary Outcome	Secondary Outcomes	Population	Results	Study Quality
Combination Therapies								
Greenwald et al., 2011[55] TAME[55]	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	Fair

Abbreviations. ACR 20/50/70: American College of Rheumatology, percentage improvement; BIW: dose delivered twice weekly; DAS28-CRP: Disease Activity Score 28 C-reactive protein; DAS28-ESR: Disease Activity Score 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; QM: dose delivered monthly; Q2M: dose delivered every 2 months; QW: dose delivered weekly; Q2W: dose delivered every 2 weeks; 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.

Abatacept Compared to Rituximab

We included 1 new, poor-methodological-quality RCT for this update.[38] The previous report included 1 poor-methodological-quality, pragmatic RCT that assessed the comparative effectiveness of abatacept and rituximab in participants who had an inadequate response to a TNF-α inhibitor.[52] Overall, the studies provide data on 174 participants.[38,52]

The poor-methodological-quality, open-label effectiveness trial conducted in the Netherlands and described previously also compared abatacept with rituximab.[52] At 12 months, DAS28-ESR scores were similar between treatment groups (3.8 for abatacept, 3.4 for rituximab; *P* value NR).[52] Likewise, health-related QoL measures (HAQ, SF-36) did not show any statistically significant differences between treatment groups.[52]

The second trial, SWITCH, was a publicly funded, open-label, noninferiority trial in the U.K.[38] 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 to 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).[38] Because funding was withdrawn after 2 years, the study enrolled only 122 participants (TNF-α inhibitor: n = 41; abatacept: n = 41; rituximab: n = 40).[38] Consequently, statistical analyses were likely underpowered and rendered nonstatistically significant, uncertain results.[38] 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).[38]

Abatacept Compared to Tocilizumab

We included 1 new study for this comparison. A poor-methodological-quality, open-label RCT enrolled 132 female Saudi Arabian participants with moderate-to-severe RA despite treatment with TNF-α inhibitors.[26] 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.[26] All participants were on methotrexate background therapy. The study did not report a registered protocol, primary outcomes, or the funding source.[26] 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).[26]

TNF-α Inhibitors Compared to 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.[53]

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%).[53] 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.[53] The choice of the treatment within

each randomized group was left to the treating clinician. The study did not analyze comparisons of individual treatments.[53]

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%; odds ratio [OR], 2.06; 95% CI, 1.27 to 3.37).[53] 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).[53] 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).[53]

Combination Therapies

We did not include any new RCTs for this update. The previous report included the fair-methodological-quality 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 that 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.[55] The control group maintained the adalimumab and etanercept therapies and received placebo infusions.[55] The primary endpoint of the study was the proportion of patients developing at least 1 serious infection during 24 weeks of treatment.[55] The study also assessed efficacy as a secondary outcome.[55] 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.[55] Likewise, DAS28-ESR remission rates (< 2.6) were higher for the rituximab combination group (18% vs. 6%; *P* value NR).[55]

Effectiveness and Harms of Pipeline TIM Agents

We identified 9 RCTs evaluating effectiveness and harms of pipeline TIM agents for the treatment of RA.[17-20,22,23,35-37] These studies provided evidence on filgotinib compared to placebo,[19,22,23] peficitinib compared to placebo,[17,18,20,36,37] peficitinib compared to etanercept,[36] and one combination treatment of certolizumab pegol plus bimekizumab compared to certolizumab pegol monotherapy.[35] Appendix B, Table B1 and Table B2 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	Quality of Evidence	Relationship	Rationale
Filgotinib Compared to Placebo			
Quality of life (1 RCT [23])	High ●●●●	Greater improvements for filgotinib than placebo	Not downgraded

Outcome	Quality of Evidence	Relationship	Rationale
Clinical improvement (3 RCTs[19,22,23])	High ●●●●	Higher proportion with improvement for filgotinib than placebo	Not downgraded
Disease remission (3 RCTs[19,22,23])	High ●●●●	Higher proportion of remission with filgotinib than placebo	Not downgraded
Overall AEs (3 RCTs[19,22,23])	Moderate ●●●○	No difference between groups	Downgraded 1 level for imprecision
SAEs (3 RCTs[19,22,23])	Low ●●○○	No difference between groups	Downgraded 2 levels for very serious imprecision
Peficitinib Compared to Placebo			
Clinical improvement (5 RCTs[17,18,20,36,37])	High ●●●●	Higher proportion with improvement for peficitinib than placebo	Not downgraded
Disease remission (4 RCTs[17,18,36,37])	High ●●●●	Higher proportion of remission with peficitinib than placebo	Not downgraded
Overall AEs (5 RCTs[17,18,20,36,37])	Moderate ●●●○	No difference between groups	Downgraded 1 level for imprecision
SAEs (5 RCTs[17,18,20,36,37])	Moderate ●●●○	No difference between groups	Downgraded 1 level for imprecision
Peficitinib Compared to Etanercept			
Clinical improvement (1 RCT[36])	Moderate ●●●○	Lower proportion with improvement for peficitinib than etanercept	Downgraded 1 level for study limitations
Disease remission (1 RCT[36])	Moderate ●●●○	Lower proportion with remission for peficitinib than etanercept	Downgraded 1 level for study limitations
Overall AEs (1 RCT[36])	Low ●●○○	No difference between groups	Downgraded 1 level for imprecision; downgraded 1 level for study limitations
SAEs (1 RCT[36])	Low ●●○○	No difference between groups	Downgraded 1 level for imprecision; downgraded 1 level for study limitations
Combination Therapy (Certolizumab pegol + Bimekizumab Compared to Certolizumab pegol)			
Clinical improvement (1 RCT[35])	Low ●●○○	Higher proportion of response for combination therapy than certolizumab pegol alone	Downgraded 2 levels for very serious imprecision
Disease remission (1 RCT[35])	Low ●●○○	Higher proportion of remission with combination therapy than certolizumab pegol alone	Downgraded 2 levels for very serious imprecision
Overall AEs (1 RCT[35])	Low ●●○○	Higher proportion of overall AEs for combination therapy than certolizumab pegol alone	Downgraded 2 levels for very serious imprecision
SAEs (1 RCT[35])	Low ●●○○	Lower proportion of serious AEsfor 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; SAE: serious adverse event; TIM: targeted immune modulator.

Filgotinib Compared to Placebo

We identified 3 double-blinded, randomized, placebo-controlled trials with data on 1,326 participants assessing the benefits and harms of filgotinib in patients with RA.[19,22,23] Two trials were phase 2 studies, and 1 trial was a phase 3 study.[23] We rated all 3 studies as of fair-methodological quality because of extensive manufacturer involvement in study design, execution, and reporting.[19,22,23] All studies included participants with moderate-to-severe RA for at least 6 months.[19,22,23] One study included participants with inadequate response or intolerance to 1 or more prior TIM agents.[23] Most participants in the other 2 studies were naïve to TIM agents.[19,22]

The phase 3 double-blinded multicenter RCT (FINCH 2) enrolled 449 participants with active RA and inadequate response or intolerance to 1 or more prior TIM agents.[23] Participants were randomized to 24 weeks of treatment with filgotinib (100 or 200 mg once daily) or placebo.[23] Most patients (82%) received concomitant methotrexate.[23] The primary outcome was the ACR20 response after 12 weeks.[23] As secondary outcomes, this trial assessed changes on the HAQ-DI, DAS28-CRP, SF-36 PCS, and Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-F) scores after 24 weeks of treatment.[23] After 12 weeks, significantly more participants in the intervention groups achieved an ACR20 response compared to participants in the placebo group (filgotinib 100 mg, 58%; filgotinib 200 mg, 66%; placebo, 31%; $P < .001$ for both comparisons with placebo).[23] Likewise, mean change from baseline in SF-36 at 12 weeks showed statistically significant differences between filgotnib groups compared to placebo (filgotinib 100 mg, 6.8; filgotinib 200 mg, 7.6; placebo, 3.6; $P < .001$ for both comparisons with placebo).[23] Participants in the filgotinib 100 mg and 200 mg groups had greater improvements on the HAQ-DI score than participants treated with placebo (filgotinib 100 mg, −0.60; filgotinib 200 mg, −0.75; placebo, −0.42; $P = .003$ and $P < .001$, respectively) and more participants achieved DAS28-CRP < 2.6 at week 24 (filgotinib 100 mg, 26%; filgotinib 200 mg, 31%; placebo, 12%; $P = .003$ and $P < .001$, respectively).[23] An improvement of −0.20 on the HAQ-DI is often considered a clinically relevant difference.[105]

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

Authors, Year Trial Registration 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	Study Quality
Filgotinib Compared to Placebo					
Genovese et al., 2019[23] NCT02873936 FINCH 2	Filgotinib 200 mg QD; Filgotinib 100 mg QD; Placebo Total N = 449	ACR20 response at 12 weeks: • Filgotinib 200 mg: *97* of 147 (66.0%), compared to placebo; *P* < .001 • Filgotinib 100 mg: *88* of 153 (57.5%), compared to placebo; *P* < .001 • Placebo: *46* of 148 (31.1%)	• Filgotinib 200 mg: 6 of 147 (4.1%) • Filgotinib 100 mg: 8 of 153 (5.2%) • Placebo: 5 of148 (3.4%)	• Filgotinib 200 mg: 5 of 147 (3.4%) • Filgotinib 100 mg: 6 of 153 (3.9%) • Placebo: 3 of148 (2.0%)	Fair
Westhovens et al., 2016[22] NCT01888874 DARWIN 1	Filgotinib 50, 100 or 200 mg QD or twice daily; Placebo At week 12, patients on placebo who had not achieved a 20% improvement in SJC66 and TJC68 were reassigned to receive filgotinib 100 mg QD or 50 mg twice daily; patients who had not achieved this target who were receiving filgotinib 50 mg QD were reassigned to receive filgotinib 100 mg QD, and patients on filgotinib 25 mg twice daily received filgotinib 50 mg twice daily, continuing on their new dose until week 24. Total N = 594	ACR20 response at 12 weeks: • Filgotinib 100 mg: 57 of 85 (63.5%) compared to placebo; *P* = .04 • Filgotinib 200 mg: 59 of 86 (66.6%) compared to placebo; *P* = .007, • Placebo: 38 of 86 (44.2%)	• Filgotinib 100 mg: 4 of 85 (4.7%) • Filgotinib 200 mg: 2of 86 (2.3%) • Placebo: 4 of 56 (7.1%)	• Filgotinib 100 mg: • 5 of 85 (5.9%) • Filgotinib 200 mg: 3 of 86 (3.5%) • Placebo: 2 of 56 (3.6%)	Fair

Authors, Year Trial Registration 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	Study Quality
Kavanaugh et al., 2017[19] NCT01894516 DARWIN 2	Filgotinib 50mg, 100mg, or 200mg QD + MTX; Placebo At week 12, all patients in the placebo group, and patients in the Filgotinib 50-mg group who had not achieved at least a 20% improvement in SJC66 and TJC68, were reassigned to receive filgotinib 100 mg and continued on this dose until week 24. Total N = 283	ACR20 response at 12 weeks: • Filgotinib 100 mg: 46 of 70 (65.7%) • Filgotinib 200 mg: 50 of 69 (72.5%) Placebo: 21 of 72 (29.2%) • *P* value NR	• Filgotinib 100 mg: 0 of 70 (0%) • Filgotinib 200 mg: 3 of 69 (4.3%) • Placebo: 1 of 72 (1.4%)	• Filgotinib 100 mg: 0 of 70 (0%) • Filgotinib 200 mg: 1 of 69 (1.4%) • Placebo: 4 of 72 (5.6%)	Fair
Peficitinib Compared to Placebo					
Takeuchi et al., 2019[37] 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%)	Fair

Authors, Year Trial Registration 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	Study Quality
Tanaka et al., 2019[36] 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%)	Fair
Kivitz et al., 2017[20] 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%)	Fair
Genovese et al., 2017[18] 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%)	Fair
Takeuchi et al, 2015[17] 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%)	Fair

Authors, Year Trial Registration 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	Study Quality
Peficitinib Compared to Etanercept					
Tanaka et al., 2019[36] 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%)	Fair
Combination Therapy					
Glatt et al., 2019[35] 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 + bimekizumab 240 mg: 2 of 52 (4%) • Certolizumab pegol 200 mg+ placebo: 3 of 27 (11%)	• Certolizumab pegol 200 mg + bimekizumab 240 mg: 4 of 52 (8%) • Certolizumab pegol 200 mg + placebo: 3 of 27 (11%)	Fair

Abbreviations. ACR20: American College of Rheumatology, number refers to percentage improvement; AE,:adverse event; CI: confidence interval; DAS28-CRP: 28-Joint Disease Activity Score, C-reactive protein; ET: early termination; mg: milligram; LD: loading dose; mTSS25: van der Heijde-modified total Sharp score; MTX: methotrexate; NCT: U.S. National Clinical Trial; NR: not reported; QD: dose delivered daily; QW: dose delivered weekly; Q2W: dose delivery every 2 weeks; RA: rheumatoid arthritis; RCT: randomized controlled trial; SAE: serious adverse event; SJC66: swollen joint count based on 66 joints; TIM: targeted immune modulator; TJC68: tender joint count based on 68 joints.

The two phase 2 studies (DARWIN 1 and DARWIN 2) reported similar results for response, remission, and functional capacity as the phase 3 FINCH trial.[19,22] In addition, we identified a publication that presented patient-reported outcomes from these 2 trials.[106] After 24 weeks of treatment with filgotinib, more patients reported rapid and sustained improvements compared to placebo in all evaluated outcomes, including mental health, pain, functional status, physical wellbeing, and fatigue.[106]

Two RCTs assessed general and specific AEs at 24 weeks,[22,23] and 1 RCT assessed AEs at 12 weeks.[19] Findings related to any or serious treatment-emergent AEs were consistent across the 3 studies.[19,22,23] No significant differences were found between filgotinib and placebo groups in AEs or SAEs.[19,22,23]

Peficitinib Compared to Placebo

We identified 5 double-blinded, randomized, placebo-controlled trials with data on 1,977 participants assessing the benefits and harms of peficitinib in patients with RA.[17,18,20,36,37] Three trials were phase 2 studies, and two trials were phase 3 studies.[36,37] We rated all 5 studies as of fair methodological quality because of extensive manufacturer involvement in study design, execution, and reporting.[17,18,20,36,37] All studies included participants with moderate-to-severe RA for at least 6 months.[17,18,20,36,37] Two studies included participants with inadequate response to or intolerance of at least one DMARD agent[18,36]; in the other 2 studies, participants had an inadequate response to methotrexate.[20,37]

The phase 3 double-blinded multicenter RCTs (RAJ 4 and RAJ 3 trials) enrolled 1,028 participants with active RA.[36,37] Participants were randomized to 12 weeks of treatment with peficitinib (100 or 150 mg once daily), or placebo.[36,37] All participants from 1 study[37] and 59% from the other[36] received concomitant methotrexate. The primary outcome was the ACR20 response after 12 weeks.[36,37] 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.[36,37] Both studies reported similar results.[36,37] After 12 weeks, significantly more participants in the intervention group achieved an ACR20 response compared to 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).[36,37] 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).[36,37]

Two of three phase 2 studies reported similar significant results for response, remission, and functional capacity as the phase 3 trials.[17,18] The third phase 2 study did not identify statistically significant clinical improvements for peficitinib 100 mg and 150 mg compared to placebo.[20]

All 5 RCTs assessed general and specific AEs at 12 weeks.[17,18,20,36,37] Findings related to any or serious treatment-emergent AEs were consistent across the 5 studies.[17,18,20,36,37] No significant differences were found between peficitinib and placebo groups in AEs or SAEs.[17,18,20,36,37]

Peficitinib Compared to Etanercept

One fair-methodological-quality double-blinded multicenter RCT assessed the efficacy and harms of peficitinib compared to open-label etanercept in participants with RA.[36] Participants were randomized to peficitinib 100 mg, peficitinib 150 mg, etanercept 50 mg, or placebo for 52 weeks.[36] The primary endpoint was the response rate according to ACR20 at 12 weeks.[36] 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.[36] At 12 weeks, a numerically lower proportion of participants in peficitinib groups achieved an ACR20 response compared to participants in the etanercept group (peficitinib 100 mg, 58%; peficitinib 150 mg, 75%; etanercept 50 mg, 84%; *P* value NR).[36] Treatment with etanercept also appeared to provide numerically greater improvements than either peficitinib 100 mg or 150 mg, across all outcomes measured.[36]

Combination Therapy (Certolizumab pegol Compared to Certolizumab pegol + Bimekizumab)

One fair-methodological-quality double-blinded RCT assessed 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.[35] The control group was maintained on the certolizumab pegol 200 mg therapy and also received placebo.[35] The primary endpoint was the change in DAS28-CRP at 12 weeks of treatment.[35] Key secondary endpoints were DAS28-CRP < 2.6 and ACR20/50/70 responses, together with safety outcomes.[35] 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).[35] Likewise, DAS28-CRP remission rates (< 2.6) were higher for the bimekizumab combination group (26% vs.8%; *P* value NR).[35] Significantly more participants experienced treatment-emergent AEsin the combination group compared to the certolizumab pegol monotherapy group (79% vs. 59%; *P* value NR).[35]

Comparative Harms (Key Question 2)

In this section, we describe harm findings of RCTs and cohort studies. Appendix B, Table B1 and Table B2 provide detailed study characteristics and results from the included RCTs, and Appendix B, Table B3 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 6 new RCTs with data on the overall incidence of AEs, discontinuation due to AEs, and SAEs.[21,24-26,31,38] Overall, we describe harm findings of 20 included RCTs.[21,24-26,31,38-42,44-48,50-52,54,55] Of these, 4 RCTs evaluated combination

strategies.[50,51,54,55] Table 8 presents the Summary of Findings (GRADE) for comparisons with data on harms. Appendix C, Table C1 and Table C2 provide detailed evidence profiles.

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

Outcome	Quality of Evidence	Relationship	Rationale
Abatacept Compared to Adalimumab			
Overall AEs (1 RCT[39])	Low ●●○○	No difference between groups	Downgraded 1 level for study limitations and 1 level for imprecision
SAEs(1 RCT[39])	Very low ●○○○	No difference between groups	Downgraded 1 level for study limitations and 2 levels for very serious imprecision
Abatacept Compared to Infliximab			
Overall AEs(1 RCT[40])	Moderate ●●●○	No difference between groups	Downgraded 1 level for imprecision
SAEs(1 RCT[40])	Low ●●○○	Lower proportion of SAEs with abatacept than infliximab	Downgraded 2 levels for very serious imprecision
Abatacept Compared to Rituximab			
Overall AEs (2 RCTs[38,52])	Low ●●○○	No difference between groups	Downgraded 1 level for study limitations and 1 level for imprecision
SAEs (1 RCT[38])	Very low ●○○○	No difference between groups	Downgraded 1 level for study limitations and 2 levels for very serious imprecision
Abatacept Compared to Tocilizumab			
Overall AEs (1 RCT[26])	Low ●●○○	Lower proportion of overall AE for abatacept than tocilizumab	Downgraded 1 level for study limitations and 1 level for imprecision
SAEs (1 RCT[26])	Very low ●○○○	Lower proportion of SAEs for abatacept than tocilizumab	Downgraded 1 level for study limitations and 2 levels for very serious imprecision
Adalimumab Compared to Baracitinib			
Overall AEs (1 RCT[21])	High ●●●●	No difference between groups	Not downgraded
SAEs (1 RCT[21])	Low ●●○○	Lower proportion of SAEs with adalimumab than baracitinib	Downgraded 2 levels for very serious imprecision
Adalimumab Compared to Certolizumab pegol			
Overall AEs(1 RCT[41])	High ●●●●	No difference between groups	Not downgraded
SAEs (1 RCT[41])	Low ●●○○	No difference between groups	Downgraded 2 levels for very serious imprecision
Adalimumab Compared to Etanercept			
SAEs(1 RCT[42])	Very low ●○○○	No difference between groups	Downgraded 1 level for study limitations and 2 levels for very serious imprecision
Adalimumab Compared to Sarilumab			
Overall AEs (1 RCT[44])	Moderate ●●●○	No difference between groups	Downgraded 1 level for imprecision

Outcome	Quality of Evidence	Relationship	Rationale
SAEs(1 RCT[44])	Low ●●○○	No difference between groups	Downgraded 2 levels for very serious imprecision
Adalimumab Compared to Tocilizumab			
Overall AEs (1 RCT[45])	Low ●●○○	No difference between groups	Downgraded 1 level for indirectness and 1 level imprecision
SAEs (1 RCT[45])	Low ●●○○	No difference between groups	Downgraded 1 level for indirectness and 1 level imprecision
Adalimumab Compared to Tofacitinib			
Overall AEs (3 RCTs[46-48])	High ●●●●	No difference between groups	Not downgraded
SAEs(3 RCTs[46-48])	Moderate ●●●○	No difference between groups	Downgraded 1 level for imprecision
Adalimumab Compared to Upadacitinib			
Overall AEs (1 RCT[24])	High ●●●●	No difference between groups	Not downgraded
SAEs(1 RCT[24])	Low ●●○○	No difference between groups	Downgraded 2 levels for very serious imprecision
Etanercept Compared to Tocilizumab			
SAEs (1 RCT[25])	Moderate ●●●○	No difference between groups	Downgraded 1 level for study limitations
Combination Therapies			
Etanercept + Abatacept Compared to Etanercept; Etanercept+Anakinra Compared to Etanercept			
Overall AEs (2 RCTs[50,51])	Moderate ●●●○	No difference between groups	Downgraded 1 level for imprecision
SAEs (2 RCTs[50,51])	Low ●●○○	More SAEs for combination of etanercept and abatacept or anakinra than etanercept alone	Downgraded 2 levels for very serious imprecision
Rituximab Plus Adalimumab or Etanercept Compared to Adalimumab Alone or Etanercept Alone			
Overall AEs (1 RCT[55])	Low ●●○○	More overall AEs for combination of rituximab with TNF-α inhibitors than TNF-α inhibitor maintenance	Downgraded 2 levels for very serious imprecision
SAEs (1 RCT[55])	Low ●●○○	More SAEs for combination of rituximab with TNF-α inhibitors than TNF-α inhibitor maintenance	Downgraded 2 levels for very serious imprecision
Abatacept Plus Other TIMs (Adalimumab, Anakinra, Etanercept, or infliximab) Compared to Other TIM Alone			
Overall AEs (1 RCT[54])	Low ●●○○	No difference between groups	Downgraded 2 levels for very serious imprecision
SAEs (1 RCT[54])	Low ●●○○	More SAEs for combination of abatacept with other TIM than other TIM 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; SAE: serious adverse event; TIM: targeted immune modulator.

The pharmaceutical industry funded the majority of RCTs included for this key question. 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 5 comparisons, studies reported some statistically significant differences (see Table 9).[21,26,31,40,102] However, these findings are all based on single trials, some of which were of poor methodological quality. Therefore, findings should be interpreted with cautious.

We identified 4 RCTs that randomized patients to a combination of TIMs.[50,51,54,55] The combination of TNF-α inhibitors with a TIM of a different mechanism of action substantially increased the frequency of SAEs.[50,51,55] For example, in a fair-methodological-quality 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).[50]

Similarly, 2 fair-methodological-quality studies revealed that combination therapies were associated with a substantial increase in SAEs.[51,54] One 1 RCT compared a combination of abatacept (2 mg/kg) and etanercept (25 mg twice weekly) to etanercept monotherapy (25 mg twice weekly).[51] The combination was associated with a substantial increase in SAEs (16.5% vs. 2.8%; *P* value NR).[51] The second RCT studied the addition of abatacept to another TIM (background adalimumab, anakinra, etanercept, or infliximab) compared to a background TIM agent and placebo in 167 RA patients.[54] SAEs and serious infections were higher in the combination group (22.3% vs. 12.5%, and 5.8% vs. 1.6%, respectively).[54]

In a small, fair-methodological-quality trial of rituximab added to either etanercept or adalimumab for RA, the combination therapy resulted in 6% of patients with SAEs compared to 0% in the control group, and 5.5% withdrawing due to AEs compared to 0%.[55] 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.[55]

Specific Serious Adverse Events Findings from Cohort Studies

For this update, we identified 6 new cohort studies reporting on specific SAEs.[27,28,30,32-34] Overall, we describe harm findings of 41 included cohort studies.[27,28,30,32-34,56-91] Many of the observational studies were independently funded (national funders). 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. Appendix B, Table B3 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	Study Quality
Abatacept Compared to Adalimumab							
Weinblatt et al., 2013[39] 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	Fair
Schiff et al., 2014[102] 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 compared to adalimumab	
Abatacept Compared to Infliximab							
Schiff et al., 2008[40,107] 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 compared to infliximab	Fair
Abatacept Compared to Rituximab							
Manders et al., 2015[52]	93	52 weeks	*1.14 (0.65 to 2.02)*	NR	NR	No significant differences	Poor
Brown et al. 2018[38] 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	Poor

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	Study Quality
Abatacept Compared to Tocilizumab							
Elmedany et al., 2019[26]	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 compared to tocilizumab	Poor
Adalimumab Compared to Baracitinib							
Taylor et al., 2017[21] 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 compared to baracitinib	Fair
Adalimumab Compared to Certolizumab pegol							
Smolen et al., 2016[41] 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	Fair
Adalimumab Compared to Etanercept							
Jobanputra et al., 2012[42] RED SEA	125	52 weeks	NR	*0.83 (0.39 to 1.78)*	*0.86 (0.31 to 2.40)*	No significant differences	Poor
Adalimumab Compared to Sarilumab							
Burmester et al., 2017[44] 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	Fair
Adalimumab Compared to Tocilizumab							
Gabay et al., 2013[45] 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	Fair

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	Study Quality
Adalimumab Compared to Tofacitinib							
van Vollenhoven et al., 2012[46] 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	Fair
Fleischmann et al., 2012[47]	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	Fair
Fleischmann et al., 2017[48] 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	Fair
Adalimumab Compared to Upadacitinb							
Fleischmann et al., 2019[24] 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	Fair
Etanercept Compared to Tocilizumab							
Giles et al., 2019[25] 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	Fair
Tocilizumab Compared to Sarilumab							
Emery et al., 2018[31] 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 compared to sarilumab 200 mg	Poor

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	Study Quality
Combination Strategies							
Anakinra Plus Etanercept Compared to Etanercept							
Genovese et al., 2004[50]	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	Fair
Abatacept Plus Etanercept Compared to Etanercept							
Weinblatt et al., 2007[51]	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	Fair
Abatacept Plus other TIM[f] Compared to other TIM[f] alone							
Weinblatt et al., 2006[54]	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	Fair
Rituximab Plus Adalimumab or Etanercept Compared to Adalimumab Alone or Etanercept Alone							
Greenwald et al., 2011[55] TAME	54	24 weeks	*1.13 (0.90 to 1.41)*	*Not estimable*[e]	*Not estimable*[e]	No significant differences	Fair

Note. [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 compared to 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 compared to sarilumab 200 mg. [e] RR not estimable with OpenEpi due to no events in one group. [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: relative risk; SAE: serious adverse event; TIM: targeted immune modulator.

