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DERP VI Surveillance: Targeted Immune Modulators for Rheumatoid Arthritis and Ankylosing Spondylitis

April 2021

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Objectives

The purpose of this Drug Effectiveness Review Project (DERP) surveillance report is to preview the volume and nature of new research and relevant clinical information that has emerged since the last systematic review on targeted immune modulators (TIMs) for the treatment of rheumatoid arthritis (RA) and ankylosing spondylitis. The literature search for this report focuses on new randomized controlled trials (RCTs), retrospective and prospective cohort studies of harms, and actions taken by the US Food and Drug Administration (FDA) since the last report, including approval of new drugs, formulations, or indications and identification of serious harms. Comprehensive searches, risk of bias assessment, and synthesis of evidence would follow only if DERP participants commission an update review or another research product type for this topic. Comprehensive searches might identify additional eligible studies.

Topic History and Context

This report is the first surveillance document on this topic since the completion of the seventh systematic review update of TIMs for the treatment of RA and ankylosing spondylitis (April 2020). The search strategy for that systematic review was through September 2019.

Table 1. Topic History and Search Dates

Document Type	Date Presented	Search Dates
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

PICOS

Population

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

Interventions

Table 2. Included Drugs and Biosimilars

Generic Name	Brand Name	Mechanism	Route	Approved Population(s)[a]	Date of FDA Approval
Abatacept	Orencia	CD80/86–CD28 T-cell costimulation modulator	IV, SC	RA	12/23/2005
Adalimumab	Humira	TNF-α Inhibitor	SC	RA, ankylosing spondylitis	12/31/2002

Generic Name	Brand Name	Mechanism	Route	Approved Population(s)[a]	Date of FDA Approval
Adalimumab-atto	Amjevita	TNF-α Inhibitor	SC	RA, ankylosing spondylitis	12/23/2016
Adalimumab-adaz	Hyrimoz	TNF-α Inhibitor	SC	RA, ankylosing spondylitis	10/30/2018
Adalimumab-adbm	Cyltezo	TNF-α Inhibitor	SC	RA, ankylosing spondylitis	08/25/2017
Anakinra	Kineret	IL-1 inhibitor	SC	RA	11/14/2001
Baricitinib	Olumiant	JAK inhibitor	PO	RA	05/31/2018
Certolizumab pegol	Cimzia	TNF-α Inhibitor	SC	RA, ankylosing spondylitis	04/22/2008
Etanercept	Enbrel	TNF-α Inhibitor	SC	RA, ankylosing spondylitis	11/02/1998
Etanercept-szzs	Erelzi	TNF-α Inhibitor	SC	RA, ankylosing spondylitis	08/30/2016
Golimumab	Simponi	TNF-α Inhibitor	SC	RA, ankylosing spondylitis	04/24/2009
Golimumab	Simponi ARIA	TNF-α Inhibitor	IV	RA, ankylosing spondylitis	07/18/2013
Infliximab	Remicade	TNF-α Inhibitor	IV	RA, ankylosing spondylitis	08/24/1998
Infliximab-abda	Renflexis	TNF-α Inhibitor	IV	RA, ankylosing spondylitis	04/21/2017
Infliximab-dyyb	Inflectra	TNF-α Inhibitor	IV	RA, ankylosing spondylitis	04/05/2016
Infliximab-qbtx	Ixifi	TNF-α Inhibitor	IV	RA, ankylosing spondylitis	12/13/2017
Rituximab	Rituxan	Anti-CD20 antibody	IV	RA	11/26/1997
Sarilumab	Kevzara	IL-6 receptor inhibitor	SC	RA	05/22/2017
Secukinumab	Cosentyx	IL-17A receptor inhibitor	SC	Ankylosing spondylitis	01/21/2015
Tocilizumab	Actemra	IL-6 receptor inhibitor	IV, SC	RA	10/21/2013
Tofacitinib	Xeljanz	JAK inhibitor	PO	RA	11/16/2012
Tofacitinib	Xeljanz XR	JAK inhibitor	PO	RA	02/23/2016
Upadacitinib	Rinvoq	JAK inhibitor	PO	RA[b]	08/16/2019
Pipeline Drugs					
ABBV-3373	NA	TNF-α inhibitor	IV	Under investigation for RA	NA
Bimekizumab	NA	IL-17A and IL-17F receptor inhibitor	IV	Under investigation for ankylosing spondylitis	NA

