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OHSU Drug Effectiveness Review Project Summary Reports – (1) Targeted Immune Modulators for Rheumatoid Arthritis and Ankylosing Spondylitis (March 2022) (2) Targeted Immune Modulators for Plaque Psoriasis and Psoriatic Arthritis (April 2022)

Date of Review: Oct 2022

Date of Last Review: Oct 2021
Literature Search: 01/01/19-07/22/21 (RA/AS) and 05/01/19-08/25/22 (PsO/PsA)

Current Status of PDL Class:
See **Appendix 1**.

Research Questions:
March 2022 Report:

1. What is the comparative effectiveness of targeted immune modulators (TIMs) to treat rheumatoid arthritis (RA) or ankylosing spondylitis (AS)?
2. What are the comparative harms of TIMs to treat RA or AS?
3. Do the included drugs differ in their effectiveness or harms for managing RA or AS based on age, race, ethnicity, gender, patients with comorbidities, patients taking other commonly prescribed drugs, or in patients with early versus established disease?

April 2022 Report:

1. What is the comparative effectiveness of targeted TIMs to treat plaque psoriasis (PsO) or psoriatic arthritis (PsA)?
2. What are the comparative harms of TIMs to treat PsO or PsA?
3. Do the included drugs differ in their effectiveness or harms for managing PsO or PsA based on age and race, ethnicity, gender, patients with comorbidities, patients taking other commonly prescribed drugs, or in patients with early versus established disease?

Conclusions:
Targeted Immune Modulators for Rheumatoid Arthritis and Ankylosing Spondylitis

- There is moderate certainty evidence that there is no difference in response (America College of Rheumatology [ACR]50) or remission (ACR70) of RA between certolizumab pegol, tocilizumab, and abatacept when used as first-line treatment.[1] As second-line treatment, abatacept is less effective than upadacitinib for achieving response in RA based on the Disease Activity Score-28 joints-C-reactive protein [DAS-28-CRP] mean change from baseline (-2.0 vs. -2.52 respectively; p<0.001; 95% Confidence Interval [CI] not reported [NR]) and RA remission (percent of patients achieving DAS-28-CRP <2.6, 13% vs. 30% respectively; p<0.001; 95% CI NR) at 24 weeks.[1] (High certainty of evidence [CoE] for response; moderate CoE for remission).[1]
- Three new randomized clinical trials (RCTs) provide data on the overall incidence of adverse effects (AEs) and serious adverse effects (SAEs) for TIMS when used to treat RA.[1] Moderate to very low CoE from RCTs indicate a lower incidence of overall AEs and SAEs with abatacept and certolizumab pegol compared with tocilizumab.[1] Overall AEs were less frequent for abatacept compared with tocilizumab (80% vs. 95%, respectively; RR 0.48; 95% CI, 0.31 to 0.74) at 24

weeks; however no differences in SAEs were reported at 24 weeks (RR 0.42; 95% CI, 0.14 to 1.29; low CoE for AEs; very low CoE for SAEs).[1] When certolizumab pegol was compared with tocilizumab, a lower incidence of overall AEs was reported at 24 weeks (83% vs. 95%, respectively; RR 0.87; 95% CI, 0.81 to 0.93); however, no differences in SAEs were reported at 24 weeks (RR 1.72; 95% CI, 0.79 to 3.76; moderate CoE for overall AEs; low CoE for SAEs).[1]

- Most observational studies have not found statistically significant differences in mortality, malignancies, cardiovascular events or heart failure between TIMs.[1] However, some studies suggest, based on moderate CoE, that infliximab may be associated with higher incidence of serious infections compared to other TIMs, and tocilizumab may be associated with higher incidence of gastrointestinal perforations compared to other TIMs, when used in the treatment of RA.
- New comparative evidence for the efficacy of TIMs in treatment of AS was sparse.[1] Only one RCT with high risk of bias that compared etanercept and infliximab was identified.[1] Although etanercept was less effective for clinical improvement compared to infliximab at 12 weeks, no statistically significant differences in response were observed at weeks 54 and 104 (very low CoE).[1]
- No new evidence was identified to evaluate comparative harms of TIMs when used to treat AS.[1]
- No studies were identified that addressed differences in effectiveness or harms of TIMs when used to manage RA or AS in specific populations based on age, gender, race, comorbidities, concomitant medications, or different disease stages.[1]

Targeted Immune Modulators for Plaque Psoriasis and Psoriatic Arthritis

- New head-to-head RCTs were published for certolizumab pegol, etanercept, ixekizumab, guselkumab, secukinumab and risankizumab in the treatment of moderate-to-severe PsO.[2] No differences were found between ixekizumab and secukinumab for disease remission of PsO at 24 weeks (moderate CoE).[2] The following head-to-head comparisons found statistically significant results:
    - In one RCT, 200 mg and 400 mg doses of certolizumab pegol were compared with etanercept.[2] At 12 weeks, 61.3% of certolizumab 200 mg patients, 66.7% of certolizumab 400 mg patients and 53.3% of etanercept patients achieved a Psoriasis Area and Severity Index (PASI) 75 response. The PASI 75 response rate was higher for certolizumab pegol 400 mg versus etanercept (calculated RR 1.2; 95% CI, 0.04 to 1.5).[2] (Moderate CoE).[2]
    - At 12 weeks, ixekizumab achieved higher PASI 100 remission versus guselkumab (41% vs. 25%, respectively; calculated RR 1.7; 95% CI 1.4 to 2.0; high CoE).[2] However, no differences were noted between ixekizumab and guselkumab for disease remission at 24 weeks (PASI 100: 50% vs. 52%, respectively; calculated RR 0.96; 95% CI, 0.85 to 1.1; high CoE).
    - No difference in disease remission was observed between risankizumab and secukinumab at 16 weeks (PASI 90: 73.8% vs. 65.6%, respectively; absolute risk difference [ARD] 8.2%; 95% CI, -2.2 to 18.6). However at 52 weeks, risankizumab achieved higher PASI 90 remission than secukinumab (PASI 90: 86.6% vs. 57.1%, respectively; ARD 29.8; 95% CI, 20.8 to 38.8; moderate CoE).[2]
- Few differences in harms were found between certolizumab pegol, etanercept, ixekizumab, guselkumab, secukinumab, and risankizumab when used to treat PsO based on low and moderate CoE.[2] No differences in AEs, SAEs, or withdrawals due to AEs were observed between these agents in recently published RCTs.[2] A higher risk of injection-site reactions was observed for ixekizumab compared with guselkumab (RR, 3.4; 95% CI 2.1 to 5.6) over 24 weeks (moderate CoE).[2]
- Most of the new cohort studies evaluated patients receiving TIMs for either PsO or PsA.[2] Only one cohort study evaluated TIMs used to treat PsO and no cohort studies just evaluated PsA. When used to managed PsO or PsA, one cohort study found a lower risk of hospitalization for serious infections for ustekinumab compared with adalimumab (HR 0.62; 95% CI 0.56 to 0.76) and infliximab (HR 2.3; 95% CI 1.9 to 2.8) with no difference with certolizumab pegol (HR 1.09; 95% CI, 0.68 to 1.75; very low CoE).[2] Another cohort study reported similar results; fewer serious infections with ustekinumab (HR 0.59; 95% CI 0.39 to 0.90) compared with TNF inhibitors in patients treated for PsO or PsA (very low CoE).[2] A French cohort study observed that compared with etanercept, the risk for serious infection was increased with adalimumab (HR 1.22; 95% CI, 1.07 to 1.38) and infliximab (HR 1.79; 95% CI, 1.49 to 2.16) and decreased for ustekinumab (HR 0.79; 95% CI, 0.67 to 0.94; very low CoE for all comparisons) when these TIMs were used to treat PsO.[2]

- In patients with PsA, the efficacy of ixekizumab, secukinumab, and upadacitinib were all superior to adalimumab for improving skin disease based on moderate CoE, but only higher doses of upadacitinib (30 mg) were superior for improving arthritis symptoms.[2]
- Few differences in harms were found between TIMs when used to treat PsA based on low to moderate CoE; however, upadacitinib had more AEs compared with adalimumab over 24 weeks (RR 1.1; 95% CI, 1.02 to 1.20; moderate CoE).[2]
- Subgroup analyses found notable differences for a comparison for PsO and a comparison for PsA:[2]
    - Guselkumab vs. secukinumab for PsO*:* guselkumab was superior to secukinumab overall and in all subgroups evaluated based on age, weight, body mass index (BMI), severity of disease, body area affected and prior medication use.[2]
    - Ixekizumab vs. adalimumab for PsA*:* ixekizumab was more effective than adalimumab for individuals with and without concomitant use of methotrexate (MTX), but this difference was not statistically significant in concomitant users of MTX.[2]

Targeted Immune Modulators Expanded Indications

- Risankizumab received expanded approval by the U.S. Food and Drug Administration (FDA) for treatment of moderately to severely active Crohn's disease.[3]
- Baricitinib received expanded approval for inpatient treatment of coronavirus disease-2019 (COVID-19) and outpatient treatment of alopecia areata.[4] Alopecia areata is not funded by the Oregon Health Plan (OHP).[5]
- Ustekinumab received expanded approval for the treatment of children aged 6 years and older with active PsA.[6]

Recommendations:

- After clinical review, no changes to the Preferred Drug List (PDL) are recommended.
- Modify prior authorization (PA) criteria to reflect updated indications for risankizumab, baricitinib, and ustekinumab.
- After review of costs in executive session, no changes were made to the PDL.

Summary of Prior Reviews and Current Policy

- The TIMs for autoimmune conditions were last reviewed by the Pharmacy and Therapeutics (P & T) Committee at the October 2021 meeting. After clinical review, no changes to the PDL were recommended. After review of costs in executive session, secukinumab was made preferred on the PDL. Prior authorization (PA) criteria were modified to reflect expanded ages and indications for FDA-approvals that occurred in 2021. The PA criteria were recently updated after the June 2022 meeting to reflect FDA approvals in the first 6 months of 2022.
- Currently, adalimumab, etanercept, and secukinumab are preferred medications on the PDL (see **Appendix 1** for PDL status of all TIMS for autoimmune conditions). All preferred and nonpreferred TIMs require PA to ensure appropriate utilization. A 3-month trial and failure of adalimumab or etanercept is required for management of AS, RA, PsO or PsA before advancing to another TIM. Current clinical PA criteria are outlined in **Appendix 3.** In the second quarter of 2022, 51% of pharmacy claims for TIMs for autoimmune conditions were for the preferred agents adalimumab, etanercept and secukinumab. For the non-preferred agents, 9% of claims were for apremilast, 9% were for tocilizumab, and 5% each were for certolizumab pegol, ustekinumab, guselkumab, tofacitinib, and anakinra. About 1-2% of claims were for abatacept, risankizumab, and canakinumab. In the first quarter of 2022, there were 56 claims for physician administered TIMs (reflects decreased utilization from 71 claims in the first quarter of 2021). The most frequent claims for physician administered drugs were for infliximab, golimumab, tocilizumab, rituximab, and vedolizumab.

Methods:

The March 2022 drug class report on TIMs for RA and AS[1] and the April 2022 drug class report on TIMs for PsO and PsA[2] by the Drug Effectiveness Review Project (DERP) at the Center for Evidence Based Policy at the Oregon Health & Science University (OHSU) were used to inform recommendations for this drug class. The original report is available to Oregon P & T Committee members upon request.

The purpose of the DERP reports is to make available information regarding the comparative clinical effectiveness and harms of different drugs. DERP reports are not guidelines, nor should they be read as an endorsement of or recommendation for any particular drug, use, or approach. OHSU does not recommend or endorse any guideline or recommendation developed by users of these reports.

Background:
Targeted immune modulators include biologic disease-modifying antirheumatic drugs (DMARDs) and targeted synthetic DMARDs. Biologic DMARDs are large, complex, proteins that must be administered parentally. The biologic DMARDs include tumor necrosis factor (TNF) inhibitors (e.g., adalimumab, certolizumab pegol, etanercept, golimumab, and infliximab), IL antagonists (e.g., anakinra, sarilumab, tocilizumab, ustekinumab, secukinumab, brodalumab, ixekizumab, secukinumab guselkumab, risankizumab and tildrakizumab), and lymphocyte antagonists (e.g., rituximab and abatacept). FDA-approved biosimilars are available for adalimumab, etanercept, infliximab, and rituximab.[7] Targeted synthetic DMARDs are small chemical molecules that can be taken orally. The Janus kinase (JAK) inhibitors (e.g., tofacitinib, baricitinib, and upadacitinib), and the phosphodiesterase (PDE)-4 inhibitor (apremilast) are classified as targeted synthetic DMARDs. **Table 1** summarizes the TIMs indicated for management of AS, RA, PsA, and PsO discussed in this report.