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

Authors, Year Registry Name, Country	Number of Patients	Follow-up	Comparison	Population	Outcome	Results	Study Quality
Mortality							
Kim et al., 2018[27] IMS PharMetrics, MarketScan and Medicare	20,922	16,280 PY	Tocilizumab vs. abatacept	RA	Mortality	No significant differences	Fair
Listing et al., 2015[78] RABBIT, Germany	8,908	31,378 PY 42.4 months	Adalimumab or infliximab vs. etanercept	RA	Mortality	No significant differences	Good
Simard et al., 2012[82] ARTIS, Sweden	5,212	19,118 PY	Adalimumab or infliximab vs. etanercept	RA	Mortality	No significant differences.	Fair
Serious Infections							
Pawar et al., 2019[34] IMS PharMetrics, MarketScan and Medicare	49,183	42,139 PY	Tocilizumab vs. pooled TNF-α inhibitors	RA	Serious infections	No significant differences	Fair
	20,828	17,693 PY	Tocilizumab vs. abatacept			Significantly higher for tocilizumab compared to abatacept (aHR, 1.40; 95% CI, 1.20 to 1.63)	
Gron et al., 2019[33] ARTIS, Sweden and DANBIO, Denmark	6,648	24 months	Abatacept vs. tocilizumab vs. rituximab	RA	Serious infections	No significant differences	Poor
Rutherford et al., 2018[32] BSRBR, U.K.	19,282	46,771 PY	Adalimumab, infliximab, certolizumab, tocilizumab, or rituximab vs. etanercept	RA	Serious infections	Significantly higher for tocilizumab compared to etanercept (aHR, 1.22; 95% CI, 1.02 to 1.47) Significantly lower with certolizumab pegol compared to etanercept (aHR, 0.75; 95% CI, 0.58 to 0.97)	Fair

Authors, Year Registry Name, Country	Number of Patients	Follow-up	Comparison	Population	Outcome	Results	Study Quality
Mori et al., 2017[81] SARABA, Japan	1,596 new treatment episodes	1,239 PY	Adalimumab, abatacept, infliximab, or tocilizumab vs. etanercept	RA	Serious infections	No significant differences	Poor
Aaltonen et al., 2015[56] ROB-FIN, Finland	3,532	7,875 PY	Pooled TNF-α inhibitors (adalimumab, etanercept, infliximab) vs. rituximab	RA	Serious infections	No significant differences	Good
Yun et al., 2015 and 2016[88,89] Medicare, U.S.	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) compared with abatacept	Good
Chiang et al., 2014[62] NHIRD, Taiwan	2,144	12 months	Adalimumab vs. etanercept	RA	Infections	Significantly higher for etanercept compared to adalimumab (aHR, 2.04; 95% CI, 1.13 to 3.61)	Good
Curtis et al., 2014[66] VHA, U.S.	3,152	1 year	Abatacept, adalimumab, infliximab, or rituximab vs. etanercept	RA	Hospitalized bacterial infections	Significantly higher for infliximab compared to etanercept (aHR, 2.3; 95% CI, 1.3 to 4.0)	Good
Flouri et al., 2014[70] Hellenic Registry of Biologic Therapies, Greece	1,208	Median follow-up 2.9 to 3 years	Adalimumab vs. etanercept vs. enfliximab	RA	Serious infections	Significantly higher for infliximab compared to adalimumab and etanercept (IR, 4.0 vs. 2.7 vs. 2.1 per 100 PY; $P < .001$)	Good

Authors, Year Registry Name, Country	Number of Patients	Follow-up	Comparison	Population	Outcome	Results	Study Quality
Chiu et al., 2014[63] NHIRD, Taiwan	2,238	NR	Adalimumab vs. etanercept	RA	Serious bacterial infections	Significantly higher for adalimumab compared to etanercept (IRR, 1.83; 95% CI, 1.19 to 2.77)	Good
Van Dartel et al., 2013[83] DREAM, Netherlands	2,356	4,832 PY	Adalimumab vs. etanercept vs. infliximab	RA	Serious infections	Significantly lower for etanercept compared to adalimumab (aHR, 1.83; 95% CI, 1.49 to 2.26) and infliximab (aHR, 2.04; 95% CI, 1.62 to 2.58)	Fair
Johnston et al., 2013[77] SABER, U.S.	4,332	Abatacept: 1,005 PY; adalimumab: 1,772 PY; etanercept: 1,392 PY; infliximab: 7,89 PY; rituximab: 463 PY	Abatacept vs. adalimumab vs. etanercept vs. infliximab vs. rituximab	RA	Severe infections	Significantly higher for infliximab compared to rituximab (aHR, 1.62; 95% CI, 1.03 to 2.55)	Good
Atzeni et al., 2012[60] GISEA, Italy	2,769	NR	Adalimumab vs. etanercept vs. infliximab	RA	Serious infections	Significantly higher for adalimumab compared to etanercept (aHR, 2.22; 95% CI, 1.12 to 4.42) Significantly higher for infliximab compared to etanercept (aHR, 4.92; 95% CI, 2.71 to 8.91)	Fair

Authors, Year Registry Name, Country	Number of Patients	Follow-up	Comparison	Population	Outcome	Results	Study Quality
Curtis et al., 2012[65] Medicare, U.S.	11,657	10,240 PY	Adalimumab vs. etanercept vs. infliximab	RA	Serious infections	Significantly higher for infliximab compared to adalimumab (aHR, 1.49; 95% CI, 1.05 to 2.10) and for infliximab compared to etanercept (aHR, 1.52; 95% CI, 1.08 to 2.12	Fair
Galloway et al., 2011[72] BSRBR, U.K.	11,881	NR	Adalimumab vs. etanercept vs. infliximab	RA	Serous septic arthritis	No significant differences	Fair
Galloway et al., 2013[73] BSRBR, U.K.	11,181	17,048 PY	Adalimumab vs. etanercept vs. infliximab	RA	Serious skin and soft tissue infections	No significant differences	Fair
Tuberculosis							
Rutherford et al., 2018[30] BSRBR, U.K.	19,282	106,347 PY	Rituximab or tocilizumab vs. pooled TNF-α inhibitors	RA	Tuberculosis	Significantly lower for rituximab compared to pooled TNF-α inhibitors (aHR, 0.16; 95% CI, 0.04 to 0.67)	Fair
	7,243	21,015 PY	Etanercept vs. rituximab			Significantly higher for etanercept compared to rituximab (aHR, 4.63; 95% CI, 1.06 to 20.2)	
Arkema et al., 2015[58] SWEDISH, Sweden	10,800	48,228 PY; mean 4.5 ± 2.8 years	Adalimumab, infliximab, rituximab vs. etanercept	RA	Tuberculosis	No significant differences	Fair
Chiu et al., 2014[63] NHIRD, Taiwan	2,238	NR	Adalimumab vs. etanercept	RA	Tuberculosis	Significantly higher for adalimumab compared to etanercept (IRR, 2.35; 95% CI, 1.29 to 4.15)	Good

Authors, Year Registry Name, Country	Number of Patients	Follow-up	Comparison	Population	Outcome	Results	Study Quality
Dixon et al., 2010[67] BSRBR, U.K.	10,712	34,025 PY	Adalimumab or infliximab vs. etanercept	RA	Tuberculosis	Significantly higher for adalimumab (aIRR, 4.2; 95% CI, 1.4 to 12.4) and infliximab compared to etanercept (aIRR, 3.1; 95% CI, 1.0 to 9.5)	Fair
Opportunistic Infections							
Pawar et al., 2019[34] IMS PharMetrics, MarketScan and Medicare	49,183	42,139 PY	Tocilizumab vs. pooled TNF-α inhibitors	RA	Opportunistic infections	No significant differences	Fair
Rutherford et al., 2018[30] BSRBR, U.K.	19,282	106,347 PY	Rituximab or tocilizumab vs. pooled TNF-α inhibitors	RA	Opportunistic infections	No significant differences	Fair
Baddley et al., 2014[61] SABER, U.S.	24,384	NR	Adalimumab or infliximab vs. etanercept	RA and other indications	Opportunistic infections	Significantly higher for infliximab compared to etanercept (aHR, 2.9; 95% CI, 1.5 to 5.4)	Fair
Varicella Zoster							
Curtis et al., 2016[64] Marketscan and Medicare, U.S.	69,726	44,987 PY	Adalimumab, certolizumab, pegol, etanercept, golimumab, infliximab, rituximab, tocilizumab, or tofacitinib, vs. abatacept	RA	Herpes zoster and herpes simplex	Significantly higher for tofacitinib compared to abatacept (aHR, 1.40; 95% CI, 1.09 to 1.81)	Fair
Galloway et al., 2013[73] BSRBR, U.K.	11,881	17,048 PY	Adalimumab vs. etanercept vs. infliximab	RA	Shingles	Significantly higher for infliximab compared to adalimumab (aHR, 1.5; 95% CI, 1.1 to 2.0)	Fair

Authors, Year Registry Name, Country	Number of Patients	Follow-up	Comparison	Population	Outcome	Results	Study Quality
Winthrop et al., 2013[84] SABER, U.S.	33,324	28,392 PY	Adalimumab or etanercept vs. infliximab	RAand other indications	Herpes zoster	No significant differences	Fair
Malignancies							
Kim et al., 2019[28] IMS PharMetrics, MarketScan and Medicare	16,930	14,491 PY	Toacilizumab vs. abatacept	RA	Malignancy (excluding non-melanoma skin cancer)	No significant differences	Fair
Harigai et al., 2016[75] SECURE, Japan	14,440	5 years	Adalimumab, etanercept, or tocilizumab vs. infliximab	RA	Malignant lymphoma; Nonhemato-poietic malignancy	Significantly higher for infliximab compared to etanercept (IR 2.32 per 1,000 PY vs. IR 0.70 per 1,000 PY; $P < .001$; on drug analysis) Significantly higher for infliximab compared to etanercept (IR 3.38 per 1,000 PY vs. IR 1.30 per 1,000 PY; $P < .001$; ever-exposed analysis) No significant differences	Poor
Aaltonen et al., 2015[56] ROB-FIN, Finland	3,532	7,875 PY	Pooled TNF-α inhibitors (adalimumab, etanercept, infliximab) vs. rituximab	RA	Malignancies	No significant differences	Good
Askling et al., 2009[59] SWEDSIH, Sweden	6,366	25,693 PY	Adalimumab vs. etanercept vs. infliximab	RA	Malignancy	No significant differences	Good

Authors, Year Registry Name, Country	Number of Patients	Follow-up	Comparison	Population	Outcome	Results	Study Quality
Wolfe et al., 2007[86] National Databank for Rheumatic Diseases, U.S.	13,001	49,000 PY	Adalimumab vs. etanercept vs. infliximab vs. anakinra	RA	Lymphoma	No significant differences	Good
Non-melanoma and Melanoma Skin Cancer							
Merce, et al., 2012[79] BSRBR, U.K.	13,784	43,798 PY	Adalimumab or etanercept vs. infliximab	RA	Basal cell carcinoma	No significant differences	Fair
Amari et al., 2011[57] Veterans Affairs, (Austin Automation Center [AAC]), U.S.	4,088	11,084 PY	Adalimumab or infliximab vs. etanercept	RA	Non-melanoma skin cancers	Significantly higher for adalimumab compared to etanercept (IR, 0.036 per PY vs. 0.021 per PY; $P < .001$)	Fair
Wolfe et al., 2007[86] National Databank for Rheumatic Diseases, U.S.	13,001	49,000 PY	Adalimumab vs. etanercept vs. infliximab vs. anakinra	RA	Non-melanoma skin cancers; Melanoma	No significant differences	Good
Cardiovascular Events and Congestive Heart Failure							
Kim et al. 2019[27] IMS PharMetrics, MarketScan and Medicare	20,922	16,280 PY	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	Fair

Authors, Year Registry Name, Country	Number of Patients	Follow-up	Comparison	Population	Outcome	Results	Study Quality
Iannone et al., 2017[76] GISEA, Italy	7,539	2 years	Pooled TNF-α inhibitors (Adalimumab, etanercept, infliximab) vs. tocilizumab or abatacept	RA	Cardiovascular events	No significant differences	Poor
Zhang et al., 2016[90] Medicare, U.S.	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	No significant differences for abatacept compared to other drugs Significantly higher for etanercept compared to abatacept (aHR, 1.33; 95% CI, 1.01 to 1.76) and infliximab compared to abatacept (aHR, 1.30; 95% CI, 1.03 to 1.64)	Fair
Wolfe et al., 2004[85] National Databank for Rheumatic Diseases, U.S.	13,171	2 years	Etanercept vs. infliximab	RA	Heart failure	No significant differences.	Poor
Gastrointestinal Perforations							
Monemi et al., 2016[80] MarketScan, U.S.	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 compared to any TNF-α inhibitor (aIRR, 4.0; 95% CI, 1.1 to 14.1) No significant differences for Tocilizumab compared to any TNF-α inhibitor	Fair

Authors, Year Registry Name, Country	Number of Patients	Follow-up	Comparison	Population	Outcome	Results	Study Quality
Xie et al., 2016[87] MarketScan and Medicare, U.S.	167,113	TNF-α inhibitors: 130 324 PY; abatacept: 39,227 PY; tocilizumab: 10,293; tofacitinib: 2,329; rituximab: 4,134 PY	Pooled TNF-α inhibitors (adalimumab, certolizumab, etanercept, golimumab, infliximab) vs. abatacept, tocilizumab, tofacitinib, or rituximab	RA	Lower gastrointestinal tract perforation	Significantly higher for tocilizumab compared to any TNF-α inhibitor (aHR, 2.51; 95% CI, 1.31 to 4.80)	Fair

Abbreviations. aHR, adjusted hazard ratio; aIRR: adjusted incidence rate ratio; ARTIS: antirheumatic therapy in Sweden biologics registry; BSRBR: British Society for Rheumatology biologics register; CABG: coronary artery bypass grafting; CI: confidence interval; DANBIO: nationwide registry of biological therapies in Denmark; DREAM: Dutch rheumatoid arthritis monitoring registry; GISEA: Italian Group for the Study of Early Arthritis; IR: unadjusted incidence rate; IRR: incidence rate ratio; LOHREN: Lombard Rheumatology Network; NHIRD: National Health Insurance Research Database Taiwan; NR: not reported; PCI: percutaneous coronary intervention; PY: 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; SAE: serious adverse event; SARABA: SAfety profile of RA patients receiving Biological Agents study; SECURE: SafEty of biologics in Clinical Use in Japanese patients with RhEumatoid arthritis; SCQM-RA: Swiss Clinical Quality Management in Rheumatic Diseases; 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; U.K.: United Kingdom; vs.: versus.

Mortality

We located 3 publications of comparative data from observational studies on mortality.[27,78,82] Two studies did not report statistically significant differences in mortality among TNF-α inhibitors.[78,82] Specifically, 1 publication reported data from 5,212 patients (19,118 patient-years) from the Swedish ARTIS (Antirheumatic Therapy in Sweden biologics registry) database.[82] Overall, 179 patients died.[82] No statistically significant differences were found in adjusted hazard ratio (aHR) of death for adalimumab or infliximab compared to etanercept (aHR, 1.3; 95% CI, 0.9 to 2.0; aHR, 1.1; 95% CI, 0.7 to 1.7, respectively).[82]

A second study in RA patients analyzed data from 8,908 patients (31,378 patient-years) from the German biologics register (RABBIT).[78] Overall, 463 patients died during this observation period.[78] No statistically significant differences were found in the unadjusted hazard ratios (HRs) for mortality between the TNF-α inhibitors (adalimumab compared to etanercept: HR, 0.94; 95% CI, 0.75 to 1.18; infliximab compared to etanercept: HR, 1.05; 95% CI, 0.79 to 1.38).[78] One multidatabase cohort study including 20,922 patients (16,280 patient-years) found no difference in all-cause mortality for tocilizumab compared to abatacept (aHR, 0.99; 95% CI, 0.62 to 1.60).[27]

Serious Infections

We identified 20 observational studies containing data on the comparative risk of TIMs for serious infections.[32-34,56,60,62,63,65,66,69-74,77,81,83,88,89,91] 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, 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.[60,65,66,74,77,88,89]

A recent observational study that used propensity score-matched data of more than 49,000 patients from 3 U.S. databases (Medicare, IMS, and MarketScan) reported no statistically significant difference in serious infections for tocilizumab (N = 16,074) compared to TNF-α inhibitors (N = 33,109; 3 databases combined: HR, 1.05; 95% CI, 0.95 to 1.16).[34] Propensity matching was applied to control for more than 70 baseline covariates (i.e., potential prognostic factors or confounders) within each database.[34] Serious infections included bacterial, viral, or opportunistic infection based on discharge diagnoses.[34] The authors also reported a statistically significant higher risk of serious infections in patients treated for RA with tocilizumab (N = 10,414) compared to abatacept (N = 10,414; 3 databases combined: HR, 1.40; 95% CI, 1.20 to 1.63).[34]

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	Study Quality
TNF-α Inhibitor Compared to TNF-α inhibitor		
Adalimumab Compared to Etanercept		
Favalli et al., 2009[69]	No significant difference	Fair
Galloway et al., 2011[71]	No significant difference	Good
Atzeni et al., 2012[60]	Significantly higher for adalimumab compared to etanercept (aHR, 2.20; 95% CI, 1.10 to 4.40)	Fair
van Dartel et al., 2013[83]	Significantly higher for adalimumab compared to etanercept (aHR, 1.83; 95% CI, 1.49 to 2.26)	Fair
Chiang et al., 2014[62]	Significantly higher for etanercept compared to adalimumab (aHR, 0.49; 95% CI, 0.28 to 0.88)[a]	Good
Mori et al., 2017[81]	No significant difference	Fair
Rutherford et al., 2018[32]	No significant difference	Fair
Adalimumab Compared to Infliximab		
Galloway et al., 2011[71]	No significant difference	Good
Grijalva et al., 2011[74]	Significantly lower for adalimumab compared to infliximab (aHR, 0.81; 95% CI, 0.68 to 0.98)[a]	Fair
Curtis et al., 2011[91]	Significantly lower for adalimumab compared to infliximab (aHR, 0.52; 95% CI, 0.39 to 0.71)	Fair
Curtis et al., 2012[65]	Significantly lower for adalimumab compared to infliximab (aHR, 0.67; 95% CI, 0.48 to 0.95)[a]	Fair
Etanercept Compared to Infliximab		
Favalli et al., 2009[69]	No significant difference	Fair
Galloway et al., 2011[71]	No significant difference	Good
Grijalva et al., 2011[74]	Significantly lower for etanercept compared to infliximab (aHR, 0.79; 95%, 0.68 to 0.93)[a]	Fair
Curtis et al., 2011[91]	Significantly lower for etanercept compared to infliximab (aHR, 0.64; 95% CI, 0.49 to 0.84)	Fair
Atzeni et al., 2012[60]	Significantly lower for etanercept compared to Infliximab (aHR, 0.20; 95% CI, 0.11 to 0.37)[a]	Fair
Curtis et al., 2012[65]	Significantly lower for etanercept compared to infliximab (aHR, 0.66; 95% CI, 0.47 to 0.93)[a]	Fair
van Dartel et al., 2013[83]	Significantly lower for etanercept compared to infliximab (aHR, 0.49; 95% CI, 0.39 to 0.62)[a]	Fair
Mori et al., 2017[81]	No significant difference	Fair
Rutherford et al., 2018[32]	No significant differences	Fair
Certolizumab pegol Compared to Etanercept		
Rutherford et al., 2018[32]	Significantly lower for certolizumab pegol compared to etanercept (aHR, 0.75; 95% CI, 0.58 to 0.97)	Fair
TNF-α Inhibitor Compared to Abatacept		
Adalimumab Compared to Abatacept		
Yun et al., 2016[89]	No significant difference	Good
Certolizumab pegol Compared to Abatacept		
Yun et al., 2016[89]	No significant difference	Good

Authors, Year	Result	Study Quality
Etanercept Compared to Abatacept		
Yun et al., 2016[89]	Significantly higher for etanercept compared to abatacept (aHR, 1.24; 95% CI, 1.07 to 1.45)	Good
Mori et al., 2017[81]	No significant difference	Fair
Golimumab Compared to Abatacept		
Yun et al., 2016[89]	No significant difference	Good
Infliximab Compared to Abatacept		
Yun et al., 2016[89]	Significantly higher for infliximab compared to abatacept (aHR, 1.39; 95% CI, 1.21 to 1.60)	Good
Curtis et al., 2011[91]	Significantly higher for adalimumab compared to abatacept (aHR, 1.47; 95% CI, 1.04 to 2.08)[a]	Fair
TNF-α Inhibitor Compared to Rituximab		
Adalimumab Compared to Rituximab		
Johnston et al., 2013[77]	No significant difference	Good
Aaltonen et al., 2015[56]	No significant difference	Good
Etanercept Compared to Rituximab		
Johnston et al., 2013[77]	No significant difference	Good
Curtis et al., 2014[66]	No significant difference	Good
Aaltonen et al., 2015[56]	No significant difference	Good
Rutherford et al., 2018[32]	No significant difference	Fair
Infliximab Compared to Rituximab		
Curtis et al., 2011[91]	No significant difference	Fair
Johnston et al., 2013[77]	Significantly higher for Infliximab compared to rituximab (aHR, 1.62; 95% CI, 1.03 to 2.55)	Good
Aaltonen et al., 2015[56]	No significant difference	Good
TNF-α Inhibitor Compared to Tocilizumab		
Etanercept Compared to Tocilizumab		
Mori et al., 2017[81]	No significant difference	Fair
Non-TNF-α inhibitor Compared to Non-TNF-α inhibitor		
Abatacept Compared to Rituximab		
Johnston et al., 2013[77]	No significant difference	Good
Yun et al., 2016[89]	Significantly lower for abatacept compared to rituximab (aHR, 0.73; 95% CI, 0.65 to 0.83)[a]	Good
Gron et al., 2019[33]	No significant difference	Poor
Tocilizumab Compared to Abatacept		
Yun et al., 2016[89]	No significant difference	Good
Gron et al., 2019[33]	No significant difference	Poor
Pawar et al. 2019[34]	Significantly higher for tocilizumab compared to abatacept (aHR, 1.40; 95% CI, 1.20 to 1.63)	Fair
Tocilizumab Compared to Rituximab		
Gron et al., 2019[33]	No significant difference	Poor

Note. [a] *Direction of comparison was reversed compared to 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.*

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.[89] The outcome of interest was the first hospitalized infection during 12 months of follow-up.[89] 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)[89]. 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.[89] No statistically significant differences could be detected among other TIM agents.[89] A subgroup analysis of patients who were previously hospitalized because of an infection confirmed a higher risk of infliximab compared to abatacept and etanercept.[88]

Another analysis of Medicare data (more than 4,000 patients) in patients with RA who switched from TNF-α inhibitors to a second-line treatment (other TNF-α inhibitor, abatacept, or rituximab) found a statistically significantly higher risk for serious infections for infliximab than rituximab (aHR,1.62; 95% CI, 1.03 to 2.55).[77] The study did not find any statistically significant differences in serious infections when comparing abatacept, adalimumab, or etanercept to rituximab.[77]

A prospective 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.[32] Authors reported that compared to etanercept, incidence of serious infection 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).[32] However, authors found no statistically significant differences for infliximab, adalimumab, or rituximab compared to etanercept.[32]

In a Japanese analysis of 1,596 new treatment episodes among RA patients with no prior biological therapy from 8 community hospitals, the HRs for serious infections were not significantly different between infliximab (1.54; 95% CI, 0.78 to 3.04), adalimumab (1.72; 95% CI, 0.88 to 3.34), abatacept (1.11; 95% CI, 0.55 to 2.21), and tocilizumab (1.02; 95% CI, 0.55 to 1.87) compared to etanercept.[81] However, the authors reported a significantly higher rate of pulmonary hospitalized infections for adalimumab compared to tocilizumab (HR, 4.43; 95% CI, 1.72 to 11.37).[81] For the comparison of adalimumab and etanercept, results conflict with 3 other cohort studies (Table 11).[60,62,83]

An analysis from the Danish (DANBIO) and Swedish (ARTIS) registries included more than 8,000 treatment courses of 6,648 patients with non-TNF-α inhibitors, abatacept, rituximab, and tocilizumab.[33] Within 12 months after treatment start, in pooled analyses of both registries the incidence of serious infections was not statistically significant different for abatacept compared to tocilizumab (adjusted RR, 1.13; 95% CI, 0.91 to 1.42) or rituximab (adjusted RR, 0.88; 95% CI, 0.69 to 1.12) as well as for tocilizumab compared to rituximab (adjusted RR, 0.78; 95% CI, 0.61 to 1.01).[33]

Tuberculosis

We located 4 retrospective studies that reported on the comparative risk of tuberculosis in patients taking TIMs.[30,58,63,67] The larger studies provided data on 10,712[67] and 19,282[30] RA patients from the British Society for Rheumatology Biologics Register, and 10,800 RA

patients from Swedish registers.[58] The smallest study analyzed 2,238 matched patients from the Taiwan's National Health Insurance Research Database.[63] In this study patients treated with etanercept were propensity score-matched with adalimumab patients to control for covariates.[63] The results of these 4 studies consistently showed that etanercept is associated with a lower risk of developing tuberculosis than adalimumab or infliximab, although baseline risk of tuberculosis differed between settings.[30,58,63,67]

Specifically, in 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).[67] A comparative analysis showed a statistically significant increased risk of tuberculosis for patients treated with adalimumab compared to those on etanercept (aIRR, 4.2; 95% CI, 1.4 to 12.4).[67] 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).[67] The median time to event was 13.4 months from start of therapy.[67] Considering that the rates of tuberculosis infection in Britain are higher than in the U.S., the absolute rates may be lower, but it is unlikely that the relative rates across the drugs would differ.

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 to those treated with TNF-α inhibitors (65 events per 100,000 patient-years; aHR, 0.16; 95% CI, 0.04 to 0.67).[30]

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.[58] 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).[58] In these databases, no cases of tuberculosis were seen in patients treated with abatacept, anakinra, certolizumab pegol, golimumab, and tocilizumab.[58] Adjusted HRs did not detect any statistically significant differences in the risk for tuberculosis among any of the treatments.[58] However, these results might be due to lack of statistical power, as this study analyzed fewer patient-years than the studies reported above.