Generic Name	Brand Name	Mechanism	Route	Approved Population(s)[a]	Date of FDA Approval
Filgotinib	Jyseleca	JAK inhibitor	PO	Under investigation for RA and ankylosing spondylitis	NA[c]
Peficitinib	Smyraf	JAK inhibitor	PO	Under investigation for RA and ankylosing spondylitis	NA[d]

Notes. [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 ankylosing spondylitis; [b] Upadacitinib is under investigation for ankylosing spondylitis and axial spondyloarthritis; [c] Filgotinib is currently approved for the treatment of RA in the UK, Europe, and Japan; [d] Peficitinib is currently only approved in Japan. Abbreviations. IL: interleukin; IV: intravenous; JAK: Janus kinase; NA: not applicable; PO: by mouth (orally); RA: rheumatoid arthritis; SC: subcutaneous; TNF-α: tumor necrosis factor alpha.

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
  - 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

Study Designs

- 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

Key Questions

KQ1. What is the comparative effectiveness of TIMs to treat RA or ankylosing spondylitis?
KQ2. What are the comparative harms of TIMs to treat RA or ankylosing spondylitis?
KQ3. 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?
KQ4. What are the characteristics of ongoing studies for TIMs to treat RA or ankylosing spondylitis?

Methods

Using the PICOS outlined above, researchers at the Center for Evidence-based Policy (Center) searched for eligible RCTs and retrospective or prospective cohort studies of harms in ClinicalTrials.gov, the ISRCTN Registry, and the FDA website. Using relevant clinical trial numbers and other identifiers, we then searched Epub Ahead of Print, Ovid MEDLINE, and Ovid MEDLINE In-Process & Other Non-Indexed Citations from September 2019 through February 2021. We used the Google search engine to identify studies published since the implementation of the search strategy in the most recent systematic review of TIMs for the treatment of RA and ankylosing spondylitis (April 2020). We used limits for English language and human participants. We searched the FDA website to identify newly approved drugs, formulations, indications, and new serious harms (e.g., boxed warnings) or warnings for included interventions. We also searched IPD Analytics to identify new FDA actions.

Findings

FDA Actions

New Drugs or Formulations

During this surveillance period, the FDA approved 6 new biosimilars of existing TIMs therapies for the treatment of RA and ankylosing spondylitis (Table 3).

- Adalimumab-bwwd (Hadlima), adalimumab-afzb (Abrilada), and adalimumab-fkjp (Hulio) are the fourth, fifth, and sixth biosimilars of adalimumab, respectively. All adalimumab biosimilars are approved for adults with RA or ankylosing spondylitis.[1,2]
- Etanercept-ykro (Eticovo) is the second biosimilar of etanercept and is approved for adults with RA or ankylosing spondylitis.[1]
- Infliximab-axxq (Avsola) is the fourth biosimilar of infliximab and is approved for adults with RA or ankylosing spondylitis.[1]
- Several biosimilars of rituximab have been approved since the last systematic review update, but only 1 – rituximab-abbs (Truxima) – was approved for the treatment of RA in adults. Raibni is the first biosimilar of its reference product.[1]

Table 3. Newly-Approved TIMs for the Treatment of Rheumatoid Arthritis or Ankylosing Spondylitis

Generic Name	Brand Name	Mechanism	Route	Approved Population[a]	Date of FDA Approval
Adalimumab-bwwd[3]	Hadlima	TNF-α Inhibitor	SC	RA, AS	07/23/2019
Adalimumab-afzb[4]	Abrilada	TNF-α Inhibitor	SC	RA, AS	11/18/2019
Adalimumab-fkjp[5]	Hulio	TNF-α Inhibitor	SC	RA, AS	07/06/2020
Etanercept-ykro[6]	Eticovo	TNF-α Inhibitor	SC	RA, AS	04/25/2019
Infliximab-axxq[7]	Avsola	TNF-α Inhibitor	SC	RA, AS	12/06/2019
Rituximab-abbs[8]	Truxima	Anti-CD20 antibody	IV	RA	11/28/2018[b]

Notes. [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 ankylosing spondylitis. [b] Approved for RA in December 2019. Abbreviations. AS: ankylosing spondylitis; IV: intravenous; RA: rheumatoid arthritis; SC: subcutaneous; TNF-α: tumor necrosis factor alpha.

New Indications

No new indications were identified since the searches in the last systematic review update.

New Serious Harms or Warnings

We identified 4 new instances of a serious harm or warning issued by the FDA since the last systematic review update for approved and pipeline TIMs therapies to treat RA or ankylosing spondylitis.