Table 1. FDA-Approved Targeted Immune Modulators for Selected Auto-Immune Diseases[8,9]

Drug – Route of Administration	Molecular Target	Approved Indication(s)
Biologic DMARDs		
Adalimumab (HUMIRA) - SC	TNF	AS, RA, PsA, PsO
Certolizumab Pegol (CIMZIA) - SC		AS, RA PsA, PsO,
Etanercept (ENBREL) - SC		AS, RA, PsA, PsO
Golimumab - (SIMPONI and SIMPONI ARIA) – SC or IV		AS, RA, PsA
Infliximab (REMICADE) - IV		AS, RA, PsA, PsO
Anakinra (KINERET) - SC	IL-1	RA
Sarilumab (KEVZARA) - SC	IL-6	RA
Tocilizumab (ACTEMRA) – IV or SC		RA
Ustekinumab (STELARA) – IV or SC	IL-12 and IL-23	PsA, PsO
Brodalumab (SILIQ) - SC	IL-17	PsO
Ixekizumab (TALTZ) - SC		AS, PsA, PsO
Secukinumab (COSYNTEX) - SC		AS, PsA, PsO
Guselkumab (TREMFYA) - SC	IL-23	PsA, PsO
Risankizumab (SKYRIZI) - SC		PsO
Tildrakizumab (ILUMYA) - SC		PsO
Abatacept (ORENCIA) - IV or SC	T-lymphocyte	RA, PsA

Rituximab (RITUXAN) - IV	B-lymphocyte	RA
Targeted Synthetic DMARDs		
Baricitinib (OLUMIANT) - PO	JAK 1,2	RA
Tofacitinib (XELJANZ)- PO	JAK 1,2,3	RA, PsA
Upadacitinib (RINVOQ) - PO	JAK 1	RA, PsA
Apremilast (OTEZLA) - PO	PDE4	PsA, PsO
Abbreviations: AS=ankylosing spondylitis; FDA=Food and Drug Administration; IL=interleukin; IV=intravenous; JAK=Janus Kinase; PDE=phosphodiesterase; PO=oral; PsA=psoriatic arthritis; PsO=plaque psoriasis; RA=rheumatoid arthritis; SC=subcutaneous; TNF=tumor necrosis factor		

Rheumatoid Arthritis and Ankylosing Spondylitis

The hallmarks of RA are inflammation of the synovial tissues with progressive erosion of bone leading to malalignment of the joint and, in most cases, disability.[10] Tumor necrosis factor plays a central role in the pathophysiology of RA.[10] The 2019 European League against Rheumatism (EULAR) recommendations suggest RA treatment begin with a conventional synthetic DMARD such as methotrexate (MTX) as soon as diagnosis of RA is established.[11] Other conventional synthetic DMARDs recommended to treat RA include sulfasalazine and leflunomide.[11] Biologic DMARDs or targeted synthetic DMARDs are recommended for patients with a suboptimal response or intolerance to conventional synthetic DMARDs.[11] Monotherapy with biologic DMARDs or targeted synthetic DMARDs or combination therapy that includes MTX can be initiated as second-line therapy, depending on the patient's response to previous therapy and any pertinent comorbidities.[11] Primary endpoints used in RA clinical trials are American College of Rheumatology (ACR) response, EULAR response, the Health Assessment Questionnaire Disability Index (HAQ-DI), and the DAS-28. Outcomes used to assess RA in clinical trials are summarized in **Appendix 2**.

Ankylosing spondylitis is a chronic rheumatic disorder that primarily affects the sacroiliac joints and spine.[12] Diagnosis is based on radiologic confirmation of sacroiliitis and the presence of at least one clinical symptom: low back pain for at least 3 months, limited lumbar spine motion, or decreased chest expansion.[13] All TNF inhibitors are proven to provide sustained improvement in patient functioning and reduced disease activity as assessed by the Bath Ankylosing Spondylitis Disease Activity Index (BASDI) and Functional Index (BASFI) scores.[14] More details for these 2 outcomes are presented in **Appendix 2.** Two IL-antagonists, secukinumab and ixekizumab, have also demonstrated efficacy in treating AS.[15] However, ACR/ Spondylitis Association of America (SAA) guidance recommends a TNF inhibitor as the first TIM for use after nonsteroidal anti-inflammatory drug (NSAID) therapy over secukinumab or ixekizumab.[15] Co-administration of low-dose MTX with a TNF inhibitor is not recommended for AS management.[15]

Plaque Psoriasis and Psoriatic Arthritis

Plaque psoriasis is a chronic, immune-mediated inflammatory disorder of the skin, scalp and nails that affects about 2 to 3% of the population.[16] The development of the disease is driven by multiple pathways of immune mediators, including TNF, IL-23 and IL-17 cytokines.[17] Psoriasis ranges from mild to severe disease. The severity of PsO is classified based on the percentage of body surface area (BSA) involved. Moderate PsO affects 5 to 10% of BSA; severe PsO affects more than 10% of BSA. Mild PsO (less than 5% of BSA) is not a funded condition per the Health Evidence Review Commission (HERC) Guideline Note 57.[18] Per 2017 NICE guidance, first-line agents for PsO include: topical medications including corticosteroids, vitamin D analogs (e.g., calcipotriene), retinoids (e.g., tazarotene) or calcineurin inhibitors (e.g., tacrolimus or pimecrolimus).[19] Biologics including TNF inhibitors, IL-12/23 antagonists, IL-23 antagonists, or IL-17 antagonists, may be added for patients with moderate-to-severe PsO not controlled by other therapies.[19]

Psoriatic arthritis is a disease with heterogeneous manifestations in patients who have manifest or latent psoriasis.[20] Symptoms included pain and stiffness in the affected joint, swelling, and loss of range of motion.[2] Psoriatic arthritis comprises both musculoskeletal as well as non-musculoskeletal manifestations; the latter

particularly include the skin and the nails, but also potentially the gut (inflammatory bowel disease) or the eyes (uveitis).[20] First-line treatment for PsA includes NSAIDs, although in most cases conventional synthetic DMARDs (MTX, sulfasalazine or leflunomide) are necessary.[20]

Several tools have been developed to evaluate symptom improvement and quality of life in patients with psoriasis. In clinical trials, symptom improvement is often evaluated using the PASI, the static Physician's Global Assessment scale (sPGA), or the Psoriasis Symptom Inventory (PSI). There is no consensus on the most reliable scale, but the PASI is used most often in clinical trials and is considered the most validated scale.[21] The most commonly reported outcome in clinical trials is improvement of greater than 75% in the PASI score. However, an improvement of 100%, indicating complete disease clearance, is considered more clinically significant.[22] Additional outcomes used to assess PsO and PsA in clinical trials are summarized in **Appendix 2.**

Summary Findings:

Targeted Immune Modulators for Rheumatoid Arthritis or Ankylosing Spondylitis

The DERP authors identified comparative RCTs with at least 12 weeks duration and cohort studies with a minimum sample size of 10,000 patients to evaluate the effectiveness and harms of TIM agents FDA-approved for the treatment of RA and AS.[1] Outcomes of interest included measures of clinical improvement (ACR20, ACR50), disease remission (ACR70), quality of life (HAQ-DI), AEs, and SAEs.[1] Descriptions of the clinical outcomes used in the RA trials are presented in **Appendix 2**. Literature was searched through July 22, 2021.[1] Nine new studies were identified for the 2022 update; one RCT in patients with AS, and 8 RCTs in patients with RA.[1] Fifty-one studies were carried forward from the previous report for a total of 60 studies.[1] Of the 60 eligible studies, 35 were RCTs and 25 were cohort studies.[1] Among the 35 RCTs, 8 RCTs were rated as high risk of bias, 3 RCTs as low risk of bias, and the others were rated as moderate risk of bias, primarily due to extensive manufacturer involvement in study design, execution, and reporting.[1] Manufacturers sponsored nearly all the RCTs.[1] Among the 25 cohort studies, one study had high risk of bias, 3 studies were at low risk of bias and the rest were evaluated as having moderate risk of bias.[1]

A. Comparative Effectiveness of TIMs as First-Line Rheumatoid Arthritis Treatments

Fifteen head-to-head comparisons provided evidence for the effectiveness of TIMs used as first-line RA treatments (i.e., no prior treatment with TIMs).[1] Two studies evaluated combination TIM treatment with TIM monotherapy.[1] All RCTs enrolled subjects with moderate-to-severe RA despite treatment with DMARDs.[1]

New Evidence:

- ***Abatacept vs. Certolizumab Pegol (n = 407); Abatacept vs. Tocilizumab (n = 392); and Certolizumab Pegol vs. Tocilizumab (n = 391):*** a single low risk-of-bias RCT was identified.[1] The Nordic Rheumatic Diseases Strategy Trials and Registries (NORD-STAR) was a multicenter, pragmatic, open-label, observer-blinded, phase 4 trial conducted at 29 sites in Denmark, Finland, Iceland, the Netherlands, and Sweden in 812 adults.[23] The NORD-STAR study compared abatacept 125 mg subcutaneously (SC) once weekly (n = 204) versus certolizumab 200 mg every 2 weeks SC (after 400 mg loading dosing x 3 doses; n = 203) versus tocilizumab 8 mg/kg every 4 weeks intravenously (IV) or 162 mg SC once weekly (n = 188) versus conventional treatment (either MTX plus oral prednisolone or oral sulfasalazine combined with hydroxychloroquine and intra-articular corticosteroids).[23] Methotrexate was given as background therapy to all patients who received a TIM.[23] Participants were treatment-naïve, with early RA (less than 2 years).[23] The primary outcome was Clinical Disease Activity Index (CDAI) less than or equal to 2.8 at 24 weeks for conventional treatment compared to the selected TIMs.[23] Secondary outcomes at 24 weeks included DAS-28 remission and EULAR response. The following results were reported by DERP authors:
    - ***Abatacept vs. Certolizumab Pegol:*** No difference in EULAR response (84.9% vs. 86.7%; p-value not reported [NR]) or remission (CDAI <2.8; 56.3% vs. 52.6%; p-value NR) at 24 weeks (moderate CoE for response and remission).[1]

- ***Abatacept vs. Tocilizumab:*** No difference in EULAR response (84.9% vs. 82.2%; p-value NR) or remission (CDAI <2.8; 56.3% vs. 48.7%, p-value NR) at 24 weeks (moderate CoE for response and remission).[1]
- ***Certolizumab Pegol vs. Tocilizumab:*** No difference in EULAR response (84.9% vs. 82%; p-value NR) or remission (CDAI <2.8; 53% vs. 49%, p-value NR) at 24 weeks (moderate CoE for response and remission).[1]

- ***Anakinra vs. TNF-Inhibitors (adalimumab, etanercept, infliximab, golimumab, or certolizumab pegol); (n = 39):*** One new, high risk-of-bias, open-label RCT was identified. The trial enrolled 39 patients with type 2 diabetes mellitus who had moderate-to-severe RA and an inadequate response to MTX.[1] Patients received weekly anakinra SC injections (n = 22) or TNF-inhibitors at unreported doses (n = 17).[1] The primary outcome was the change in percent glycated hemoglobin (Hb1c) levels.[1] No significant differences in the secondary outcomes of EULAR response (95% vs. 63%; odds ratio [OR] 1.47; 95% CI, 0.95 to 2.26) or EULAR remission (50% vs. 25%; OR 1.93; 95% CI, 0.73 to 5.10) at 24 weeks were reported (very low CoE for response and remission).[1]

Previously Reported Evidence:

No new RCTs were identified for the head-to-head comparisons listed below,[1] previous conclusions are included for context. No differences were identified for over half of the head-to-head comparisons.

- ***Abatacept vs. Adalimumab (1 RCT; n = 646):*** No differences were found in response (ACR50; 46% vs. 46%), remission (ACR70; 29% vs. 26%; p-value NR), or improvement in functional capacity (HAQ-DI; -0.60 vs.-0.58; p-value NR) at 48 weeks.[1] (Low CoE for response, functional improvement, and remission).[1]
- ***Abatacept vs. Infliximab (1 RCT*; *n = 431):*** No differences were found in response (ACR50; 40% vs. 37%; p-value NR) or remission (ACR70; 21% vs. 24%; p-value NR) at 24 weeks.[1] (Low CoE for response and remission).[1]
- ***Adalimumab vs. Baricitinib (1 RCT; n = 1,305):*** Adalimumab was less effective than baricitinib for achieving response (ACR20, 61% vs. 70%; p=0.01; 95% CI NR) and improvement in functional capacity (HAQ-DI $\geq$ 0.22, 58% vs. 68%; p<0.01; 95% CI NR) at 52 weeks.[1] No difference in remission was found (Simplified Disease Activity Index [SDAI] < 3.3; 7% vs. 8%; p-value NR).[1] (High CoE for response and functional capacity; low CoE for remission).[1]
- ***Adalimumab vs. Certolizumab Pegol (1 RCT; n = 915):*** No difference in response was found (ACR20; 71% vs. 69%; p=0.47) at 12 weeks (high CoE).[1]
- ***Adalimumab vs. Etanercept (1 RCT; n = 64);*** No differences in disease activity (DAS-28; -2.12 vs. -2.84; p-value NR) or improvement in functional capacity (HAQ-DI; 0.69 vs. 0.68; p-value NR) at 24 weeks was found (very low CoE for both outcomes).[1]
- ***Adalimumab vs. Sarilumab (1 RCT; n = 369):*** Adalimumab was less effective than sarilumab for achieving response (ACR 50, 30% vs. 46%; p=0.002; 95% CI NR), remission (CDAI, 3% vs. 7%; p=0.047; 95% CI NR), improvement in functional capacity (HAQ-DI, -0.43 vs. -0.61; p<0.005; 95% CI NR), and quality of life (Short Form 36-item Health Survey [SF-36], 6.09 vs. 8.75; p<0.001; 95% CI NR) at 24 weeks.[1] (Moderate CoE for response, functional improvement, and quality of life; low CoE for remission).[1]
- ***Adalimumab vs. Tocilizumab (1 RCT; n = 326):*** Adalimumab was less effective than tocilizumab for achieving response (ACR50, 28% vs. 47%; p<0.001; 95% CI NR) and remission (ACR70, 18% vs. 33%; p=0.002; 95% CI NR) at 24 weeks.[1] No difference in quality of life was found (SF-36; 7.6 vs. 9.2; p=0.16) at 24 weeks.[1] Tocilizumab was used at higher doses than are FDA-approved.[1] (Low CoE for all 3 measures).[1]
- ***Adalimumab vs. Tofacitinib (1 RCT; n = 1,146):*** No differences in response (ACR50, 44% vs. 46%; p-value NR), remission (ACR70, 28% vs. 31%; p-value NR), or improvement in functional capacity (HAQ-DI; -0.54 vs -0.58%; p-value NR) were found at 24 weeks.[1] (High CoE for response, remission, and functional improvement).[1]