In addition, data from Taiwan (Taiwan's National Health Insurance Research Database) support the findings of a higher risk of tuberculosis with adalimumab compared to etanercept (aIRR, 2.35; 95% CI, 1.29 to 4.15).[63]

Opportunistic Infections

Three cohort studies provided data on opportunistic infections.[30,34,61] The fair-methodological-quality SABER study (SAfety Assessment of Biologic ThERapy) included U.S. 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 two large observational studies including more than 69,000 patients reported no statistically significant difference for TNF-α inhibitors (different pooled drugs) compared to tocilizumab or rituximab.[30,34] In general, the number of opportunistic infections was low.[30,34] 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 to rituximab (aHR, 0.96; 95% CI, 0.62 to 1.50) or tocilizumab (aHR, 0.52; 95% CI, 0.17 to 1.65).[30] Overall, the incidence of opportunistic infections (excluding tuberculosis) was 134 per 100,000 patient-years.[30] The most common were herpes zoster (n = 54), pneumocystis jirovecii (n = 15), and legionella (n = 11).[30]

Varicella Zoster

Three 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.[64,73,84] All studies performed statistical adjustment for baseline risk including age, sex, race, residence, disease duration, disease severity, and others.[64,73,84]

The largest study used Medicare and MarketScan data for almost 58,000 patients with RA;[64] it assessed the risk for herpes zoster and herpes simplex in patients treated with abatacept, adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, rituximab, tocilizumab, and tofacitinib.[64] Patients treated with tofacitinib had the numerically highest risk for herpes zoster and herpes simplex infections (incidence rate per 100 person-years, 7.61; 95% CI, 6.06 to 9.55).[64] Compared to abatacept, the risk for tofacitinib was significantly higher (aHR, 1.40, 95% CI, 1.09 to 1.81).[64] The study used abatacept as the reference drug for all comparisons.[64] Risks of all other drugs were not significantly different than the risk of abatacept.[64] Nevertheless, results should be interpreted with cautioun because only 74 patients treated with tofacitinib had a herpes zoster or herpes simplex infection.[64]

Two studies focused on the comparative risks of the TNF-α inhibitors adalimumab, etanercept, and infliximab.[73,84] Adalimumab had the lowest HR for herpes zoster,[73,84] and this difference was significant for the comparison with infliximab in 1 study (HR, 1.5; 95% CI, 1.1 to 2.0).[73] Two studies found no significant difference between etanercept and infliximab (HR, 1.09; 95% CI, 0.82 to 1.45).[73,84]

Malignancies

We located 4 publications of large observational database studies that analyzed the incidence of any malignancy (excluding melanoma or non-melanoma skin cancer) in patients with RA.[28,56,59,86] and 1 study including non-melanoma skin cancer cases.[75]

Three studies reported no significant differences in the risk of malignancy between adalimumab, anakinra, etanercept, infliximab, and rituximab.[56,59,86] One study with pooled data from 3 U.S. databases (IMS PharMetrics, MarketScan and Medicare) found no significant difference for the risk of malignancy for tocilizumab compared to abatacept.[28]

One Japanese study of poor methodological quality reported a higher incidence of malignant lymphoma in patients receiving infliximab compared to patients treated with etanercept ($P < .001$), and no statistically significant difference between infliximab and adalimumab, or infliximab and tocilizumab.[75] The study found no significant difference in the risk of nonhematopoietic cancer among drugs.[75]

In a large U.S. database of 6,282 RA patients receiving biologic therapy, 231 cases of cancer were detected.[86] The adjusted odds ratio for the incidence of any cancer for the individual targeted immune modulators was not elevated for any drug compared to patients not receiving biologic therapy.[86] Furthermore, the results for all malignancies with more than 20 incident cases were also reported, and none of these reached statistical significance for biologics as a group, or for any single drug (cancers reported: bladder, breast, colon, leukemia, lung, lymphoma, non-Hodgkin's lymphoma, prostate).[86]

An analysis from Finland (ROB-FIN register plus a hospital registry) found no significant difference in the incidence rates of malignancy between the TNF-α inhibitors adalimumab, etanercept, infliximab, and rituximab in 3,532 RA patients (7,875 patient-years) who had 53 cases of malignancies.[56]

Non-melanoma and Melanoma Skin Cancer

We located 3 publications reporting on incidence of non-melanoma skin cancers or keratinocyte skin cancers (such as basal and squamous cell carcinomas) for patients receiving the TNF-α inhibitors adalimumab, etanercept, or infliximab.[57,79,86] In these studies, the risk of non-melanoma skin cancer was not significantly different for etanercept compared to infliximab.[57,79,86] One study suggested a higher risk of non-melanoma skin cancer for adalimumab compared to etanercept.[57] Specifically, in the analysis of the Veterans Affairs health care system database, the TNF-α inhibitor group contained 11,084 person-years of data.[57] Non-melanoma skin cancer occurred at a rate of 18.9 per 1,000 person-years.[57] In a comparative analysis, the authors determined that the risk of developing non-melanoma skin cancer was significantly higher for adalimumab compared to etanercept (0.036 vs. 0.021 per person-year, respectively; $P < .001$), but not for infliximab compared to etanercept (0.028 vs. 0.021 per patient-year, respectively; $P = .26$).[57] Similarly, in 2 other database analyses, no difference was detected between rates of basal cell carcinoma or non-melanoma skin cancer in patients receiving etanercept or infliximab.[79,86]

One database study reported on the comparative incidence of melanoma.[86] This analysis of 6,282 patients who received TIM therapy, from the U.S. National Databank for Rheumatic Diseases registry, compared the rates of melanoma in patients receiving the TNF-α inhibitors etanercept and infliximab.[86] Overall, a non-significant increase in the rate of melanoma was observed (OR, 2.3; 95% CI, 0.9 to 5.4; $P = .07$).[86]

Cardiovascular Events and Congestive Heart Failure

Four studies reported on the comparative risks of cardiovascular events in patients treated with TIMs.[27,76,85,90] The largest study, a retrospective cohort study, used data from more than 47,000 Medicare patients with RA.[90] The study assessed the risk of cardiovascular events in patients treated with abatacept compared to patients on other TIMs (adalimumab, certolizumab pegol, etanercept, infliximab, rituximab, tocilizumab, golimumab).[90] TNF-α inhibitors, in general, had higher risks of cardiovascular events than abatacept.[90] 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 to abatacept.[90]

A retrospective analysis of 3 U.S. databases (Medicare, IMS PharMetrics and MarketScan) 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 to abatacept (combined HR,

0.82; 95% CI, 0.55 to 1.22).[27] The number of events in this study, however, was low (tocilizumab 32 events, abatacept 112 events).[27]Two retrospective cohort studies of poor-methodological quality did not detect significant differences in risk for incident heart failure between etanercept and infliximab,[85] or in risk for cardiovascular events among abatacept, tocilizumab, and TNF-α inhibitors.[76]

Gastrointestinal Perforations

Two retrospective cohort studies examined the comparative risk for lower gastrointestinal perforations.[80,87] Both studies showed a significantly higher incidence of lower gastrointestinal perforations in patients using tocilizumab compared to any TNF-α inhibitor (aHR, 2.51; 95% CI, 1.31 to 4.80[87]; aIRRs, 4.0; 95% CI, 1.1 to 14.1[80]). One study used MarketScan and Medicare data for 167,113 patients with RA, of whom 106 patients experienced lower gastrointestinal perforations.[87] Authors of a second study using data from the U.S. health care claims database MarketScan analyzed the incidence rates of gastrointestinal perforations, including 27,255 patients with RA.[80] In addition to the higher risk for lower gastrointestinal perforations in patients using tocilizumab compared to any TNF-α inhibitor, the authors found no significant differences among the drugs for perforations in the entire gastrointestinal tract.[80] However, depending on the definition of the condition, only 16 to 23 cases of lower gastrointestinal perforations occured in this study.[80] We did not find any information on the number of patients experiencing these events.[80]

Ankylosing Spondylitis

Comparative Efficacy (Key Question 1)

We identified 1 open-label, head-to-head study for the treatment of ankylosing spondylitis.[16] 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 B2 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	Quality of Evidence	Relationship	Rationale
Etanercept Compared to Infliximab			
Clinical improvement (1 RCT[16])	Very Low ●○○○	Higher proportion with improvement for infliximab than etanercept	Downgraded 1 level for study limitations and 2 levels for imprecision

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

Etanercept Compared to Infliximab

We included 1 poor-methodological-quality open-label RCT that enrolled 50 participants with ankylosing spondylitis, who not responded to nonsteroidal anti-inflammatory drugs (NSAIDs). [16] All patients were naïve to DMARDs and TIMs. 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.[16] Authors do not report whether dose adjustments for infliximab were allowed.[16] The primary endpoints were the Assessment of Spondylarthritis International Society (ASAS) 20 and ASAS 40 responses at 12, 54, and 102 weeks.[16] 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).[16] 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.[16]

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	Study Quality
Etanercept Compared to Infliximab							
Giardina et al., 2010[16]	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 anti-inflammatory drugs; mean duration of disease: 15 years	Better efficacy for infliximab than etanercept	Poor

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 placebo-controlled RCT on filgotinib for the treatment of ankylosing spondylitis.[44] Appendix B, Table B1 and Table B2 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	Quality of Evidence	Relationship	Rationale
Filgotinib Compared to Placebo			
Quality of life (1 RCT[29])	Moderate ●●●○	Higher improvements for filgotinib than placebo	Downgraded 1 level for imprecision
Clinical improvement (1 RCT[29])	Moderate ●●●○	Higher proportion with improvement for filgotinib than placebo	Downgraded 1 level for imprecision
Disease remission (1 RCT[29])	Low ●●○○	Higher proportion of response for filgotinib than placebo	Downgraded 2 levels for very serious imprecision
Overall AEs (1 RCT[29])	Low ●●○○	No difference between groups	Downgraded 2 levels for very serious imprecision
SAEs (1 RCT[29])	Low ●●○○	No difference between groups	Downgraded 2 levels for very serious imprecision

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

Filgotinib Compared to Placebo

One fair-methodological-quality RCT, the TORTUGA trial, assessed the efficacy and harms of filgotinib compared to placebo in 116 participants with active ankylosing spondylitis and an inadequate response or intolerance to 2 or more NSAIDs.[29] The study randomized participants to filgotinib 200 mg daily or placebo, with the main outcome being the change from baseline to week 12 in ankylosing spondylitis disease activity score (ASDAS).[29] Participants treated with filgotinib significantly improved on the ASDAS compared to placebo (−1.47 vs.−0.57; $P < .001$).[29] More participants reported major improvement (decrease of ASDAS from baseline ≥ 2.0) and clinically significant improvement (decrease of ASDAS from baseline of at least 1.1) in the filgotinib group compared to the placebo group (33% vs. 2%, and 66% vs. 26%; $P < .001$ for both comparisons).[29] Participants in the filgotinib group also had greater improvements on the Ankylosing Spondylitis Quality of Life score than participants treated with placebo (filgotinib 200 mg, −4.76; placebo, −2.24; $P = .004$).[29] No differences in any treatment-emergent AEs were reported.[29] The incidence of treatment-emergent SAEs was numerically higher in filgotinib group compared to placebo (2% vs.0%; *P* value not reported).[29]

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)	N (%) With at Least 1 SAE	N (%) With AE Leading to Discontinuation	Study Quality
Filgotinib Compared to Placebo					
van der Heijde et al., 2018[29] NCT03117270 TORTUGA[29]	Filgotinib 200 mg daily; placebo Total N = 116	ASDAS mean change from baseline (SD) at 12 weeks: • Filgotinib 200 mg: −1.47 (1.04) • Placebo: −0.57 (0.82) Difference between groups: −0.85 (95% CI, −1.17 to −0.53); *P* < .001	• Filgotinib 200 mg: 1 of 58 (2%) • Placebo: 0 of 58 (0%)	• Filgotinib 200 mg: 1 of 58 (2%) • Placebo: 1 of 58 (2%)	Fair

Abbreviations. AE: adverse event; ASDAS: ankylosing spondylitis disease activity score; CI: confidence interval; mg: milligram; RCT: randomized controlled trial; SAE: serious adverse event; SD: standard deviation; TIM: targeted immune modulator.

Comparative Harms (Key Question 2)

General Tolerability Findings from RCTs

For this update, we identified 1 new RCT that reported on general tolerability; the study had no discontinuations due to AEs; however, toverall AEs and SAEs (Table 16).[16] Appendix B, Table B1 and Table B2 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 Randomized Patients (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	Study Quality
Etanercept Compared to Infliximab							
Giardina et al., 2010[16]	50	102 weeks	NR	Not estimable due to no events in both groups	NR	No significant differences.	Poor

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.

Ongoing Studies (Key Question 4)

We identified 24 ongoing head-to-head studies evaluating the comparative effectiveness or harms of TIM agents, and 3 ongoing placebo-controlled trials on pipeline drugs (Table 17) for ankylosing spondylitis. Of the 27 studies, 23 studies are RCTs and 4 are prospective cohort studies. Sixteen studies include participants with RA, 4 include participants with ankylosing spondylitis, and 4 include mixed populations. The pharmaceutical industry is funding all of the identified studies.

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 Enrolled Treatment Duration	Study Completion Date[a]	Primary Outcome(s)
Abatacept Compared to Adalimumab [RA]				
NCT02557100* A Randomized, Head-to-Head, Single-Blinded Study to Assess Changes in the Immune Profile in Response to Treatment With Subcutaneous Abatacept in Combination With Methotrexate Versus Subcutaneous Adalimumab in Combination With Methotrexate in Adults With Early RA Who Are Naive to Biologic Disease-Modifying Antirheumatic Drugs Phase 4	Abatacept, adalimumab Blinded	N = 120 24 weeks	March 2019 (Actual)	Changes from baseline in levels of autoantibody levels (anti-CCP2 and ACPA) at 24 weeks
NCT03619876 Effects of Abatacept on Myocarditis in RA (AMiRA) Phase 4	Abatacept adalimumab Open	N = 20 16 weeks	July 2021 (Estimated)	Change in myocardial FDG uptake at 16 weeks
Abatacept Compared to Certolizumab pegol Compared to Tocilizumab [RA]				
NCT01491815 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 56 weeks	December 2021 (Estimated)	Remission according to CDAI at week 24

Registration Number Trial Name Phase	Treatment Groups; Blinded vs. Open	N Enrolled Treatment Duration	Study Completion Date[a]	Primary Outcome(s)
ABBV-3373 Compared to Adalimumab Compared to Placebo [RA]				
NCT03823391 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 = 45 22 weeks	June 2021 (Estimated)	Change in DAS28-CRP from baseline for ABBV-3373 and adalimumab at 12 weeks
Abatacept Compared to Tocilizumab [RA]				
NCT03227419 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 52 weeks	November 2022 (Estimated)	Change of the CDAI at 6 months
Abatacept Compared to Tocilizumab Compared to TNF-α Inhibitor [RA]				
NCT02353780 Mechanistic Studies of B- and T-Cell Function in RA Patients Treated With TNF antagonists, Tocilizumab, or Abatacept Phase 4	Abatacept, tocilizumab, TNF-α inhibitor (etanercept, adulimumab, infliximab, certolizumab pegol, golimumab) Blinded	N = 10 30 weeks	May 2020 (Estimated)	Mechanistic comparisons (changes in frequencies of peripheral blood immune cell subsets following institution of a subcutaneously administered TNF antagonist, tocilizumab or abatacept) at 6 months
Abatacept Compared to Upadacitinib [RA]				
NCT03086343 A Phase 3, Randomized, Active-Controlled, Double-Blind Study Comparing Upadacitinib (ABT-494) to Abatacept in Subjects With Moderately to Severely Active RA With Inadequate Response or Intolerance to Biologic DMARDs (bDMARDs) on Stable Conventional Synthetic Disease-Modifying Antirheumatic Drugs (csDMARDs) (SELECT-CHOICE) Phase 3	Abatacept, upadacitinib Blinded	N = 657 24 weeks	June 2022 (Estimated)	Change in DAS28-CRP at week 12

Registration Number Trial Name Phase	Treatment Groups; Blinded vs. Open	N Enrolled Treatment Duration	Study Completion Date[a]	Primary Outcome(s)
Adalimumab Compared to Baricitinib Compared to Etanercept [RA]				
NCT03915964 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 = 2600 5.5 years	February 2026 (Estimated)	Time from first dose of study treatment to first event of venous thromboembolis
Adalimumab Compared to Etanercept Compared to Tofacitinib [RA]				
NCT02092467 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 = 4414 5 years	September 2020 (Estimated)	Malignancies, excluding non-melanoma skin cancer at 5 years
Adalimumab Compared to Sarilumab [RA]				
NCT02332590 A Randomized, Double-blind, Parallel-group Study Assessing the Efficacy and Safety of Sarilumab Monotherapy Versus Adalimumab Monotherapy in Patients With RA Phase 3	Adalimumab, sarilumab, placebo Blinded	N = 369 310 weeks	December 2020 (Estimated)	Change from baseline in DAS28-ESR score at 24 weeks
Baricitinib Compared to Etanercept [RA]				
EudraCT number: 2018-004558-30 Synovial ultrasound as Primary Outcome in a 3-Arm, Randomized, Open-Label, Parallel Active-Controlled, 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	Baricitinib, etanercept Open	N = 186 24 weeks	NR	Decrease in join inflammation detected by musculoskeletal ultrasound (B-mode and doppler mode synovitis)
Etanercept Compared to Tofacitinib [RA]				
NCT03976245 Advanced Therapeutics in RA Phase 4	Etanercept, tofacitinib Open	N = 144 24 months	September 2021 (Estimated)	Retention rates at 24 months
Etanercept Compared to Rituximab Compared to Tocilizumab [RA]				
ISRCTN43336433 Stratification of biologic Therapies for RA by Pathobiology: A Randomised, Open-Labelled Biopsy-Driven Stratification Trial in DMARD Inadequate Responder Patients	Etanercept, rituximab, tocilizumab Open	N = 226 48 weeks	December 2020 (Estimated)	Response using ACR20 at week 16

Registration Number Trial Name Phase	Treatment Groups; Blinded vs. Open	N Enrolled Treatment Duration	Study Completion Date[a]	Primary Outcome(s)
Randomised to Etanercept, Tocilizumab or Rituximab (STRAP-EU) NR				
ISRCTN10618686; 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, Phase 3	Etanercept, rituximab, tocilizumab Open	N = 219 48 weeks	NR	Response using ACR20 at week 16
Filgotinib Compared to Placebo [RA]				
NCT02886728* A Randomized, Double-blind, Placebo- and Active-controlled, Multicenter, Phase 3 Study to Assess the Efficacy and Safety of Filgotinib Administered for 52 Weeks Alone and in Combination With Methotrexate (MTX) to Subjects With Moderately to Severely Active RA Who Are Naïve to MTX Therapy (FINCH 3) Phase 3	Filgotinib, placebo Open	N = 1252 52 weeks	May 2019 (Actual)	ACR20 response at week 24
NCT03025308 A Multicenter, Open-label, Long-Term Extension Study to Assess the Safety and Efficacy of Filgotinib in Subjects With RA (FINCH 4) Phase 3	Filgotinib, placebo Open	N = 2731 6 years	May 2025 (Estimated)	Proportion of participants experiencing AEs at 6 years
Rituximab Compared to Tocilizumab [RA]				
ISRCTN97443826*; EudraCT Number: 2012-002535-28 A Randomised, open-labelled study in anti-TNFa inadequate responders to investigate the mechanisms for Response - Resistance to Rituximab versus Tocilizumab in RA (R4-RA) Phase 4	Rituximab, tocilizumab Open	N = 160 96 weeks	May 2019 (Estimated)	Improvement in CDAI at 16 weeks
Tocilizumab Compared to TNF-α Inhibitor [RA]				
NCT03100253 Open-label, Randomized Controlled Trial Comparing Tocilizumab to Anti-TNF Treatment and Discovery of Biomarkers for Treatment Selection in RA Patients With	Tocilizumab, TNF-α inhibitor (etanercept, infliximab, adalimumab, golimumab,:	N = 400 96 weeks	October 2021 (Estimated)	Proportion of patients with good EULAR at 24 weeks

Registration Number Trial Name Phase	Treatment Groups; Blinded vs. Open	N Enrolled Treatment Duration	Study Completion Date[a]	Primary Outcome(s)
Inadequate Response to a First Anti-TNF (RAFTING), Phase 4	certolizumab pegol)			
Adalimumab Compared to Secukinumab [Ankylosing Spondylitis]				
NCT03906136 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 36 weeks	June 2022 (Estimated)	Clinical response assessments in ASAS 40 at week 24
NCT03259074 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 to 2 Years in Patients With Active Ankylosing Spondylitis (SURPASS) Phase 3	Adalimumab, secukinumab 150 mg, secukinumab 300 mg Blinded	N = 837 104 weeks	December 2021 (Estimated)	Radiographic progression as measured by mSASSS
Bimekizumab Compared to Certolizumab pegol [Ankylosing Spondylitis]				
NCT03215277 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	May 2020 (Estimated)	Change from baseline in ASDAS at week 12
Filgotinib Compared to Placebo [RA, Ankylosing Spondylitis]				
NCT03926195 A Randomized, Double-blind, Placebo-controlled Phase 2 Study to Evaluate the Effect of Filgotinib on Semen Parameters in Adult Males With Active RA, Psoriatic Arthritis, Ankylosing Spondylitis or Nonradiographic Axial Spondyloarthritis Phase 2	Filgotinib, placebo Blinded	N = 250 52 weeks	October 2024 (Estimated)	Percentage of participants with a ≥ 50% decrease from baseline in sperm concentration at week 13
Secukinumab Compared to TNF-α inhibitor [Ankylosing Spondylitis]				
NCT03445845	Secukinumab, TNF-α inhibitor (infliximab,	N = 300 52 weeks	June 2021 (Estimated)	Clinical response assessments in

Registration Number Trial Name Phase	Treatment Groups; Blinded vs. Open	N Enrolled Treatment Duration	Study Completion Date[a]	Primary Outcome(s)
Rotation or Change of Biotherapy After TNF-Blocker Treatment Failure for Axial Spondyloarthritis (ROC-SPA) Phase 4	etanercept, adalimumab, certolizumab, golimumab) Blinded			ASAS 40 at week 24
Various Biologic Treatments Evaluated Through Cohort Studies [RA, Ankylosing Spondylitis]				
NCT02728934 Comparative and Pragmatic Study of Simponi Aria Versus Remicade in RA	Golimumab, infliximab	N = 1279 3 years	January 2020 (Estimated)	Proportion of patients with an infusion reaction through week 52
NCT01932372 Xeljanz (Registered) Tablets 5mg Special Investigation (All-Cases Surveillance)	Tofacitinib, etanercept, other biologics, DMARDs	N = 10477 36 months	December 2020 (Estimated)	DAS28 score at 24 months
NCT03440892 Longitudinal Observational Study on RA Patients: Effects of Antirheumatic Treatment on Serum Levels of Survivin (SurviTreat)	Abatacept, tocilizumab, tofacitinib, baricitinib	N = 2500 6 months	January 2020 (Estimated)	Survivor status at 6 months
NCT01081717* A Large U.S. Health Insurance Claims Database Will be Used to Estimate the Incidence of Serious Outcomes in Patients With RA, Psoriatic Arthritis, or Ankylosing Spondylitis Treated With Golimumab and Other Types of Biological and Systemic Nonbiological Treatments	Golimumab, TNF-α inhibitor, non-anti-TNF-α TIMs, systemic nonbiological treatments	N = 1064 Up to 8 years	May 2015	Estimate incidence of serious infections, malignancies at 8 years

*Note. [a] as reported in ClinicalTrials.gov[108],the European Clinical Trials Register[109], or the International Clinical Trials Registry Platform[110]; *indicates completed, but not published yet. Abbreviations. ACPA: anticyclic citrullinated peptide antibody; ACR20: American College of Rheumatology, 20% improvement; AE: adverse event; ASAS 40: Assessment of Spondylarthritis International Society, 40% improvement; ASDAS, Ankylosing Spondylitis Disease Activity Score; CCP: cyclic citrullinated peptide; CDAI: Clinical Disease Activity Index; DAS28-CRP: 28-Joint Disease Activity Score C-Reactive Protein; DAS28-ESR: 28-Joint Disease Activity Score Erythrocyte Sedimentation Rate; DMARD: disease-modifying antirheumatic drug; EULAR: European League Against Rheumatism response; FDG: F-fluordesoxyglucose; mg: milligram; mSASSS: modified Stroke Ankylosing Spondylitis Spine Score; MTX: methotrexate; N: number of participants; NCT: U.S. National Clinical Trial; NR: not reported; RA: rheumatoid arthritis; TIM: targeted immune modulator; TNF-α: tumor necrosis factor alpha.*

Discussion

The evidence for the comparative effectiveness and harms of TIM agents includes data for 12 comparisons of TIMs as first-line treatments and 6 comparisons as second-line treatments for the treatment of RA. Most comparisons are limited to single RCTs. Consequently, the quality of evidence (QoE) for many outcomes is very low or low, precluding definitive conclusions. Evidence rated as moderate- or high-quality indicates that baricitinib, sarilumab, and updacitinib are more efficacious than adalimumab as first-line treatments for RA. 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 QoE indicates no differences in the incidence of overall AEs and SAEs. Significant differences in AEs and SAEs for the incidence of some comparisons were rated as very low or low QoE, 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, however, 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 compared to established disease.

For ankylosing spondylitis, the only head-to-head evidence we identified was 1 poor-methodological-quality RCT.

Two pipeline drugs (filgotinib and peficitinib), in 8 published trials, showed superior efficacy for the treatment of RA (filgotinib and peficitinib) or ankylosing spondylitis (filgotinib) compared to placebo. In addition, 27 ongoing head-to-head studies or placebo-controlled trials of pipeline drugs highlight the rapidly evolving scientific dynamic in this field. About 10 studies are scheduled to be completed before 2021.

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

We identified 5 relevant network meta-analyses that provided indirect comparisons of TIM agents in patients with RA.[111-115] The search periods in these studies were up to November 2018. 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

was available. If 2 network meta-analyses reported results on the same comparison, we present the comparison with the most recent literature search.

In this section, we briefly summarize findings from the 2 most comprehensive network meta-analyses by Ma et al.[112] and Carmean-Castillo et al.[111] Both used a Bayesian approach; one reported results as odds ratios (ORs) with corresponding 95% credible intervals (CrIs),[112] while the other reported ORs with 95% confidence intervals (CIs).[111] Ma et al. analyzed 67 RCTs with data on abatacept, adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, and tocilizumab,[112] and searched publications from 1997 to 2016. Overall, analyses yielded few statistically significant differences.[112] Compared to 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).[112] All comparisons included background methotrexate therapy.[112] Overall, AEs were similar among evaluated treatments.[112] Patients taking abatacept plus methotrexate had fewer SAEs compared to 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).[112] Because of limitations inherent in network meta-analyses, results should be interpreted with caution.[112]

Carmean-Castillo et al. analyzed 27 double-blinded RCTs to assess the comparative efficacy of abatacept, adalimumab, anakinra, golimumab, infliximab, baricitinib, certolizumab, etanercept, tocilizumab, and tofacitinib in patients with active RA, despite previous treatment with conventional DMARDs.[111] The literature was searched up to June 2017, and the main outcome was the ACR50 response.[111] Certolizumab pegol was significantly less efficacious in achieving an ACR50 response compared to anakinra (OR, 0.36; 95% CI, 0.14 to 0.89).[111]

Ankylosing Spondylitis

We identified 1 relevant network meta-analysis that provided indirect comparisons of TNF-α inhibitors for treatment of ankylosing spondylitis.[116] 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, Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and Bath Ankylosing Spondylitis Functional Index (BASFI).[116] Wang et al. 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.[116] None of the comparisons yielded statistically significant differences between TNF-α inhibitors in reducing BASDAI or BASFI at 24 weeks.[116]

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.[117] 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 poor methodological quality 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 1,000 participants, 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 did not reevaluate the methodological study quality for the previously included studies, except for RCTs that were previously assessed as good quality. We reassessed these good-quality RCTs to determine the influence of manufacturer involvement on study design and execution, consistent with current Center methodology. Lastly, the previous report used a modified GRADE approach whereby the lowest quality rating was termed *insufficient;* we converted all previous insufficient quality of evidence ratings to *very low* for consistency with current GRADE methods.

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-atto*, *Anakinra*, *Baricitinib*, *Certolizumab pegol*, *Etanercept*, *Etanercept-szzs*, *Golimumab*, *Infliximab*, *Infliximab-abda*, *Infliximab-dyyb*, *Infliximab-qbtx*, *Rituximab*, *Sarilumab*, *Secukinumab*, *Tocilizumab*, *Tofacitinib*, *ABBV-3373*, *Bimekizumab*, *Filgotinib*, *Upadacitinib*), and study designs (if appropriate). We limited searches of evidence sources to citations published since January 1, 2017 through September 5, 2019.