- Infliximab (Remicade) and biosimilars: An RCT observed higher rates of mortality and hospitalizations in individuals with heart failure who received a 10 mg/kg dose of infliximab, and higher rates of cardiovascular adverse events in patients who received a 5 mg/kg dose compared with placebo.[9] In response, the FDA issued a label amendment in May 2020 for infliximab and all biosimilars with a contraindication for doses > 5 mg/kg in patients with moderate to severe heart failure.[10]
- Abatacept (Orencia): In June 2020, the FDA issued a warning for increased risk of infections and malignancies with abatacept, due to T-cell inhibition, after higher rates of infections were observed in adults with RA randomized to treatment with abatacept compared with placebo in clinical trials.[11]
- Baricitinib (Olumiant): In July 2020, the FDA issued a warning for increased risk of hypersensitivity reactions, including serious reactions, in people treated with baricitinib. Reactions may include angioedema, urticaria, and rash.[12]
- Filgotinib: In August 2020, the FDA rejected Gilead's New Drug Application (NDA) for filgotinib for moderate to severe RA, citing concerns over testicular toxicities demonstrated in earlier animal trials and the overall safety profile of filgotinib at doses of 200 mg or greater.[13] Two placebo-controlled trials evaluating male reproductive safety with filgotinib, MANTA[14] and MANTA-RAy,[15] are underway with full results expected in the first half of 2021. The FDA has requested these trial results before completing its review of the NDA.[13] In December 2020, Gilead announced it would no longer continue to seek FDA approval for

filgotinib for the treatment of RA and suspended enrollment in 2 recently initiated trials, SEALION1[16] and SEALION2,[17] evaluating filgotinib for ankylosing spondylitis.[18]

Clinical Evidence

Randomized Controlled Trials

We identified 3 new RCTs assessing the effectiveness of included interventions in participants with RA published during this surveillance period (Table 4). We did not find any new published studies evaluating TIMs in participants with ankylosing spondylitis.

- In the SELECT CHOICE trial,[19] Rubbert-Roth et al. assessed the effectiveness of intravenous abatacept compared with extended-release upadacitinib in participants with moderate to severe RA. This is the first published study of this treatment comparison we have identified.
- In the R4RA trial,[20] Humby et al. assessed the effectiveness of tocilizumab compared with rituximab in participants with RA who had an inadequate response to at least 1 anti-TNF therapy. This is the first published study of this comparison we have identified.
- In the FINCH 3 trial,[21] Westhovens et al. assessed the effectiveness of filgotinib in combination with methotrexate, or as monotherapy in comparison with placebo (and methotrexate monotherapy) for participants with RA. This is the fourth published study of filgotinib for the treatment of RA we have identified and follows the DARWIN 1,[22] DARWIN 2,[23] and FINCH 2[24] trials, which were captured in the last systematic review update.

Burmester et al.[25] published the first study comparing the effectiveness and safety of adalimumab monotherapy with sarilumab monotherapy for the treatment of RA (MONARCH) in May 2017. This study and a secondary analysis of patient-reported outcomes[26] were captured in the last systematic review update. Since that time, several additional secondary analyses of MONARCH have also been published.[27-31] Secondary analyses are not considered to be new, original research, so we do not provide additional details on these studies.

Table 4. Published RCTs of TIMs for Rheumatoid Arthritis

Author, Year Study Name NCT Number	Population Sample Size (N) Study duration	Treatment Groups	Outcomes
Rubbert-Roth et al., 2020[19] SELECT-CHOICE NCT03086343	Participants with moderate to severe RA refractory to biologic DMARDs N = 613 24 weeks	• Abatacept IV (dose dependent on weight) • Upadacitinib 15 mg	• Clinical improvement • Disease activity
Humby et al., 2021[20] R4RA ISRCTN97443826	Anti-TNF inadequate responder participants with RA N = 164 48 weeks	• Rituximab 1000 mg (twice every 2 weeks) • Tocilizumab 8 mg/kg (once every 4 weeks)	• Clinical improvement • Functional capacity • Quality of life • Adverse events • Serious adverse events

Author, Year Study Name NCT Number	Population Sample Size (N) Study duration	Treatment Groups	Outcomes
Westhovens et al., 2021[21] FINCH 3 NCT02886728	Participants with active RA N = 1,252 52 weeks	• Filgotinib 200 mg + methotrexate • Filgotinib 100 mg + methotrexate • Filgotinib 200 mg + placebo methotrexate • Methotrexate + placebo filgotinib	• Clinical improvement • Quality of life • Adverse events • Serious adverse events