- ***Adalimumab vs. Upadacitinib (1 RCT; n = 1,629):*** Adalimumab was less effective than upadacitinib for achieving response (ACR50, 29% vs. 45%; p<0.001; 95% CI NR), remission (DAS-28-CRP<2.6; 18% vs. 29%; p<0.001; 95% CI NR), and improvement in functional capacity (HAQ-DI, -0.49 vs. -0.60; p<0.01; 95% CI NR) at 12 weeks.[1] (High CoE for response, remission, and functional improvement).[1]
- ***Etanercept vs. Infliximab (1 RCT; n = 32):*** Etanercept achieved higher response than infliximab (ACR20, 74% vs. 60%; p-value NR) and more improved functional capacity (HAQ-DI, -32.30 vs. -21.60; p-value NR) at 54 weeks.[1] (Very low CoE for clinical improvement and functional capacity).[1]
- ***Etanercept vs. Tocilizumab (1 RCT; n = 64):*** No differences in clinical improvement (DAS-28; -2.84 vs. -2.10; p-value NR) or improvement in functional capacity (HAQ-DI 0.68 vs. 0.70; p-value NR) was found at 24 weeks.[1] (Very low CoE for clinical improvement and functional capacity).[1]
- ***Combination Therapies (2 RCTs; total n = 365):*** No additional benefits (response, remission) from the combination of etanercept with abatacept or anakinra was identified compared with etanercept monotherapy.[1] (Moderate CoE for response and remission).[1]

B. Comparative Effectiveness of TIMs as Second-Line Rheumatoid Arthritis Treatments

Six head-to-head comparisons provided evidence of TIM agents as second-line treatment for RA (i.e., at least one inadequate response to a TIM).[1] Two studies evaluated TIM combination treatment with TIM monotherapy.[1]

New Evidence:

- ***Abatacept vs. Upadacitinib:*** One multinational , double-blinded, non-inferiority, low risk-of-bias RCT (n = 613) was identified.[1] Abatacept 500 to 1,000 mg IV once a month was compared with oral upadacitinib 15 mg once daily over 24 weeks in patients with active RA and moderate-to-high disease activity with an inadequate response to a TNF-inhibitor.[1] Abatacept was less effective than upadacitinib for achieving response (DAS-28 C-reactive protein [CRP] mean change from baseline, -2.0 vs. -2.52 respectively; p<0.001; 95% CI NR) and remission (DAS-28-CRP <2.6, 13% vs. 30% respectively; p<0.001; 95% CI NR) at 24 weeks.[1] (High CoE for response; moderate CoE for remission).[1]

- ***Rituximab vs. Tocilizumab:*** One open-label, noninferiority, high risk-of-bias RCT (n = 164) was identified.[1] Rituximab 1,000 mg IV every 2 weeks was compared with tocilizumab 8 mg/kg IV once monthly in patients with RA, despite treatment with a TNF inhibitor.[1] All patients continued MTX while enrolled in the study. No difference in clinical improvement (CDAI 50% improvement; 45.2% vs. 55.7%; OR, 0.81; 95% CI 0.59 to 1.10) at 16 weeks was observed between rituximab and tocilizumab (very low CoE).[1]

Previously Reported Evidence:

No new RCTs were identified for the head-to-head comparisons listed below,[1] previous conclusions are included for context. No significant differences were identified for most of the head-to-head comparisons.

- ***Abatacept vs. TNF-Inhibitors (adalimumab, etanercept, infliximab, golimumab, or certolizumab pegol; 2 RCTs; n = 93 and 176):*** No difference in clinical improvement (DAS-28; 3.8 vs. 3.5; p-value NR) at 52 weeks (low CoE).[1]
- ***Abatacept vs. Rituximab (2 RCTs; n = 93 and 122):*** No difference in clinical improvement (DAS-28; 3.8 vs. 3.4; p-value NR) at 52 weeks (low CoE).[1]
- ***Abatacept vs. Tocilizumab (1 RCT; n = 132):*** No significant differences in clinical improvement (DAS-28; 2.8 vs. 2.5; p=0.06) or functional improvement (HAQ-DI; 1.01 vs. 0.89; p=0.56) at 24 weeks.[1] (Low CoE for both outcomes).[1]
- ***TNF-Inhibitors (adalimumab, etanercept, infliximab, or certolizumab pegol) vs. Other TIMs (abatacept, rituximab, tocilizumab); (1 RCT; n = 300):*** Non-TNF-inhibitors were more effective than TNF-inhibitors for achieving EULAR response (69% vs. 52%; OR 2.06; 95% CI, 1.27 to 3.37) and remission (DAS-28 <2.6; 27% vs. 14%; p<0.01; 95% CI NR) at 52 weeks.[1] (Low CoE for response and remission).[1]

- ***Combination Therapy (rituximab plus adalimumab or etanercept; 1 RCT, n = 54):*** Combination treatment was more effective than monotherapy for achieving response (ACR50, 12% vs. 6%; p-value NR) and remission (DAS-28 <2.6, 18% vs. 6%; p-value NR) at 24 weeks.[1] (Low COE for response and remission).[1]
- ***Combination Therapy (abatacept added to existing TIM therapy; 1 RCT, n = 167):*** No difference in functional capacity (HAQ-DI; 0.33 vs. 0.22; p-value NR) at 52 weeks (low CoE).[1]

C. Comparative Harms of TIMs When Used to Manage Rheumatoid Arthritis

Three new RCTs provided data on the overall incidence of AEs, discontinuation due to AEs, and SAEs. Seventeen head-to-head comparisons and 4 comparisons of TIM combination treatment with TIM monotherapy provided evidence for comparative harms between TIMs.[1] Overall, few differences in AE incidence, discontinuation due to AEs, or SAEs were observed in head-to-head comparisons of TIMs.[1] Twenty-five cohort studies also provided data.[1]

New Evidence (RCTs):

- ***Abatacept vs. Certolizumab pegol (1 RCT; n = 812):*** No differences between groups for overall AEs (risk ratio [RR], 0.97; 95% CI 0.88 to 1.06) or SAEs (RR, 0.58; 95% CI 0.27 to 1.24) were observed at 24 weeks.[1] (Moderate CoE for AEs; low CoE for SAEs).[1]
- ***Abatacept vs. Tocilizumab (1 RCT, n = 132; first line treatment):*** lower incidence of overall AEs for abatacept was observed versus tocilizumab (80% vs. 95%; RR 0.48 95% CI, 0.31 to 0.74) at 24 weeks.[1] No difference in SAEs (RR, 0.42; 95% CI 0.14 to 1.29) at 24 weeks was observed.[1] (Low CoE for overall AEs; very low CoE for SAEs).[1]
- ***Certolizumab Pegol vs. Tocilizumab (1 RCT, n = 812):*** lower incidence of overall AEs for certolizumab pegol was observed versus tocilizumab (83% vs. 95%; RR 0.87; 95% CI, 0.81 to 0.93) at 24 weeks.[1] No difference in SAEs (RR, 1.72; 95% CI 0.79 to 3.76) was observed at 24 weeks.[1] (Moderate CoE for overall AEs; low CoE for SAEs).[1]

Previously Reported Evidence (RCTs):

No new RCTs were identified for the head-to-head comparisons listed below,[1] previous conclusions are included for context.

- ***Abatacept vs. Adalimumab (1 RCT; n = 646*)**: No difference between groups for overall AEs (RR 1.02; 95% CI, 0.98 to 1.05) or SAEs (RR, 1.10; 95% CI, 0.69 to 1.77) was observed at 48 weeks (low CoE for AEs; very low CoE for SAEs).[1] At 96 weeks, the incidence of discontinuation due to AEs was lower for abatacept versus adalimumab (RR 0.40; 95% CI, 0.21 to 0.76; low CoE).[1]
- ***Abatacept vs. Infliximab (1 RCT, n = 321):*** fewer SAEs with abatacept were observe versus infliximab (5% vs. 12%; RR 0.45; 95% CI, 0.20 to 0.99) at 24 weeks.[1] No difference in overall AEs (RR 0.97; 95% CI, 0.88 to 1.07) was found at 24 weeks.[1] (Low CoE for SAEs; moderate CoE for overall AEs).[1]
- ***Abatacept vs. Tocilizumab (1 RCT, n = 812; second-line treatment):*** lower incidence of overall AEs for abatacept versus tocilizumab (28% vs. 60%; RR 0.84; 95% CI, 0.78 to 0.92) at 24 weeks.[1] No difference in SAEs (RR, 1.00; 95% CI 0.42 to 2.41) was observed at 24 weeks.[1] (Low CoE for overall AEs; very low CoE for SAEs).[1]
- ***Adalimumab vs. Baricitinib (1 RCT, n = 817):*** fewer SAEs with adalimumab were observed versus baricitinib (4% vs. 8%; RR 0.50; 95% CI, 0.27 to 0.93) at 52 weeks.[1] No difference in overall AEs (RR 0.97; 95% CI, 0.90 to 1.05) was observed at 52 weeks.[1] (Low CoE for SAEs; high CoE for overall AEs).[1]
- ***Adalimumab vs. Certolizumab pegol (1 RCT; n = 915):*** No difference between groups for overall AEs (RR 0.98; 95% CI, 0.91 to 1.05) or SAEs (RR 0.85; 95% CI, 0.61 to 1.19) was observed at 12 weeks.[1] (High CoE for AEs; low CoE for SAEs.)
- ***Tocilizumab vs. Sarilumab (1 RCT, n = 202):*** No differences in overall AEs (RR 0.94; 95% CI, 0.75 to 1.18) or SAEs (RR 1.17; 95% CI, 0.31 to 4.32) were observed at 24 weeks.[1] (Low CoE for overall AEs; very low CoE for SAEs).[1]
- ***Combination Therapies vs. Monotherapy (3 RCTs):***

- ***Anakinra plus Etanercept vs. Etanercept monotherapy (1 RCT; n = 244):*** No differences in SAEs (RR 1.98; 95% CI, 0.37 to 10.48) or overall AEs (RR 1.06; 95% CI, 0.97 to 1.15) observed over 24 weeks (moderate CoE).[1]
- ***Abatacept plus other TIMs vs. TIM monotherapy (1 RCT, n = 167):*** No differences in SAEs (RR 1.79; 95% CI, 0.85 to 3.75) or AEs (RR 1.07; 95% CI 0.97 to 1.18) observed when abatacept plus other TIMs (adalimumab, anakinra, etanercept, or infliximab) were compared with other TIMs alone over 52 weeks (low CoE).[1]
- ***Rituximab plus Adalimumab or Etanercept vs. Adalimumab or Etanercept Monotherapy (1 RCT, n = 54):*** No difference in overall AEs (94% vs. 83%; RR, 1.13; 95% CI 0.90 to 1.41) observed for combination rituximab with TNF-inhibitor (adalimumab or etanercept) compared with adalimumab monotherapy or etanercept monotherapy (low CoE).[1] SAEs were not estimable due to no events in 1 or both groups.[1]

