Targeted Immune Modulators for Rheumatoid Arthritis and Ankylosing Spondylitis

Surveillance Report

Washington P&T Committee Meeting

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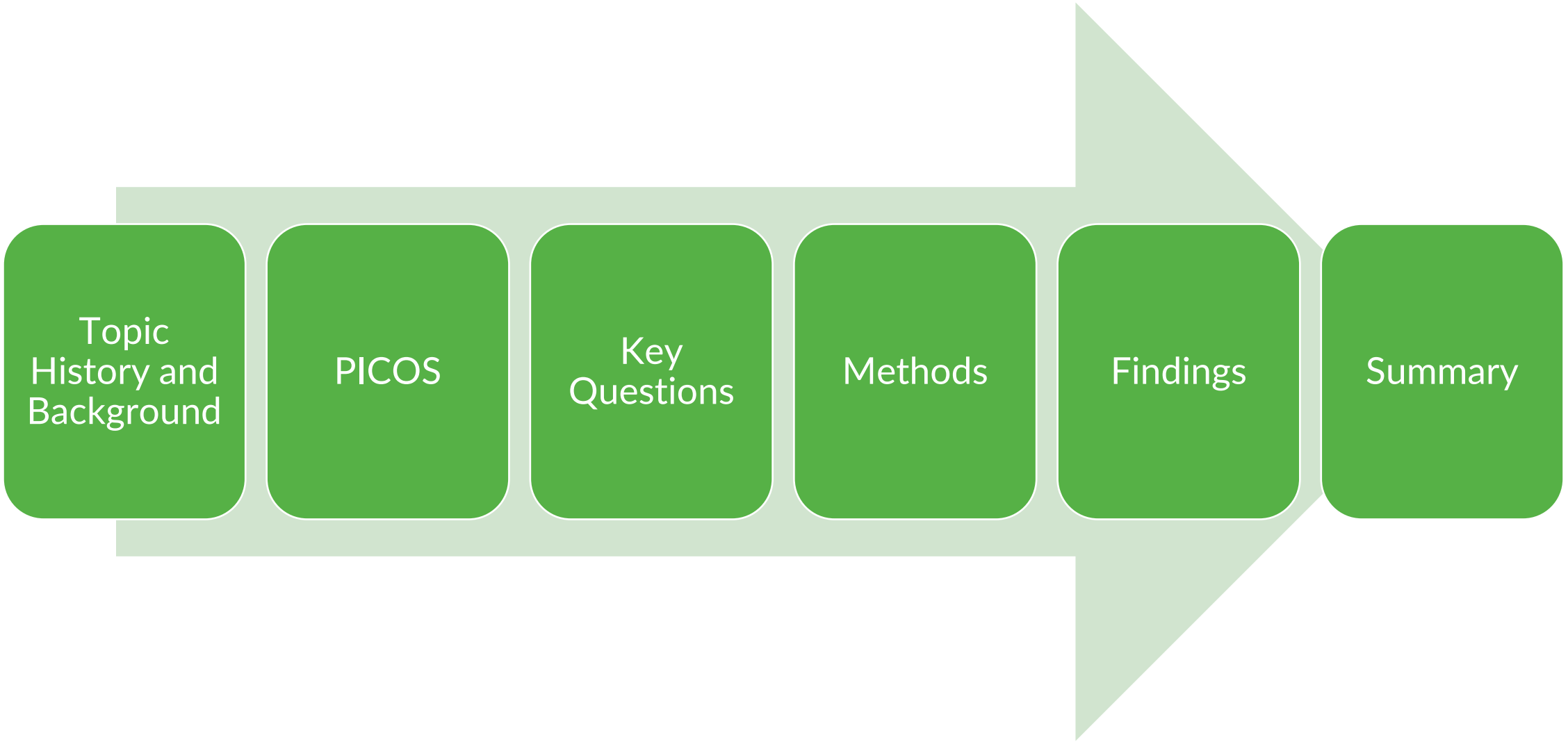
OHSU