Abbreviations. DMARDs: disease-modifying antirheumatic drugs; RA: rheumatoid arthritis; RCT: randomized controlled trial; TIM: targeted immune modulator; TNF: tumor necrosis factor

Ongoing Studies

We identified 24 ongoing studies[15,32-53] evaluating the comparative effectiveness or harms of eligible TIMs conducted among adults with RA or ankylosing spondylitis (Table 5). Of the 24 ongoing studies, 20 studies are RCTs,[15,32-43,46,48,50-54] (16 head-to-head trials of FDA-approved TIMs[32-34,36-38,40-43,46,48,51-54] and 4 placebo-controlled trials of pipeline drugs[15,35,39,50]) and 4 are comparative cohort studies.[44,45,47,49] Eighteen studies limit enrollment to adults with RA,[32-40,44-49,52-54] 5 studies limit enrollment to adults with ankylosing spondylitis,[42,43,50] and 1 study includes adults with either condition.[15] Sample sizes range from 20 to 9,968 participant and primary completion dates range from 2019 to 2025.

Table 5. Ongoing Studies of TIMs for Rheumatoid Arthritis and Ankylosing Spondylitis

NCT Number Trial Name	Condition	Treatment Groups Blinded vs. Open	Eligible Outcomes	N Enrolled Study Duration	Primary Completion Date[a]
Abatacept vs. Adalimumab					
NCT02557100[46]	RA	• Abatacept • Adalimumab Blinded	• Adverse events • Serious adverse events • Study withdrawal due to adverse events • Mortality	N = 80 (actual) 40 weeks	March 2019* (actual) Preliminary data have been reported.
NCT03619876[32] AMiRA	RA	• Abatacept • Adalimumab Open	• Clinical improvement	N = 20 (estimated) 16 weeks	July 2021 (estimated)
NCT04255134[48] BIORA-PAIN	RA	• Abatacept • Adalimumab Open	• Pain	N = 60 (estimated) 52 weeks	January 2023 (estimated)

NCT Number Trial Name	Condition	Treatment Groups Blinded vs. Open	Eligible Outcomes	N Enrolled Study Duration	Primary Completion Date[a]
Abatacept vs. Certolizumab Pegol vs. Tocilizumab					
NCT01491815[33]	RA	• Abatacept • Certolizumab pegol • Tocilizumab • Nonbiological DMARDs Open	• Remission • Joint destruction	N = 812 (actual) 56 weeks	June 2021 (estimated)
Abatacept vs. Tocilizumab					
NCT03227419[34] SUNSTAR	RA	• Abatacept • Tocilizumab Open	• Clinical improvement • Quality of life • Pain • Hospitalizations • Joint destruction • Adverse events • Serious adverse events • Study withdrawal due to adverse events	N = 224 (estimated) 52 weeks	September 2021 (estimated)
ABBV-3373 vs. Adalimumab vs. Placebo					
NCT03823391[35]	RA	• ABBV-3373 • Adalimumab • Placebo Blinded	• Disease activity • Clinical improvement • Remission	N = 48 (actual) 22 weeks	April 2020* (actual)
Adalimumab vs. Baricitinib vs. Etanercept					
NCT03915964[36] RA-BRIDGE	RA	• Baricitinib–low dose • Baricitinib–high dose • TNF-α inhibitor (adalimumab or etanercept) Open	• Adverse events • Serious adverse events	N = 2,600 (estimated) 5.5 years	April 2025 (estimated)

NCT Number Trial Name	Condition	Treatment Groups Blinded vs. Open	Eligible Outcomes	N Enrolled Study Duration	Primary Completion Date[a]
Adalimumab vs. Secukinumab					
NCT03906136[41] AScalate	AS	• Adalimumab-biosimilar • Secukinumab 150 mg • Secukinumab 300 mg • Standard of care Open	• Clinical improvement • Remission • Functional capacity • Quality of life • Pain	N = 300 (estimated) 36 weeks	December 2021 (estimated)
NCT03259074[42] SURPASS	AS	• Adalimumab-biosimilar • Secukinumab 150 mg • Secukinumab 300 mg Blinded	• Clinical improvement • Joint swelling • Joint destruction	N = 860 (actual) 104 weeks	September 2021 (estimated)
Baricitinib vs. Etanercept					
EudraCT number: 2018-004558-30	RA	• Baricitinib • Etanercept Open	• Clinical improvement • Joint swelling • Quality of life	N = 186 24 weeks	NR
Bimekizumab vs. Certolizumab pegol					
NCT03215277[43]	AS	• Bimekizumab/ placebo loading dose • Certolizumab pegol Blinded	• Clinical improvement • Pain • Remission • Adverse events • Serious adverse events • Study withdrawal due to adverse events	N = 76 (actual) 64 weeks	May 2020* (actual)
Bimekizumab vs. Placebo					
NCT03928743[50] BE MOBILE 2	AS	• Bimekizumab • Placebo Blinded	• Clinical improvement • Functional capacity • Pain • Quality of life • Adverse events • Serious adverse events	N = 300 (estimated) 72 weeks	August 2021 (estimated)