Data from Cohort Studies

- ***Mortality:*** One retrospective cohort study (n = 20,922) found no difference in all-cause mortality for tocilizumab compared with abatacept (adjusted hazard ratio [HR] 0.99; 95% CI 0.62 to 1.60).[1]
- ***Serious Infections:*** Ten observational studies provided data on the comparative risk of serious infections associated with TIMs when used to treat RA.[1] Definitions of serious infections included deaths, hospitalizations, and use of IV antibiotics associated with infections.[1]
    - One comparative study evaluated abatacept, rituximab, tocilizumab, tofacitinib and TNF inhibitors (adalimumab, certolizumab pegol, etanercept, golimumab, and infliximab).[1] Infliximab was associated with the highest incidence of serious infections.[1]
    - The largest cohort study (n = 130,000) from 3 U.S. databases compared tofacitinib, TNF inhibitors, abatacept and tocilizumab.[1] Risk of serious infections was higher for tofacitinib versus etanercept (HR 1.41; 95% CI, 1.15 to 1.73).[1] No differences were identified between tofacitinib and other TNF inhibitors (adalimumab, certolizumab pegol golimumab, and infliximab) or tocilizumab and abatacept.[1]
    - Another observational study (n = 49,000) reported no differences in serious infections for tocilizumab compared with TNF inhibitors (HR 1.05; 95% CI, 0.95 to 1.16).[1] A higher risk of serious infections was noted with tocilizumab versus abatacept (HR 1.40; 95% CI, 1.20 to 1.63).[1]
    - A British cohort study (n = 19,000) reported the incidence of serious infections was higher with tocilizumab compared with etanercept (HR 1.22; 95% CI, 1.02 to 1.47), but lower when etanercept was compared with certolizumab pegol (HR 0.75; 95% CI, 0.58 to 0.97).[1] No differences were identified when etanercept was compared with infliximab, adalimumab, or rituximab.[1]
- ***Tuberculosis:*** Three retrospective studies reported on the comparative risk of tuberculosis in patients taking TIMs.[1] The evidence was collected from British and Swedish registries.[1]
    - The British registry (n = 10,000) provided data on patients treated with adalimumab, etanercept, or infliximab.[1] A comparative analysis showed increased risk of tuberculosis with adalimumab compared with etanercept (adjusted incidence rate ratio [RR] 4.2; 95% CI, 1.4 to 12.4).[1]
    - Another study based on British registry data found lower incidence of tuberculosis for patients receiving rituximab (12 events per 100,000 patient years) compared with those treated with TNF inhibitors (65 events per 100,000 patient years; HR 0.16; 95% CI, 0.04 to 0.67).[1]
    - Data from Swedish registries (n = 10,800) compared the risk of tuberculosis for abatacept, adalimumab, anakinra, certolizumab pegol, etanercept, golimumab, infliximab, rituximab, and tocilizumab.[1] 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).[1] No cases of tuberculosis were reported in patients treated with abatacept, anakinra, certolizumab pegol, golimumab, and tocilizumab.[1] Adjusted hazard ratios did not detect any statistically significant differences in the risk for tuberculosis among any of the treatments.

- ***Opportunistic Infections:*** Three cohort studies provided data on opportunistic infections.[1]
  - An American study included patients with different autoimmune diseases treated with TNF inhibitors. An analysis of 24,384 patients treated for RA indicated a higher incidence of nonviral opportunistic infections for infliximab than etanercept (HR 2.9; 95% CI, 1.5 to 5.4).[1] In the same study, no differences were reported between adalimumab and etanercept (HR 1.8; 95% CI, 0.8 to 4.0).[1]
  - Another study (n = 69,000) reported no differences for TNF inhibitors (adalimumab, certolizumab pegol, etanercept, infliximab) compared with tocilizumab (HR 0.52; 95% CI, 0.17 to 1.65) or rituximab (HR 0.96; 95% CI, 0.62 to 1.50).[1] In general, the number of opportunistic infections was low (134 per 100,000 patient-years).[1] The most common infections were from herpes (n = 54), *Pneumocystis jirovecii* (n = 15), and *Legionella* (n = 11).[1]
- ***Varicella Zoster:*** Five observational studies provided evidence on the comparative risk of varicella zoster virus infections (herpes zoster, chicken pox, or shingles).[1]
  - Three cohort studies found the numerically highest risk for herpes zoster in patients treated with tofacitinib.[1] The largest of these studies (n = 130,000) analyzed data from 3 U.S. databases.[1] A higher risk of herpes zoster was found for tofacitinib versus other TIMs: adalimumab (aHR 1.99; 95% CI, 1.63 to 2.43); certolizumab pegol (aHR 2.24; 95% CI, 1.68 to 2.99); etanercept (aHR 2.12; 95% CI, 1.73 to 2.58); golimumab (aHR, 1.84; 95% CI 1.35 to 2.50); infliximab (aHR 1.94; 95% CI, 1.51 to 2.50); tocilizumab (aHR 2.14; 95% CI, 1.53 to 2.99); or abatacept (aHR 1.94; 95% CI, 1.53 to 2.44).[1]
  - Another study (n = 58,000) assessed the risk for herpes zoster and herpes simplex in patients treated with abatacept, adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, rituximab, tocilizumab, and tofacitinib.[1] Abatacept was used as the reference drug for all comparisons.[1] Compared with abatacept, risk for herpes infection was higher for tofacitinib (HR 1.40; 95% CI, 1.09 to 1.81).[1] Risks of all other drugs did not differ from the risk associated with abatacept.[1] Only 74 patients treated with tofacitinib had a herpes zoster or herpes simplex infection.[1]
  - A smaller study (n = 10,019) observed higher risk of herpes zoster with tofacitinib (HR 2.16; 95% CI, 1.09 to 4.28), tocilizumab (HR 1.98; 95% CI, 1.06 to 3.68), and rituximab (HR 1.82; 95% CI, 1.02 to 3.24) compared with abatacept.[1] The overall number of events was low.[1]
- ***Malignancies***: One large observational study pooled data from 3 U.S. databases and no found no significant difference or the risk of malignancy for tocilizumab compared with abatacept.[1]
- ***Nonmelanoma and Melanoma Skin Cancer:*** One publication reported on the incidence of nonmelanoma skin cancers for patients receiving adalimumab, etanercept, or infliximab.[1] The risk of basal cell carcinoma did not differ between these drugs.[1]
- ***Cardiovascular Events and Congestive Heart Failure:*** Three studies reported on the comparative risks of cardiovascular events:[1]
  - The largest study (n = 47,000) used data from Medicare patients with RA.[1] The retrospective study assessed the risk of cardiovascular events in patients treated with abatacept compared with adalimumab, certolizumab pegol, etanercept infliximab, rituximab, tocilizumab, and golimumab. Etanercept (HR 1.33; 95% CI, 1.01 to 1.76) and infliximab (HR 1.30; 95% CI 1.03 to 1.64) were associated with higher risks of myocardial infarction compared with abatacept (moderate CoE).[1]

- In another analysis, no differences were found between tocilizumab and abatacept (HR 0.82; 95% CI, 0.55 to 1.22) for the incidence of composite cardiovascular endpoint of hospitalization due to myocardial infarction or stroke.[1] The number of events in this study was low (tocilizumab n=32; abatacept n=112).[1]
- One retrospective study with high risk of bias did not detect differences in incident heart failure between etanercept and infliximab.[1]

- ***Gastrointestinal Perforations:*** Two retrospective cohort studies examined the comparative risk for gastrointestinal perforations.[1] Both studies showed a higher incidence of lower gastrointestinal perforation in patients using tocilizumab compared with any TNF inhibitor (HR 2.51; 95% CI, 1.31 to 4.80; RR 4.0; 95% CI, 1.1 to 14.1).[1] However, one study did not find differences between the drugs in any perforation within the entire gastrointestinal tract.[1] Only 16 to 23 cases of lower gastrointestinal perforations occurred in this study.[1]
- ***Venous Thromboembolism:*** One cohort study (n = 87,653) provided data on the incidence of venous thromboembolism (VTE), a composite of pulmonary embolism or deep venous thrombosis).[1] Overall, 365 cases of VTE were diagnosed in 80,879 patients treated with a TNF-inhibitor (incidence rate 0.48 per 100 person-years) and 29 in 6,744 patients receiving the JAK inhibitor tofacitinib (incidence rate 0.55 per 100 person-years).[1] In propensity score weighted analysis, no difference was found for the incidence of VTE for tofacitinib versus any TNF inhibitor.

  Data from long-term extension trials resulted in an FDA advisory warning for the use of tofacitinib at a higher dose (10 mg twice daily) due to an increased risk of VTE.[24] In September 2021, the FDA issued a drug safety communication warning providers and patients about the increased risk of serious heart-related events, cancer, blood clots, and death for JAK inhibitors (i.e., tofacitinib, upadacitinib, baricitinib) used to treat RA, PsA, and ulcerative colitis.[25]

D. Comparative Effectiveness of TIMS for Ankylosing Spondylitis Treatments

One new open-label, high risk of bias, head-to-head comparison of etanercept versus infliximab (n = 50) was identified for the treatment of AS.[1] Enrolled participants had not responded to NSAIDs and were naïve to treatment with DMARDs or TIMs.[1] Etanercept 50 mg once weekly was compared to infliximab 5 mg/kg at weeks 0, 2, 6, and every 6 weeks over 102 weeks.[1] After 12 weeks, fewer participants on etanercept than on infliximab achieved ASAS 40 response (43% vs. 55%; p-value NR). Etanercept was less effective for clinical improvement compared with infliximab (BASDAI, 5.9 vs. 4.8; p<0.005; 95% CI NR) at 12 weeks (very low CoE).[1] Overall AEs or SAEs were not reported.[1]

E. Comparative Harms of TIMS for Ankylosing Spondylitis Treatment

In the previous DERP report, one high risk of bias RCT was identified that reported on general tolerability of TIMs when used to treat AS in 50 patients over 102 weeks.[1] The study had no discontinuations due to AEs, but overall AEs and SAEs were not reported.[1] No eligible cohort studies or RCTs were identified to evaluate comparative harms of TIMs when used for AS treatment.[1]

F. Differences In Effectiveness or Harms by Subgroup Analysis

No studies were identified to address the research question focused on differences in effectiveness or harms by subgroup analysis based on specific demographic characteristics in patients with RA or AS (age, race, ethnicity, gender, patients with comorbidities, patients taking other commonly prescribed drugs, or in patients with early versus established disease).[1]

Targeted Immune Modulators for Plaque Psoriasis or Psoriatic Arthritis

The DERP authors identified comparative RCTs with at least a 12 week duration and cohort studies with a minimum sample size of 1,000 subjects to evaluate the effectiveness and harms of TIMs FDA-approved for the treatment of PsO and PsA.[2] Literature for the DERP report was searched through August 25, 2021.[2] Eighteen new studies were identified and 33 studies were carried forward from the previous DERP report focused on TIMs for management of PsO and PsA.[2] Of the included studies, 40 were RCTs and 11 were cohort studies.[2] Forty-two studies evaluated TIMs for treatment of PsO and 9 studies focused on TIMs for PsA.[2] Three RCTs and 2 cohort studies were rated as high risk of bias; the rest of the studies were evaluated as moderate risk of bias, primarily because of extensive manufacturer involvement in study design, execution, and reporting.[2] Outcomes of interest included measures of clinical improvement and disease remission (PASI, PGA, ACR), quality of life (DLQI,HAQ), AEs and SAEs.[2] Outcomes of interest are described in more detail in **Appendix 2**. When the statistical analysis was not reported by the original authors, the DERP team calculated risk ratios and associated confidence intervals based on data provided in the study.[2]

A. Comparative Effectiveness of TIMs for Plaque Psoriasis

Eighteen head-to-head comparisons were conducted in patients with PsO.[2] Most of the studies enrolled patients with a history of at least 6 months of moderate-to-severe PsO.[2] Four new RCTs and 5 new cohort studies were identified for this updated DERP report.[2] One RCT comparing etanercept with infliximab was rated as high risk of bias due to insufficient blinding and switching of treatments.[2] The DERP authors rated the rest of the RCTs as moderate risk of bias.[2]

New Evidence

- ***Certolizumab pegol vs. Etanercept (1 RCT; n = 502 without placebo arm):*** Higher dose of certolizumab pegol (400 mg) was more effective than etanercept for clinical improvement (PASI 75: 66.7% vs. 53.3%; calculated RR 1.2; 95% CI, 1.04 to 1.5).[2] No differences between lower dose of certolizumab (200 mg) and etanercept for clinical improvement (PASI 75: 61.3% vs. 53.3%; statistics NR because primary comparison was vs. placebo).[2] (Moderate CoE for both outcomes).[2]
- ***Ixekizumab vs. Guselkumab (1 RCT; n = 1,027):*** Ixekizumab was more effective than guselkumab for disease remission (PASI 100: 41% vs. 25%; calculated RR 1.7; 95% CI, 1.4 to 2.0; high CoE) at 12 weeks.[2] No differences were noted between ixekizumab and guselkumab for disease remission at 24 weeks (PASI 100: 50% vs. 52%; calculated RR 0.96; 95% CI, 0.85 to 1.1; high CoE).[2]
- ***Ixekizumab vs. Secukinumab (1 RCT; n = 54):*** No differences were noted between ixekizumab and secukinumab for disease remission at 24 weeks (PGA 0 or 1: 85.7% vs. 84.6%; calculated RR 1.01; 95% CI, 0.81 to 1.3; moderate CoE).[2]
- ***Risankizumab vs. Secukinumab (1 RCT, n = 327):*** No difference in disease remission at 16 weeks (PASI 90: 73.8% vs. 65.6%; ARD, 8.2%; 95% CI -2.2 to 18.6). At 52 weeks, risankizumab was more effective that secukinumab (PASI 90: 86.6% vs. 57.1%; ARD, 29.8; 95% CI 20.8 to 38.8; moderate CoE).[2]

Previously Reported Evidence

No new RCTs were identified for the head-to-head comparisons listed below,[2] previous conclusions are included for context. Orange text indicates the intervention was significantly less effective than the comparison and blue text indicates the intervention was significantly more effective than the comparison.[2]