Overview


Topic History and Background
PICOS
Key Questions
Methods
Findings
Summary

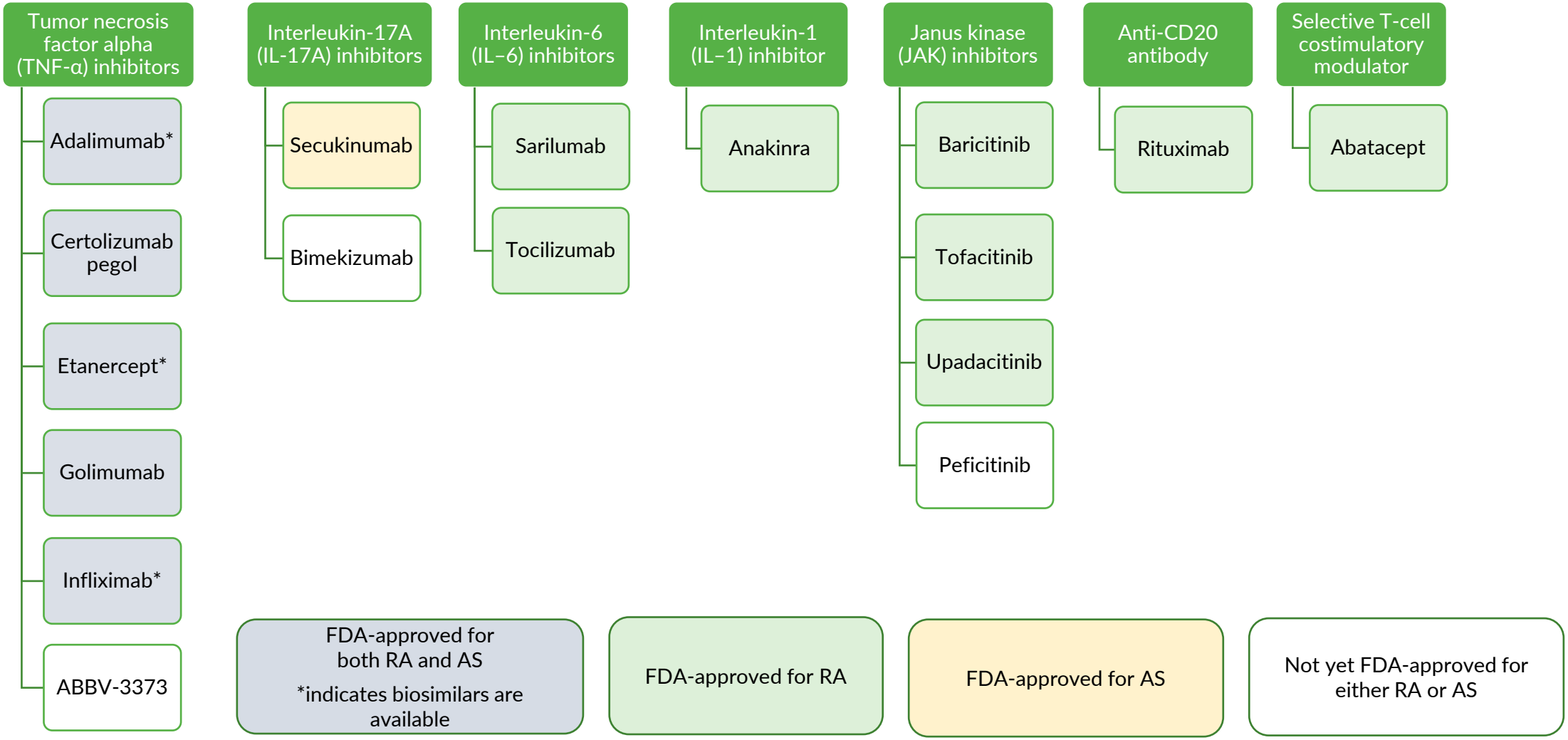
Topic History

Research Product Type	Date Presented	Search Dates
Systematic Review - Update 8	March 2022	January 2019 through July 2021
Systematic Review - Update 7	April 2020	January 2017 through September 2019
Systematic Review - Update 6	June 2018	January 2016 through November 2017
Systematic Review - Update 5	April 2016	November 2013 through January 2016
Systematic Review - Update 4	June 2014	October 2011 through November 2013
Systematic Review - Update 3	March 2012	January 2009 through October 2011
Systematic Review - Update 2	November 2009	August 2006 through April 2009
Systematic Review - Update 1	January 2007	March 2005 through August 2006
Original Systematic Review	December 2005	January 1980 through March 2005