NCT Number Trial Name	Condition	Treatment Groups Blinded vs. Open	Eligible Outcomes	N Enrolled Study Duration	Primary Completion Date[a]
Etanercept vs. Tofacitinib					
NCT03976245[38]	RA	• Etanercept 50 mg • Tofacitinib 5 mg Open	• Clinical improvement	N = 144 (estimated) 24 months	September 2020 (estimated)
Etanercept vs. Rituximab vs. Tocilizumab					
ISRCTN43336433[52] STRAP-EU	RA	• Etanercept • Rituximab • Tocilizumab Open	• Remission	N = 226 (actual) 48 weeks	January* 2020 (estimated)
ISRCTN10618686[53] STRAP	RA	• Etanercept • Rituximab • Tocilizumab Open	• Remission	N = 187 (actual) 48 weeks	January 2021 (estimated)
Filgotinib vs. Placebo					
NCT03025308[39] FINCH 4	RA	• Filgotinib 100 mg • Filgotinib 200 mg • Placebo Open	• Adverse events • Laboratory abnormalities • Clinical improvement	N = 2,731 (actual) 6 years	April 2025 (estimated)
NCT03926195[15] MANTA-RAy	RA, AS	• Filgotinib 200 mg • Placebo Blinded	• Testicular toxicities	N = 109 (actual) 52 weeks	August 2020* (actual)
Secukinumab vs. TNF-α inhibitor					
NCT03445845[51] ROC-SPA	AS	• Secukinumab 150 mg • TNF-α inhibitor (infliximab, etanercept, adalimumab, certolizumab, golimumab) Blinded	• Clinical improvement • Remission • Adverse events	N = 300 (estimated) 52 weeks	November 2021 (estimated)

NCT Number Trial Name	Condition	Treatment Groups Blinded vs. Open	Eligible Outcomes	N Enrolled Study Duration	Primary Completion Date[a]
Tocilizumab vs. TNF-α Inhibitor					
NCT03100253[40] RAFTING	RA	• Tocilizumab 8 mg/kg • TNF-α inhibitor (etanercept, infliximab, adalimumab, golimumab, certolizumab pegol) Open	• Clinical improvement • Remission • Joint destruction • Quality of life	N = 208 (estimated) 96 weeks	December 2021 (estimated)
Tofacitinib vs. TNF-α Inhibitor					
NCT02092467[37]	RA	• Tofacitinib 5 mg • Tofacitinib 10 mg • TNF-α inhibitor (adalimumab or etanercept) • Open	• Disease activity • Remission • Functional capacity • Serious adverse events • Mortality	N = 4,369 (actual) 5 years	July 2020* (actual)
Various Biologic Treatments Evaluated Through Cohort Studies					
NCT02728934[44] AWARE	RA	• Golimumab • Infliximab and infliximab biosimilar	• Adverse events • Serious adverse events • Study withdrawal due to adverse events	N =1,279 (actual) 3 years	January* 2020 (actual)
NCT01932372[45]	RA	• Tofacitinib 5mg • Etanercept, other biologics, DMARDs	• Adverse events • Serious adverse events	N = 9,968 (actual) 36 months	March 2021 (estimated)
NCT04449224[47]	RA	• bDMARDs (Adalimuab, Etanercept, Tocilizumab, or Abatacept) • Small molecule inhibitors (Tofacitinib or Baricitinib)	• Adverse events	N = 506 (estimated) 48 weeks	August 2023 (estimated)
NCT04115423[49]	RA	• Tocilizumab • TNF-α inhibitor (etanercept, infliximab, adalimumab, golimumab)	• Serious adverse events (i.e., infections)	N = 9,508 (actual) 5 years	October 2021 (estimated)

Note. [a] *as reported in ClinicalTrials.gov, the European Clinical Trials Register, or the International Clinical Trials Registry Platform; * likely to publish results in 2021. Abbreviations. AE: adverse event; AS: ankylosing spondylitis; DMARD: disease-modifying antirheumatic drug; 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.*