- ***Apremilast vs. Etanercept (1 RCT; n = 250):*** Apremilast 30 mg twice daily was compared with etanercept 50 mg once weekly. The etanercept dose is the standard labeled dose in Europe, but it is less than the recommended FDA dose (twice weekly for 3 months, followed by 50mg once a week).[2] No difference in clinical improvement (PASI 75: 40% vs. 48%; p=0.26) at 16 weeks was observed (low CoE).[2]
- ***Brodalumab vs. Ustekinumab (2 RCTs; n = 1,831 and n = 1881):*** Two large RCTs (AMAGINE-2 and AMAGINE-3) contributed data for this head-to-head comparison.[2] Brodalumab was more effective for achieving disease remission compared with ustekinumab (PASI 100: 44% vs. 22%; p<0.001; 95% CI NR [AMAGINE-2 results] and 37% vs. 19%; p<0.001; 95% CI NR [AMAGINE-3 results]) at 12 weeks (high CoE).[2]

- ***Etanercept vs. Infliximab (1 RCT; n = 50):*** Etanercept was less effective than infliximab for achieving clinical improvement (PASI 75: 35% vs. 72%; p=0.01; 95% CI NR) at 24 weeks (very low CoE).[2]
- ***Etanercept vs. Ixekizumab (2 RCTs; n = 1,224 and n = 1,346):*** Etanercept was less effective than ixekizumab for achieving clinical improvement (PASI 75: absolute risk differences [ARDs], 34% to 47%) and for improving quality of life (proportion of subjects achieving DLQI 0 or 1: ARDs, 20% to 30%) at 12 weeks.[2] (High CoE for both outcomes).[2]
- ***Etanercept vs. Secukinumab (1 RCT; n = 1,306):*** Etanercept was less effective than secukinumab for achieving clinical improvement (PASI 75: 44% [etanercept] vs. 77% [secukinumab 300 mg] vs. 67% [secukinumab 150 mg]; p<0.001 for both secukinumab doses vs. etanercept; 95% CI NR) at 12 weeks (high CoE).[2] Etanercept was less effective than secukinumab for improving quality of life (mean change DLQI : -7.9 [etanercept] vs. -10.4 [secukinumab 300 mg] vs. -9.7 [secukinumab 150 mg]); p-value NR at 12 weeks (moderate CoE).[2] Etanercept was less effective than secukinumab for maintaining disease remission at 52 weeks (PASI 75 : 73% [etanercept] vs. 84%; p<0.001 [secukinumab 300 mg]; vs. 82%; p<0.009 [secukinumab 150 mg]; high CoE).[2]
- ***Etanercept vs. Ustekinumab (1 RCT; n = 903):*** Etanercept was less effective than ustekinumab for achieving clinical improvement (PASI 75: 57% [etanercept] vs. 74%; p=0.01 [ustekinumab 90 mg] vs. 68%; p<0.001 [ustekinumab 45 mg]) at 12 weeks; moderate CoE).[2]
- ***Guselkumab vs. Adalimumab (3 RCTs; n = 251; n = 663; n = 744):*** Guselkumab was more effective than adalimumab for disease remission (PGA 0 or 1: ARD range, 16% to 28%; high CoE) and improving quality of life at 16 weeks (DLQI 0 or 1: ARD range 13 to 15%; moderate CoE).[2]
- ***Guselkumab vs. Secukinumab (1 RCT; n = 1,048):*** Guselkumab was more effective than secukinumab for disease remission (PASI 90: 84% vs. 70%; p<0.001; 95% CI NR) at 48 weeks (moderate CoE).[2] Guselkumab was noninferior to secukinumab for a clinical improvement at a combined endpoint that included 12 and 48 weeks (PASI 75: 85% vs. 80% p<0.001 for noninferiority; p=0.06 for superiority; CoE NR).
- ***Ixekizumab vs. Ustekinumab (1 RCT; n = 302):*** Ixekizumab was more effective than ustekinumab for disease remission at 12 weeks (PASI 90: 73% vs. 42%; p<0.001; 95% CI NR) and at 52 weeks (PASI 90: 77% vs. 59%; moderate CoE for both time intervals).[2] Ixekizumab was more effective than ustekinumab for improving quality of life at 12 weeks (DLQI 0 or 1: 61% vs. 45%; p=0.01) and at 52 weeks (DLQI 0 or 1: 71% vs. 57%; p-value NR; moderate CoE for both time intervals).[2]
- ***Risankizumab vs. Adalimumab (1 RCT; n = 605):*** Risankizumab was more effective than adalimumab for disease remission (PASI 90: 72% vs. 47%; p-value NR) and quality of life (DLQI 0 or 1: 66% vs. 49%; p<0.001) at 16 weeks.[2] (Moderate CoE for both outcomes).[2]
- ***Risankizumab vs. Ustekinumab (3 RCTs; n = 166; n = 506; n = 393):*** Risankizumab was more effective than ustekinumab for disease remission (PASI 90: ARD range 28% to 37%) and improving quality of life (DLQI 0 or 1: ARD range 19% to 23%) at 12 to 16 weeks.[2] (Moderate CoE for both outcomes).[2]
- ***Secukinumab vs. Ustekinumab (2 RCTs; n = 676 and n = 1,102):*** Secukinumab was more effective than ustekinumab for disease remission at 16 weeks (PASI 90: ARDs 21% to 22%) and 52 weeks (PASI 90: ARDs 14% to 13%) at 16 weeks.[2] (High CoE for both time frames).[2]
- ***Tildrakizumab vs. Etanercept (1 RCT; n = 934):*** Tildrakizumab was more effective than etanercept for clinical improvement at 12 weeks (PASI 75: 66%; p<0.001 [tildrakizumab 200 mg] vs. 61%; p=0.001 [tildrakizumab 100 mg] vs. 48% [etanercept]).[2] (High CoE).[2]

B. Comparative Harms of TIMs When Used To Manage Plaque Psoriasis

All the RCTs that evaluated efficacy also reported on harms of TIM agents; few differences in harms for TIMs were reported in head-to-head comparisons.[2] Five cohort studies were new to the updated DERP report.[2] One new cohort study was rated as high risk of bias, the rest were evaluated as moderate risk of text indicates the intervention was more harmful than the comparison and blue text indicates the intervention was significantly less harmful.[2]

New Evidence (RCTs)

- ***Certolizumab 200 mg and 400 mg vs. Etanercept (1 RCT; n= 502 without placebo arm):*** No significant differences in AEs between etanercept and certolizumab pegol (200 mg: RR 1.02; 95% CI, 0.81 to 1.3 and 400 mg: RR 1.06; 95% CI, 0.85 to 1.3) SAEs (200 mg: RR 1.02; 95% CI, 0.06 to 16.1 and 400 mg: RR 4.0; 95% CI, 0.45 to 35.6), or withdrawals due to AEs (200 mg: RR 0.25; 95% CI, 0.03 to 2.3 and 400 mg: RR 0.25; 95% CI, 0.03 to 2.2) over 12 weeks (moderate CoE for all reported harms at both doses).[2]
- ***Ixekizuamb vs. Guselkumab (1 RCT; n = 1,027):*** Higher risk of injection-site reactions for ixekizumab than guselkumab (RR 3.4; 95% CI, 2.1 to 5.6) over 24 weeks. No significant differences in AEs (RR 1.1; 95% CI, 0.99 to 1.2), SAEs (RR 1.1; 95% CI, 0.6 to 2.1), or withdrawals due to AEs (RR 1.8; 95% CI, 0.8 to 4.3) over 24 weeks (moderate CoE for all harms).[2]
- ***Ixekizumab vs. Secukinumab (1 RCT; n = 54):*** No significant differences in AEs (RR 1.04; 95% CI, 0.71 to 1.5), SAEs (none reported), or withdrawals due to AEs (none reported) over 24 weeks (moderate CoE).[2]
- ***Risankizumab vs. Secukinumab (1 RCT; n = 327):*** No significant differences in AEs (RR 1.002; 95% CI, 0.87 to 1.2), SAEs (RR 1.5; 95% CI, 0.54 to 4.1), or withdrawals due to AEs (RR 0.98; 95% CI, 0.06 to 15.07) over 52 weeks (moderate CoE).[2]

Previously Reported Evidence (RCTs)

This section describes findings where at least one statistically significant difference was observed in AEs, SAEs, or specific serious harms.[2]

- ***Apremilast vs. Etanercept (1 RCT; n = 250):*** Higher incidence of AEs apremilast compared with etanercept (71% vs. 53%; calculated RR 1.3; 95% CI, 1.05 to 1.7; low CoE) over 16 weeks.[2] No difference in SAEs (RR 1.5; 95% CI, 0.26 to 0.87) over 16 weeks (very low CoE).[2]
- ***Etanercept vs. Secukinumab (1 RCT; n = 1,306):*** Higher risk of injection-site reactions for etanercept than secukinumab 300 mg dose (11% vs. 1%: RR 14.9; 95% CI, 6.7 to 33.2) over 52 weeks.[2] No significant differences in AEs, SAEs, or withdrawals due to AEs (moderate CoE for all harms).[2]
- ***Etanercept vs. Tofacitinib (1 RCT; n = 1,106):*** Higher incidence of withdrawal due to AEs for etanercept than tofacitinib 5 mg twice daily (3% vs. 1%; RR 3.6; 95% CI, 1.01 to 12.8) over 12 weeks.[2] No significant differences in overall AEs or SAEs for either tofacitinib 5 mg or 10 mg twice daily moderate CoE for all harms).[2]
- ***Guselkumab vs. Adalimumab (3 RCTs; n = 251, n = 663, and n=744):*** Lower incidence of injection-site reactions with guselkumab compared to adalimumab over 16 weeks reported in 2 RCTs (RR 0.7; 95% CI, 0.01 to 0.33 and RR 0.38; 95% CI, 0.19 to 0.74; moderate CoE).[2] No significant differences in AEs, SAEs, or withdrawals due to AEs (moderate CoE for all harms).[2]
- ***Risankizumab vs. Ustekinumab (3 RCTs; n = 166, n = 506, n = 393):*** One RCT reported no significant differences in AEs or SAEs.[2] Two RCTs reported some differences, but not across all time periods evaluated.[2] In one RCT, fewer AEs were observed for risankizumab compared with ustekinumab over 17 to 52 weeks (RR 0.75; 95% CI, 0.11 to 0.77; low CoE).[2] In another RCT, fewer SAEs were observed with risankizumab compared with ustekinumab over 0 to 16 weeks (RR 0.29; 95% CI, 0.11 to 0.66; low CoE).[2]
- ***Tildrakizumab vs. Etanercept (1 RCT):*** Fewer overall AEs for tildrakizumab versus etanercept during weeks 13 to 28 (RR 0.80; 95% CI, 0.68 to 0.93); fewer AEs for the 100 mg tildrakizumab dose, but not the 200 mg dose during weeks 0 to 12 (moderate CoE).[2] No difference in incidence of SAEs during either time period (low CoE).[2]

Data from Cohort Studies

Most of the recent cohort studies evaluated patients receiving TIMs for either PsO or PsA. Only one cohort study evaluated TIMs used to treat PsO and no observational studies focused just on PsA.