Background

- **Rheumatoid arthritis (RA):** Chronic inflammatory autoimmune disease of the joint-lining tissues with progressive erosion of the bone, leading to a destruction of the joints and disability
- **Ankylosing spondylitis (AS):** Chronic inflammatory arthritis of the axial skeleton, with prominent involvement of spine and sacroiliac joints
- **Targeted immune modulators (TIMs):** Biologic drugs used to treat RA and AS by selectively blocking mechanisms involved in the inflammatory and immune responses
  - First TIM approved by US Food and Drug Administration (FDA) for RA in 1998 (etanercept)
  - First TIM FDA-approved for AS in 2003 (etanercept)
  - Additional agents, including biosimilars, have since been approved for both conditions

TIM Agents for RA and AS



PICOS

- Populations:
  - Adults with moderate-to-severe RA
  - Adults with AS (a type of axial spondyloarthropathy)
- Interventions:
  - FDA-approved TIMs and respective biosimilars or pipeline drugs
- Comparators:
  - For FDA-approved drugs: another listed TIM intervention (head-to-head comparison)
  - For pipeline drugs: any listed TIM, standard of care, placebo

PICOS

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

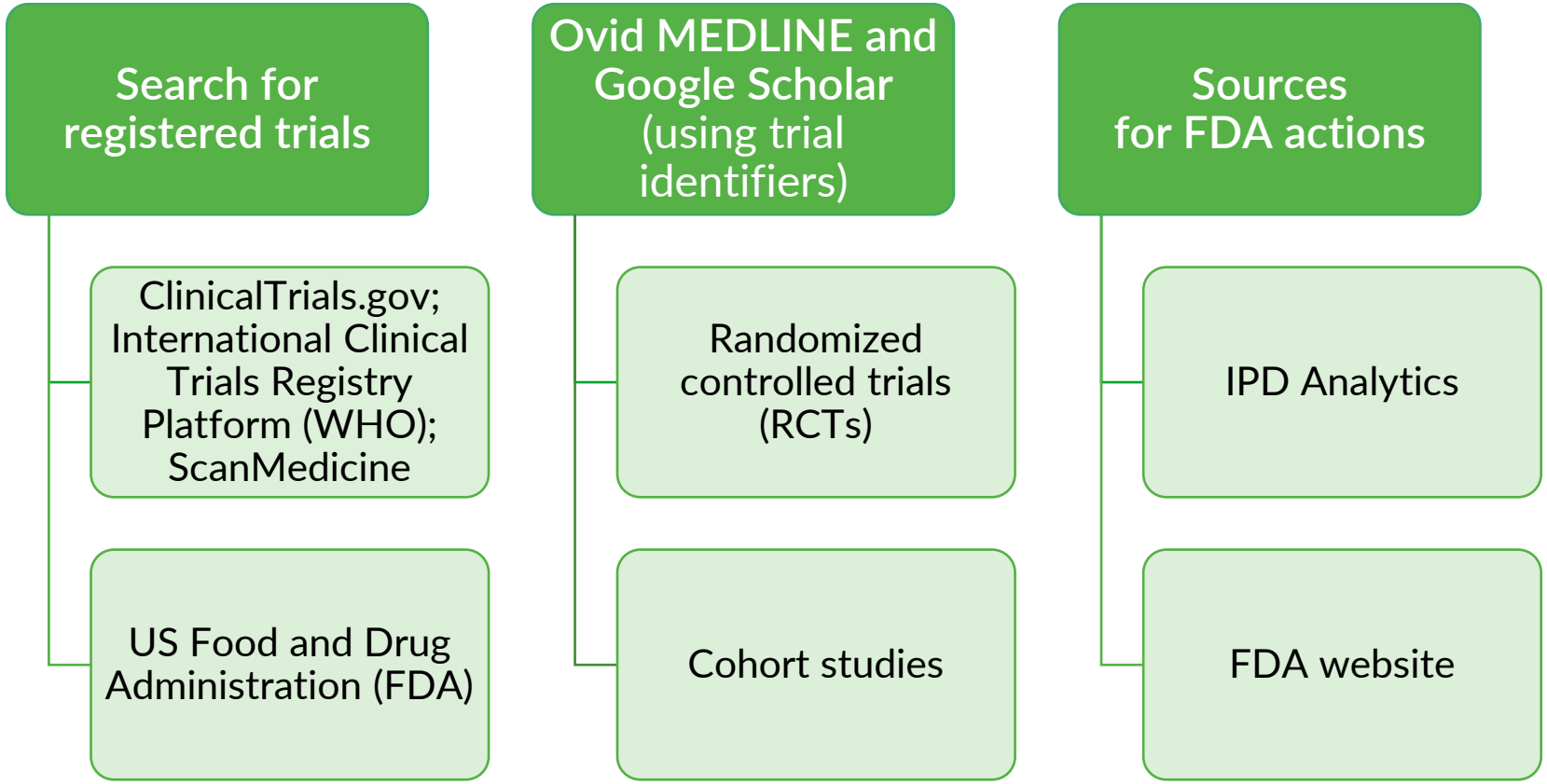
PICOS

- Study designs
  - Randomized controlled trials (RCTs) with ≥ 12-week study duration
  - Retrospective and prospective cohort studies comparing an intervention type to another for harms outcomes
    - ≥ 12-week study duration
    - Minimum total sample size of 1,000
    - Statistical analysis adjusted for any confounders
    - Studies providing direct statistical comparisons between drugs

Key Questions

1. Comparative effectiveness
2. Comparative harms
3. Variation by subgroups
   - Age and racial groups
   - Gender
   - Comorbidities
   - Patients taking other commonly prescribed drugs
   - Patients with early vs. established disease
4. Characteristics of ongoing studies

Methods



- All searches covered July 2021 through February 2023

Findings

Findings: New Published Studies

- 3 RCTs (in 7 publications) evaluating TIMs in patients with RA and AS during this surveillance period