Summary

Since the completion of the DERP systematic review update for TIMs to treat RA and ankylosing spondylitis (April 2020), we identified:

- 6 new biosimilars
  - Adalimumab-bwwd (Hadlima): approved in July 2019 for the treatment of RA and ankylosing spondylitis.
  - Adalimumab-afzb (Abrilada): approved in November 2019 for the treatment RA and ankylosing spondylitis.
  - Adalimumab-fkjp (Hulio): approved in July 2020 for the treatment of RA and ankylosing spondylitis.
  - Etanercept-ykro (Eticovo): approved in April 2019 for the treatment of RA.
  - Infliximab-axxq (Avsola): approved in December 2019 for the treatment of RA and ankylosing spondylitis.
  - Rituximab-abbs (Truxima): approved in December 2019 for the treatment of RA.
- 4 new warnings
  - Abatacept: infections and malignancies (June 2020)
  - Baricitinib: hypersensitivity reactions (July 2020)
  - Filgotinib: testicular toxicities (August 2020)
    - Cited as reason for rejection of NDA for RA
  - Infliximab: heart failure (May 2020)
- No new indications or formulations
- 3 new RCTs (all in participants with RA)
  - 2 head-to-head studies
    - Abatacept vs. upadacitinib (SELECT-CHOICE)
    - Rituximab vs. Tocilizumab (R4RA)
  - 1 placebo-controlled trial
    - Filgotinib vs. placebo (FINCH 3)
- 24 ongoing studies
  - 16 head-to-head studies of approved TIMs
  - 4 placebo-controlled trials of pipeline drugs
  - 4 prospective and retrospective cohort studies of harms

Using the *Is There a There There Scale* (ITS) (Table 5), we rated this topic as *Maybe* (see Appendix B for ratings and definitions).

Table 5. Summary and ITS Rating

Clinical Evidence	Yes How many?	No
New Comparative Trial	☑ 2	
New Placebo-Controlled Trial	☑ 1	
New Meaningful[a] Study	☑ 2	
Ongoing Study Likely to be Published in the Next Year	☑ 7 Abatacept vs. adalimumab: 1 ABBV-3373 vs. Placebo: 1 Bimekizumab vs. certolizumab pegol: 1 Etanercept vs. rituximab vs. tocilizumab: 1 Filgotinib vs. Placebo: 1 Golimumab vs. infliximab: 1 Tofacitinib vs. TNF inhibitors: 1	
FDA Actions	**Yes** **Description**	**No**
New Drug or Formulation	☑ Adalimumab-bwwd (Hadlima) Adalimumab-afzb (Abrilada) Adalimumab-fkjp (Hulio) Etanercept-ykro (Eticovo) Infliximab-axxq (Avsola) Rituximab-abbs (Truxima)	
New Indication		☒
New Serious Harm or Warning	☑ Infliximab: heart failure Abatacept: infections and malignancies Baricitinib: hypersensitivity reactions Filgotinib: testicular toxicities	
ITS Rating: *Maybe*		

Abbreviation. ITS: Is There a There There Scale. Note. [a] *Large studies (≥ 150 participants), studies that have long-term follow-up (≥ 12 months), studies that compare one drug with another that is considered the standard of care or has not been reported and is clinically important, and studies that include an intervention or outcome that is not previously reported in the literature or is clinically important (e.g., mortality) and adds to the body of literature.*

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Appendix A. Abstracts of New Eligible Studies

Humby F, Durez P, Buch MH, et al. Rituximab versus tocilizumab in anti-TNF inadequate responder patients with rheumatoid arthritis (R4RA): 16-week outcomes of a stratified, biopsy-driven, multicentre, open-label, phase 4 randomised controlled trial. *Lancet*. 2021;397(10271):305-317. doi: 10.1016/s0140-6736(20)32341-2.