The following DERP evidence sources were searched:

- Agency for Healthcare Research and Quality (AHRQ)
- Evidence-based Practice Centers (EPC) Reports
- Effective Health Care (EHC) Program
- Canadian Agency for Drugs and Technologies in Health (CADTH)
- Cochrane Library (Wiley Interscience)
- National Institute for Health and Care Excellence (NICE)
- Ovid MEDLINE
- Veterans Administration Evidence-based Synthesis Program (ESP)
- Embase
- Clinical Trials.gov
- European Medicines Agency
- ISRCTN

Ovid MEDLINE Search Strategy

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) 1946 to September 05, 2019

#	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.
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/

#	Searches
15	monoclonal antibod*.ti,ab.
16	Adalimumab/
17	(adalimumab or Humira or Amjevita or Hyrimoz or Cyltezo).mp.
18	Certolizumab Pegol/
19	(Certolizumab or Cimzia).mp.
20	(golimumab or simponi or CNTO148 or "CNTO 148").af.
21	Infliximab/
22	(infliximab or Remicade or Renflexis or Inflectra or Ixifi).mp.
23	Interleukin 1 Receptor Antagonist Protein/
24	(Anakinra or Kineret).mp.
25	Rituximab/
26	(Rituximab or Rituxan).mp.
27	(Sarilumab or Kevzara or "REGN 88" or REGN88 or "SAR 153191" or SAR153191).af.
28	(Tocilizumab or Actemra or Atlizumab or RoActemra or "R 1569" or R1569).af.
29	Abatacept/
30	(Abatacept or Orencia).mp.
31	Etanercept/
32	(Etanercept or Enbrel or Erelzi).mp.
33	(Secukinumab or Cosentyx or "AIN 457" or AIN457).af.
34	(Tofacitinib or Xeljanz or "CP 690550" or CP690550).af.
35	or/6-34
36	limit 35 to yr = "2017 -Current"
37	(Upadacitinib or ABT494 or "ABT 494").af.
38	(Baricitinib or Olumiant or "INCB 028050" or INCB028050 or LY 3009104 or LY3009104).af.
39	(Filgotinib or GLPG-0634 or GLPG0634 or GS-6034 or GS6034).af.
40	(ABBV-3373 or ABBV3373).af.
41	(Bimekizumab or UCB-4940 or UCB4940 or CDP-4940 or CDP4940).af.
42	or/36-41
43	5 and 42
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 of publication or retracted publication).pt.)

#	Searches
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) – September 05, 2019

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 ^"Adalimumab"]
#7	(adalimumab or Humira or Amjevita or Hyrimoz or Cyltezo):ti,ab,kw
#8	[mh ^"Certolizumab Pegol"]
#9	(Certolizumab or Cimzia):ti,ab,kw
#10	(golimumab or simponi or CNTO148 or "CNTO 148"):ti,ab,kw
#11	[mh ^"Infliximab"]
#12	(infliximab or Remicade or Renflexis or Inflectra or Ixifi):ti,ab,kw
#13	[mh ^"Interleukin 1 Receptor Antagonist Protein"]
#14	(Anakinra or Kineret):ti,ab,kw
#15	[mh ^"Rituximab"]

ID	Search
#16	(Rituximab or Rituxan):ti,ab,kw
#17	(Sarilumab or Kevzara or "REGN 88" or REGN88 or "SAR 153191" or SAR153191):ti,ab,kw
#18	(Tocilizumab or Actemra or Atlizumab or RoActemra or "R 1569" or R1569):ti,ab,kw
#19	[mh ^"Abatacept"]
#20	(Abatacept or Orencia):ti,ab,kw
#21	[mh ^"Etanercept"]
#22	(Etanercept or Enbrel or Erelzi):ti,ab,kw
#23	(Secukinumab or Cosentyx or "AIN 457" or AIN457):ti,ab,kw
#24	(Tofacitinib or Xeljanz or "CP 690550" or CP690550):ti,ab,kw
#25	{or #6-#24} with Cochrane Library publication date Between Oct 2017 and Sep 2019
#26	(Upadacitinib or ABT494 or "ABT 494"):ti,ab,kw
#27	(Baricitinib or Olumiant or "INCB 028050" or INCB028050 or LY 3009104 or LY3009104):ti,ab,kw
#28	(Filgotinib or GLPG-0634 or GLPG0634 or GS-6034 or GS6034):ti,ab,kw
#29	(ABBV-3373 or ABBV3373):ti,ab,kw
#30	(Bimekizumab or UCB-4940 or UCB4940 or CDP-4940 or CDP4940):ti,ab,kw
#31	{or #25-#30}
#32	#5 and #31
#33	[mh "age groups"] not [mh adult]
#34	#32 not #33
#35	(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
#36	#34 not #35

Embase Search Strategy

Embase.com (Elsevier) – September 05, 2019

No.	Query
#1	'rheumatoid arthritis'/exp
#2	'ankylosing spondylitis'/exp
#3	'rheumatoid arthritis':ti,ab
#4	(ankylosing NEAR/1 (arthritis OR spondyl*)):ti,ab
#5	#1 OR #2 OR #3 OR #4
#6	'adalimumab'/exp/mj
#7	adalimumab:ti,ab OR humira:ti,ab OR amjevita:ti,ab OR hyrimoz:ti,ab OR cyltezo:ti,ab
#8	'certolizumab pegol'/exp/mj
#9	certolizumab:ti,ab OR cimzia:ti,ab
#10	'golimumab'/exp/mj
#11	golimumab:ti,ab OR simponi:ti,ab OR cnto148:ti,ab OR 'cnto 148':ti,ab
#12	'infliximab'/exp/mj
#13	infliximab:ti,ab OR remicade:ti,ab OR renflexis:ti,ab OR inflectra:ti,ab OR ixifi:ti,ab
#14	'anakinra'/exp/mj
#15	anakinra:ti,ab OR kineret:ti,ab
#16	'rituximab'/exp/mj

No.	Query
#17	rituximab:ti,ab OR rituxan:ti,ab
#18	'sarilumab'/exp/mj
#19	sarilumab:ti,ab OR kevzara:ti,ab OR 'regn 88':ti,ab OR regn88:ti,ab OR 'sar 153191':ti,ab OR sar153191:ti,ab
#20	'tocilizumab'/exp/mj
#21	tocilizumab:ti,ab OR actemra:ti,ab OR atlizumab:ti,ab OR roactemra:ti,ab OR 'r 1569':ti,ab OR r1569:ti,ab
#22	'abatacept'/exp/mj
#23	abatacept:ti,ab OR orencia:ti,ab
#24	'etanercept'/exp/mj
#25	etanercept:ti,ab OR enbrel:ti,ab OR erelzi:ti,ab
#26	'secukinumab'/exp/mj
#27	secukinumab:ti,ab OR cosentyx:ti,ab OR 'ain 457':ti,ab OR ain457:ti,ab
#28	'tofacitinib'/exp/mj
#29	tofacitinib:ti,ab OR xeljanz:ti,ab OR 'cp 690550':ti,ab OR cp690550:ti,ab
#30	#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
#31	#30 AND [2017-2019]/py
#32	'upadacitinib'/exp/mj
#33	upadacitinib:ti,ab OR abt494:ti,ab OR 'abt 494':ti,ab
#34	'baricitinib'/exp/mj
#35	(baricitinib:ti,ab OR olumiant:ti,ab OR 'incb 028050':ti,ab OR incb028050:ti,ab OR ly:ti,ab) AND 3009104:ti,ab OR ly3009104:ti,ab
#36	'filgotinib'/exp/mj
#37	filgotinib:ti,ab OR 'glpg 0634':ti,ab OR glpg0634:ti,ab OR 'gs 6034':ti,ab OR gs6034:ti,ab
#38	'abbv 3373':ti,ab OR abbv3373:ti,ab
#39	'bimekizumab'/exp/mj
#40	bimekizumab:ti,ab OR 'ucb 4940':ti,ab OR ucb4940:ti,ab OR 'cdp 4940':ti,ab OR cdp4940:ti,ab
#41	#31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40
#42	#5 AND #41
#43	'animal'/exp NOT 'human'/exp
#44	#42 NOT #43
#45	'groups by age'/exp NOT 'adult'/exp
#46	#44 NOT #45
#47	'systematic review'/exp OR 'meta analysis'/exp
#48	(((systematic OR 'state of the art' OR scoping OR umbrella) NEXT/1 (review* OR overview* OR assessment*)):ti,ab) OR 'review* of reviews':ti,ab OR 'meta analy*':ti,ab OR metaanaly*:ti,ab OR (((systematic OR evidence) NEAR/1 assess*):ti,ab) OR 'research evidence':ti,ab OR metasynthe*:ti,ab OR 'meta synthe*':ti,ab
#49	#47 OR #48
#50	#46 AND #49
#51	'randomized controlled trial'/exp OR random*:ti,ab OR placebo:ti,ab
#52	#46 AND #51
#53	'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

No.	Query
	'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
#54	'adverse drug reaction'/de
#55	((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
#56	(drug NEXT/1 (survival OR retention OR longevity OR adherence)):ti,ab
#57	harms:ti OR safety:ti OR complication$:ti
#58	toxicity:ti OR ((('injection site' OR infusion) NEXT/1 reaction$):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)
#59	#53 OR #54 OR #55 OR #56 OR #57 OR #58
#60	#46 AND #59
#61	#50 OR #52 OR #60
#62	#61 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 – September 05, 2019

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 03/01/2019 to 09/05/2019
"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 03/01/2019 to 09/05/2019
"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 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 03/01/2019 to 09/05/2019
"Rheumatoid Arthritis" OR "Ankylosing Spondylitis" | Filgotinib 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 | Adult, Older Adult | Last update posted from 03/01/2019 to 09/05/2019
Total
Total after deduplication

- ISRCTN Registry – September 05, 2019

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 OR 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 | filter within Condition: " Rheumatoid Arthritis" OR " Ankylosing Spondylitis"| filter Participant age range: Adult | filter Date applied: from: 01/11/2017 | filter Date applied: to: 05/09/2019
Secukinumab OR Cosentyx OR "AIN 457" OR AIN457 OR Tofacitinib OR Xeljanz OR "CP 690550" OR CP690550 OR Upadacitinib OR ABT494 OR "ABT 494" OR Baricitinib OR Olumiant OR "INCB 028050" OR INCB028050 OR "LY 3009104" OR LY3009104 | filter within Condition: " Rheumatoid Arthritis" OR " Ankylosing Spondylitis"| filter Participant age range: Adult | filter Date applied: from: 01/11/2017 | filter Date applied: to: 05/09/2019
Filgotinib 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 | filter within Condition: " Rheumatoid Arthritis" OR " Ankylosing Spondylitis"| filter Participant age range: Adult | filter Date applied: from: 01/11/2017 | filter Date applied: to: 05/09/2019
Total
Total after deduplication

Inclusion Criteria

Population

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

Interventions

- Table 1 presents the TIMs and respective biosimilars that the FDA has approved 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 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
  - ~~o~~ Reduction in disease-specific mortality

- Rebound/flare
- Joint destruction
- Steroid withdrawal
- Dose escalation

- Harms
  - Overall adverse events (AEs)
  - Withdrawals due to adverse events
  - Serious adverse events (SAEs)
  - Specific adverse events (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 outcomes on harms
  - > 12-week study duration
  - Minimum total sample size of 1,000

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 - Methodological Quality of Included Studies

We assessed the methodological quality 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 where we disagreed about the methodological quality of a study, we resolved the disagreement through discussion.

Randomized Controlled Trials

Good-quality 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. Good-quality RCTs also have low potential for bias from conflicts of interest and funding source(s). Fair-quality RCTs have incomplete information about

methods that might mask important limitations or a meaningful conflict of interest. Poor-quality RCTs have clear flaws that could introduce significant bias.

Cohort Studies

Good-quality 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. Good-quality cohort studies also list their funding source(s) and have a low potential of bias from conflicts of interest. Fair-quality 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. Poor-quality cohort studies have a clear, high risk of bias that would affect findings.

Quality of Evidence Assessment - Overall Quality of Evidence

We assigned each outcome a summary judgment for the overall quality of evidence based on the system developed by the Grading of Recommendations, Assessment, Development, and Evaluation Working Group (GRADE).[118,119] Two independent experienced researchers assigned ratings, with disagreements resolved through discussion. The GRADE system defines the overall quality 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)

Author, Year Country Trial Name Trial Number Study Quality	Population	Age Gender Ethnicity	Other Population Characteristics	Funding
Brown et al., 2018[38] 35 sites in the United Kingdom SWITCH NR Poor	Adults with RA ≥ 24 weeks with inadequate response to TNFi treatment	Age: 57 (12); range 24–81 Alternative TNFi: 54 (10) Abatacept 125 mg: 58 (14) Rituximab 1 g: 58 (12) Female: 102 (84%) Alternative TNFi: 33 (81) Abatacept 125 mg: 39 (95) Rituximab 1 g: 30 (75) Race/ethnicity: 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 TNFi 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

Author, Year Country Trial Name Trial Number Study Quality	Population	Age Gender Ethnicity	Other Population Characteristics	Funding
			• Patients with active current infection or any major episode of infection requiring hospitalisation 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[44]; Strand et al., 2018[92] 86 centres in Europe, Israel, Russia, South Africa, South America, South Korea, and the U.S. MONARCH NCT02332590 Fair	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[26]	Adult females with active RA with moderate-to-severe disease	Age: 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)	None

Author, Year Country Trial Name Trial Number Study Quality	Population	Age Gender Ethnicity	Other Population Characteristics	Funding
1 site in Saudi Arabia NR NR Poor	activity who failed to respond to at least one anti-TNF drug.	Female, n (%): 132 (100%) Tocilizumab 8 mg/kg: 68 (100%) Abatacept 500/750/1000 mg: 64 (100%) Race/ethnicity, n (%): NR	Inclusion: • 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 one 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/mm^3, an absolute neutropenia < 1200 cells/mL, or lymphopenia < 750 cells/mL, and GFR < 40 mL/min • Male patients	
Emery et al., 2018[31] U.S., South	Adults with RA for ≥ 3 months	Age, mean (SD): 52 (NR) Sarilumab 150 mg: 55 (12)	Concomitant medication: • In both studies, all patients received concomitant csDMARDs.	Sanofi Genzyme and Regeneron Pharmaceuticals, Inc.

Author, Year Country Trial Name Trial Number Study Quality	Population	Age Gender Ethnicity	Other Population Characteristics	Funding
America, Western Europe, Eastern Europe, and Russia ASCERTAIN NR Poor		Sarilumab 200 mg: 52 (13) Tocilizumab 4 mg/kg: 50 (13) Female, n (%): > 80% 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%)	Inclusion: • ≥ 18 years of age • With an RA diagnosis for ≥ 3 months as determined by the 2010 revised ACR criteria as well as functional class I–III as categorized by the 1991 revised ACR criteria • Continuous treatment with one 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[47] 63 centers in the U.S., Europe, Latin America, and the Republic of Korea NR NCT00550446 Fair	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	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)	Key inclusion criteria: • Failure of at least one 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 10^9/L, absolute neutrophil count < 1.2 x 10^9/L, or platelet count < 100 x 10^9/L); estimated glomerular filtration rate < 50 mL/min; total bilirubin, AST, or ALT levels < 2 x ULN; untreated	Pfizer, Abbott, Actelion, Mundipharma

Author, Year Country Trial Name Trial Number Study Quality	Population	Age Gender Ethnicity	Other Population Characteristics	Funding
	above the ULN or a CRP level > 7 mg/L	Adalimumab 40 mg: 45 (84.9) Placebo: 52 (88.1) White, n (%): Tofacitinib 1 mg: 44 (81.5) 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)	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.	
Fleischmann et al., 2017[48] 194 centres in 25 countries ORAL – Strategy NCT02187055 Fair	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 four 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%) 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 randomisation. 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 randomisation; had exclusionary morbidities, HIV, hepatitis B or C, inadequately treated or undocumented treatment of TB; had more than one episode of herpes zoster, one episode of disseminated herpes zoster or herpes simplex; any clinically significant laboratory abnormalities; or were pregnant. Patients who had	Pfizer

Author, Year Country Trial Name Trial Number Study Quality	Population	Age Gender Ethnicity	Other Population Characteristics	Funding
			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	
Fleischmann et al., 2019[24] 286 sites in 41 countries in Europe, South and Central America, North America, Europe, Asia SELECT-COMPARE NCT02629159 Fair	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: 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), a hsCRP level of ≥ 5 mg/L (ULN, 2.87 mg/L), and at least one 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	AbbVie, Inc

Author, Year Country Trial Name Trial Number Study Quality	Population	Age Gender Ethnicity	Other Population Characteristics	Funding
			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	
Gabay et al., 2013[45] 76 centres in 15 countries in North and South America, Australasia, and Europe ADACTA NCT01119859 Fair	Adults with RA for ≥ 6 months who were intolerant to MTX or for whom continuation of MTX was deemed inappropriate	Age, mean (SD): NR 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%) White, n (%): NR Tocilizumab 8 mg/kg: 145 (89%) Adalimumab 40 mg: 133 (82%)	Patients previously treated with a biological DMARDs were excluded. Patients had to stop taking all synthetic DMARDs except leflunomide 2 weeks or more before baseline; leflunomide had to be withdrawn 12 weeks or more before baseline or after standard washout	LA Roche
Genovese et al., 2017[18] 41 sites in 6 countries (U.S. [20 sites], Poland [6 sites], Hungary [5 sites], Czech Republic [4 sites], Mexico [4 sites], and Bulgaria [3 sites])	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: Peficitinib 25 mg: 46 of 59 (78.0%) Peficitinib 50mg: 48 of 57 (84.2%)	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	Astellas Pharma Global Development

Author, Year Country Trial Name Trial Number Study Quality	Population	Age Gender Ethnicity	Other Population Characteristics	Funding
NR NR Fair		Peficitinib 100 mg: 51 of 58 (87.9%) Peficitinib 150 mg: 50 of 64 (78.1%) Placebo: 42 of 51 (82.4%) Race/ethnicity: NR	• Active disease Exclusion: • Previous csDMARD therapy, biologic agents approved for the treatment of RA, intraarticular or parenteral corticosteroids, more than10 mg oral prednisone (or 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	
Genovese et al., 2019[23] 114 sites in Europe, North and South America, Asia, Australia FINCH 2 NR Fair	Adults with active RA despite ongoing treatment with csDMARDs and an inadequate response or intolerance to 1 or more prior bDMARDs.	Age: Filgotinib 200 mg: 56 (12.5) Filgotinib 100 mg: 55 (12.0) Placebo: 56 (12.1) Female: Filgotinib 200 mg: 120 of 147 (82%) Filgotinib 100 mg: 119 of 153 (78%) Placebo: 121 of 148 (82%) Race/ethnicity: *White:*	Concomitant medication: Most patients (81.9%) were receiving concomitant MTX on the first dosing date and the mean (SD) dose was 15.8 (5.25) mg/week. Inclusion: • 18 years of age or older at the time of consent with a diagnosis of RA • ≥ 6 swollen joints (SJC66) and ≥ 6 tender joints (TJC68) at both screening and baseline • Serum CRP level of 4 mg/L or greater based on central laboratory assessment at screening	Gilead Sciences Inc.

Author, Year Country Trial Name Trial Number Study Quality	Population	Age Gender Ethnicity	Other Population Characteristics	Funding
		Filgotinib 200 mg: 110 of 147 (75%) Filgotinib 100 mg: 109 of 153(71%) Placebo: 97 of 148 (66%) *Asian:* Filgotinib 200 mg: 15 of 147 (10%) Filgotinib 100 mg: 20 of 153 (13%) Placebo: 15 of 148 (10%) *Black/African American:* Filgotinib 200 mg: 14 of 147 (10%) Filgotinib 100 mg: 12 of 153 (8%) Placebo: 21 of 148 (14%) *American Indian/Alaska* Native: Filgotinib 200 mg: 7 of 147 (5%) Filgotinib 100 mg: 9 of 153 (6%) Placebo: 10 of 148 (7%)	• Active RA despite ongoing treatment with csDMARDs and an inadequate response or intolerance to 1 or more prior bDMARDs. • Patients with evidence of latent TB could enroll only if appropriate prophylaxis was initiated prior to first dose of study drugs. Exclusion: • Previous treatment with a JAK inhibitor • Specified abnormal laboratory results • Pregnancy • Recent or active infection	
Giardina et al., 2010[16] Italy NR NR	Adults with ankylosing spondylitis and inadequate response to oral NSAIDs	Age: Overall: 32.2 (8) Etanercept: 32.6 (6.8) Infliximab: 31.9 (9.2) Female: Overall: 21% Etanercept: 5 of 25 Infliximab: 6 of 25	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	NR

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Poor		Ethnicity: NR	Exclusion: • Complete ankylosis (fusion) of the spine	
Giles et al., 2019[25] NR ENTRACTE NR Fair	Patients were seropositive for RF or anti-CCP, ≥ 8 swollen joints (SJC66) and 8 tender joints (TJC68) at screening, and CRP > 0.3 mg/dL.	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%) Race/ethnicity: Nonwhite population, n (%): Tocilizumab 8 mg/kg: 378 (25%) Etanercept 50 mg: 355 (23%)	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 • ≥ 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%	F. Hoffmann-La Roche Ltd.
Glatt et al., 2019[35] NR NR	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)	Concomitant medication: • Certolizumb pegol Inclusion: • Adults (18–69 years) with moderate-to-severe RA for at least 6 months	The authors have not declared a specific grant for this research

Author, Year Country Trial Name Trial Number Study Quality	Population	Age Gender Ethnicity	Other Population Characteristics	Funding
NCT02430909 Fair		Female, n (%): Certolizumab pegol plus bimekizumab: 45 of 52 (87%) Certolizumab pegol plus placebo: 23 of 27 (85.2) Ethnicity, n (%): Nonwhite population: 0%	• Body mass index 18–35 kg/m^2, 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 • Active/high risk of infection, active or latent TB, known central nervous system demyelinating disorder or neoplastic disease within 5 years of study entry	from any funding agency in the public, commercial or not-for-profit sectors
Gottenberg et al., 2016[53] 47 clinical centers in France NR NCT01000441 Fair	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	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: 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,	French Ministry of Health (Programme Hospitalier de Recherche Clinique National

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	another anti-TNF drug) was added to the regimen of an already prescribed anti-TNF drug.		or tocilizumab; contraindication to all anti-TNF agents and other biologics, as well as pregnancy and breastfeeding.	
van der Heijde et al., 2018[29] 30 sites in 7 countries (Belgium, Bulgaria, Czech Republic, Estonia, Poland, Spain, and Ukraine) TORTUGA NR Fair	Active ankylosing spondylitis and an inadequate response or intolerance to two or more NSAIDs	Age: Filgotinib 200 mg: 41 (11.6) Placebo: 42 (9.0) Female: Filgotinib 200 mg: 13 of 58 (22%) Placebo: 17 of 58 (29%) Race/ethnicity: NR	Concomitant medication: • csDMARDs during the study (which must have been taken for at least 12 weeks before screening, with a stable dose for at least 4 weeks before baseline): MTX, leflunomide, sulfasalazine, and hydroxychloroquine. Use of one NSAID or a cyclooxygenase-2 inhibitor was permitted provided that the drug was used at a stable dose for at least 2 weeks before baseline • Previous use of one TNF-α inhibitor was allowed (capped at 30% of enrolled patients), with a minimum washout period before screening of 4 weeks (for etanercept), 8 weeks (for adalimumab, certolizumab pegol, and golimumab), or 12 weeks (for infliximab) Inclusion: • 18 years of age or older and active ankylosing spondylitis that fulfilled the modified New York classification criteria (with sacroiliitis confirmed by radiography within 12 months of screening) • BASDAI of 4 or higher and spinal pain scored as 4 or more at screening and baseline • High-sensitivity CRP concentration of 3.0 mg/L or higher at screening • Inadequate response to two or more NSAIDs given at the therapeutic dose range for 4 weeks or more	Galapagos and Gilead Sciences

Author, Year Country Trial Name Trial Number Study Quality	Population	Age Gender Ethnicity	Other Population Characteristics	Funding
			Exclusion: • Patients who were receiving high-potency opioid analgesics (methadone, hydromorphone, morphine, or oxycodone) at the time of the study or had received previous treatment with more than one TNF-α inhibitor, any alkylating agent, JAK inhibitors, or other investigational or approved biological drug at any time.	
Jobanputra et al., 2012[42] England RED SEA NR Poor	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: 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 two DMARDs including MTX Exclusion: • Patients treated previously with any licensed or experimental biological TNF-α inhibitor • Noncompliant or unsuitable patients for TNF-α inhibitors treatment	Queen Elizabeth Hospital Birmingham Charity
Kavanaugh et al., 2017[19]; Genovese et al., 2018[106] 59 sites in 18 countries (Argentina,	Adults with moderate to severely active RA for more than 6 months prior the screening	Age, mean (SD): Placebo: 52 (1.4) Filgotinib 50 mg: 52 (1.6) Filgotinib 100 mg: 53 (1.4) Filgotinib 200 mg: 52 (1.4) Female, n (%): Placebo: 56 (77.8%) Filgotonib 50 mg: 62 (86.1%)	Concomitant medication: • Corticosteroid treatment and antimalarial treatment Inclusion: • Adults ≥ 18 years of age with a diagnosis of RA for ≥ 6 months prior to screening meeting the 2010 ACR/EULAR criteria and ACR functional class I–III • 6/SJC66 or more and 8/TJC68 or more, a screening serum CRP 0.7 × ULN or more	Galapagos NV

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Austria, Bulgaria, Chile, Columbia, Germany, Guatemala, Hungary, Latvia, Mexico, Moldova, New Zealand, Poland, Romania, Russian Federation, Spain, Ukraine, and the U.S.) DARWIN 2 NR Fair		Filgotinib 100 mg: 53 (75.7%) Filgotinib 200 mg: 60 (87.0%) Race/ethnicity: NR	• Inadequate response to MTX and agreed to be washed out from MTX for ≥ 4 weeks before or during screening • Patients receiving oral glucocorticoids (≤ 10 mg/day) or NSAIDs were on a stable dose for ≥ 4 and ≥ 2 weeks, respectively, prior to baseline and a medically acceptable means of contraception Exclusion: • Current therapy with any DMARD (with the exception of antimalarials), or previous RA treatment with a bDMARD (excepting if the biological agent had been received in a single clinical study more than 6 months prior to enrollment and if the drug had been effective) • Any kind of JAK inhibitor used or a cytotoxic agent other than MTX or had received intra-articular or parenteral corticosteroid injection within 4 weeks of screening • Pregnant or immunocompromised patients	
Kivitz et al., 2017[20] 43 sites in 8 countries (the U.S., Poland, Colombia Mexico, Bulgaria, Czech Republic, Hungary, and Belgium) NR	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 of 66 (83.3%) Peficitinib 50 mg: 65 of 78	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	Astellas Pharma Global Development