  - Buttgereit and colleagues compared the efficacy and safety of ABBV-3373 vs. adalimumab in patients with moderate to severe RA
  - SURPASS trial compared the effectiveness of secukinumab versus SDZ-ADL (an adalimumab biosimilar) on spinal radiographic progression
  - Balanescu and colleagues focused on the safety outcomes of tofacitinib vs. other TNF inhibitors (in several publications)
- 2 new retrospective cohort studies assessed the safety (specifically cardiovascular events and risk of malignancies) in patients with RA treated with tofacitinib and TNF inhibitors

Characteristics of RCTs

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Author (Year) Trial Name Trial Number	Population Sample Size	Treatment Groups	Outcomes	Trial Duration
Buttgereit et al., 2022 NCT03823391	Adults with moderate/ severe RA N = 48	• ABBV-3373 100 mg IV • Adalimumab 80 mg SC • Placebo	• Disease activity	24 weeks
Baraliakos et al., 2020 SURPASS NCT03259074	Biologic-naïve patients with AS N = 858	• Secukinumab 150 mg SC • Secukinumab 300 mg SC • GP2017 (adalimumab biosimilar) 40 mg	• Disease activity • Remission	104 weeks
Balanescu et al., 2022 ORAL Surveillance Investigators NCT02092467	Patients with RA, aged ≥ 50 years with ≥ 1 additional cardiovascular risk factor N = 4,362	• Tofacitinib 5 mg twice daily • Tofacitinib 10 mg twice daily • TNF inhibitor	• Treatment-emergent adverse events	6 years

Abbreviations. AS: ankylosing spondylitis; IV: intravenous; RA: rheumatoid arthritis; RCT: randomized controlled trial; SC: subcutaneous; TNF: tumor necrosis factor.

Characteristics of Cohort Studies

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Author (Year) Trial Name Trial Number	Population Sample Size	Interventions	Outcomes
Khosrow-Khavar et al., 2022 STAR-RA NCT04772248	Patients with RA N = 102,263	• Tofacitinib • TNF inhibitor	Cardiovascular events
Khosrow-Khavar et al., 2022 STAR-RA NCT04798287	Patients with RA N = 83,295	• Tofacitinib • TNF inhibitor	Risk of malignancy

Abbreviations. RA: rheumatoid arthritis; TNF: tumor necrosis factor.