- One cohort study (n = 123,383) reported a significantly lower risk of hospitalization for serious infection for ustekinumab compared with adalimumab and infliximab with no difference compared with certolizumab pegol (very low CoE) when used to manage PsO and PsA.[2] Additional data from this study is summarized below.
    - ***Certolizumab pegol vs. Ustekinumab:*** No differences in the incidence of serious infection (HR 1.09; 95% CI, 0.68 to 1.75; very low CoE).[2]
    - ***Infliximab vs. Ustekinumab:*** Higher incidence of serious infection with infliximab (HR 2.3; 95% CI 1.9 to 2.8; very low CoE).[2]
    - ***Ixekizumab vs. Infliximab:*** Lower incidence of serious infection with ixekizumab compared with infliximab (HR 0.46; 95% CI, 0.27 to 0.77; very low CoE).[2]
    - ***Secukinumab vs. Adalimumab:*** Lower incidence of serious infection with secukinumab compared with adalimumab (HR 0.77; 95% CI, 0.62 to 0.96; very low CoE).[2]
    - ***Secukinumab vs. Infliximab:*** Lower incidence of serious infection with secukinumab compared with infliximab (HR 0.53; 95% CI 0.41 to 0.68; very low CoE).[2]
    - ***Ustekinumab vs. Adalimumab:*** Fewer serious infections with ustekinumab compared with adalimumab (HR 0.70; 95% CI, 0.49 to 1.00; very low CoE).[2]
- In another cohort study (n = 11,560), fewer serious infections with ustekinumab (HR 0.59; 95% CI 0.39 to 0.90; very low CoE) compared with TNF inhibitors (adalimumab, certolizumab pegol, etanercept, golimumab, and infliximab) in patients treated for PsO and PsA.[2]
- A French cohort study (n = 44,239) observed that compared with etanercept, the risk for serious infection was increased with adalimumab (HR 1.22; 95% CI, 1.07 to 1.38) and infliximab (HR 1.79; 95% CI, 1.49 to 2.16) and decreased for ustekinumab (HR 0.79; 95% CI, 0.67 to 0.94; very low CoE for all comparisons) when these TIMs were used to treat PsO.[2] In the same study, no statistically significant differences were observed on the outcome of serious infections for etanercept compared with apremilast, brodalumab, certolizumab pegol, guselkumab, ixekizumab, and secukinumab (very low CoE).[2] Additional data from this study is summarized below.
    - ***Certolizumab pegol vs. Ustekinumab:*** Higher incidence of serious infection for certolizumab pegol compared with ustekinumab (HR 1.45; 95% CI, 1.03 to 2.04).[2]
    - ***Apremilast vs. Infliximab:*** Lower incidence of serious infection for apremilast compared with infliximab (HR 0.46; 95% CI, 0.34 to 0.63; very low CoE).[2]
    - ***Certolizumab pegol vs. Infliximab:*** Lower incidence of serious infection for certolizumab pegol compared with infliximab (HR 0.64; 95% CI, 0.46 to 0.91; very low CoE).[2]
    - ***Infliximab vs. Adalimumab:*** Higher incidence of serious infection for infliximab compared with adalimumab (HR 1.47; 95% CI 1.24 to 1.74; very low CoE).[2]
- A prospective, multi-center, Spanish cohort study (n = 3,171) focused on the incidence of hepatic AEs.[2] Compared with TNF inhibitors, a higher incidence of nonalcoholic fatty liver disease was observed for users of ixekizumab or secukinumab (adjusted incidence rate ratio [IRR] 4.16; 95% CI, 1.36 to 12.70) and no difference for users of interleukin (IL)-23 antagonists (guselkumab, risankizumab; low CoE).[2] Overall, no statistically significant differences were reported in liver test abnormalities or overall hepatic AEs for IL-17 antagonists and IL-23 antagonists compared with TNF inhibitors (very low CoE).[2]

C. Comparative Effectiveness of TIMs for Psoriatic Arthritis

Six head-to-head comparisons provided data for the effectiveness of TIMs in PsA.[2] Three RCTs provided new evidence.[2] All studies enrolled patients with active PsA.[2] Two RCTs were rated as high risk of bias for various critical methodological flaws, the rest of the studies had moderate risk of bias because of extensive manufacturer involvement in study design, execution and reporting.[2]

New Evidence

- ***Ixekizumab vs. Adalimumab (1 RCT, n = 566):*** The primary outcome for this RCT was simultaneous ACR50 and PASI 100 at 24 weeks. The proportion of participants achieving clinical improvement was greater in the ixekizumab group compared with the adalimumab group (36% vs. 28%; RR 1.3; 95% CI, 1.01 to 1.60; moderate CoE).[2]
- ***Secukinumab vs. Adalimumab (1 RCT; n = 853):*** No difference in arthritis clinical improvement at 52 weeks (ACR 20: calculated RR 1.1; 95% CI, 0.98 to 1.20).[2] Larger clinical improvement in skin disease with secukinumab compared with adalimumab (PASI 90: calculated RR 1.5; 95% CI, 1.3 to 1.7; moderate CoE for both outcomes).[2]
- ***Upadacitinib vs. Adalimumab (1 RCT; n = 1,281):*** At 12 weeks, a larger proportion of participants showed arthritis improvement with upadacitinib 30 mg compared with adalimumab (ACR 20: 78.5% vs. 65%; calculated RR 1.2; 95% CI, 1.1 to 1.3), but no differences were observed between adalimumab versus upadacitinib 15 mg (moderate CoE).[2]

Previously Reported Evidence

- ***Adalimumab vs. Etanercept or Infliximab (1 RCT; n = 100):*** No difference in ACR20 response at 1 year (adalimumab: 70%; etanercept: 72%; infliximab: 75%; p-value NR; very low CoE).[2]
- ***Adalimumab vs. Tofacitinib 10 mg and 5 mg (1 RCT; n = 422):*** No differences between adalimumab and tofacitinib 10 mg or tofacitinib 5 mg in ACR20 response at 1 year (adalimumab: 60%; tofacitinib 10 mg: 70%; tofacitinib 5 mg: 68%; p-value NR; low CoE).[2]
- ***Ixekizumab vs. Adalimumab (1 RCT; n = 417):*** No difference between adalimumab compared with ixekizumab administered every 2 or 4 weeks in ACR20 response at 24 weeks (adalimumab: 57%; ixekizumab every 2 weeks: 62%; ixekizumab every 4 weeks: 58%; p value NR; low CoE).[2]
- ***Ustekinumab vs. TNF inhibitors (specific TNF inhibitors not reported; 1 RCT; n = 47):*** At 24 weeks, a higher proportion of participants achieved enthesitis remission with ustekinumab compared with TNF inhibitors (Spondyloarthritis Research Consortium of Canada Enthesitis Index [SPARCC EI]: 74% vs 42%; p=0.02; 95% CI NR) and skin disease remission (PASI 100: 50% vs. 29%; p=0.04; 95% CI NR), but not arthritis remission (tender joint count: 54% vs. 46%; p=0.78; swollen joint count: 59% vs. 46%; p=0.38; very low CoE for all outcomes).[2]

D. Comparative Harms of TIMs When Used to Manage Psoriatic Arthritis

All of the RCTs included for efficacy assessment also reported harms observed with TIMs when used to treat PsA.[2] Few differences in harms were observed (very low to moderate CoE) for overall AEs and SAEs.[2] No new cohort studies were identified that just focused on harms of TIMs when used to manage PsA.[2]

New Evidence

- ***Ixekizumab vs. Adalimumab (1 RCT, n = 566):*** Fewer SAEs, but more injection site reactions with ixekizumab versus adalimumab.[2] No statistically significant differences in overall AEs, or withdrawals due to AEs were observed (moderate CoE for all harms).[2]
- ***Secukinumab vs. Adalimumab (1 RCT; n = 853):*** Less withdrawals due to AE reported with secukinumab compared with adalimumab (4% vs. 7%; RR 0.53; 95% CI, 0.30 to 0.94) over 52 weeks. Injection site reactions were also less frequent with secukinumab vs. adalimumab (4% vs. 11%; RR 0.36; 95% CI, 0.21 to 0.62).[2] No statistically significant differences in overall AEs and SAEs were observed (moderate CoE for all harms).[2]

- ***Upadacitinib vs. Adalimumab (1 RCT; n = 1,281):*** More AEs observed with upadacitinib versus adalimumab over 24 weeks (RR 1.1; 95% CI, 1.02 to 1.20; moderate CoE); no difference in SAEs was reported (RR 1.6; 95% CI, 0.9 to 3.0; low CoE).[2]

Previously Reported Evidence

- ***Adalimumab vs. Etanercept or Infliximab (1 RCT; n = 100):*** Fewer AEs were observed with adalimumab versus etanercept (RR 0.38; 95% CI, 0.17 to 0.84); fewer AEs were observed with adalimumab versus infliximab (RR 0.23; 95% CI, 0.11 to 0.49); and more AEs were observed with infliximab versus etanercept over 12 months (RR 1.6; 95% CI, 1.1 to 2.4; very low CoE for all comparisons).[2]
- ***Adalimumab vs. Tofacitinib 10 mg and 5 mg (1 RCT; n = 422):*** No statistically significant differences in AEs, SAEs, or withdrawals due to AEs over 12 months (moderate CoE for all harms).[2]
- ***Ixekizumab vs. Adalimumab (1 RCT; n = 417):*** Injection site reactions were more frequently reported with ixekizumab versus adalimumab (13.9% vs. 2%; RR 0.14; 95% CI, 0.03 to 0.59) over 24 weeks. No statistically significant differences in overall AEs, SAEs, or withdrawals due to AEs (moderate CoE for all harms).[2]

E. Differences In Effectiveness or Harms by Subgroup Analysis

Relevant subgroup analyses were available for 3 comparisons for PsO and 1 comparison for PsA.[2]

- ***Brodalumab vs. Ustekinumab for PsO:*** No differences in comparative efficacy or safety in post hoc subgroup analysis of patients with BMI less than 30 kg/m^2 versus those with BMI 30 kg/m^2 and greater.[2]
- ***Guselkumab vs. Secukinumab for PsO:*** Guselkumab was superior to secukinumab overall and in all subgroups evaluated based on age, weight, BMI, severity of disease, body area affected and prior medication use.[2]
- ***Tildrakizumab vs. Etanercept for PsO:*** No differences in comparative efficacy for participants with metabolic syndrome compared with those without metabolic syndrome.[2]
- ***Ixekizumab vs. Adalimumab for PsA:*** Ixekizuamb was more effective than adalimumab for individuals with and without concomitant use of MTX, although the difference was not statistically significant in concomitant users.[2]

New Indications:

May 2022: Baricitinib (OLUMIANT) received FDA approval for treatment of COVID-19 in hospitalized adults requiring supplemental oxygen, non-invasive or invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO).[4] The recommended dose for COVID-19 is 4 mg orally once daily for up to 14 days.[4] Inpatient treatment is not subject to prior authorization.

June 2022: Baricitinib received expanded FDA-approval for the treatment of adult patients with severe alopecia areata.[4] Alopecia areata is a chronic autoimmune disorder characterized by rapid onset of hair loss, typically on the scalp, eyebrows, and eyelashes.[26] Disorders of the hair and nails are not funded by the Health Evidence Review Commission on line 587.[5]

June 2022: Risankizumab (SKYRIZI) received expanded FDA-approval for treatment of moderately to severely active Crohn's disease in adults.[3] Risankizumab is also approved for treatment of moderate-to-severe PsO and active PsA in adults.[3] For PsO and PsA, risankizumab is initiated at 150 mg SC every 4 weeks for 2 doses, followed by 150 mg SC every 12 weeks thereafter.[3] The risankizumab dosing for Crohn's disease is higher than the recommended dose for psoriasis. For CD, the risankizumab induction dose is 600 mg via IV infusion every 4 weeks for 3 doses. The recommended maintenance dose is 360 mg SC at week 12 after induction is completed, followed by 360 mg SC every 8 weeks thereafter.[3]

Drug induced hepatotoxicity during induction therapy for Crohn's disease with risankizumab has been reported.[3] Therefore, the manufacturer recommends obtaining liver enzymes and bilirubin prior to starting risankizumab and during induction dosing, up to 12 weeks of treatment.[3] During maintenance dosing liver enzymes should monitored according to routine patient management.[3] Other AEs reported during induction dosing for CD included: upper respiratory infections, headache and arthralgia.[3] During maintenance dosing additional AEs included: injection site reactions, abdominal pain, anemia, pyrexia, back pain, and urinary tract infections.[3]

August 2022: Ustekinumab (STELARA) received expanded approval for treatment of children aged 6 years and older with active PsA.[6] Due to the limited availability of pediatric patients with PsA for clinical trials, researchers used an extrapolation strategy based on previous pharmacokinetic, efficacy and safety observations from a closely adjacent population of children with moderate-to-severe PsO who also had active PsA, as well as adults with moderate-to-severe PsO or active PsA.[6] The safety and effectiveness of ustekinumab have not been established in pediatric patients less than 6 years old.[6]

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Appendix 1: Current Preferred Drug List

Generic	Brand	Route	Form	PDL
adalimumab	HUMIRA PEN	SUBCUT	PEN IJ KIT	Y
adalimumab	HUMIRA PEN CROHN'S-UC-HS	SUBCUT	PEN IJ KIT	Y
adalimumab	HUMIRA PEN PSOR-UVEITS-ADOL HS	SUBCUT	PEN IJ KIT	Y
adalimumab	HUMIRA(CF) PEN	SUBCUT	PEN IJ KIT	Y
adalimumab	HUMIRA(CF) PEN CROHN'S-UC-HS	SUBCUT	PEN IJ KIT	Y
adalimumab	HUMIRA(CF) PEN PEDIATRIC UC	SUBCUT	PEN IJ KIT	Y
adalimumab	HUMIRA(CF) PEN PSOR-UV-ADOL HS	SUBCUT	PEN IJ KIT	Y
adalimumab	HUMIRA	SUBCUT	SYRINGEKIT	Y
adalimumab	HUMIRA(CF)	SUBCUT	SYRINGEKIT	Y
adalimumab	HUMIRA(CF) PEDIATRIC CROHN'S	SUBCUT	SYRINGEKIT	Y
etanercept	ENBREL MINI	SUBCUT	CARTRIDGE	Y
etanercept	ENBREL SURECLICK	SUBCUT	PEN INJCTR	Y
etanercept	ENBREL	SUBCUT	SYRINGE	Y
etanercept	ENBREL	SUBCUT	VIAL	Y
secukinumab	COSENTYX PEN	SUBCUT	PEN INJCTR	Y
secukinumab	COSENTYX PEN (2 PENS)	SUBCUT	PEN INJCTR	Y
secukinumab	COSENTYX (2 SYRINGES)	SUBCUT	SYRINGE	Y
secukinumab	COSENTYX SYRINGE	SUBCUT	SYRINGE	Y
abatacept	ORENCIA CLICKJECT	SUBCUT	AUTO INJCT	N
abatacept	ORENCIA	SUBCUT	SYRINGE	N
abatacept/maltose	ORENCIA	INTRAVEN	VIAL	N
anakinra	KINERET	SUBCUT	SYRINGE	N
apremilast	OTEZLA	ORAL	TAB DS PK	N
apremilast	OTEZLA	ORAL	TABLET	N
baricitinib	OLUMIANT	ORAL	TABLET	N
brodalumab	SILIQ	SUBCUT	SYRINGE	N
canakinumab/PF	ILARIS	SUBCUT	VIAL	N
certolizumab pegol	CIMZIA	SUBCUT	KIT	N
certolizumab pegol	CIMZIA	SUBCUT	SYRINGEKIT	N
golimumab	SIMPONI ARIA	INTRAVEN	VIAL	N
golimumab	SIMPONI	SUBCUT	PEN INJCTR	N
golimumab	SIMPONI	SUBCUT	SYRINGE	N
guselkumab	TREMFYA	SUBCUT	AUTO INJCT	N
guselkumab	TREMFYA	SUBCUT	SYRINGE	N
infliximab	INFLIXIMAB	INTRAVEN	VIAL	N
infliximab	REMICADE	INTRAVEN	VIAL	N
infliximab-abda	RENFLEXIS	INTRAVEN	VIAL	N
infliximab-axxq	AVSOLA	INTRAVEN	VIAL	N