Author, Year Country Trial Name Trial Number Study Quality	Population	Age Gender Ethnicity	Other Population Characteristics	Funding
NR Fair		(83.3%) Peficitinib 100 mg: 68 of 84 (81.0%) Peficitinib 150 mg: 64 of 78 (82.1%) Placebo: 63 of 72 (87.5%) <u>Race/ethnicity:</u> Non-Hispanic/Non-Latino 66-77% Peficitinib 25 mg: 45 of 66 (68%) Peficitinib 50 mg: 52 of 78 (67%) Peficitinib 100 mg: 56 of 84 (67%) Peficitinib 150 mg: 60 of 78 (77%) Placebo: 52 of 72 (72%)	<u>Exclusion:</u> • 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	
Kume et al., 2011[43] Japan NR NR Fair	Patients with active RA with no prior treatment with MTX, steroids or biologics and stable dosage of all DMARDs for at least 8 weeks prior to enrollment	<u>Age, mean (SD):</u> Tocilizumab 8 mg/kg: 62 (16) Etanercept 25 mg: 61 (15) Adalimumab 40 mg: 63 (17) <u>Female:</u> Tocilizumab 8 mg/kg: 19 (86%) Etanercept 25 mg: 18 (86%) Adalimumab 40 mg: 18 (86%) <u>Race/ethnicity:</u> NR	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, were allowed to leave the group (by clinician's judgment). Only patients who completed the study at 24 weeks were analyzed	NR
Manders et al., 2015[52]	Patients with treatment failure with their first	<u>Age, mean (SD):</u> 56.34 (11.24) Abatacept 500-1000 mg IV:	<u>Inclusion criteria:</u> • Patients with treatment failure with their first TNFi, moderate-to-high disease activity DAS28 > 3.2) and	Netherlands Organisation for Health Research

Author, Year Country Trial Name Trial Number Study Quality	Population	Age Gender Ethnicity	Other Population Characteristics	Funding
Multicenter trial in the Netherlands NR NR Poor	TNFi, moderate-to-high disease activity and no previous treatment with abatacept or rituximab	56.16 (9.95) Rituximab 1000 mg IV: 57.09 (11.08) TNFi: 55.81 (12.53) <u>Female, n (%):</u> 104 (74.8) Abatacept 500-1000 mg IV: 38 (88.4) Rituximab 1000 mg IV: 29 (63.0) TNFi: 37 (74.0) <u>Race/ethnicity:</u> NR	no previous treatment with abatacept or rituximab were included in this study. Patients were randomized in 3 groups: abatacept, rituximab and TNFi, with each medication mentioned in "Interventions" not being either rituximab or abatacept being a TNFi. Type of TNFi was individually chosen by the treating physician and the patient <u>Exclusion criteria:</u> • 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 one of the treatment agents or did not want to be randomized	and Development
Schiff et al., 2007[40] 86 sites in 14 countries in North, South, and Central America, Europe, and Africa ATTEST NCT00095147 Fair	Patients with RA who had the disease for at least 1 year and had an inadequate response to MTX	<u>Age, mean (SD):</u> Abatacept: 49.0 (12.5) Infliximab 3 mg/kg: 49.1 (12.0) Placebo: 49.4 (11.5) <u>Female, n (%):</u> NR Abatacept: 130 (83.3%) Infliximab 3 mg/kg: 136 (82.4%) Placebo: 96 (87.3%) <u>Caucasian, n (%):</u> NR Abatacept: 126 (80.8%%) Infliximab 3 mg/kg: 133 (80.6%) Placebo: 84 (76.4%)	<u>Concomitant medications</u> • Permitted between days 1–197: oral corticosteroids (10 mg of prednisone or equivalent daily (stable for > 25 out of 28 days prior to randomisation)), 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) <u>Inclusion:</u> • 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	Bristol-Myers Squibb, Princeton, New Jersey, USA

Author, Year Country Trial Name Trial Number Study Quality	Population	Age Gender Ethnicity	Other Population Characteristics	Funding
			MTX > 15 mg/week for > 3 months prior to randomization (stable 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[41] 151 centers in Europe, Australia, and North America EXXELERATE NCT01500278 Fair	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,	UCB Pharma

Author, Year Country Trial Name Trial Number Study Quality	Population	Age Gender Ethnicity	Other Population Characteristics	Funding
			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)	
Takeuchi et al., 2015[17] 43 sites in Japan NR NCT01649999 Fair	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 of 55 (83.6%) Peficitinib 50 mg: 46 of 57 (80.7%) Peficitinib 100 mg: 42 of 55 (76.4%) Peficitinib 150 mg: 51 of 58 (87.9%) Placebo: 43 of 56 (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: • 20–75 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[37] 161 centers in Japan NR Fair	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 of 518 (70.3%) Placebo: 121 of 170 (71.2%) Peficitinib 100 mg: 118 of 174	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:	Astellas Pharma, Inc

Author, Year Country Trial Name Trial Number Study Quality	Population	Age Gender Ethnicity	Other Population Characteristics	Funding
		(67.8%) Peficitinib 150 mg: 125 of 174 (71.8%) Race/ethnicity: NR	• Previous biological DMARDs or other JAK inhibitors, infections or laboratory abnormalities, or a history of or concurrent malignant tumor	
Tanaka et al. 2019[36] 165 sites in 3 countries (Japan, Korea, and Taiwan) NR NR Fair	Adults with active RA and inadequate response to, or intolerance of, at least one DMARD	Age, mean (SD): 55.3 Placebo: 56.3 (11.7) Peficitinib 100 mg: 54.1 (12.2) Peficitinib 150 mg: 55.0 (12.8) Etanercept: 55.5 (11.6) Female, n (%): 366 of 507 (72.2%) Placebo: 73 of 101 (72.3%) Peficitinib 100 mg: 77 of 104 (74.0%) Peficitinib 150 mg: 78 of 102 (76.5%) Etanercept : 138 of 200 (69.0%) Race/ethnicity: NR	Concomitant medication: DMARDs Inclusion: • 20 years of age or older and active RA • Inadequate response to, or intolerance of, at least one 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	Astellas Pharma, Inc.
Taylor et al., 2017[21] 281 centers in 26 countries in North and South America, Europe, and Asia	Adults with active RA and inadequate response to MTX	Age: Baricitinib 4 mg: 54 (2) Adalimumab 40 mg: 53 (12) Placebo: 53 (2) Female: 1008 (77%) Baricitinib 4 mg: 375 (77%)	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	Eli Lilly and Incyte

Author, Year Country Trial Name Trial Number Study Quality	Population	Age Gender Ethnicity	Other Population Characteristics	Funding
RA-BEAM NR Fair		Adalimumab 40 mg: 251 (76%) Placebo: 382 (78%) Race/ethnicity: NR	• 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	
Vollenhofen et al., 2013[46] 115 centers worldwide ORAL Standard NCT00853385 Fair	Patients were eligible for enrollment if they were 18 years of age or older and had received a diagnosis of active RA, as defined according to the ACR 1987 Revised Criteria.	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) 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) White, n (%): Tofacitinib 5 mg: 151 (74.0) Tofacitinib 10 mg: 143 (71.1) Adalimumab 40 mg: 148 (72.5)	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 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	Pfizer

Author, Year Country Trial Name Trial Number Study Quality	Population	Age Gender Ethnicity	Other Population Characteristics	Funding
		Placebo + Tofacitinib 5 mg: 40 (71.4) Placebo + Tofacitinib 10 mg: 35 (67.3)		
Weinblatt et al., 2013[39]; Schiff et al., 2013[102] 120 sites in North and South America AMPLE NCT00929864 Fair	Adults with confirmed diagnosis of RA for less than 5 years, inadequate response to MTX, and nor previous bDMARD therapy	<u>Age, mean (SD):</u> Abatacept 125 mg SC: 51.4 (12.6) Adalimumab 40 mg SC: 51.0 (12.8) <u>Female, n (%):</u> Abatacept 125 mg SC: 259 (81.4%) Adalimumab 40 mg SC: 270 (82.3%) <u>White, n (%):</u> Abatacept 125 mg SC: 257 (80.8%) Adalimumab 40 mg SC: 256 (78.0%)	<u>Concomitant medication:</u> • 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 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 <u>Inclusion:</u> • 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 one or both of the following features: 1)	Bristol-Myers Squibb and Abbott

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			seropositivity for anticyclic citrullinated peptide antibodies or rheumatoid factor, and/or 2) an elevated ESR or CRP level	
Westhovens et al., 2016[22]; Genovese et al., 2018[106] 106 sites in 21 countries in North and South America, Europe, Asia, Australia, and New Zealand DARWIN 1 NR Fair	Adults with moderate-to-severe active RA for 6 months or more, receiving a stable dose of MTX	Age: NR Placebo: 52 (1.4) Filgotinib once-daily dose groups Filgotinib 50 mg: 53 (1.5) Filgotinib 100 mg: 52 (1.4) Filgotinib 200 mg: 55 (1.3) Filgotinib twice-daily dose groups Filgotinib 2×25 mg: 52 (1.4) Filgotinib 2×50 mg: 55 (1.3) Filgotinib 2×100 mg: 54 (1.3) Female: NR Placebo: 70 of 86 (81.4%) Filgotinib once-daily dose groups Filgotinib 50 mg: 69 of 82 (84.1%) Filgotinib 100 mg: 65 of 85 (76.5%) Filgotinib 200 mg: 74 of 86 (86.0%) Filgotinib twice-daily dose groups Filgotinib 2×25 mg: 68 of 86 (79.1%) Filgotinib 2×50 mg: 65 of 85	Concomitant medication: • MTX, corticosteroids Inclusion: • Adults (18 years of age or older) with a diagnosis of RA for ≥6 months prior to screening, meeting the 2010 ACR/ EULAR criteria for and ACR functional class I–III • 6/66 or more SJC and 8/68 or more TJC, a screening serum CRP ≥ 0.7 × ULN (changed from ≥ 1.5 × ULN in May 2014 to facilitate recruitment) • Treatment with MTX for 6 months or more and on a stable dose (15–25 mg/week, oral or parenteral) 4 weeks prior to screening • Oral glucocorticoids (≤ 10 mg/day) or NSAIDs on a stable dose for ≥ 4 and ≥ 2 weeks, respectively, prior to baseline • Females of childbearing potential were required to be using a medically acceptable means of contraception Exclusion: • Current therapy with any DMARD other than MTX • Previous RA treatment with a bDMARD (excepting if the biological agent had been received in a single clinical study > 6 months prior to enrollment and if the drug was effective) • Treatment with JAK inhibitor, a cytotoxic agent other than MTX or parenteral glucocorticoids within 4 weeks of screening	Galapagos NV

Author, Year Country Trial Name Trial Number Study Quality	Population	Age Gender Ethnicity	Other Population Characteristics	Funding
		(76.5%) Filgotinib 2×100 mg: 70 of 84 (83.3%) <u>Race/ethnicity:</u> NR		

Abbreviations. ACR 20/50/70: American College Of Rheumatology, numbers refer to percentage improvement; 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; 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: U.S. National Clinical Trial Identifier; NR: not reported; NSAID: nonsteroidal anti-inflammatory drug; 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; TNFi: tumor necrosis factor inhibitor; ULN: upper limit of laboratory normal; VAS: Visual Analogue Scale.

Table B2. Evidence Table RCTs (Intervention and Results)

Author, Year Country Trial Name Trial Number Study Quality	Interventions	N	Efficacy/Effectiveness Outcomes	AEs General	AEs Specific
Brown et al., 2018[38] 35 sites in the United Kingdom SWITCH NR Poor	• Abatacept 125 mg SC weekly (minimum 24 weeks) • Rituximab 1 g IV at days 0 (week 0) and 15 (week 2) • Alternative TNFi: 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	Total N = 122 Alternative TNFi = 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 TNFi: -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 Abatacept vs. rituximab: 0.06 (–0.59 to 0.71) *P* = .86	Week 48: Any AE: Rituximab 1 g: 31 of 40 Abatacept 125 mg: 31 of 41 SAEs: Rituximab 1 g: 4 of 40 Abatacept 125 mg: 4 of 41 Withdrawal because of AEs: Rituximab 1 g: 4 of 40 (10%) Abatacept 125 mg: 2 of 41 (5%)	Week 48: Death: Rituximab 1 g: 1 of 40 (3%*) Abatacept 125 mg: 1 of 41 (2%*) Melanoma skin cancer: Rituximab 1 g: 1 of 40 (3%*) Abatacept 125 mg: 0 of 41 (2%*) Pneumonia: Rituximab 1 g: 1 of 40 (3%*) Abatacept 125 mg: 1 of 41 (2%*) Injection site reactions (angioedema): Rituximab 1 g: 0 of 40 (0%*) Abatacept 125 mg: 1 of 41 (2%*) * self-calculated

Author, Year Country Trial Name Trial Number Study Quality	Interventions	N	Efficacy/Effectiveness Outcomes	AEs General	AEs Specific
	thereafter for a minimum of 24 weeks), golimumab (50 mg SC every 4 weeks for a minimum of 24 weeks) • 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; two intravenous infusions administered at a 2-week interval. Prior to receiving rituximab, 100 mg of IV methylpredniso-		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 (3%) Abatacept 125 mg: 1 of 41 (2%) ACR20: Rituximab 1 g: 12 of 28 (43%) Abatacept 125 mg: 11 of 31 (36%) ACR50: Rituximab 1 g: 6 of 29 (21%) Abatacept 125 mg: 6 of 32 (19%) ACR70: Rituximab 1 g: 3 of 30 (10%) Abatacept 125 mg: 3 of 32 (9%) DAS28 remission:		

Author, Year Country Trial Name Trial Number Study Quality	Interventions	N	Efficacy/Effectiveness Outcomes	AEs General	AEs Specific
	lone was given as a premedication.		Rituximab 1 g: 2 (5%) Abatacept 125 mg: 2 (5%) EULAR good response: Rituximab 1 g: 2 of 40 (5%) Abatacept 125 mg: 2 of 41 (5%) 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)		
Burmester et al., 2016[44]; Strand et al., 2018[92] 86 centers in Europe, Israel, Russia, South Africa, South	• 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:	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	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%)

Author, Year Country Trial Name Trial Number Study Quality	Interventions	N	Efficacy/Effectiveness Outcomes	AEs General	AEs Specific
America, South Korea and the U.S. MONARCH NCT02332590 Fair			Week 24 DAS28-ESR < 2.6: Adalimumab 40 mg: 13 (7.0) Sarilumab 200 mg: 49 (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 (58.4) Sarilumab 200 mg: 132 (71.7) *P* = .007 ACR50 response Adalimumab 40 mg: 55 (29.7) Sarilumab 200 mg: 84 (45.7) *P* = .002 ACR70 response Adalimumab 40 mg: 22 (11.9) Sarilumab 200 mg: 43 (23.4) *P* = .004	184 (4.9%) Withdrawal because of AEs: Adalimumab 40 mg: 13 of 184 (7.1%) Sarilumab 200 mg: 11 of 184 (6.0%)	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%)
Elmedany et al., 2019[26] 1 site in Saudi Arabia	• Tocilizumab IV 8 mg/kg every 4 weeks • Abatacept IV 500 mg for patients less than 60 kg	Total N = 132 Tocilizumab 8 mg/kg = 68 Abatacept 500/750/1000 mg = 64	Week 24: DAS28-ESR: mean change from baseline: Tocilizumab 8 mg/kg: -3.3 Abatacept 500/750/1000 mg: -2.6	Week 24: Any AE: Tocilizumab 8 mg/kg: 40 of 68 (60.3%) Abatacept 500/750/1000 mg: 18 of 64 (28.1%)	Injection site reaction: Tocilizumab 8 mg/kg: 12 of 68 (18%) Abatacept 500/750/1000 mg: 10 of64 (16%)

Author, Year Country Trial Name Trial Number Study Quality	Interventions	N	Efficacy/Effectiveness Outcomes	AEs General	AEs Specific
NR NR Poor	body weight, 750 mg for 60–100 kg, and 1000 mg for patients more than 100 kg body weight on days 1, 15, and 29 and then every 4 weeks		*P* = .049 DAS28-ESR mean (SD): Tocilizumab 8 mg/kg: 2.4 (0.84) Abatacept 500/750/1000 mg: 2.8 (0.78) *P* = .055 HAQ (VAS) mean (SD): Tocilizumab 8 mg/kg: 15.95 (7.86) Abatacept 500/750/1000 mg: 20.74 (8.82) *P* = .001 HAQ-DI mean (SD): Tocilizumab 8 mg/kg: 0.89 (1.12) Abatacept 500/750/1000 mg: 1.01 (1.24) *P* = .56	Withdrawal because of AEs: Tocilizumab 8 mg/kg: 10 of 68 (14.7%) Abatacept 500/750/1000 mg: 4 of 64 (6.3%) SAEs: Tocilizumab 8 mg/kg: 10 of 68 (14.7%) Abatacept 500/750/1000 mg: 4 of 64 (6.3%)	Herpes zoster: Tocilizumab 8 mg/kg: 0 of 68 (0%) Abatacept 500/750/1000 mg: 0 of 64 (0%) New cancer incidence: Tocilizumab 8 mg/kg: 0 of 68 (0%) Abatacept 500/750/1000 mg: 0 of 64 (0%) Major adverse cardiovascular events: Tocilizumab 8 mg/kg: 0 of 68 (0%) Abatacept 500/750/1000 mg: 0 of 64 (0%) Gastrointestinal perforation: Tocilizumab 8 mg/kg: 0 of 68 (0%) Abatacept 500/750/1000 mg: 0 of 64 (0%)

Author, Year Country Trial Name Trial Number Study Quality	Interventions	N	Efficacy/Effectiveness Outcomes	AEs General	AEs Specific
Emery et al., 2018[31] U.S., South America, Western Europe, Eastern Europe and Russia ASCERTAIN NR Poor	• 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 (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%)	Week 24 Infection: Sarilumab 150 mg: 20 of 49 (41%) Sarilumab 200 mg: 11 of 51 (22%) Tocilizumab 4 mg/kg: 32 of 102 (31%) Serious infection Sarilumab 150 mg: 0 of 49 (0%) Sarilumab 200 mg: 1 of 51 (2%) Tocilizumab 4 mg/kg: 2 of 102 (2%) Death Sarilumab 150 mg: 0 of 49 (0%) Sarilumab 200 mg: 0 of 51 (0%) Tocilizumab 4 mg/kg: 1 of 102 (1%)
Fleischmann et al., 2012[47] 63 centers in the U.S., Europe, Latin America, and the Republic of Korea	• Tofacitinib 1 mg twice a day • Tofacitinib 3 mg twice a day • Tofacitinib 5 mg twice a day,	Total n = 384 Tofacitinib 1 mg = 54, Tofacitinib 3 mg = 51, Tofacitinib 5 mg = 49,	Primary outcome: 12 weeks ACR20 response: *P*-value compared to placebo Tofacitinib 1 mg: 31.5% Tofacitinib 3 mg: 39.2% (*P* < .05) Tofacitinib 5 mg: 59.2% (*P* <	AEs: Tofacitinib 1 mg: 19 of 37 (51.4%) Tofacitinib 1 mg reassigned*: 5 of 17 (29.4%) Tofacitinib 3 mg: 18 of 34	Infections: Tofacitinib 1 mg: 11 of 37 (29.7%) Tofacitinib 1 mg reassigned*: 2 of 17 (11.8%) Tofacitinib 3 mg: 7 of

Author, Year Country Trial Name Trial Number Study Quality	Interventions	N	Efficacy/Effectiveness Outcomes	AEs General	AEs Specific
NR NCT00550446 Fair	• Tofacitinib 10 mg twice a day, • Tofacitinib 15 mg twice a day • Adalimumab 40 mg SC every 2 weeks • Placebo	Tofacitinib 10 mg = 61, Tofacitinib 15 mg = 57, Adalimumab 40 mg = 53 Placebo = 59	.0001) Tofacitinib 10 mg: 70.5% (*P* < .0001) Tofacitinib 15 mg: 71.9% (*P* < .0001) Adalimumab 40 mg: 35.9% Placebo: 22% 24 weeks ACR20 response: *P* -value compared to placebo Tofacitinib 1 mg: 24.1% Tofacitinib 3 mg: 37.3% Tofacitinib 5 mg: 51.0% (*P* < .05) Tofacitinib 10 mg: 65.6% (*P* < .0001) Tofacitinib 15 mg: 66.7% (*P* < .0001) Adalimumab 40 mg: NR Placebo: 25.4% Secondary outcomes: 12 weeks ACR50 response: *P*-value compared to placebo Tofacitinib 1 mg: 11.1% Tofacitinib 3 mg: 23.5% Tofacitinib 5 mg: 36.7% (*P* < .001) Tofacitinib 10 mg: 44.3% (*P* < .0001) Tofacitinib 15 mg: 50.9% (*P* <	(52.9%) Tofacitinib 3 mg 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 17 (0%) Tofacitinib 5 mg: 0 of 49 (0%) Tofacitinib 10 mg: 1 of 61 (1.6%)	34 (20.6%) Tofacitinib 3 mg 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

Author, Year Country Trial Name Trial Number Study Quality	Interventions	N	Efficacy/Effectiveness Outcomes	AEs General	AEs Specific
			.0001) Adalimumab 40 mg: 18.9% Placebo: 10.2% ACR70 response: *P*-value compared to placebo Tofacitinib 1 mg: 5.6% Tofacitinib 3 mg: 11.8% Tofacitinib 5 mg: 12.2% Tofacitinib 10 mg: 24.6% (*P* < .001) Tofacitinib 15 mg: 26.3% (*P* < .001) Adalimumab 40 mg: 3.8% Placebo: 3.4% 24 weeks ACR50 response: *P* -value compared to placebo Tofacitinib 1 mg: 7.4% Tofacitinib 3 mg: 27.5% (*P* < .05) Tofacitinib 5 mg: 34.7% (*P* < .05) Tofacitinib 10 mg: 44.3% (*P* < .0001) Tofacitinib 15 mg: 54.4% (*P* < .0001) Placebo: 10.2% ACR70 response: *P* -value compared to placebo Tofacitinib 1 mg: 5.6% Tofacitinib 3 mg: 13.7%	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%) 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	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%) Adalimumab 40 mg reassigned*: 1 of 44 (2.3%) Placebo: 1 of 34 (2.9%) Placebo reassigned*: 0 of 25 (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

Author, Year Country Trial Name Trial Number Study Quality	Interventions	N	Efficacy/Effectiveness Outcomes	AEs General	AEs Specific
			Tofacitinib 5 mg: 20.4% (*P* < .05) Tofacitinib 10 mg: 37.7% (*P* < .0001) Tofacitinib 15 mg: 33.3% (*P* < .001) Placebo: 6.8%	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[48] 194 centers in 25 countries. ORAL – Strategy NCT02187055 Fair	Tofacitinib 5 mg twice daily Tofacitinib 5 mg twice daily + background MTX Adalimumab 40 mg every 2 weeks + background MTX	Total n = 1146 Tofacitinib 5 mg = 384 Tofacitinib 5 mg + MTX = 376 Adalimumab 40 mg + MTX = 386	Primary outcome: 6 months ACR50 response Tofacitinib 5 mg: 147 of 384 ((38%) 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	AEs: Tofacitinib 5 mg: 226 of 384 (59%) Tofacitinib 5 mg + MTX: 231 of 376 (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%)	Serious infections: Tofacitinib 5 mg: 6 of 384 (2%) Tofacitinib 5 mg + MTX: 10 of 376 (3%) Adalimumab 40 mg + MTX: 6 of 386 (2%) Herpes zoster: Tofacitinib 5 mg: 4 of 384 (1%) Tofacitinib 5 mg + MTX: 8 of 376 (2%) Adalimumab 40 mg + MTX: 6 of 386 (2%) Opportunistic infections: Tofacitinib 5 mg: 2 of 384 (1%) Tofacitinib 5 mg + MTX: 1 of 376 (< 1%) Adalimumab 40 mg + MTX: 2 of 386 (1%) Malignancies:

Author, Year Country Trial Name Trial Number Study Quality	Interventions	N	Efficacy/Effectiveness Outcomes	AEs General	AEs Specific
			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: Tofacitinib 5 mg: 40 of 384 (10%) Tofacitinib 5 mg + MTX: 45 of 376 (12%) Adalimumab 40 mg + MTX: 48 of 386 (12%)		Tofacitinib 5 mg: 1 of 384 (< 1%) Tofacitinib 5 mg + MTX: 0 of 376 (0%) Adalimumab 40 mg + MTX: 0 of 386 (0%) Deaths: Tofacitinib 5 mg: 2/384 (1%) Tofacitinib 5 mg + MTX: 0 of 376 (0%) Adalimumab 40 mg + MTX: 0 of 386 (0%)
Fleischmann et al., 2019[24] 286 sites in 41 countries in Europe, North, South and Central America, Europe, Asia SELECT-COMPARE NCT02629159	• Upadacitinib 15 mg once daily • Adalimumab 40 mg SC every 2 weeks • Placebo	Total N = 1629 Upadacitinib 15 mg = 651 Adalimumab 40 mg = 327 Placebo = 651	Primary outcomes: Week 12: ACR20 response: Upadacitinib 15 mg: 71% Adalimumab 40 mg: 63% *P* ≤ .05 DAS28-CRP score of < 2.6: Upadacitinib 15 mg: 29% Adalimumab 40 mg: 18% *P* ≤ .001 Secondary outcomes: Week 12: ACR50 response:	Week 26: Any AE: 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:	Week 26: Infection: 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:

Author, Year Country Trial Name Trial Number Study Quality	Interventions	N	Efficacy/Effectiveness Outcomes	AEs General	AEs Specific
Fair			Upadacitinib 15 mg: 45% Adalimumab 40 mg: 29% *P* ≤ .001 DAS28-CRP score of ≤ 3.2: Upadacitinib 15 mg: 45% Adalimumab 40 mg: 29% *P* ≤ .001 HAQ-DI: mean change from baseline Upadacitinib 15 mg: -0.60 Adalimumab 40 mg: -0.49 *P* ≤ .01	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, along with background MTX, before discontinuing the treatment; this patient was included in the placebo group for safety assessments	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%)
Gabay et al., 2013[45] 76 centers in 15 countries in North and South America, Australasia and Europe ADACTA NCT01119859 Fair	• 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: 39.9% Adalimumab 40 mg: 10.5% *P* < .0001 DAS28 score of ≤ 3.2:	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%) Adalimumab 40 mg: 134 of 162 (83%) SAEs: Tocilizumab 8 mg/kg: 23 of 162 (14%) Adalimumab 40 mg: 21 of 162 (13%)	Week 24: Infection: Tocilizumab 8 mg/kg: of 162 (70%) Adalimumab 40 mg: 106 of 162 (65%) At least one infection: Tocilizumab 8 mg/kg: 77/162 (48%) Adalimumab 40 mg: 68 of 162 (42%) At least one serious infection: Tocilizumab 8 mg/kg: 5 of 162 (3%)

Author, Year Country Trial Name Trial Number Study Quality	Interventions	N	Efficacy/Effectiveness Outcomes	AEs General	AEs Specific
			Tocilizumab 8 mg/kg: 51.5% Adalimumab 40 mg: 19.8% *P* < .0001 EULAR response good or moderate: Tocilizumab 8 mg/kg: 77.9% Adalimumab 40 mg: 54.9% *P* < .0001 EULAR response good: Tocilizumab 8 mg/kg: 51.5% Adalimumab 40 mg: 19.8% *P* < .0001 ACR20 response: Tocilizumab 8 mg/kg: 65.0% Adalimumab 40 mg: 49.4% *P* = .0038 ACR50 response: Tocilizumab 8 mg/kg: 47.2% Adalimumab 40 mg: 27.8% *P* = .0002 ACR70 response: Tocilizumab 8 mg/kg: 32.5% Adalimumab 40 mg: 17.9% *P* = .0023		Adalimumab 40 mg: 5 of 162 (3%) Cancers: Tocilizumab 8 mg/kg: 1 of 162 (1%) Adalimumab 40 mg: 1 of 162 (1%) Deaths: Tocilizumab 8 mg/kg: 2 of 162 (1%) Adalimumab 40 mg: 0 of 162 (0%).
Genovese et al., 2017[18]	Peficitinib 25 mg, 50 mg, 100 mg, 150 mg once a day	Total N = 289 Peficitinib 25 mg = 59	Week 12: ACR20 response: Peficitinib 25 mg: *13* of 59	Week 12: Any AE: Peficitinib 25 mg: 22 of 59	Week 12: Deaths: Peficitinib 25 mg: 0 of