BACKGROUND: Although targeted biological treatments have transformed the outlook for patients with rheumatoid arthritis, 40% of patients show poor clinical response, which is mechanistically still unexplained. Because more than 50% of patients with rheumatoid arthritis have low or absent CD20 B cells-the target for rituximab-in the main disease tissue (joint synovium), we hypothesised that, in these patients, the IL-6 receptor inhibitor tocilizumab would be more effective. The aim of this trial was to compare the effect of tocilizumab with rituximab in patients with rheumatoid arthritis who had an inadequate response to anti-tumour necrosis factor (TNF) stratified for synovial B-cell status. METHODS: This study was a 48-week, biopsy-driven, multicentre, open-label, phase 4 randomised controlled trial (rituximab vs tocilizumab in anti-TNF inadequate responder patients with rheumatoid arthritis; R4RA) done in 19 centres across five European countries (the UK, Belgium, Italy, Portugal, and Spain). Patients aged 18 years or older who fulfilled the 2010 American College of Rheumatology and European League Against Rheumatism classification criteria for rheumatoid arthritis and were eligible for treatment with rituximab therapy according to UK National Institute for Health and Care Excellence guidelines were eligible for inclusion in the trial. To inform balanced stratification, following a baseline synovial biopsy, patients were classified histologically as B-cell poor or rich. Patients were then randomly assigned (1:1) centrally in block sizes of six and four to receive two 1000 mg rituximab infusions at an interval of 2 weeks (rituximab group) or 8 mg/kg tocilizumab infusions at 4-week intervals (tocilizumab group). To enhance the accuracy of the stratification of B-cell poor and B-cell rich patients, baseline synovial biopsies from all participants were subjected to RNA sequencing and reclassified by B-cell molecular signature. The study was powered to test the superiority of tocilizumab over rituximab in the B-cell poor population at 16 weeks. The primary endpoint was defined as a 50% improvement in Clinical Disease Activity Index (CDAI50%) from baseline. The trial is registered on the ISRCTN database, ISRCTN97443826, and EudraCT, 2012-002535-28. FINDINGS: Between Feb 28, 2013, and Jan 17, 2019, 164 patients were classified histologically and were randomly assigned to the rituximab group (83 [51%]) or the tocilizumab group (81 [49%]). In patients histologically classified as B-cell poor, there was no statistically significant difference in CDAI50% between the rituximab group (17 [45%] of 38 patients) and the tocilizumab group (23 [56%] of 41 patients; difference 11% [95% CI -11 to 33], p=0·31). However, in the synovial biopsies classified as B-cell poor with RNA sequencing the tocilizumab group had a significantly higher response rate compared with the rituximab group for CDAI50% (rituximab group 12 [36%] of 33 patients vs tocilizumab group 20 [63%] of 32 patients; difference 26% [2 to 50], p=0·035). Occurrence of adverse events (rituximab group 76 [70%] of 108 patients vs tocilizumab group 94 [80%] of 117 patients; difference 10% [-1 to 21) and serious adverse events (rituximab group 8 [7%] of 108 vs tocilizumab group 12 [10%] of 117; difference 3% [-5 to 10]) were not significantly different between treatment groups. INTERPRETATION: The results suggest that RNA sequencing-based stratification of rheumatoid arthritis synovial tissue showed stronger associations with clinical responses compared with histopathological classification. Additionally, for patients with low or absent B-cell lineage

expression signature in synovial tissue tocilizumab is more effective than rituximab. Replication of the results and validation of the RNA sequencing-based classification in independent cohorts is required before making treatment recommendations for clinical practice. FUNDING: Efficacy and Mechanism Evaluation programme from the UK National Institute for Health Research.

Rubbert-Roth A, Enejosa J, Pangan AL, et al. Trial of upadacitinib or abatacept in rheumatoid arthritis. *N Engl J Med.* 2020;383(16):1511-1521. doi: 10.1056/NEJMoa2008250.

BACKGROUND: Upadacitinib is an oral selective Janus kinase inhibitor to treat rheumatoid arthritis. The efficacy and safety of upadacitinib as compared with abatacept, a T-cell costimulation modulator, in patients with rheumatoid arthritis refractory to biologic disease-modifying antirheumatic drugs (DMARDs) are unclear. METHODS: In this 24-week, phase 3, double-blind, controlled trial, we randomly assigned patients in a 1:1 ratio to receive oral upadacitinib (15 mg once daily) or intravenous abatacept, each in combination with stable synthetic DMARDs. The primary end point was the change from baseline in the composite Disease Activity Score for 28 joints based on the C-reactive protein level (DAS28-CRP; range, 0 to 9.4, with higher scores indicating more disease activity) at week 12, assessed for noninferiority. Key secondary end points at week 12 were the superiority of upadacitinib over abatacept in the change from baseline in the DAS28-CRP and the percentage of patients having clinical remission according to a DAS28-CRP of less than 2.6. RESULTS: A total of 303 patients received upadacitinib, and 309 patients received abatacept. From baseline DAS28-CRP values of 5.70 in the upadacitinib group and 5.88 in the abatacept group, the mean change at week 12 was -2.52 and -2.00, respectively (difference, -0.52 points; 95% confidence interval [CI], -0.69 to -0.35; P<0.001 for noninferiority; P<0.001 for superiority). The percentage of patients having remission was 30.0% with upadacitinib and 13.3% with abatacept (difference, 16.8 percentage points; 95% CI, 10.4 to 23.2; P<0.001 for superiority). During the treatment period, one death, one nonfatal stroke, and two venous thromboembolic events occurred in the upadacitinib group, and more patients in the upadacitinib group than in the abatacept group had elevated hepatic aminotransferase levels. CONCLUSIONS: In patients with rheumatoid arthritis refractory to biologic DMARDs, upadacitinib was superior to abatacept in the change from baseline in the DAS28-CRP and the achievement of remission at week 12 but was associated with more serious adverse events. Longer and larger trials are required in order to determine the effect and safety of upadacitinib in patients with rheumatoid arthritis. (Funded by AbbVie; SELECT-CHOICE Clinicaltrials.gov number, NCT03086343.).