infliximab-dyyb	INFLECTRA	INTRAVEN	VIAL	N
ixekizumab	TALTZ AUTOINJECTOR	SUBCUT	AUTO INJCT	N
ixekizumab	TALTZ AUTOINJECTOR (2 PACK)	SUBCUT	AUTO INJCT	N
ixekizumab	TALTZ AUTOINJECTOR (3 PACK)	SUBCUT	AUTO INJCT	N
ixekizumab	TALTZ SYRINGE	SUBCUT	SYRINGE	N
natalizumab	TYSABRI	INTRAVEN	VIAL	N
risankizumab-rzaa	SKYRIZI PEN	SUBCUT	PEN INJCTR	N
risankizumab-rzaa	SKYRIZI	SUBCUT	SYRINGE	N
risankizumab-rzaa	SKYRIZI (2 SYRINGES) KIT	SUBCUT	SYRINGEKIT	N
rituximab	RITUXAN	INTRAVEN	VIAL	N
rituximab-abbs	TRUXIMA	INTRAVEN	VIAL	N
rituximab-arrx	RIABNI	INTRAVEN	VIAL	N
rituximab-pvvr	RUXIENCE	INTRAVEN	VIAL	N
sarilumab	KEVZARA	SUBCUT	PEN INJCTR	N
sarilumab	KEVZARA	SUBCUT	SYRINGE	N
tildrakizumab-asmn	ILUMYA	SUBCUT	SYRINGE	N
tocilizumab	ACTEMRA	INTRAVEN	VIAL	N
tocilizumab	ACTEMRA ACTPEN	SUBCUT	PEN INJCTR	N
tocilizumab	ACTEMRA	SUBCUT	SYRINGE	N
tofacitinib citrate	XELJANZ	ORAL	SOLUTION	N
tofacitinib citrate	XELJANZ XR	ORAL	TAB ER 24H	N
tofacitinib citrate	XELJANZ	ORAL	TABLET	N
upadacitinib	RINVOQ	ORAL	TAB ER 24H	N
ustekinumab	STELARA	INTRAVEN	VIAL	N
ustekinumab	STELARA	SUBCUT	SYRINGE	N
ustekinumab	STELARA	SUBCUT	VIAL	N
vedolizumab	ENTYVIO	INTRAVEN	VIAL	N

Appendix 2: Selected Outcomes Used for Assessment of Disease Progression in Clinical Trials[27,28]

Ankylosing Spondylitis		
Outcome Measure	**Domains**	**Scale and Scoring**
Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) BASDI 50	Level of symptoms: 1. Fatigue 2. Pain in hips, back and neck 3. Pain in joints other than hips, back or neck 4. Discomfort in areas tender to touch or pressure Mean measurements of: 5. Intensity of morning stiffness 6. Duration of morning stiffness (0 to 2 hours scored on a 0-10 scale) • ≥ 50% improvement in BASDAI	VAS scale 0-10: 0 is no symptoms, 10 is very severe BASADI score calculation: 1.Add scores for first 4 questions 2. Add one half of the sum of question 5 and 6 3. Divide the result by 5 A BASDI score ≥ 4 (on a scale of 0-10) indicates active disease that warrants consideration of therapy
Bath Ankylosing Spondylitis Functional Index (BASFI)	Severity of 10 functional abilities: 1. Putting on socks 2. Bend from the waist to pick up a pen from the floor 3. Reaching up to a high shelf 4. Getting up from an armless chair 5. Getting up off the floor 6. Standing unsupported 7. Climbing 12-15 steps unaided 8. Looking over shoulder 9. Doing physically demanding activities 10. Doing a full day's activities	VAS scale 0-10: easy (0) to impossible (10) BASFI score calculation: Total all 10 items and divide by 10 for final score Reported as change in score from baseline
Assessment of Spondyloarthritis International Society (ASAS) Response ASAS 20 ASAS 40 ASAS Partial Remission	Combines measures of symptoms and disability in 4 disease measures: 1. Spinal inflammation (BASDI questions 5 and 6) 2. Spinal pain 3. Patient global assessment of spondylitis 4. Functional impairment (BASFI score) • Improvement of ≥ 20% and ≥ 1 unit in ≥ 3 of disease measures above • No worsening of ≥ 20% and ≥ 1 unit in remaining unimproved measure • Improvement of ≥ 40% and ≥ 2 units in ≥ 3 of disease measures above • No worsening at all in remaining measure	Scale of 0-10: 0 is no symptoms, 10 is very severe Assessment of response to therapy by percent in symptom improvement Value of ≤ 2 in each of the 4 domains

	• Reflects low disease activity	
Ankylosing Spondylitis Disease Activity Score (ASDAS)	Measures severity of symptoms and signs of inflammation including: 1. Back pain 2. Patient global assessment of spondylitis 3. Peripheral pain and swelling (BASDAI score) 4. Duration of morning stiffness (BASDI score) 5. CRP or ESR	Scale of 0-10: 0 is no symptoms, 10 is very severe ASDAS scores: < 1.3 – Inactive Disease 1.4 to 2.1 – Moderate Disease Activity 2.2 to 3.4 – High Disease Activity >3.5 – Very High Disease Activity Improvement Criteria: Change ≥ 1.1 – Clinically Important Improvement Change ≥ 2.0 – Major Improvement
Rheumatoid Arthritis		
Outcome Measure	**Domains**	**Scale and Scoring**
Disease Activity Score (DAS)-28	Clinical assessment of disease activity in combination with an acute phase reactant level 1. Assessment of 28 joints for swelling and tenderness - swollen joint count (SJC) - tender joint count (TJC) 2. General health (GH) - patient assessment of disease on a 0-100 scale where 100 means maximal disease activity 3. Either ESR or CRP adjusted with SJC and TJC scores	DAS-28 scoring ranges from 0 to 9.4: <2.6: Remission ≥2.6 and ≤3.2: Low Disease Activity >3.2 and ≤5.1: Moderate Disease Activity >5.1: High disease activity • DAS-28 reduction by 0.6 represents a moderate improvement. • DAS-28 reduction more than 1.2 represents a major improvement.
Health Assessment Questionnaire Disability Index (HAQ-DI)	Assess 8 domains of daily activity – patient self-reported 1. Dressing and Grooming 2. Arising 3. Eating 4. Walking 5. Hygiene 6. Reach 7. Grip 8. Chores or Activities	Scored 0 to 3: 0 - no difficulty 1 - with some difficulty 2- with much difficulty 3 - unable to do HAQ-DI calculation: Sum of all domains then divided by 8 to give total score ranging from 0 (best) to 3 (worst)
CDAI (Clinical Disease Activity Index)	A clinical composite index composed of the sum of: • Swollen joint count (0-28) • Tender joint count (0-28) • Patient's global score of disease activity (0-10) • Investigator's global score (0-10)	0 to 76, lower scores are better CDAI remission ≤ 2.8

American College of Rheumatology (ACR)
 	
ACR 20
 	
ACR 50
 	
ACR 70
	Definition of improvement in RA symptoms
	
	• 20% improvement in tender and swollen joint counts
	• 20% improvement in 3 of 5 remaining ACR core set measures
	  ○ patient global assessment (VAS score)
	  ○ physician global assessment (VAS score)
	  ○ self-reported physical disability (HAQ score)
	  ○ an acute phase reactant (ESR or CRP)
	  ○ patient pain assessment (VAS score)
	
	• 50% improvement in tender and swollen joint counts
	• 50% improvement in 3 of 5 remaining ACR core set measures
	
	• 70% improvement in tender and swollen joint counts
	• 70% improvement in 3 of 5 remaining ACR core set measures
		
		20% improvement
		
		50% improvement
		
		70% improvement

European League Against Rheumatism (EULAR)	• 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 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 other DAS28 > 5.1 (high disease activity).	Lower is better
Simplified Disease Activity Index (SDAI)	A sum of 5 outcome parameters • Tender and swollen joint count • Patient and physician global assessment of disease activity and level of C-reactive protein) used to monitor activity	0 to 86, lower is better
Short Form 36 (SF-36)	Measure of general level of well-being, consists of 8 domains reflecting 8 dimensions of life: • Physical functioning • Physical role • Bodily pain • General health • Vitality • Social functioning • Emotional role • Mental health	0 to 100, higher is better
Plaque Psoriasis and Psoriatic Arthritis		
Outcome Measure	**Domains**	**Scale and Scoring**

Static Physician's Global Assessment Scale (sPGA)	The static PGA is a 0-5 ordinal rating ranging from "clear" to "very severe psoriasis" as evaluated by the provider	Scale of 0 – 5: 0 = clear; scores 1–5 = increasing severity Response to therapy indicated by a score of 0 or 1
Psoriasis Symptom Inventory (PSI)	Patient reported outcome in 8 areas: 1. Itch 2. Redness 3. Scaling 4. Burning 5. Cracking 6. Stinging 7. Flaking 8. Pain of Lesions	Scale of 0-4: 0 = not at all severe, 1 = mild, 2 = moderate, 3 = severe, and 4 = very severe Score ranges from 0 – 32 Response to therapy indicated by scores < 8 with no single item rated higher than 1
Psoriasis Area and Severity Index (PASI) PASI 75 PASI 90	Measure of overall psoriasis severity and coverage on head, upper extremities, trunk and lower extremities • Erythema • Induration • Scaling 75% Improvement in PASI score 90% Improvement in PASI score – clear or almost clear skin	Scale of 0-4: 0 is clear, 1-4 increasing severity PASI score: 1. Sum rows 1, 2, and 3 for each area of the body using 0-4 scale 2. Add an area score based on percentage involvement from 0 (clear) to 6 (≥90% coverage) 3. Multiply score as rated for each body area (0.1, 0.2, 0.3, 0.4 for head, arms, trunk, and legs, respectively) 4. Add all the scores together Composite score ranges from 0 -72: 0 = normal 72 = maximal disease
PsA Response Criteria (PsARC)	Used by the National Institute of Health Care Excellence (NICE) to continue TNF inhibitor therapy with an assessment at baseline and 12 weeks 1. 66 swollen joint score 2. 68 tender joint score 3. Patient global assessment 4. Physician global assessment	**Response** = improvement in ≥ 2 of the 4 tests: -One of which must be the joint tenderness or swelling score -No worsening in any of the four measures • **Improvement** is defined as a decrease ≥ 30% in the swollen or tender joint score and ≥1 in either of the global assessments

Dermatology Quality of Life (DQLI)	10 question patient self-reported assessment 1. How itchy has your skin been? 2. How embarrassed are because of your skin? 3. Has your skin interfered with activities? 4. Has your skin influenced the clothes you wear/ 5. Has your skin affected social activities? 6. How your skin impacted your ability to participate in a sport? 7. Has your skin prevented you from working? 8. Has your skin caused any problems with friends? 9. Has your skin impacted sexual activities? 10. How much has the treatment for your skin affected your daily activities?	Scale of 0-3: 0 not at all, 1 a little, 2 a lot, and 3 very much Interpretation of DQLI score: 0 – 1 no effect at all on patient's life 2 – 5 small effect on patient's life 6 – 10 moderate effect on patient's life 11 – 20 very large effect on patient's life 21 – 30 extremely large effect on patient's life
Abbreviations: CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; VAS = visual analog scale		

Targeted Immune Modulators for Autoimmune Conditions

Goal(s):

- Restrict use of targeted immune modulators to OHP-funded conditions and according to OHP guidelines for use.
- Promote use that is consistent with national clinical practice guidelines and medical evidence.
- Promote use of cost-effective products.