Author, Year Country Trial Name Trial Number Study Quality	Interventions	N	Efficacy/Effectiveness Outcomes	AEs General	AEs Specific
41 sites in 6 countries (the U.S., Poland, Hungary, Czech Republic, Mexico, and Bulgaria NR NR Fair	for 12 weeks Placebo	Peficitinib 50mg = 57 Peficitinib 100 mg = 58 Peficitinib 150 mg = 64 Placebo = 51	(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%) *P* > .05 DAS28-CRP < 2.6	(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 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%)	of 59 (0%) Peficitinib 50 mg: 0 of 57 (0%) Peficitinib 100 mg: 0 of 58 (0%) Peficitinib 150 mg: 0 of 64 (0%) Placebo: 0 of 51 (0%) Serious infections: Peficitinib 25 mg: 1 of 59 (1.7%) Peficitinib 50 mg: 0 of 57 (0%) Peficitinib 100 mg: 0 of 58 (0%) Peficitinib 150 mg: 0 of 64 (0%) Placebo: 0 of 51 (0%)

Author, Year Country Trial Name Trial Number Study Quality	Interventions	N	Efficacy/Effectiveness Outcomes	AEs General	AEs Specific
			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%)		
Genovese et al., 2019[23] 114 sites in Europe, North and South America, Asia, and Australia FINCH 2 NR Fair	• Filgotinib 200 mg once daily • Filgotinib 100 mg once daily • Placebo	Total N = 449 Filgotinib 200 mg = 148 Filgotinib 100 mg = 153 Placebo = 148	Week 12 Primary endpoint: ACR20 response: Filgotinib 200 mg: *97* of 147 (66.0%), compared to placebo, *P* < .001 Filgotinib 100 mg: *88* of 153 (57.5%), compared to placebo, *P* < .001 Placebo: *46* of 148 (31.1%) Week 24 Key secondary endpoints: HAQ-DI, mean change from baseline (SD): Filgotinib 200 mg: −0.75 (0.62), compared to placebo, *P* < .001 Filgotinib 100 mg: −0.60 (0.66), compared to placebo, *P* = .003 Placebo: −0.42 (0.60) HAQ-DI reduction ≥0.22: Filgotinib 200 mg: *99* of 144 (68.8%), compared to placebo, *P* < .001	Week 24: Any treatment-emergent AE: Filgotinib 200 mg: 102 of 147 (69.4%) Filgotinib 100 mg: 97 of 153 (63.4%) Placebo: 100 of 148 (67.6%) Withdrawal because of treatment-emergent AEs: Filgotinib 200 mg: 5 of 147 (3.4%) Filgotinib 100 mg: 6 of 153 (3.9%) Placebo: 3 of 148 (2.0%) Serious treatment-emergent AEs: Filgotinib 200 mg: 6 of 147 (4.1%) Filgotinib 100 mg: 8 of 153 (5.2%) Placebo: 5 of 148 (3.4%)	Week 24: Death: Filgotinib 200 mg: 0 of 147 (0%) Filgotinib 100 mg: 0 of 153 (0%) Placebo: 0 of 148 (0%) Infection: Filgotinib 200 mg: 53 of 147 (36.1%) Filgotinib 100 mg: 52 of 153 (34.0%) Placebo: 38 of 148 (25.7%) Herpes zoster: Filgotinib 200 mg: 2 of 147 (1%) Filgotinib 100 mg: 2 of 153 (1%) Placebo: 0 of 148 (0%)

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			Filgotinib 100 mg: *80* of 148 (54.1%), compared to placebo, *P* = .001 Placebo: *51* of 144 (35.4%) DAS28-CRP ≤ 3.2: Filgotinib 200 mg: *66* of 136 (48.3%), compared to placebo, *P* < .001 Filgotinib 100 mg: *52* of 137 (37.9%), compared to placebo, *P* = .003 Placebo: *27* of 128 (20.9%)		Opportunistic infection: Filgotinib 200 mg: 0 of 147 (0%) Filgotinib 100 mg: 0 of 153 (0%) Placebo: 0 of 148 (0%) Serious infection: Filgotinib 200 mg: 1 of 147 (0.7%) Filgotinib 100 mg: 3 of 153 (2.0%) Placebo: 2 of 148 (1.4%)
Giardina et al., 2010[16] Italy NR NR Poor	Etanercept vs. infliximab	Total N = 50 Etanercept = 25 Infliximab = 25	12 weeks: ASAS 20: Etanercept = 15 of 25 (60%) Infliximab = 19 of 25 (75%) ASAS 40: Etanercept = 43% Infliximab = 55% BASFI: Etanercept = 5 Infliximab = 3.5 *P* < .005 BASDAI: Etanercept = 5.6	Week 104: Overall AEs: NR Discontinuation due to AEs: Etanercept: 0 of 25 Infliximab: 0 of 25 SAEs: NR	Week 104: Injection site reactions: Etanercept: 5 of /25 (25%) Infliximab:1 of 25 (4%) *P* < .005 Severe infections: Etanercept: 1 of 25 (4%) Infliximab: 2 of 25 (8%) *P* = NS

Author, Year Country Trial Name Trial Number Study Quality	Interventions	N	Efficacy/Effectiveness Outcomes	AEs General	AEs Specific
			Infliximab = 3.5 *P* < .005		
Giles et al., 2019[25] NR ENTRACTE NR Fair	• Tocilizumab 8 mg/kg intravenous every 4 weeks • Etanercept 50 mg subcutaneous weekly	Total N = 3080 Tocilizumab 8 mg/kg = 1538 Etanercept 50 mg = 1542	NR	Overall AEs: NR SAEs: Tocilizumab 8 mg/kg: 421 of 1538 (27%), 666 events, IR per 100 patient-years 15.7 Etanercept 50 mg: 356 of 1542 (23%), 631 events, IR per 100 patient-years 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 1538 (5%), 120 events, IR per 100 patient-years 2.8 Etanercept 50 mg: 105 of 1542 (7%), 105 events, IR per 100 patient-years 2.4 Tocilizumab vs. etanercept HR, 1.15 (95% CI, 0.89 to 1.49)	MACE, including undetermined cause of death: Tocilizumab 8 mg/kg: 83 of 1538 (5%), events/100 pys 1.82 (95% CI, 1.46 to 2.24) Etanercept 50 mg: 78 of 1542 (5%), 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 /1538 (2%), events/100 pys 0.61 (95% CI, 0.41 to 0.87) Etanercept 50 mg: 32 of 1542 (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)

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					Nonfatal and fatal stroke, all types: Tocilizumab 8 mg/kg: 26 of 1538 (2%), events/100 pys 0.53 (95% CI, 0.35 to 0.78) Etanercept 50 mg: 16 of 1542 (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 1538 (4%), events/100 pys 1.31 (95% CI, 1.01 to 1.67) Etanercept 50 mg: 64 of 1542 (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) * self-calculated

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Glatt et al., 2019[35] NR NR NCT02430909 Fair	Combination therapy (certolizumab pegol plus bimekizumab vs. certolizumab pegol plus placebo)	Totan 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 (79%) Certolizumab pegol plus placebo: 16 of 27 (59%) Serious treatment-emergent AEs: Certolizumab pegol plus bimekizumab: 2 of 52 (4%) Certolizumab pegol plus placebo: 3 of 27 (11%) Discontinuation due to AEs: Certolizumab pegol plus bimekizumab: 4 of 52 (8%) Certolizumab pegol plus placebo: 3 of 27 (11%)	Death: Certolizumab pegol plus bimekizumab: 0 of 52 (0%) Certolizumab pegol plus placebo: 1 of 27 (4%) Infections: Certolizumab pegol plus bimekizumab: 26 of 52 (50%) Certolizumab pegol plus placebo: 6 of 27 (22%)
Gottenberg et al., 2016[53] 47 clinical centers in France NR NCT01000441 Fair	Non-TNF biologics: • Abatacept: 500 - 1000 mg IV in weeks 0, 2, and 4 and once monthly from week 4 on. • Rituximab: 1000 mg IV in weeks 0 and 2 • Tocilizumab: 8 mg/kg IV every month	Total n = 292 Non-TNF-biologic = 146 Second anti-TNF drug = 146	Primary outcome: Week 24: EULAR response good or moderate: Non-TNF-biologic: 101 of 146 (69%) Second anti-TNF drug: 76 of 146 (52%) *P* = .004 Secondary outcomes: Week 12:	AEs: NR SAEs: Non-TNF-biologic: 16 of 146 (11%) Second anti-TNF drug: 8 of 146 (5%) Withdrawal because of AEs: Non-TNF-biologic: 1 of	Deaths: Non-TNF-biologic: 1 of 146 0.7(%) Second anti-TNF drug: 0 of 146 (0%) Cancer: Non-TNF-biologic: 1 of 146 (0.7%) Second anti-TNF drug: 0 of 146 (0%)

Author, Year Country Trial Name Trial Number Study Quality	Interventions	N	Efficacy/Effectiveness Outcomes	AEs General	AEs Specific
	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 thereafter		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 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	146 (0.7%) Second anti-TNF drug: 1 of 146 (0.7%)	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%) Tuberculosis Non-TNF-biologic: 0 of 146 (0%) Second anti-TNF drug: 1 of 146 (0.7%) Cardiovascular events: Non-TNF-biologic: 6 of 146 (4.11%) Second anti-TNF drug: 1 of 146 (0.7%)

Author, Year Country Trial Name Trial Number Study Quality	Interventions	N	Efficacy/Effectiveness Outcomes	AEs General	AEs Specific
			(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: /130 (%) Second anti-TNF drug: /133 (%)		
van der Heijde et al., 2018[29] 30 sites in 7 countries (Belgium, Bulgaria, Czech Republic, Estonia, Poland, Spain, and Ukraine) TORTUGA	• Filgotinib 200 mg daily for 12 weeks • Placebo	Total N = 116 Filgotinib 200 mg = 58 Placebo = 58	Week 12: ASDAS: mean change from baseline (SD): Filgotinib 200 mg: −1.47 (1.04) Placebo: −0.57 (0.82) difference between groups −0.85 (95% CI, −1.17 to 0.53) *P* < .001 ASDAS: Number of patients with major improvement: Filgotinib 200 mg: 19 of 58 (33%)	Week 12: Any treatment-emergent AE: Filgotinib 200 mg: 18 of 58 (31%) Placebo: 18 of 58 (31%) Treatment-emergent AEs leading to discontinuation: Filgotinib 200 mg: 1 of 58 (2%) Placebo: 1 of 58 (2%)	Week 12: Serious treatment-emergent infection: Filgotinib 200 mg: 1 of 58 (2%) Placebo: 0 of 58 (0%) Infection: Filgotinib 200 mg: 7 of 58 (12%) Placebo: 7 of 58 (12%)

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NR Fair			Placebo: 1 of 58 (2%) Difference between groups: 31% (95% CI, 18 to 44) *P* < .001 ASDAS: Number of patients clinically significant improvement Filgotinib 200 mg: 38 of 58 (66%) Placebo: 15 of 58 (26%) Difference between groups: 40% (95% CI, 22 to 54) *P* < .001 Inactive disease: Filgotinib 200 mg: 3 of 58 (5%) Placebo: 0 of 58 (0%) Difference between groups: 5% (95% CI,−2 to 14) *P* = .09 ASAS20 : Filgotinib 200 mg: 44 of 58 (76%) Placebo: 23 of 58 (40%) Difference between groups: 36% (95% CI, 18 to 51) *P* < .001 ASAS40 : Filgotinib 200 mg: 22 of 58 (38%) Placebo: 11 of 58 (19%) Difference between groups: 19%	Treatment-emergent AEs Grade 3 or higher: Filgotinib 200 mg: 2 of 58 (3%) Placebo: 0 of 58 (0%) Serious treatment-emergent AE: Filgotinib 200 mg: 1 of 58 (2%) Placebo: 0 of 58 (0%)	Death: Filgotinib 200 mg: 0 of 58 (0%) Placebo: 0 of 58 (0%) Opportunistic infection: Filgotinib 200 mg: 0 of 58 (0%) Placebo:0 of 58 (0%) Tuberculosis: Filgotinib 200 mg: 0 of 58 (0%) Placebo: 0 of 58 (0%) Malignancies including lymphoma: Filgotinib 200 mg: 0 of 58 (0%) Placebo: 0 of 58 (0%)

Author, Year Country Trial Name Trial Number Study Quality	Interventions	N	Efficacy/Effectiveness Outcomes	AEs General	AEs Specific
			(95% CI, 3 to 34) *P* < .02 ASAS 5/6: Filgotinib 200 mg: 34 of 58 (59%) Placebo: 12 of 58 (21%) Difference between groups: 38% (95% CI, 20 to 52) *P* < .001 ASAS partial remission: Filgotinib 200 mg: 7 of 58 (12%) Placebo: 2 of 58 (3%) Difference between groups: 9% (95% CI, −2 to 20) *P* = .1 BASDAI: Mean change from baseline (SD): Filgotinib 200 mg: −2.41 (2.01) Placebo: −1.44 (2.02) Least squares mean difference −1,,00 (95% CI, −1.69 to −0.30) *P* = .005 BASFI: Mean change from baseline (SD): Filgotinib 200 mg: −2.45 (1.90) Placebo: −1.23 (1.88) Least squares mean difference: −1.11 (95% CI, −1.78 to −0·43) *P* = .002		

Author, Year Country Trial Name Trial Number Study Quality	Interventions	N	Efficacy/Effectiveness Outcomes	AEs General	AEs Specific
			BASMI: Mean change from baseline (SD): Filgotinib 200 mg: −0.75 (1.02) Placebo: −0.39 (0.70) Least squares mean difference: −0.39 (95% CI, −0·68 to −0·10) *P* = .009 ASQoL: Mean change from baseline (SD): Filgotinib 200 mg: −4.76 (4.50) Placebo: −2.24 (3.97) Least squares mean difference: −2.35, 95% CI, −3.92 to −0.77 *P* = .004 SF-36 PCS: Mean change from baseline (SD): Filgotinib 200 mg: 8.44 (8.18) Placebo: 3.84 (7.10) Least squares mean difference 4.41 (95% CI, 1.88 to 6.93) *P* < .001 SF-36 MCS: Mean change from baseline (SD): Filgotinib 200 mg: 3.95 (7.05) Placebo: 1.00 (9.83) Least squares mean difference: 2.54 (95% CI, −0.21 to 5.29) *P* < .07		

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Jobanputra et al. 2012[42] England RED SEA NR Poor	• Adalimumab 40 mg SC every other week • Etanercept 50 mg IV weekly	Total N = 125 Adalimumab 40 mg = 63 (60 received treatment) Etanercept 50 mg = 62 (60 received treatment)	Primary endpoint: Week 52: Retention in treatment: Adalimumab 40 mg: 39 of 60 (65%) 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: NR/60 (71.7%) Etanercept 50 mg: NR/60 (71.7%) Week 52 DAS28 (CRP4): Good: Adalimumab 40 mg: 26.3% Etanercept 50 mg: 16.7% Moderate:	Any AE*: Adalimumab 40 mg: NR Etanercept 50 mg: NR Withdrawal because of AEs: Baricitinib 4 mg: NR Adalimumab 40 mg: NR SAEs: Adalimumab 40 mg: NR Etanercept 50 mg: NR *Number of patients with at least one AE not reported. Overall number of AEs reported.	Injection site reaction: Adalimumab 40 mg: 9 of 60 (15%) Etanercept 50 mg: 19 of 60 (32%) Cardiovascular events: Adalimumab 40 mg: 5 of 60 (8%) Etanercept 50 mg: 6 of 60 (10%) Death: Adalimumab 40 mg: 2 of 60 (3%) Etanercept 50 mg: 0 of 60 (0%) Malignancy Adalimumab 40 mg: 1 of 60 (2%) Etanercept 50 mg: 1 of 60 (2%)

Author, Year Country Trial Name Trial Number Study Quality	Interventions	N	Efficacy/Effectiveness Outcomes	AEs General	AEs Specific
			Adalimumab 40 mg: 33.3% Etanercept 50 mg: 31.7% Nonresponders: Adalimumab 40 mg: 40.4% Etanercept 50 mg: 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 1 year		
Kavanaugh et al., 2017[19]; Genovese et al., 2018[106]	• Placebo • Filgotinib 50 mg, 100 mg, or 200 mg once daily	Total N = 283 Placebo = 72 Filgotinib 50 mg = 72	Week 12: Primary endpoint: ACR20 response: Placebo: 21 of 72 (29.2%)	Week 12: Any treatment-emergent related AE: Placebo: 28 of 72 (38.9%)	Week 12: Serious treatment-emergent infections: Placebo: 0 of 72 (0%)

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59 sites in 18 countries (Argentina, Austria, Bulgaria, Chile, Columbia, Germany, Guatemala, Hungary, Latvia, Mexico, Moldova, New Zealand, Poland, Romania, Russian Federation, Spain, Ukraine, and the U.S.) DARWIN 2 NR Fair	At week 12, all patients in the placebo group, and patients in the filgotinib 50 mg group who had not achieved at least a 20% improvement in SJC66 and TJC68, were reassigned to receive filgotinib 100 mg and continued on this dose until week 24	Filgotinib 100 mg = 70 Filgotinib 200 mg = 69	Filgotinib 50 mg: 48 of 72 (66.7%) Filgotinib 100 mg: 46 of 70 (65.7%) Filgotinib 200 mg: 50 of 69 (72.5%) Secondary endpoints: ACR50: Placebo: 8 of 72 (11.1) Filgotinib 50 mg: 25 of 72 (34.7%) Filgotinib 100 mg: 26 of 70 (37.1%) Filgotinib 200 mg: 30 of 69 (43.5%) ACR70: Placebo: 2 of 72 (2.8%) Filgotinib 50 mg: 6 of 72 (8.3%) Filgotinib 100 mg: 13 of 70 (18.6%) Filgotinib 200 mg: 9 of 69 (13%) ACR-N, mean change (SE): Placebo: 16.28 (2.723) Filgotinib 50 mg: 35.03 (3.178) Filgotinib 100 mg: 38.35 (3.533) Filgotinib 200 mg: 41.00 (3.477) TJC68, mean change (SE): Placebo: −5.8 (1.48)	Filgotinib 50 mg: 29 of 72 (40.3%) Filgotinib 100 mg: 23 of 70 (32.9%) Filgotinib 200 mg: 30 of 69 (43.5%) Serious treatment-emergent AEs: Placebo: 1 of 72 (1.4%) Filgotinib 50 mg: 1 of 72 (1.4%) Filgotinib 100 mg: 0 of 70 (0%) Filgotinib 200 mg: 3 of 69 (4.3%) Withdrawal because of treatment-AEs: Placebo: 4 of 72 (5.6%) Filgotinib 50 mg: 1 of 72 (1.4%) Filgotinib 100 mg: 0 of 70 (0%) Filgotinib 200 mg: 1 of 69 (1.4%)	Filgotinib 50 mg: 1/72 (1.4%) Filgotinib 100 mg: 0 of 70 (0%) Filgotinib 200 mg: 1 of 69 (1.4%) Death: Placebo: 0 of 72 (0%) Filgotinib 50 mg: 0 of 72 (0%) Filgotinib 100 mg: 0 of 70 (0%) Filgotinib 200 mg: 0 of 69

Author, Year Country Trial Name Trial Number Study Quality	Interventions	N	Efficacy/Effectiveness Outcomes	AEs General	AEs Specific
			Filgotinib 50 mg: −12.7 (1.38) Filgotinib 100 mg: −15.1 (1.53) Filgotinib 200 mg: −17.4 (1.48) TJC28, mean change (SE): Placebo: −4.1 (0.88) Filgotinib 50 mg: −7.6 (0.80) Filgotinib 100 mg: −8.8 (0.95) Filgotinib 200 mg: −10.7 (0.86) SJC66, mean change (SE): Placebo: −4.1 (1.22) Filgotinib 50 mg: −9.3 (1.00) Filgotinib 100 mg: −11.4 (1.20) Filgotinib 200 mg: −10.5 (0.98) SJC28, mean change (SE): Placebo: −3.7 (0.78) Filgotinib 50 mg: −7.2 (0.72) Filgotinib 100 mg: −8.1 (0.79) Filgotinib 200 mg: −7.4 (0.66) DAS28-CRP, mean change (SE): Placebo: −0.99 (0.162) Filgotinib 50mg: −1.75 (0.145) Filgotinib 100mg: −2.04 (0.162) Filgotinib 200mg: −2.32 (0.155) DAS28-CRP remission Placebo: 5 of 72 (6.9%) Filgotinib 50 mg: 9 of 72 (12.5%) Filgotinib 100 mg: 10 of 70		

Author, Year Country Trial Name Trial Number Study Quality	Interventions	N	Efficacy/Effectiveness Outcomes	AEs General	AEs Specific
			(14.3%) Filgotinib 200 mg: 12 of 69 (17.4%) DAS28-CRP EULAR response (good): Placebo: 10 of 72 (14%) Filgotinib 50 mg: 17 of 72 (24%) Filgotinib 100 mg: 19 of 72 (27%) Filgotinib 200 mg: 31 of 69 (45%) ACR/EULAR remission: Placebo: 1 of 72 (1.4%) Filgotinib 50 mg: 1 of 72 (1.4%) Filgotinib 100 mg: 3 of 72 (4.3%) Filgotinib 200 mg: 3 of 69 (4.3%) SDAI mean change, (SE): Placebo): −12.6 (1.98) Filgotinib 50 mg: −21.4 (1.80) Filgotinib 100 mg: −25.3 (1.99) Filgotinib 200 mg: −26.5 (1.75) SDAI remission: Placebo: 2 of 72 (2.8%) Filgotinib 50 mg: 2 of 72 (2.8%) Filgotinib 100 mg: 5 of 70 (7.1%) Filgotinib 200 mg: 5 of 69 (7.2%) CDAI, mean change (SE): Placebo: −11.7 (1.88) Filgotinib 50 mg: −21.0 (1.72)		

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			Filgotinib 100 mg: −24.0 (1.97) Filgotinib 200 mg: −25.1 (1.74) CDAI remission: Placebo: 2 of 72 (2.8%) Filgotinib 50 mg: 2 of 72 (2.8%) Filgotinib 100 mg: 4 of 70 (5.7%) Filgotinib 200 mg: 6 of 69 (8.7%) HAQ-DI, mean change (SE): Placebo: −0.226 (0.07) Filgotinib 50 mg: −0.661 (0.08) Filgotinib 100 mg: −0.677 (0.08) Filgotinib 200 mg: −0.739 (0.08)		
Kivitz et al., 2017[20] 43 sites in 8 countries (U.S. [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])	• 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	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%)	Week 12: Serious infections: Peficitinib 25 mg: 0 of 66 (0%) Peficitinib 50 mg: 0 of 78 (0%) Peficitinib 100 mg: 1 of 84 (1.2%) Peficitinib 150 mg: 1 of 78 (1.3%) Placebo: 0 of 72 (0%). Death: Peficitinib 25 mg: 0 of 66 (0%) Peficitinib 50 mg: 0 of 78 (0%) Peficitinib 100 mg: 0

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NR NR Fair			(33.3%) Peficitinib 150 mg: *29* of 78 (37.2%) Placebo: *19* of 72 (26.4%) *P* > .05	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 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%)	of 84 (0%) Peficitinib 150 mg: 0 of 78 (0%) Placebo: 0 of 72 (0%)
Kume et al., 2011[43] Japan NR NR Fair	• 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	NR	NR

Author, Year Country Trial Name Trial Number Study Quality	Interventions	N	Efficacy/Effectiveness Outcomes	AEs General	AEs Specific
			DAS28-ESR score: Mean change from baseline (SD) Tocilizumab 8 mg/kg: -2.10 (0.35) Etanercept 25 mg: -2.84 (0.42) 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[52] Multicenter trial in the Netherlands NR NR	• 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	Total n = 139 Abatacept 500-100 mg IV = 43 Rituximab 1000 mg IV = 46 TNFi = 50	Primary outcome: 12 months DAS28 score: mean (SD) Abatacept 500-1000 mg IV: 3.8 (1.2) Rituximab 1000 mg IV: 3.4 (1.2) TNFi: 3.5 (1.5)	Total AEs: Abatacept 500-1000 mg IV: 16 of 43 (37.21%) Rituximab 1000 mg IV: 15 of 46 (32.61%) TNFi: 20 of 50 (40%)	Infections: Abatacept 500-1000 mg IV: 6 of 43 (13.95%) Rituximab 1000 mg IV: 4 of 46 (8.70%) TNFi: 7 of 50 (14.00%) Malignancies:

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Poor	loading doses given at 0, 2, and 6 weeks • Golimumab 50 mg every 4 weeks • 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 1000 mg IV at weeks 0 and 2 with a second course after 6 months in responders				Abatacept 500-1000 mg IV: 0 of 43 (0%) Rituximab 1000 mg IV: 3/46 (6.52%) TNFi: 0/50 (0%)
Schiff et al., 2007[40] 86 sites in 14 countries in North, South, and Central	• Abatacept: Dosage according to body weight: < 60 kg receive 500 mg; 60-100 kg receive 750 mg; > 100 kg receive	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 197: AEs: Abatacept: 129 of 156 (82.7%) Infliximab 3 mg/kg: 140 of 165 (84.8%)	Day 197: Deaths: Abatacept: 1 of 156 (0.64%) Infliximab 3 mg/kg: 1 of 165 (0.61%)

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America, Europe, and Africa ATTEST NCT00095147 Fair	1000 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 IV simultaneously and at the remaining visits • Placebo		Day 365 DAS28 score: Mean change from baseline Abatacept: -2.88 Infliximab 3 mg/kg: -2.25 *P* < .05 Secondary outcomes: Day 365 EULAR response good Abatacept: 32.0% Infliximab 3 mg/kg: 18.5% *P* < .05 DAS28 defined remission Abatacept: 18.7% Infliximab 3 mg/kg: 12.2% PCS & MCS: mean difference from baseline Abatacept vs. Infliximab : 1.93 *P* < .05	SAEs: Abatacept: 8 of 156 (5.13%) Infliximab 3 mg/kg: 19 of 165 (11.52%) Withdrawal because of AEs: Abatacept: 2 of 156 (1.28% Infliximab 3 mg/kg: 4 of 165 (2.42%)	Serious infections Abatacept: 2 of 156 (1.28%) Infliximab 3 mg/kg: 7 of 165 (4.24%) Malignant symptoms and disorders: Abatacept: 1 of 156 (0.64%) Infliximab 3 mg/kg: 2 of 165 (1.21%)
Smolen et al., 2016[41] 151 centres in Europe, Australia, and North America	• Certolizumab pegol SC 400 mg in weeks 0, 2, and 4 followed by 200 mg 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: 314/454 (69%) Adalimumab 40 mg: 324 of 454 (71%) 95% CI (0.67- 1.20)	Treatment-emergent AEs: Certolizumab pegol 200 mg: 389 of 516 (75%) Adalimumab 40 mg: 386 of 523 (74%) Serious treatment-emergent AEs:	Serious infections: Certolizumab pegol 200 mg: 17 of 516 (3%) Adalimumab 40 mg: 16 of 523 (3%) Serious cardiac