Findings: Ongoing Studies

We identified 18 ongoing studies eligible for this topic, if published:

- 2 RCTs on axial spondyloarthritis
  - Sample sizes: 300 and 305
  - Estimated completion dates: February 2022 and November 2024
- 1 multi-class TIMs
  - Sample size: 75
  - Estimated completion date: December 2024
- 5 RCTs of abatacept for RA
  - Sample sizes: ranging from 20 to 300
  - Actual or estimated completion dates: November 2022 to June 2023

Findings: Ongoing Studies

- 4 RCTs of baricitinib for RA
  - Sample sizes: ranging from 178 to 2,600
  - Estimated completion dates: December 2024 to July 2025
- 3 RCTs of etanercept for RA
  - Sample sizes: ranging from 144 to 226
  - Estimated completion dates: January 2021 to March 2023
- 1 RCT of upadacitinib vs. adalimumab for RA
  - Sample size: 40
  - Estimated completion date: June 2023
- 2 RCTs of pipeline drugs
  - Sample sizes: 76 and 385
  - Estimated completion dates: May 2020 and November 2021

Findings: Ongoing Studies

Trial Number Trial Name Phase	Condition	Treatment Groups Masking	Eligible Outcomes
Axial spondyloarthritis			
NCT03906136 AScalate Phase 3	axSpA	· Secukinumab · Adalimumab biosimilar · Standard of care Open-label	· Clinical improvement
NCT03445845 Phase 4	axSpA	· Secukinumab · TNF inhibitor Open-label	· Clinical improvement · Remission · AEs
Multi-class TIMs			
NCT05305066 SUPRA Phase NA	RA	· TNF inhibitor · IL-6 inhibitor · JAK inhibitors Open-label	· Disease activity · QoL

Abbreviations. AE: adverse event; axSpA: axial spondyloarthritis; IL: interleukin; JAK: janus kinase; NA: not applicable; QoL: quality of life; RA: rheumatoid arthritis; TNF: tumor necrosis factor.

Findings: Ongoing Studies

Trial Number Trial Name Phase	Condition	Treatment Groups Masking	Eligible Outcomes
Abatacept vs. other TIMs			
NCT05428488 Phase 3	RA	· Abatacept · TNF inhibitor Open-label	· Disease remission · Disease activity · QoL · AEs
NCT05451615 Phase 3	RA	• Abatacept • JAK inhibitor Open-label	• Disease activity • Treatment-emergent AEs
NCT04909801 Phase 3	RA	• Abatacept • Adalimumab • Methotrexate Single-blinded	• Clinical improvement • Disease activity • Remission • QoL
NCT03619876 AMiRA Phase 4	RA	• Abatacept • Adalimumab Open-label	• Clinical improvement
NCT03227419[a] Phase 4	RA	• Abatacept • Tocilizumab Open-label	• Disease activity • QoL

Note. [a] *The study has not been updated on clinicaltrials.gov since 2018.*
Abbreviations. AE: adverse event; JAK: janus kinase; QoL: quality of life; RA: rheumatoid arthritis; TIM: targeted immune modulator.

Findings: Ongoing Studies

Trial Number Trial Name Phase	Condition	Treatment Groups Masking	Eligible Outcomes
Baricitinib vs. other TIMs			
NCT04870203 Phase 3	RA	• Baricitinib • Adalimumab Triple-blinded	• Disease activity • AEs • Remission
EudraCT number: 2018-004558-30 Phase 4	RA	• Baricitinib • Etanercept Open-label	• Disease progression • AEs
NCT03915964 Phase 4	RA	• Baricitinib • TNF inhibitor Open-label	• AEs • SAEs
NCT04086745 Phase 4	RA	• Baricitinib • TNF inhibitor Open-label	• AEs • SAEs

Abbreviations. AE: adverse event; RA: rheumatoid arthritis; SAE: serious adverse event; TIM: targeted immune modulator; TNF-α: tumor necrosis factor-alpha.

Findings: Ongoing Studies

Trial Number Trial Name Phase	Condition	Treatment Groups Masking	Eligible Outcomes
Etanercept vs. other TIMs			
ISRCTN43336433 STRAP-EU Phase NA	RA	• Etanercept • Rituximab • Tocilizumab Open-label	• Remission
ISRCTN10618686 STRAP Phase NA	RA	• Etanercept • Rituximab • Tocilizumab Open-label	• Remission
NCT03976245 Phase 4	RA	• Etanercept • Tofacitinib Open-label	• Retention rates • Disease activity
Upadacitinib vs. adalimumab			
NCT05153200 Phase 4	RA	• Upadacitinib • Adalimumab Single-blinded	• Retention rate • QoL • Disease activity

Abbreviations. RA: rheumatoid arthritis; QoL: quality of life; TIM: targeted immune modulator.