Westhovens R, Rigby WFC, van der Heijde D, et al. Filgotinib in combination with methotrexate or as monotherapy versus methotrexate monotherapy in patients with active rheumatoid arthritis and limited or no prior exposure to methotrexate: the phase 3, randomised controlled FINCH 3 trial. *Ann Rheum Dis.* 2021. doi: 10.1136/annrheumdis-2020-219213.

OBJECTIVES: To investigate efficacy and safety of the Janus kinase-1 inhibitor filgotinib in patients with active rheumatoid arthritis (RA) with limited or no prior methotrexate (MTX) exposure. METHODS: This 52-week, phase 3, multicentre, double-blind clinical trial (NCT02886728) evaluated once-daily oral filgotinib in 1252 patients with RA randomised 2:1:1:2 to filgotinib 200 mg with MTX (FIL200 +MTX), filgotinib 100 mg with MTX (FIL100 +MTX),

filgotinib 200 mg monotherapy (FIL200), or MTX. The primary endpoint was proportion achieving 20% improvement in American College of Rheumatology criteria (ACR20) at week 24. RESULTS: The primary endpoint was achieved by 81% of patients receiving FIL200+ MTX versus 71% receiving MTX ($p<0.001$). A significantly greater proportion treated with FIL100+ MTX compared with MTX achieved an ACR20 response (80%, $p=0.017$) at week 24. Significant improvement in Health Assessment Questionnaire-Disability Index was seen at week 24; least-squares mean change from baseline was -1.0 and -0.94 with FIL200+MTX and FIL100+MTX, respectively, versus -0.81 with MTX ($p<0.001$, $p=0.008$, respectively). Significantly higher proportions receiving FIL200+MTX (54%) and FIL100+MTX (43%) achieved DAS28(CRP) <2.6 versus MTX (29%) ($p<0.001$ for both) at week 24. Hierarchical testing stopped for comparison of ACR20 for FIL200 monotherapy (78%) versus MTX (71%) at week 24 ($p=0.058$). Adverse event rates through week 52 were comparable between all treatments. CONCLUSIONS: FIL200+MTX and FIL100+MTX both significantly improved signs and symptoms and physical function in patients with active RA and limited or no prior MTX exposure; FIL200 monotherapy did not have a superior ACR20 response rate versus MTX. Filgotinib was well tolerated, with acceptable safety compared with MTX.

Appendix B. ITS Ratings and Definitions

The *Is There a There There Scale* (ITS) consists of 3 ratings: *no*, *maybe*, and *yes*. The definitions of these ratings and methods for selection are described below. Center for Evidence-based Policy (Center) researchers will use these definitions to rate each surveillance topic. The assigned rating is offered as guidance and does not require DERP participants to follow this recommendation. Each rating is strictly based on the identified new research and clinical information and is not comprehensive to all aspects of policy decision making, such as competing priorities, budget, contracting, or internal and external state agency needs.

No

- We did not find clinical evidence or information that would indicate a need to update the report or develop a derivative research product.
- A rating of No is typically given when there are few new studies and/or no new meaningful studies, and no new serious harms.

Maybe

- We found some clinical evidence or information that might suggest a need to update the report or develop a derivative research product.
- A rating of Maybe is typically given when there are multiple new comparative trials or at least 1 new meaningful study or serious harm.

Yes

- We found clinical evidence or information that suggests a need to update the report or develop a derivative research product.
- A rating of Yes is typically given when there are multiple new comparative trials and meaningful studies and/or new serious harms, drugs, formulations, or indications.