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EXXELERATE NCT01500278 Fair	• Adalimumab 40 mg SC every 2 weeks + MTX		Week 104: DAS28-ESR < 3.2: Certolizumab pegol 200 mg: 161 of 454 (35%) Adalimumab 40 mg: 152 of 454 (33%) *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: 65% Adalimumab 40 mg: 67% ACR50 response of primary responders: Certolizumab pegol 200 mg: 53% Adalimumab 40 mg: 57% ACR70 response of primary responders: Certolizumab pegol 200 mg: 40% Adalimumab 40 mg: 41%	Certolizumab pegol 200 mg: 67 of 516 (13%) Adalimumab 40 mg: 58 of 523 (11%) Discontinuation due to AEs: Certolizumab pegol 200 mg: 65 of 516 (13%) Adalimumab 40 mg: 63 of 523 (12%)	disorders: Certolizumab pegol 200 mg: 8 of 516 (2%) Adalimumab 40 mg: 9 of 523 (2%) Malignancies: Certolizumab pegol 200 mg: 8 of 516 (2%) Adalimumab 40 mg: 7 of 523 (1%) Opportunistic infections excluding tuberculosis: Certolizumab pegol 200 mg: 3 of 516 (1%) Adalimumab 40 mg: 3 of 523 (1%) Tuberculosis Certolizumab pegol 200 mg: 0 of 516 (0%) Adalimumab 40 mg: 1 of 523 (< 1%) Deaths: Certolizumab pegol

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					200 mg: 3 of 516 (1%) Adalimumab 40 mg: 3 of 523 (1%)
Takeuchi et al., 2015[17] 43 sites in Japan NR NCT01649999 Fair	• 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 (12.1%),	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: Peficitinib 25 mg: 1 of 55 (1.8%) Peficitinib 50 mg: 2 of 57	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%)

Author, Year Country Trial Name Trial Number Study Quality	Interventions	N	Efficacy/Effectiveness Outcomes	AEs General	AEs Specific
			Placebo: *1* of 56 (1.8%) DAS28-CRP < 2.6: Peficitinib 25 mg: 0 of 45 (0%) Peficitinib 50 mg: *4* of 57 (7%) 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%)	(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[37] 161 centers in Japan NR Fair	• 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%) Peficitinib 100 mg: 54 of 172 (31.4%) Peficitinib 150 mg: 60 of 171	Week 12: AnyAE: 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%) SAEs: Placebo: 4 of 170 (2.4%) Peficitinib 100 mg: 5 of 174 (2.9%) Peficitinib 150 mg: 3 of 174 (1.7%)	Week 12: Death: Placebo: 0 of 170 (0%) Peficitinib 100 mg: 0 of 174 (0%) Peficitinib 150 mg: 0 of 174 (0%)

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			(35.1%) *P* < .001	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[36] 165 sites, 3 countries, Japan, Korea and Taiwan NR NR Fair	• Peficitinib 100 mg or 150 mg orally once daily • Etanercept 50 mg SC once weekly Placebo	Total N = 507 placebo = 101 peficitinib 100 mg = 104 peficitinib 150 mg = 102 etanercept = 200	Week 12: ACR20 response: Placebo: 31 of 101 (30.7%) Peficitinib 100 mg: 60 of 104 (57.7%), *P* < .001 compared to placebo Peficitinib 150 mg: 76 of 102 (74.5%), *P* < .001 compared to placebo Etanercept: 167 of 200 (83.5%) DAS28-ESR < 2.6 Placebo: 1 of 100 (1.0%)	Week 12: Any AE: Placebo: 54 of 101 (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%)	Infection: Placebo: 0 of 101 (0%) 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%)

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			Peficitinib 100 mg: 12 of 103 (11.7%) Peficitinib 150 mg: 18 of 101 (17.8%), *P* = .003 compared to 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 compared to placebo Peficitinib 150 mg: 35 of 101 (34.7%), *P* < .001 compared to placebo Etanercept: 91 of 200 (45.5%)	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: 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%)	Peficitinib 100 mg: 5 of 104 (4.8%) Peficitinib 150 mg: 4 of 102 (3.9%) Etanercept: 5 of 200 (2.5%)

Author, Year Country Trial Name Trial Number Study Quality	Interventions	N	Efficacy/Effectiveness Outcomes	AEs General	AEs Specific
				SAEs: Peficitinib 100mg: 7 of 104 (6.7%) Peficitinib 150 mg: 8 of 102 (7.8%) Etanercept: 18 of 200 (9.0%)	
Taylor et al., 2017[21] 281 centers in 26 countries in North and South America, Europe, and Asia RA-BEAM NR Fair	• Baricitinib 4 mg once daily Adalimumab 40 mg SC every 2 weeks • Placebo • Baricitinib 2 mg if estimated glomerular filtration rate of 40 to less than 60 mL/min/1.73 m^2 (approximately 4%) received 2 mg of baricitinib if assigned to baricitinib treatment.	Total N = 1305 Baricitinib 4 mg = 487 Adlimumab 40 mg = 330 Placebo = 488	Week 12: ACR20 response: Baricitinib 4 mg: 70% Adalimumab 40 mg: 61% *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: 39% Adalimumab 40 mg: 36% *P* > .05 SDAI ≤ 3.3: Baricitinib 4 mg: 8% Adalimumab 40 mg: 7% *P* value NR SDAI ≤ 11: Baricitinib 4 mg: 57% Adalimumab 40 mg: 49%	Week 52: Any AE: Baricitinib 4 mg: 384 of 487 (79%) Adalimumab 40 mg: 253 of 330 (77%) Withdrawal because of AEs: Baricitinib 4 mg: 36 of 487 (7%) Adalimumab 40 mg: 13 of 330 (4%) SAEs: Baricitinib 4 mg: 38 of 487 (8%) Adalimumab 40 mg: 13 of 330 (4%)	Week 52: Infection: Baricitinib 4 mg: 233 of 487 (48%) Adalimumab 40 mg: 145 of 330 (44%) Herpes zoster: Baricitinib 4 mg: 11 of 487 (2%) Adalimumab 40 mg: 5 of 330 (2%) Tuberculosis: Baricitinib 4 mg: 0 of 487 Adalimumab 40 mg: 1 of 330 (< 1%) Serious infection: Baricitinib 4 mg: 10 of 487 (2%) Adalimumab 40 mg: 5 of 330 (2%)

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			P ≤ .05 CDAI ≤ 10: Baricitinib 4 mg: 57% Adalimumab 40 mg: 49% *P* ≤ .05 HAQ-DI ≥0.22 : Baricitinib 4 mg: 68% Adalimumab 40 mg: 58% *P* ≤ .01 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: Baricitinib 4 mg: -9 Adalimumab 40 mg: -10 *P* ≤ .05		Cancer: Baricitinib 4 mg: 3 of 487 (< 1%) Adalimumab 40 mg: 0 of 330 Non-melanoma skin cancer: Baricitinib 4 mg: 0 of 487 (0%) Adalimumab 40 mg: 0 of 330 (0%) Major adverse cardiovascular event: Baricitinib 4 mg: 2 of 487 (< 1%) Adalimumab 40 mg: 1 of 330 (< 1%) Gastrointestinal perforation: Baricitinib 4 mg: 0 of 487 (0%) Adalimumab 40 mg: 0 of 330 (0%)
Vollenhofen et al., 2012[46] 115 centers worldwide	• Tofacitinib 5 mg twice daily • Tofacitinib 10 mg twice daily	Total n = 717 Tofacitinib 5 mg = 204 Tofacitinib 10 mg = 201	Primary outcomes: 6 months ACR20 response: Tofacitinib 5 mg: 51.5% Tofacitinib 10 mg: 52.6%	3 months: AEss: Tofacitinib 5 mg: 106 of 204 (52.0%) Tofacitinib 10 mg: 94 of	

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ORAL Standard NCT00853385 Fair	• Adalimumab 40 mg every 2 weeks • Placebo followed by tofacitinib 5 mg twice daily • Placebo followed by tofacitinib 10 mg	Adalimumab 40 mg = 204 Placebo + Tofacitinib 5 mg = 56 Placebo + Tofacitinib 10 mg = 52	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: Tofacitinib 5 mg: -0.55 Tofacitinib 10 mg: -0.661 Adalimumab 40 mg: -0.49 Placebo: -0.24	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 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[39]; Schiff et al., 2013[102] 120 sites, North and South America AMPLE	• Abatacept 125 mg SC every week • Adalimumab 40 mg SC every 2 week Both treatments were given in	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%	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	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%)

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NCT00929864 Fair	combination with background MTX		Adalimumab 40 mg SC: 46.0% ACR70 response: Abatacept 125 mg SC: 29.2% Adalimumab 40 mg SC: 26.2% 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:	of 318 (3.5%) Adalimumab 40 mg 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%) Withdrawal because of AEs: Abatacept 125 mg SC: 12 of 318 (3.8%) Adalimumab 40 mg SC: 31 of 328 (9.5%)	Adalimumab 40 mg SC: 4 of 328 (1.2%) Deaths: Abatacept 125 mg SC: 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

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			Abatacept 125 mg SC: 44.7% Adalimumab 40 mg SC: 46.6% 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%	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%)	Serious infections: Abatacept 125 mg SC: 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%)

Author, Year Country Trial Name Trial Number Study Quality	Interventions	N	Efficacy/Effectiveness Outcomes	AEs General	AEs Specific
Westhovens et al., 2016[22]; Genovese et al., 2018[106] 106 sites in 21 countries in North and South America, Europe, Asia, Australia and New Zealand DARWIN 1 NR Fair	• Filgotinib 50, 100 or 200 mg once or twice daily • Placebo At week 12, patients on placebo who had not achieved a 20% improvement in SJC66 and TJC68 were reassigned to receive filgotinib 100 mg once daily or 50 mg twice daily; patients who had not achieved this target who were receiving filgotinib 50 mg once daily were reassigned to receive filgotinib 100 mg once daily, and patients on filgotinib 25 mg twice daily received filgotinib 50 mg twice daily, continuing on their new dose until week 24	Total N = 594 Placebo = 86 Filgotinib 50 mg = 82 Filgotinib 100 mg = 85 Filgotinib 200 mg = 86 Filgotinib 2×25 mg = 86 Filgotinib 2×50 mg = 85 Filgotinib 2×100 mg = 84	Week 12: ACR20 response: Placebo: 38 of 86 (44.2%) Filgotinib 100 mg: 57 of 85 (63.5%) *P* =0.044, compared to placebo Filgotinib 200 mg: 59 of 86 (66.6%) *P* = .007, compared to placebo Filgotinib 2x50 mg: 51 of 85 (60.0%) Filgotinib 2x100 mg: 66 of 84 (78.6%) *P* < .001, compared to placebo Week 24: ACR20 response: Placebo: 36 of 86 (41.9%) Filgotinib 100 mg: 52 of 85 (61.2%) Filgotinib 200 mg: 63 of 86 (73.3%) Filgotinib 2x50 mg: 51 of 85 (60.0%) Filgotinib 2x100 mg: 67 of 84 (79.8%) ACR50 response: Placebo: 14 of 86 (16.3%) Filgotinib 100 mg: 40 of 85 (47.1%) Filgotinib 200 mg: 43 of 86	Continued once- and twice-daily groups Week 24: Any treatment-emergent AE: Placebo: 32 of 56 (57.1%) Filgotinib 100 mg: 37 of 85 (43.5%) Filgotinib 200 mg: 50 of 86 (58.1%) Filgotinib 2x50 mg: 46 of 85 (54.1%) Filgotinib 2x100 mg: 45 of 84 (53.6%) Serious treatment-emergent AEs: Placebo: 4 of 56 (7.1%) Filgotinib 100 mg: 4 of 85 (4.7%) Filgotinib 200 mg: 2 of 86 (2.3%) Filgotinib 2x50 mg: 0 of 85 (0%) Filgotinib 2x100 mg: 3 of 84 (3.6%) Withdrawal because of treatment-emergent AEs: Placebo: 2 of 56 (3.6%) Filgotinib 100 mg: 5 of 85	Continued once- and twice-daily groups Week 24: Serious treatment-emergent infection: Placebo: 1 of 56 (1.8%) Filgotinib 100 mg: 3 of 85 (3.5%) Filgotinib 200 mg: 1 of 86 (1.2%) Filgotinib 2x50 mg: 0 of 85 (0%) Filgotinib 2x100 mg: 1 of 84 (1.2%) Herpes zoster infection: Placebo: 1 of 56 Filgotinib 100 mg: 0 of 85 Filgotinib 200 mg: 1 of 86 Filgotinib 2x50 mg: 0 of 85 Filgotinib 2x100 mg: 2 of 84 SAEs leading to death: Placebo: 0 of 56 Filgotinib 100 mg: 0

Author, Year Country Trial Name Trial Number Study Quality	Interventions	N	Efficacy/Effectiveness Outcomes	AEs General	AEs Specific
			(50.0%) Filgotinib 2x50 mg: 30 of 85 (35.3%) Filgotinib 2x100 mg: 46 of 84 (54.8%) ACR70 response: Placebo: 8 of 86 (9.3%) Filgotinib 100 mg: 28 of 85 (32.9%) Filgotinib 200 mg: 25 of 86 (29.1%) Filgotinib 2x50 mg: 20 of 85 (23.5%) Filgotinib 2x100 mg: 33 of 84 (39.3%) ACR-N, mean (SE): Placebo: 22.06 (2.846) Filgotinib 100 mg: 50.86 (3.645) Filgotinib 200 mg: 50.40 (3.291) (3.384) Filgotinib 2x50 mg: 40.50 (3.299) Filgotinib 2x100 mg: 58.69 (3.204) TJC68, mean change from baseline (SE): Placebo: −8.9 (1.43) Filgotinib 100 mg: −17.1 (1.32) Filgotinib 200 mg: −20.6 (1.49) Filgotinib 2x50 mg: −18.1 (1.44)	(5.9%) Filgotinib 200 mg: 3 of 86 (3.5%) Filgotinib 2x50 mg: 2 of 85 (2.4%) Filgotinib 2x100 mg: 3 of 84 (3.6%)	of 85 Filgotinib 200 mg: 0 of 86 Filgotinib 2x50 mg: 0 of 85 Filgotinib 2x100 mg: 1 of 84 (1.2%)

Author, Year Country Trial Name Trial Number Study Quality	Interventions	N	Efficacy/Effectiveness Outcomes	AEs General	AEs Specific
			Filgotinib 2x100 mg: −21.4 (1.38) SJC66, mean change from baseline (SE): Placebo: −7.3 (1.00) Filgotinib 100 mg: −12.6 (0.91) Filgotinib 200 mg: −13.2 (0.87) Filgotinib 2x50 mg: −12.9 (1.29) Filgotinib 2x100 mg: −13.8 (0.85) HAQ-DI, mean change from baseline (SE): Placebo: −0.365 (0.0671) Filgotinib 100 mg: −0.783 (0.0761) Filgotinib 200 mg: −0.818 (0.0675) Filgotinib 2x50 mg: −0.659 (0.0702) Filgotinib 2x100 mg: −0.903 (0.0813) DAS28 (CRP), mean change from baseline (SE): Placebo: −1.18 (0.163) Filgotinib 100 mg: −2.70 (0.156) Filgotinib 200 mg: −2.80 (0.139) Filgotinib 2x50 mg: −2.40 (0.175) Filgotinib 2x100 mg: −3.23 (0.138) DAS28 (CRP) remission:		

Author, Year Country Trial Name Trial Number Study Quality	Interventions	N	Efficacy/Effectiveness Outcomes	AEs General	AEs Specific
			Placebo: 8 of 86 (9.3%) Filgotinib 100 mg: 31 of 85 (36.5%) Filgotinib 200 mg: 22 of 86 (25.6%) Filgotinib 2x50 mg: 20 of 85 (23.5%) Filgotinib 2x100 mg: 34 of 84 (40.5%) DAS28 (CRP) remission/LDA: Placebo: 16 of 86 (18.6%) Filgotinib 100 mg: 43 of 85 (50.6%) Filgotinib 200 mg: 44 of 86 (51.2%) Filgotinib 2x50 mg: 32 of 85 (37.6%) Filgotinib 2x100 mg: 54 of 84 (64.3%) ACR/EULAR remission: Placebo: 1 of 86 (1.2%) Filgotinib 100 mg: 7 of 85 (8.2%) Filgotinib 200 mg: 10 of 86 (11.6%) Filgotinib 2x50 mg: 3 of 85 (3.5%) Filgotinib 2x100 mg: 16 of 84 (19.0%) SDAI LDA:		

Author, Year Country Trial Name Trial Number Study Quality	Interventions	N	Efficacy/Effectiveness Outcomes	AEs General	AEs Specific
			Placebo: 17 of 86 (19.8%) Filgotinib 100 mg: 32 of 85 (37.6%) Filgotinib 200 mg: 29 of 86 (33.7%) Filgotinib 2x50 mg: 27 of 85 (31.7%) Filgotinib 2x100 mg: 34 of 84 (40.5%) SDAI remission: Placebo: 1 of 86 (1.2%) Filgotinib 100 mg: 13 of 85 (15.3%) Filgotinib 200 mg: 12 of 86 (14.0%) Filgotinib 2x50 mg: 12 of 85 (14.1%) Filgotinib 2x100 mg: 16 of 84 (19.0%) CDAI, mean change from baseline (SE): Placebo: −16.0 (1.95) Filgotinib 100 mg: −28.6 (1.63) Filgotinib 200 mg: −29.4 (1.50) Filgotinib 2x50 mg: −26.7 (1.90) Filgotinib 2x100 mg: −32.4 (1.39) CDAI remission: Placebo: 2 of 86 (2.3%) Filgotinib 100 mg: 18 of 85		

Author, Year Country Trial Name Trial Number Study Quality	Interventions	N	Efficacy/Effectiveness Outcomes	AEs General	AEs Specific
			(21.2%) Filgotinib 200 mg: 13 of 86 (15.1%) Filgotinib 2x50 mg: 13 of 85 (15.3%) Filgotinib 2x100 mg: 16 of 84 (19.0%) HAQ-DI, mean change from baseline (SE): Placebo: −0.365 (0.0671) Filgotinib 100 mg: -0.783 (0.0761) Filgotinib 200 mg: −0.818 (0.0675) Filgotinib 2x50 mg: -0.659 (0.0702) Filgotinib 2x100 mg: -0.903 (0.0813)		

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; 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; 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: U.S. 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; pys: person-years; RA: rheumatoid arthritis; 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: tumor necrosis factor; TNFi: tumor necrosis factor inhibitor; VAS: Visual Analogue Scale; vs.: versus.

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Table B3. Evidence Table for Cohort Studies of TIMs in Rheumatoid Arthritis

Author, Year Country Study Quality	Drug(s)	Sample Time Frame, Data Source	N	Population Characteristics	Harms	Funder
Kim et al., 2018[27] U.S. Fair	Tocilizumab Abatacept	Three large U.S. insurance claims databases: Medicare Parts A/B/D (2010–2013) IMS PharMetrics Plus (2011–2014) Truven MarketScan (2011—June 2015)	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 three databases: Tocilizumab: 6237 patients, 32 events, 4,596 person-years, IR per 100 person-years: 0.70 (95%, CI 0.49 to 0.97) Abatacept: 14,685 patients, 112 events, 11,684 person-years, IR per 100 person-years: 0.96 (95% CI, 0.79 to 1.15) Tocilizumab vs. abatacept : HR, 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)	Genentech
Kim et al., 2019[28] U.S. Fair	Tocilizumab Abatacept	Three large U.S. insurance claims databases: Medicare Parts A/B/D (2010-2015) IMS PharMetrics Plus (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 three databases: Tocilizumab: 8465 patients, 101 events, 7155 person-years, IR per 1000 person-years: 14.12 (95% CI, 11.36 to 16.87) Abatacept: 8465 patients, 111 events, 77336 person-years, IR per 1000 person-years: 15.13 (95% CI, 12.32 to 17.95)	Roche

Author, Year Country Study Quality	Drug(s)	Sample Time Frame, Data Source	N	Population Characteristics	Harms	Funder
		Truven MarketScan' (2011- 2015)			Tocilizumab vs. abatacept : HR, 0.97 (95% CI, 0.74 to 1.27) Intention-to-treat analysis up to 365 days: Combined data from three databases: Tocilizumab: 8465 patients, 107 events, 7069 person-years, IR per 1000 person-years: 15.14 (95% CI, 12.27 to 18.00) Abatacept: 8465 patients, 119 events, 7003 person-years, IR per 1000 person-years: 16.99 (95% CI, 13.94 to 20.05) Tocilizumab vs. abatacept : HR, 0.89 (95% CI, 0.69 to 1.16) Most common cancers (secondary outcomes) Non-Hodgkin lymphoma Tocilizumab vs. abatacept : HR, 1.31 (95% CI, 0.35 to 4.92) Melanoma Tocilizumab vs. abatacept : HR, 0.88 (95% CI, 0.39 to 2.02) HR, 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 were the individual endpoints of	

Author, Year Country Study Quality	Drug(s)	Sample Time Frame, Data Source	N	Population Characteristics	Harms	Funder
					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.	
Rutherford et al., 2018[30] NR Fair	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 patient-years Tocilizumab: 3 events, 2171 patients, 78 (95% CI, 25 to 241) IR per 100 000 patient-years Tuberculosis Rituximab: 2 events, 5072 patients, 12 (95% CI, 3 to 46) IR per 100 000 patient-years Tocilizumab: 1 event, 2171 patients, 26 (95% CI, 4 to 183) IR per 100 000 patient-years Etanercept vs. rituximab Adjusted HR, 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 two clinicians who were blinded to the treatment exposure. Differences in coding were	-

Author, Year Country Study Quality	Drug(s)	Sample Time Frame, Data Source	N	Population Characteristics	Harms	Funder
					resolved by discussion or, if consensus could not be reached, by a third clinician.	
Rutherford et al., 2018[32] United Kingdom Fair	Etanercept Infliximab Adalimumab Rituximab Tocilizumab Certolizumab	British Society for Rheumatology Biologics Register for RA (BSRBR-RA) since 2001	Total N = 19 282 Etanercept = 8630 Infliximab = 4908 Adalimumab = 7818 Rituximab = 5101 Tocilizumab = 2174 Certolizumab = 1446	Patients with RA starting a new biologic treatment	Serious infections Etanercept: 852 events, 8603 patients, 15314 years follow-up time, 5.56 (95% CI, 5.20 to 5.95) IR per 100 patient-years Infliximab: 472 events, 4908 patients, 8829 years follow-up time, 5.35 (95% CI, 4.89 to 5.85) IR per 100 patient-years Adalimumab: 709 events, 7818 patients, 13071 years follow-up time, 5.42 (95% CI, 5.04 to 5.84) IR per 100 patient-years Rituximab: 372 events, 5101 patients, 5910 years follow-up time, 6.29 (95% CI, 5.69 to 6.97) IR per 100 patient-years Tocilizumab: 137 events, 2174 patients, 1963 years follow-up time, 6.98 (95% CI, 5.90 to 8.25) IR per 100 patient-years Certolizumab: 64 events, 1446 patients, 1685 years follow-up time, 3.80 (95% CI, 2.97 to 4.85) IR per 100 patient-years Adjusted HR, 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)	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 Biovitrum and Merck

Author, Year Country Study Quality	Drug(s)	Sample Time Frame, Data Source	N	Population Characteristics	Harms	Funder
Gron et al., 2019[33] Denmark and Sweden Poor	Abatacept Rituximab Tocilizumab	Two national registers: Danish DANBIO registry (January 2010–December 2015) Swedish Antirheumatic Treatment in Sweden Register / Swedish Rheumatology Quality Register (ARTIS; January 2010 - December 2015)	Total N = 8,987 Abatacept = 2,725 Rituximab = 3,363 Tocilizumab = 2,899	Adults with RA who started treatment with abatacept, tocilizumab or rituximab either as their first bDMARD treatment course of with a history of treatment with another bDMARD (switcher)	Serious infections 0 - 12 months: Denmark: Abatacept: 40 events, 568 person-years, adjusted IR per 100 person-years: 7.1 (95% CI, 5.1 to 9.9) Rituximab: 50 events, 571 person-years, adjusted IR per 100 person-years: 8.1 (95% CI, 5.9 to 11.0) Tocilizumab: 55 events, 906 person-years, adjusted IR per 100 person-years: 6.1 (95% CI, 4.6 to 8.1) Abatacept vs. tocilizumab Adjusted RR 1.15 (95% CI, 0.69 to 1.90) Abatacept vs. rituximab Adjusted RR 0.94 (95% CI, 0.55 to 1.60) Tocilizumab vs. rituximab Adjusted RR 0.82 (95% CI, 0.50 to 1.36) Sweden: Abatacept: 90 events, 1477 person-years, adjusted IR per 100 person-years: 6.0 (95%, CI, 4.8 to 7.5) Rituximab: 156 events, 2189 person-years, adjusted IR per 100 person-years: 6.4 (95%, CI, 5.3 to 7.7) Tocilizumab: 65 events, 1426 person-years, adjusted IR) per 100 person-years: 4.7 (95%, CI, 3.7 to 6.1) Abatacept vs. tocilizumab Adjusted RR 1.14 (95% CI, 0.83 to 1.55) Abatacept vs. rituximab Adjusted RR 0.86 (95% CI, 0.66 to 1.13)	Partly funded by NordForsk and Foreum

Author, Year Country Study Quality	Drug(s)	Sample Time Frame, Data Source	N	Population Characteristics	Harms	Funder
					Tocilizumab vs. rituximab Adjusted RR 0.76 (95% CI, 0.57 to 1.02) Pooled analysis for both countries: Abatacept vs. tocilizumab Adjusted RR 1.13 (95% CI, 0.91 to 1.42), *P* = .95 Abatacept vs. rituximab Adjusted RR 0.88 (95% CI, 0.69 to 1.12), *P* = .77 Tocilizumab vs. rituximab Adjusted RR 0.78 (95% CI, 0.61 to 1.01), *P* = .83 0 - 24 months: Denmark: Abatacept: 42 events, 712 person-years, adjusted IR per 100 person-years: 6.1 (95% CI, 4.4 to 8.3) Rituximab: 69 events, 871 person-years, adjusted IR per 100 person-years: 7.5 (95% CI, 5.8 to 9.7) Tocilizumab: 70 events, 1366 person-years, adjusted IR) per 100 person-years: 5.2 (95%,CI, 4.1 to 6.7) Abatacept vs. tocilizumab Adjusted RR 1.13 (95% CI, 0.71 to 1.82) Abatacept vs. rituximab Adjusted RR 0.89 (95% CI, 0.54 to 1.47) Tocilizumab vs. rituximab Adjusted RR 0.79 (95% CI, 0.50 to 1.22) Sweden: Abatacept: 127 events, 2183 person-years,	

Author, Year Country Study Quality	Drug(s)	Sample Time Frame, Data Source	N	Population Characteristics	Harms	Funder
					adjusted IR per 100 person-years: 5.6 (95% CI, 4.6 to 6.7) Rituximab: 241 events, 3579 person-years, adjusted IR per 100 person-years: 5.8 (95% CI, 5.0 to 6.8) Tocilizumab: 90 events, 2162 person-years, adjusted IR per 100 person-years: 4.3 (95% CI, 3.4 to 5.3) Abatacept vs. tocilizumab Adjusted RR 1.15 (95% CI, 0.88 to 1.49) Abatacept vs. rituximab Adjusted RR 0.88 (95% CI, 0.70 to 1.10) Tocilizumab vs. rituximab Adjusted RR 0.77 (95% CI, 0.60 to 0.98) Outcome definition: Serious infection was defined as the first hospitalisation with a primary discharge diagnosis (or contributory, if the primary diagnosis was RA) listing infection (ICD codes) during follow-up from each treatment start. Serious infections were assessed from baseline until 12 months after treatment start, from baseline until 24 months after treatment start, and in consecutive 6-month intervals during the first 24 months after treatment start.	
Pawar et al., 2019[34] U.S. Fair	Tocilizumab Abatacept	Three large U.S. insurance claims databases: Medicare (2010-2015) IMS	Total N = 20828 Tocilizumab: 10414 Abatacept: 10414	Adults with RA	As-treated analysis: Combine data from three databases: Serious infections: Tocilizumab: 10414 patients, 388 events, 8599 person-years, IR per 100-person-years: 4.51 (95% CI, 4.06 to 4.96) Abatacept: 10414 patients, 295 events, 9094 person-years, IR per 100 person-	Roche