Findings: Ongoing Studies

Trial Number Trial Name Phase	Condition	Treatment Groups Masking	Eligible Outcomes
Pipeline drugs			
NCT03660059 Phase 3	RA	• Peficitinib • Placebo • DMARDs Quadruple-blinded	• Disease activity • Remission • QoL • AEs
NCT03215277 Phase 2	AS	• Bimekizumab • Certolizumab pegol • Placebo Quadruple-blinded	• Clinical improvement • Pain • Remission • AEs • SAEs • Study withdrawal due to AEs

Abbreviations. AE: adverse event; AS: ankylosing spondylitis; DMARD: disease-modifying antirheumatic drug; RA: rheumatoid arthritis; SAE: serious adverse event; QoL: quality of life.

New FDA Actions

Drugs, Formulations, Indications, Serious Harms, or Warnings

New Drugs and Formulations

- During this surveillance period, the FDA approved 2 new biosimilars of existing TIM therapies for the treatment of RA and AS.

Generic Name	Brand Name	Mechanism	Route	Approved Population[a]	Date of FDA Approval
Adalimumab-aacf	Idacio	TNF-α inhibitor	SC	RA, AS	12/13/2022
Adalimumab-aqvh	Yusimry	TNF-α inhibitor	SC	RA, AS	12/17/2021

Note. [a] *Details of approved indications for each drug can be found in the full prescribing information. Some agents are approved for indications other than RA or AS.*
Abbreviations. AS: ankylosing spondylitis; FDA: US Food and Drug Administration; RA: rheumatoid arthritis; SC: subcutaneous; TNF-α: tumor necrosis factor-alpha.

New Indications

- Since the last review, 2 new indications have been approved by the FDA for existing TIMs therapies for the treatment of RA and AS
  - In December 2021, the FDA expanded the indications for the Janus kinase (JAK) inhibitor tofacitinib (Xeljanz, Xeljanz XR [extended release]) to include the treatment of adult patients with active AS who have had an inadequate response or intolerance to 1 or more tumor necrosis factor (TNF) blockers.
  - In April 2022, the FDA approved the use of upadacitinib (Rinvoq), a JAK inhibitor, for AS in adults.

New Serious Harms and Warnings

- We identified 3 new serious harms or warnings issued by the FDA since the most recent systematic review update for approved and pipeline TIMs therapies to treat RA or AS
  - Tocilizumab (Actemra)
    - In December 2022, FDA issued a boxed warning for risk of serious infections leading to hospitalization or death
    - The FDA also noted the increased risk of hepatotoxicity
  - Upadacitinib (Rinvoq)
    - In April 2022, FDA issued a warning to discontinue therapy if a serious hypersensitivity reaction occurs
  - Baricitinib (Olumiant)
    - In December 2021, FDA issued a boxed warning on the increased risk of all-cause mortality, malignancies, and major adverse cardiovascular events (cardiovascular death, myocardial infarction, and stroke), based on data comparing another JAK inhibitor to TNF blockers in patients with RA

Summary

New Clinical Evidence and
FDA Actions Since the Original Report

New Clinical Evidence and FDA Actions

- 5 new original studies (in 7 publications)
  - 3 RCTs
    - 1 comparing ABBV-3373 vs. adalimumab vs. placebo in RA patients
    - 1 comparing secukinumab vs. adalimumab biosimilar in AS patients (SURPASS)
    - 1 comparing the safety of tofacitinib with TNF inhibitors in RA patients (ORAL surveillance)
  - 2 retrospective cohort studies
    - Both focused on safety of tofacitinib and TNF inhibitors in RA patients
- 18 ongoing studies
  - 16 RCTs and 2 placebo-controlled trials

New Clinical Evidence and FDA Actions

- FDA actions
  - 2 new biosimilars
    - Adalimumab-aacf (Idacio): approved in December 2022
    - Adalimumab-aqvh (Yusimry): approved in December 2021
  - 2 new indications
    - Upadacitinib (Rinvoq): approved in April 2022
    - Tofacitinib (Xeljanz, Xeljanz XR): approved in December 2021
  - 3 new warnings
    - Tocilizumab (Actemra): serious infections (December 2022)
    - Upadacitinib: hypersensitivity reactions (April 2022)
    - Baricitinib: all cause-mortality, malignancies, major adverse cardiovascular events (December 2021)

Questions?


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