Author, Year Country Study Quality	Drug(s)	Sample Time Frame, Data Source	N	Population Characteristics	Harms	Funder
		"PharMetrics" Plus (2011-2015) Truven "MarketScan" 2011-2015			years: 3.24 (95% CI, 2.87 to 3.61) Tocilizumab vs. abatacept : HR, 1.40 (95% CI, 1.20 to 1.63) Rate difference: 1.27 (95% CI, 0.69 to 1.85) Serious bacterial infections: Tocilizumab: 10414 patients, 331 events, 8619 person-years, IR per 100 person-years: 3.84 (95% CI, 3.43 to 4.25) Abatacept: 10414 patients, 234 events, 9121 person-years, IR per 100 person-years: 2.57 (95% CI, 2.24 to 2.89) Tocilizumab vs. abatacept : HR, 1.50 (95% CI, 1.27 to 1.78) Rate difference: 1.27 (95% CI, 0.74 to 1.8) Herpes zoster: Tocilizumab: 10414 patients, 13 events, 8743 person-years, IR per 100 person-years: 0.15 (95% CI, 0.07 to 0.23) Abatacept: 10414 patients, NR events, 9199 person-years, IR per 100 person-years: 0.09 (95% CI, 0.03 to 0.15) Tocilizumab vs. abatacept : HR, 1.77 (95% CI, 0.73 to 4.28) Rate difference:- Opportunistic infections: Tocilizumab: 10414 patients, 14 events, 8745 person-years, IR per 100 person-years: 0.16 (95% CI, 0.08 to 0.24) Abatacept: 10414 patients, NR events, 9202 person-years, IR per 100 person-years: 0.07 (95% CI, 0.01 to 0.12) Tocilizumab vs. abatacept :	

Author, Year Country Study Quality	Drug(s)	Sample Time Frame, Data Source	N	Population Characteristics	Harms	Funder
					HR, 2.42 (95% CI, 0.92 to 6.39) Rate difference:- Skin and soft tissue infection: Tocilizumab: 10414 patients, 21 events, 8745 person-years, IR per 100 person-years: 0.24 (95% CI, 0.14 to 0.34) Abatacept: 10414 patients, NR events, 9200 person-years, IR per 100 person-years: 0.05 (95% CI, 0.01 to 0.10) Tocilizumab vs. abatacept : HR, 2.82 (95% CI, 1.00 to 7.95) Rate difference:- Intention-to-treat analysis up to 180 days: Tocilizumab: 10414 patients, 252 events, 4661 person-years, IR per 100 person-years: 5.41 (95% CI, 4.74 to 6.07) Abatacept: 10414 patients, 188 events, 4693 person-years, IR per 100 person-years: 4.01 (95% CI, 3.43 to 4.58) Tocilizumab vs. abatacept : HR, 1.34 (95% CI, 1.11 to 1.63) Rate difference: 1.40 (95% CI, 0.52 to 2.28)	

Abbreviations. bDMARD: biologic DMARD; CI: confidence interval; DMARD: Disease-Modifying Antirheumatic Drug; HPV: human papillomavirus; HR: hazard ratio; ICD: International Classification of Disease; IR: incidence rate; N: number; NR: not reported; P*: probability value; RA: rheumatoid arthritis; RR: risk ratio; TIM: targeted immune modulator; TNF: tumor necoris 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 / Patients	Design	Study Quality	Consistency	Directness	Precision	Magnitude of Effect	Quality of Evidence
Abatacept Compared to Adalimumab							
Clinical improvement (ACR50 response at 48 weeks)							
1 study[39] / 646	Open-label RCT	Fair	NA	Direct	Imprecise	Similar between groups (46% vs. 46%)	Low[a,c]
Disease remission (ACR70 response at 48 weeks)							
1 study[39] / 646	Open-label RCT	Fair	NA	Direct	Imprecise	Similar between groups (29% vs. 26%)	Low[a,c]
Overall AEs (at 48 weeks)							
1 study[39] / 646	Open-label RCT	Fair	NA	Direct	Imprecise	Similar between groups (88% vs. 86%)	Low[a,c]
SAEs (at 48 weeks)							
1 study[39] / 646	Open-label RCT	Fair	NA	Direct	Imprecise	Similar between groups (10% vs. 9%)	Very low[b,c]
Abatacept Compared to Infliximab							
Clinical improvement (ACR50 response at 24 weeks)							
1 study[40] / 321 (431 including placebo)	RCT	Fair	NA	Direct	Imprecise	Similar between groups (40% vs. 37%)	Low[b]
Disease remission (ACR70 response at 24 weeks)							
1 study[40] / 321 (431 including placebo)1	RCT	Fair	NA	Direct	Imprecise	Similar between groups (21% vs. 24%)	Low[b]
Overall AEs(at 24 weeks)							
1 study[40] / 321 (431 including placebo)	RCT	Fair	NA	Direct	Imprecise	Similar between groups (83% vs. 85%)	Moderate[a]
SAEs (at 24 weeks)							
1 study[40] / 321 (431 including placebo)	RCT	Fair	NA	Direct	Imprecise	Lower proportion of SAEs with abatacept than infliximab (5% vs. 12%)	Low[b]

Number of Studies / Patients	Design	Study Quality	Consistency	Directness	Precision	Magnitude of Effect	Quality of Evidence
Adalimumab Compared to Baracitinib							
Clinical improvement (ACR20 response at 12 weeks)							
1 study[21] / 817 (1,307 including placebo)	RCT	Fair	NA	Direct	Precise	Lower proportion of response with adalimumab than baracitinib (61% vs. 70%)	High
Disease remission (Simplified Disease Activity Index < 3.3 at 12 weeks)							
1 study[21] / 817 (1,307 including placebo)	RCT	Fair	NA	Direct	Imprecise	Similar between groups (8% vs. 7%)	Low[b]
Overall AEs (at 52 weeks)							
1 study[21] / 817 (1,307 including placebo)	RCT	Fair	NA	Direct	Precise	Similar between groups (77% vs. 79%)	High
SAEs (at 52 weeks)							
1 study[21] / 817 (1,307 including placebo)	RCT	Fair	NA	Direct	Imprecise	Lower proportion of SAEsevents with adalimumab than baracitinib (4% vs. 8%)	Low[b]
Adalimumab Compared to Certolizumab pegol							
Clinical improvement (ACR20 response at 12 weeks)							
1 study[41] / 915	RCT	Fair	NA	Direct	Precise	Similar between groups (71% vs. 69%)	High
Disease remission							
1 study[41] / 915	RCT	Fair				Similar but data not reported	NA
Overall AEs (at 12 weeks)							
1 study[41] / 915	RCT	Fair	NA	Direct	Precise	Similar between groups (74% vs. 75%)	High
SAEs (at 12 weeks)							
1 study[41] / 915	RCT	Fair	NA	Direct	Imprecise	Similar between groups (11% vs. 13%)	Low[b]

Number of Studies / Patients	Design	Study Quality	Consistency	Directness	Precision	Magnitude of Effect	Quality of Evidence
Adalimumab Compared to Etanercept							
Clinical improvement (improvements on the DAS28-ESR at 24 weeks)							
2 studies[42,43] / 190	Open-label RCT	Poor	Consistent	Direct	Imprecise	Similar between groups (-2.12 vs. -2.84)	Very low[b,c]
SAEs (at 48 weeks)							
1 study [42] / 125	Open-label RCT	Poor	NA	Direct	Imprecise	Similar between groups (10% vs. 12%)	Very low[b,c]
Adalimumab Compared to Sarilumab							
Quality of life (SF-36 at 24 weeks)							
1 study[44] / 369	RCT	Fair	NA	Direct	Imprecise	Smaller improvements for adalimumab than sarilumab (6.09 vs. 8.75)	Moderate[a]
Clinical improvement (ACR50 at 24 weeks)							
1 study[44] / 369	RCT	Fair	NA	Direct	Imprecise	Lower proportion of response with adalimumab than sarilumab (30% vs. 46%)	Moderate[a]
Disease remission (Clinical Disease Activity Index at 24 weeks)							
1 study[44] / 369	RCT	Fair	NA	Direct	Imprecise	Lower proportion of remission with adalimumab than sarilumab (3% vs. 7%)	Low[b]
Overall AEs (at 24 weeks)							
1 study[44] / 369	RCT	Fair	NA	Direct	Imprecise	Similar between groups (64% vs. 64%)	Moderate[a]
SAEs (at 24 weeks)							
1 study[44] / 369	RCT	Fair	NA	Direct	Imprecise	Similar between groups (7% vs. 5%)	Low[b]
Adalimumab Compared to Tocilizumab							
Quality of life (SF-36 at 24 weeks)							
1 study[45] / 326	RCT	Fair	NA	Indirect	Imprecise	Similar between groups (7.6 vs. 9.2)	Low[a,d]
Clinical improvement (ACR50 at 24 weeks)							

Number of Studies / Patients	Design	Study Quality	Consistency	Directness	Precision	Magnitude of Effect	Quality of Evidence
2 studies[43,45] / 369	Open-label RCT / RCT	Fair	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[43,45] / 369	Open-label RCT / RCT	Fair	Consistent	Indirect	Imprecise	Lower proportion of remission with adalimumab than tocilizumab (18% vs. 33%)	Low[a,d]
Overall AEs (at 24 weeks)							
1 study[45] / 326	RCT	Fair	NA	Indirect	Imprecise	Similar between groups (83% vs. 82%)	Low[a,d]
SAEs (at 24 weeks)							
1 study[45] / 326	RCT	Fair	NA	Indirect	Imprecise	Similar between groups (10% vs. 12%)	Low[a,d]
Adalimumab Compared to Tofacitinib							
Clinical improvement (ACR50 at 24 weeks)							
3 studies[46-48] / 2,247	RCT	Fair	Consistent	Direct	Precise	Similar between groups (44% vs. 46%)	High
Disease remission (ACR70 at 24 weeks)							
2 studies[46,48] / 1,863	RCT	Fair	Consistent	Direct	Precise	Similar between groups (28% vs. 31%)	High
Overall AEs (at 12, 24 and 48 weeks)							
3 studies[46-48] / 2,247	RCT	Fair	NA	Direct	Precise	Similar between groups (60% vs. 58%)	High
SAEs (at 12, 24, and 48 weeks)							
3 studies[46-48] / 2,247	RCT	Fair	NA	Direct	Imprecise	Similar between groups (5% vs. 6%)	Moderate[a]
Adalimumab Compared to Upadacitinib							
Clinical improvement (ACR50 response at 12 weeks)							
1 study[24] / 978 (1,629 with placebo)	RCT	Fair	NA	Direct	Precise	Lower proportion of response with adalimumab	High

Number of Studies / Patients	Design	Study Quality	Consistency	Directness	Precision	Magnitude of Effect	Quality of Evidence
						than upadicitinib (29% vs. 45%)	
Disease remission (DAS28 < 2.6 at 12 weeks)							
1 study[24] / 978 (1,629 with placebo)	RCT	Fair	NA	Direct	Precise	Lower proportion of remission with adalimumab than upadicitinib (18% vs. 29%)	High
Overall AEs (at 12 weeks)							
1 study[24] / 978 (1,629 with placebo)	RCT	Fair	NA	Direct	Precise	Similar between groups (60% vs. 64%)	High
SAEs (at 12 weeks)							
1 study[24] / 978 (1,629 with placebo)	RCT	Fair	NA	Direct	Imprecise	Similar between groups (4% vs. 4%)	Low[b]
Etanercept Compared to Infliximab							
Clinical improvement (ACR20 response at 54 weeks)							
1 study[49] / 32	Open-label RCT	Poor	NA	Indirect	Imprecise	Higher proportion of response for etanercept than infliximab (74% vs. 60%; *P* value NR)	Very low[b,c,e]
Etanercept Compared to Tocilizumab							
Clinical improvement (DAS28-ESR at 24 weeks)							
1 study[43] / 64	Open-label RCT	Poor	NA	Direct	Imprecise	Similar between groups (-2.84 vs. -2.10)	Very low[b,c]
SAEs							
1 study[25] / 3,080	Open-label RCT	Fair	NA	Direct	Imprecise	Similar between groups (23% vs. 27%)	Moderate[c]
Combination Therapies (Etanercept + Abatacept Compared to Etanercept; Etanercept+Anakinra Compared to Etanercept)							
Clinical improvement							
2 studies[50,51] / 365	RCT	Fair	Consistent	Direct	Imprecise	No additional clinical benefit of combination therapy compared to monotherapy	Moderate[a]

Number of Studies / Patients	Design	Study Quality	Consistency	Directness	Precision	Magnitude of Effect	Quality of Evidence
Overall AEs at 24 and 52 weeks							
2 studies[50,51] / 365	RCT	Fair	Consistent	Direct	Imprecise	Similar between groups (94% vs. 90%)	Moderate[a]
SAEs at 24 and 52 weeks							
2 studies[50,51] / 365	RCT	Fair	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 study limitations; [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; DAS28: 28-joint Disease Activity Score; DAS28-ESR: 28-joint Disease Activity Score using erythrocyte sedimentation rate; FDA: U.S. Food and Drug Administration; NA: not applicable; RCT: randomized controlled trial; SAE: serious adverse event; SF-36, 36-item Short Form Health Survey; TIM: targeted immune modulator.

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

Number of Studies / Patients	Design	Study Quality	Consistency	Directness	Precision	Magnitude of Effect	Quality of Evidence
Abatacept Compared to TNF-α Inhibitors							
Quality of life (SF-36 at 52 weeks)							
1 study[52] / 93	Open-label RCT	Poor	NA	Direct	Imprecise	Similar between groups (data NR)	Very low[a,b]
Clinical improvement (DAS28 at 52 weeks)							
2 studies[38,52] / 176	Open-label RCT	Poor	NA	Direct	Imprecise	Similar between groups (difference -0.27 units)	Low[a,b]
Abatacept Compared to Rituximab							
Quality of life (SF-36 at 52 weeks)							
1 study[52] / 93	RCT	Poor	NA	Direct	Imprecise	Similar between groups (data NR)	Very low[a,b]
Clinical improvement (DAS28 at 24 weeks)							
2 studies[38,52] / 174	RCT	Poor	NA	Direct	Imprecise	Similar between groups (difference -0.40 units)*	Low[a,c]
Overall AEs (at 48 and 52 weeks)							
2 studies[38,52] / 174	RCT	Fair	NA	Direct	Imprecise	Similar between groups (56% vs. 54%)	Low[a,c]
SAEs (at 48 weeks)							
1 study[38] / 81	Open-label RCT	Poor	NA	Direct	Imprecise	Similar between groups (10% vs. 10%)	Very low[b,c]
Abatacept Compared to Tocilizumab							
Clinical improvement (DAS28-ESR at 24 weeks)							
1 study[26] / 132	Open-label RCT	Poor	NA	Direct	Imprecise	Similar between groups (2.8 vs. 2.5; *P* = .06)	Low[a,c]
Overall AEs (at 24 weeks)							
1 study[26] / 132	Open-label RCT	Poor	NA	Direct	Imprecise	Lower proportion of overall AEs for abatacept than tocilizumab (28% vs. 60%; *P* value NR)	Low[a,c]
SAEs (at 24 weeks)							
1 study[26] / 132	Open-label RCT	Poor	NA	Direct	Imprecise	Lower proportion of SAEs for abatacept than tocilizumab (6% vs. 15%; *P* value NR)	Very low[b,c]

Number of Studies / Patients	Design	Study Quality	Consistency	Directness	Precision	Magnitude of Effect	Quality of Evidence
TNF-α Inhibitors (Adalimumab, Certolizumab pegol, Etanercept, Infliximab, Golimumab) Compared to Other TIMs (Abatacept, Rituximab, Tocilizumab)							
Clinical improvement (EULAR response at 24 weeks)							
1 study[53] / 300	Open-label RCT	Fair	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,c]
Disease remission (DAS28-ESR < 2.6 at 52 weeks)							
1 study[53] / 300	RCT	Fair	NA	Direct	Imprecise	Higher proportion of remission with non-TNF- α inhibitors than TNF- α inhibitors (27% vs. 14%, *P* < .01)	Low[a,c]
Combination Therapies (Rituximab Plus Adalimumab or Etanercept)							
Clinical improvement (ACR50 response at 24 weeks)							
1 study[55]/ 54	RCT	Fair	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[55] / 54	RCT	Fair	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[55] / 54	RCT	Fair	NA	Direct	Imprecise	Higher proportion of overall AEs for combination of rituximab with TNF-α inhibitors than TNF-α inhibitor maintenance (94% vs. 83%; *P* value NR)	Low[b]
SAEs (at 24 weeks)							
1 study[55] / 54	RCT	Fair	NA	Direct	Imprecise	Higher proportion of SAEs for combination of rituximab with TNF-α inhibitors than TNF-α	Low[b]

Number of Studies / Patients	Design	Study Quality	Consistency	Directness	Precision	Magnitude of Effect	Quality of Evidence
						inhibitor maintenance (6% vs. 0%; *P* value NR)	
Combination Therapies (Abatacept Plus Other TIM [Adalimumab, Anakinra, Etanercept, or Infliximab] Compared to Other TIM Alone							
Overall AEs (at 52 weeks)							
1 study[54] / 167	RCT	Fair	NA	Direct	Imprecise	Similar between groups (95% vs.89%; *P* value NR)	Low[b]
SAEs (at 52 weeks)							
1 study[54] / 167	RCT	Fair	NA	Direct	Imprecise	Higher proportion of SAEs for combination of abatacept with other TIM than other TIM alone (22% vs. 13%; *P* value NR)	Low[b]

*Notes. * Numbers based on fair-quality trial; [a] downgraded 1 level for study limitations; [b] downgraded 2 levels for very serious imprecision; [c] 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.*

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

Number of Studies / Patients	Design	Quality	Consistency	Directness	Precision	Magnitude of Effect	Quality of Evidence
Filgotinib Compared to Placebo							
Quality of life (SF-36 at 12 weeks)							
1 study[23] / 449	RCT	Fair	NA	Direct	Precise	Greater improvements for filgotinib than placebo (filgotinib 100 mg: 6.8; filgotinib 200 mg: 7.6; placebo: 3.6; *P* < .001 for both comparisons with placebo).	High
Clinical improvement (ACR20 response at 12 weeks)							
3 studies[19,22,23] / 1,326	RCT	Fair	Consistent	Direct	Precise	Higher proportion of response for filgotinib than placebo (filgotinib 100 mg: 58%; filgotinib 200 mg: 66%; placebo: 31%; *P* < .001 for both comparisons with placebo)[a]	High
Disease remission (DAS28-CRP < 2.6)							
3 studies[19,22,23] / 1,326	RCT	Fair	Consistent	Direct	Precise	Higher proportion of remission with filgotinib than placebo (filgotinib 100 mg: 26%; filgotinib 200 mg: 31%; placebo: 12%, *P* = .003 and *P* < .001)[a]	High
Overall AEs							
3 studies[19,22,23] / 1,326	RCT	Fair	Consistent	Direct	Imprecise	No difference between groups (filgotinib 100 mg; filgotinib 200 mg: 69%: 63%; placebo: 68%, *P* value NR)[a].	Moderate[c]
SAEs							
3 studies[19,22,23] / 1,326	RCT	Fair	Consistent	Direct	Imprecise	No difference between groups (filgotinib 100 mg 5%; filgotinib 200 mg: 4%, placebo: 3%, *P* value NR)[a].	Low[d]
Peficitinib Compared to Placebo							
Clinical improvement (ACR20 response at 12 weeks)							
5 studies[17,18,20,36,37] / 1,977	RCT	Fair	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)[b]	High

Number of Studies / Patients	Design	Quality	Consistency	Directness	Precision	Magnitude of Effect	Quality of Evidence
Disease remission (DAS28-CRP < 2.6)							
4 studies[17,18,36,37] / 1,598	RCT	Fair	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							
5 studies[17,18,20,36,37] / 1,977	RCT	Fair	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[c]
SAEs							
5 studies[17,18,20,36,37] / 1,977	RCT	Fair	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[c]
Peficitinib Compared to Etanercept							
Clinical improvement (ACR20 response at 12 weeks)							
1 study[36] / 509	RCT	Fair	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[e]
Disease remission (DAS28-CRP < 2.6)							
1 study[36] /509	RCT	Fair	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[e]
Overall AEs							
1 study[36] / 509	RCT	Fair	Consistent	Direct	Imprecise	No difference between groups (peficitinib 100 mg: 57%; peficitinib 150 mg: 54%; etanercept: 60% (*P* value NR).	Low[c,e]
SAEs							
1 study[36] / 509	RCT	Fair	Consistent	Direct	Imprecise	No difference between groups (peficitinib 100 mg: 7%; peficitinib 150 mg: 8%; etanercept: 9%; *P* value NR).	Low[c,e]

Number of Studies / Patients	Design	Quality	Consistency	Directness	Precision	Magnitude of Effect	Quality of Evidence
Combination Therapy (Certolizumab pegol + Bimekizumab vs. Certolizumab pegol)							
Clinical improvement (DAS28-CRP < 3.2 at 12 weeks)							
1 study[35] / 79	RCT	Fair	NA	Direct	Imprecise	Higher proportion of response for combination therapy than TNF-α inhibitor maintenance therapy (46% vs. 29%, *P* value NR)	Low[d]
Disease remission (DAS28-CRP < 2.6)							
1 study[35] / 79	RCT	Fair	NA	Direct	Imprecise	Higher proportion of remission with combination therapy than TNF-α inhibitor maintenance therapy (26% vs. 8%, *P* value NR)	Low[d]
Overall AEs							
1 study[35] / 79	RCT	Fair	NA	Direct	Imprecise	Higher proportion of overall AEs for combination therapy than TNF-α inhibitor maintenance therapy (79% vs. 59%, *P* value NR)	Low[d]
SAEs							
1 study[35] / 79	RCT	Fair	NA	Direct	Imprecise	Lower proportion of SAEs for combination therapy than TNF-α inhibitor maintenance therapy (4% vs. 11%, *P* value NR)	Low[d]

Notes. [a] Data based on phase III FINCH 2 study; [b] Data based on phase III studies; [c] Downgraded 1 level for imprecision; [d] Downgraded 2 levels for very serious imprecision; [e] Downgraded 1 level for study limitations. 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.

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

Number of Studies / Patients	Design	Quality	Consistency	Directness	Precision	Magnitude of Effect	Overall Strength of the Evidence
Etanercept Compared to Infliximab							
Clinical improvement (BASDAI at 12 weeks)							
1 RCT[16] / 50	RCT	Poor	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 study limitation;* [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.*

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

Number of Studies / Patients	Design	Quality	Consistency	Directness	Precision	Magnitude of Effect	Overall Strength of the Evidence
Filgotinib Compared to Placebo							
Quality of life (SF-36 at 12 weeks)							
1 study [29] / 116	RCT	Fair	NA	Direct	Imprecise	Greater improvements for filgotinib than placebo (filgotinib 200 mg: 8.4; placebo: 3.8; *P* < .001)	Moderate[a]
Clinical improvement (ASDAS at 12 weeks)							
1 study [29] / 116	RCT	Fair	NA	Direct	Imprecise	Greater improvements for filgotinib than placebo (filgotinib 200 mg: –1.47; placebo: –0.57; *P* < .001)	Moderate[a]
Disease remission (ASDAS inactive disease)							
1 study [29] / 116	RCT	Fair	NA	Direct	Imprecise	Similar between groups (difference 5 percentage points; *P* = .09)	Low[b]
Overall AEs							
1 study [29] / 116	RCT	Fair	NA	Direct	Imprecise	Similar between groups (31% vs. 31%; *P* value NR)	Low[b]
SAEs							
1 study [29] / 116	RCT	Fair	NA	Direct	Imprecise	Similar between groups (2% vs. 0%; *P* value NR)	Low[b]

Notes. [a] Downgraded 1 level for imprecision; [b] Downgraded 2 levels for very serious imprecision. Abbreviations. AE: adverse event; ASDAS: ankylosing spondylitis disease activity score; 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.*

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 at least 20% improvement in TJC and in SJC, and at least 20% improvement in 3 of the 5 measures: ESR or CRP; PhGA 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% or more 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 AS 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	Ankylosing Spondylitis Functional Index	AS	Defining and monitoring functional ability in patients with AS.	0 to 10, lower 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
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
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	0 to 1, higher is better

Abbreviation	Name	Condition(s) Used in	General Description	Range and Direction
			record 3 levels of severity (no problems/some or moderate problems/extreme problems) within a particular dimension.	
HAQ	Health Assessment Questionnaire	All	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	All	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
SF–36	Medical Outcomes Study Short Form 36-item Health Survey	All	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; PhGA: 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 RA[111-115]

	ABA	ADA	ANA	BAR	CTZ	ETN	GLM	IFX	RTX	SAR	TCZ	TFB	UPA
Clinical Response (ACR50)													
ABA					0.66 (0.32 to 1.4)	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)			1.08 (0.54 to 2.23)		
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)		
RTX													

	ABA	ADA	ANA	BAR	CTZ	ETN	GLM	IFX	RTX	SAR	TCZ	TFB	UPA
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)				**0.15 (0.03 to 0.87)**		
ADA						1.32 (0.08 to 20.5)	0.8 (0.05 to 11.3)	1.2 (0.09 to 16.4)					
ANA													
BAR													
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)**		

	ABA	ADA	ANA	BAR	CTZ	ETN	GLM	IFX	RTX	SAR	TCZ	TFB	UPA
RTX													
SAR													
TCZ													
TFB													
UPA													
Overall AEs													
ABA													
ADA													
ANA													
BAR													
CTZ	1.0 (0.64 to 1.68)												
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					**0.51 (0.24 to 0.99)**	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)		1.13 (0.54 to 2.39)		
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)		

	ABA	ADA	ANA	BAR	CTZ	ETN	GLM	IFX	RTX	SAR	TCZ	TFB	UPA
RTX													
SAR													
TCZ													
TFB				0.7 (0.3 to 1.72)									
UPA												0.84 (0.18 to 2.67)	

Notes. Row drug is compared to column drug; for OR (95% CI) or OR (95% CrI), ORs > 1.0 favor the row drug for efficacy measures, and ORs < 1.0 favor the row drug for safety outcomes; Black cells mean no needed comparison; Green cells mean a direct comparison is available; Values in bold are 95% CI values that do not include the neutral value and indicate the superiority of one of the alternatives. Abbreviations. ACR: American College of Rheumatology; ABA: abatacept; AE: adverse event; ADA: adalimumab; 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[116]

	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; Black cells mean no needed comparison, or no direct comparison was found. Abbreviations. BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; ABA: abatacept; ADA: adalimumab; ANA: anakira; BAR: baricitinib; CrI: credible interval; CTZ: certolizumab; ETN: etanercept; GLM: golimumab; IFX: infliximab; IFN-dyyb: infliximab biosimilar.

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