Length of Authorization:

- Up to 12 months

Requires PA:

- All targeted immune modulators for autoimmune conditions (both pharmacy and physician-administered claims)

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Table 1. Approved and Funded Indications for Targeted Immune Modulators

Drug Name	Ankylosing Spondylitis	Crohn's Disease	Juvenile Idiopathic Arthritis	Plaque Psoriasis	Psoriatic Arthritis	Rheumatoid Arthritis	Ulcerative Colitis	Atopic Dermatitis	Other
Abatacept (ORENCIA)			≥2 yo		≥18 yo	≥18 yo			aGVHD ≥ 2 yo
Adalimumab (HUMIRA) and biosimilars	≥18 y	≥6 yo (Humira) ≥18 yo (biosimilars)	≥2 yo (Humira) ≥4 yo (biosimilars)	≥18 yo	≥18 yo	≥18 yo	≥5 yo (Humira) ≥18 yo (biosimilars)		Uveitis (non-infectious) ≥2 yo (Humira) HS ≥ 12 yo
Anakinra (KINERET)						≥18 yo			NOMID DIRA
Apremilast (OTEZLA)				≥18 yo	≥18 yo				Oral Ulcers associated with BD ≥ 18 yo
Baricitinib (OLUMIANT)						≥18 yo			COVID ≥ 18 yo (hospitalized) Severe alopecia areata is unfunded; coverage may be considered

Drug Name	Ankylosing Spondylitis	Crohn's Disease	Juvenile Idiopathic Arthritis	Plaque Psoriasis	Psoriatic Arthritis	Rheumatoid Arthritis	Ulcerative Colitis	Atopic Dermatitis	Other
									under comorbidity rule
Brodalumab (SILIQ)				≥18 yo					
Canakinumab (ILARIS)			≥2 yo						FCAS ≥4 yo MWS ≥4 yo TRAPS ≥ 4 yo HIDS ≥ 4 yo MKD ≥ 4 yo FMF ≥ 4 yo Stills Disease
Certolizumab (CIMZIA)	≥18 yo	≥18 yo		≥18 yo	≥18 yo	≥18 yo			Nr-axSpA ≥ 18 yo
Etanercept (ENBREL) and biosimilars	≥18 yo		≥2 yo	≥4 yo (Enbrel) ≥4 yo (biosimilars)	≥18 yo	≥18 yo			
Golimumab (SIMPONI and SIMPONI ARIA)	≥18 yo		≥2 yo active polyarticular course		≥2 yo	≥18 yo	≥18 yo (Simponi)		
Guselkumab (TREMFYA)				≥18 yo	≥18 yo				
Infliximab (REMICADE) and biosimilars	≥18 yo	≥6 yo		≥18 yo	≥18 yo	≥18 yo	≥6 yo		
Ixekizumab (TALTZ)	≥ 18 yo			≥6 yo	≥18 yo				Nr-axSpA ≥ 18 yo
Risankizumab-rzaa (SKYRIZI)		≥18 yo		≥18 yo	≥ 18 yo				
Rituximab (RITUXAN) and biosimilars						≥18 yo			CLL ≥18 yo DLBCL≥6 mo BL≥6 mo BLL≥6 mo B-AL≥6 mo NHL ≥18 yo GPA ≥2yo MPA ≥ 2 yo Pemphigus Vulgaris ≥18 yo (Rituxan only)
Sarilumab (KEVZARA)						≥18 yo			
Secukinumab (COSENTYX)	≥18 yo			≥6 yo	≥2 yo				ERA ≥ 4 yo Nr-AxSpA ≥18 yo

Drug Name	Ankylosing Spondylitis	Crohn's Disease	Juvenile Idiopathic Arthritis	Plaque Psoriasis	Psoriatic Arthritis	Rheumatoid Arthritis	Ulcerative Colitis	Atopic Dermatitis	Other
Tildrakizumab-asmn (ILUMYA)				≥18 yo					
Tocilizumab (ACTEMRA)			≥2 yo			≥18 yo			CRS ≥2 yo GCA ≥18 yo SSc-ILD ≥18 yo
Tofacitinib (XELJANZ)	≥18 yo		≥2 yo active polyarticular course		≥18 yo	≥18 yo	≥18 yo		
Upadacitinib (RINVOQ)	≥18 yo				≥18 yo	≥18 yo	≥18 yo	≥ 12 yo	
Ustekinumab (STELARA)		≥ 18 yo		≥6 yo	≥6 yo		≥18 yo		
Vedolizumab (ENTYVIO)		≥18 yo					≥18 yo		

Abbreviations: aGVHD = acute Graft Versus Host Disease; BD = Behcet's Disease; BL = Burkitt Lymphoma; BLL = Burkitt-like Lymphoma; B-AL = mature B-cell acute leukemia; CLL = Chronic Lymphocytic Leukemia; COVID = Covid-19 infection; CRS = Cytokine Release Syndrome; DIRA = Deficiency of Interleukin-1 Receptor Antagonist; DLBCL = Diffuse Large B-Cell Lymphoma; ERA = Enthesitis-Related Arthritis; FCAS = Familial Cold Autoinflammatory Syndrome; FMF = Familial Mediterranean Fever; GCA = Giant Cell Arteritis; GPA = Granulomatosis with Polyangiitis (Wegener's Granulomatosis); HIDS: Hyperimmunoglobulin D Syndrome; HS: Hidradenitis Suppurativa; MKD = Mevalonate Kinase Deficiency; mo = months old; MPA = Microscopic Polyangiitis; MWS = Muckle-Wells Syndrome; NHL = Non-Hodgkin's Lymphoma; NOMID = Neonatal Onset Multi-Systemic Inflammatory Disease; Nr-axSpA = Non-Radiographic Axial Spondyloarthritis; SSc-ILD = Systemic Sclerosis-Associated Interstitial Lung Disease; TRAPS = Tumor Necrosis Factor Receptor Associated Periodic Syndrome; yo = years old.

Approval Criteria		
1. What diagnosis is being treated?	Record ICD-10 code.	
2. Is the diagnosis funded by OHP? Notes: A. Mild-to-moderate psoriasis is unfunded, severe psoriasis is funded. B. Mild Hidradenitis Suppurativa (HS) is unfunded, moderate-to-severe HS (e.g., Hurley Stage II or III) is funded. C. Alopecia areata is unfunded.	**Yes:** Go to # 3	**No:** Pass to RPh. Deny; not funded by the OHP.

Approval Criteria		
3. Has the patient been annually screened for latent or active tuberculosis and if positive, started tuberculosis treatment?* *(Note: this requirement does not apply to requests for apremilast.)	**Yes:** Go to # 4	**No:** Pass to RPh. Deny; medical appropriateness. If patient meets all other criteria, pharmacist may approve once for up to 3 months to allow time for screening for ongoing therapy to avoid interruptions in care.
4. Is this a request for continuation of therapy?	**Yes**: Go to **Renewal Criteria**	**No:** Go to # 5
5. Is the request for a non-preferred product and will the prescriber consider a change to a preferred product? <u>Message</u>: • Preferred products are reviewed for comparative effectiveness and safety by the Oregon Pharmacy and Therapeutics Committee.	**Yes:** Inform prescriber of preferred alternatives. Go to #6	**No:** Go to # 6
6. Is the request for a FDA-approved medication with a corresponding diagnosis listed in the “Other” column of table 1?	**Yes:** Approve for length of treatment.	**No:** Go to # 7
7. Is the diagnosis ankylosing spondylitis and the request for a drug FDA-approved for this condition as defined in Table 1?	**Yes:** Go to # 8	**No:** Go to # 9

Approval Criteria		
8. Is this a request for a preferred agent OR if the request is for a non-preferred agent, has the patient failed to respond or had inadequate response to a Humira® branded product or an Enbrel® branded product after a trial of at least 3 months?	**Yes:** Approve for up to 6 months. Document therapy with dates.	**No:** Pass to RPh. Deny; medical appropriateness.
9. Is the diagnosis plaque psoriasis and the request for a drug FDA-approved for this condition as defined in Table 1? Note: Only treatment for *severe* plaque psoriasis is funded by the OHP.	**Yes:** Go to # 10	**No**: Go to #12
10. Is the plaque psoriasis severe in nature, which has resulted in functional impairment as indicated by Dermatology Life Quality Index (DLQI) ≥ 11 or Children's Dermatology Life Quality Index (CDLQI) ≥ 13 (or severe score on other validated tool) AND one or more of the following: • At least 10% body surface area involvement; OR • Hand, foot, face, or mucous membrane involvement?	**Yes:** Go to # 11	**No:** Pass to RPh. Deny; not funded by the OHP.

Approval Criteria		
11. Has the patient failed to respond or had inadequate response to each of the following first-line treatments: • Topical high potency corticosteroid (e.g., betamethasone dipropionate 0.05%, clobetasol propionate 0.05%, fluocinonide 0.05%, halcinonide 0.1%, halobetasol propionate 0.05%; triamcinolone 0.5%); AND • At least one other topical agent: calcipotriene, tazarotene, anthralin; AND • Phototherapy; AND • At least one other systemic therapy: acitretin, cyclosporine, or methotrexate; AND • One biologic agent: either a Humira® product or an Enbrel® product for at least 3 months?	**Yes**: Approve for up to 6 months. Document each therapy with dates.	**No:** Pass to RPh. Deny; medical appropriateness.
12. Is the request for a drug FDA-approved for atopic dermatitis as defined in Table 1? Note: only *severe* atopic dermatitis is funded by the OHP.	**Yes:** Go to # 13	**No**: Go to #15
13. Is the atopic dermatitis severe in nature, which has resulted in functional impairment as indicated by Dermatology Life Quality Index (DLQI) ≥ 11 or Children's Dermatology Life Quality Index (CDLQI) ≥ 13 (or severe score on other validated tool) AND one or more of the following: • At least 10% body surface area involvement; or • Hand and, foot, face, or mucous membrane involvement?	**Yes:** Go to # 14	**No:** Pass to RPh. Deny; not funded by the OHP.

Approval Criteria		
14. Does the patient have a documented contraindication or failed trial of the following treatments: • Moderate to high potency topical corticosteroid (e.g., clobetasol, desoximetasone, desonide, mometasone, betamethasone, halobetasol, fluticasone, or fluocinonide), AND • Topical calcineurin inhibitor (tacrolimus, pimecrolimus) or topical phosphodiesterase (PDE)-4 inhibitor (crisaborole), AND • Oral immunomodulator therapy (cyclosporine, methotrexate, azathioprine, mycophenolate mofetil, or oral corticosteroids)?	**Yes**: Document drug and dates trialed and intolerances (if applicable): 1._____(dates) 2._____(dates) 3._____(dates) Approve for length of treatment; maximum 6 months.	**No**: Pass to RPh. Deny; medical appropriateness
15. Is the diagnosis rheumatoid arthritis, juvenile idiopathic arthritis, or psoriatic arthritis and the request for a drug FDA-approved for these conditions as defined in Table 1?	**Yes:** Go to # 16	**No:** Go to # 19

Approval Criteria		
16. Has the patient failed to respond or had inadequate response to at least one of the following medications: • Methotrexate, leflunomide, sulfasalazine or hydroxychloroquine for ≥ 6 months; OR • Have a documented intolerance or contraindication to disease-modifying antirheumatic drugs (DMARDs)? AND • Had treatment failure with at least one biologic agent: a Humira® branded product or an Enbrel® branded product for at least 3 months? AND • Is the patient on concurrent DMARD therapy with plans to continue concomitant use?	**Yes:** Go to # 17 Document each therapy with dates. If applicable, document intolerance or contraindication(s).	**No:** Pass to RPh. Deny; medical appropriateness. Biologic therapy is recommended in combination with DMARDs (e.g. methotrexate) for those who have had inadequate response with DMARDs.
17. Is the request for tofacitinib, baricitinib, or upadacitinib?	**Yes:** Go to # 18	**No:** Approve for up to 6 months
18. Is the patient currently on other biologic therapy or on a potent immunosuppressant like azathioprine, tacrolimus OR cyclosporine? Note: Tofacitinib, baricitinib, and upadacitinib may be used concurrently with methotrexate or other nonbiologic DMARD drugs. Tofacitinib, baricitinib, or upadacitinib are not recommended to be used in combination with other JAK inhibitors, biologic DMARDs, azathioprine, or cyclosporine.	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Approve baricitinib or upadacitinib for up to 6 months. Approve tofacitinib for up to 6 months at a maximum dose of 10 or 11 mg daily for Rheumatoid Arthritis OR 10 mg twice daily for 8 weeks then 5 or 10 mg twice daily for Ulcerative Colitis
19. Is the request for adalimumab in an adult with moderate-to-severe Hidradenitis Suppurativa (HS)?	**Yes:** Go to # 20	**No:** Go to # 21

Approval Criteria		
20. Has the patient failed to respond, had inadequate response, or do they have an intolerance or contraindication to a 90-day trial of conventional HS therapy (e.g. oral antibiotics)? Note: Treatment of moderate-to-severe HS with adalimumab is funded on the Prioritized List of Health Services per Guideline Note 198.	**Yes:** Approve for up to 12 weeks of therapy	**No:** Pass to RPh. Deny; medical appropriateness**.**
21. Is the diagnosis Crohn's disease or ulcerative colitis and the request for a drug FDA-approved for these conditions as defined in Table 1?	**Yes:** Go to # 22	**No:** Go to # 24
22. Has the patient failed to respond or had inadequate response to at least one of the following conventional immunosuppressive therapies for ≥6 months: • Mercaptopurine, azathioprine, or budesonide; or • Have a documented intolerance or contraindication to conventional therapy?	**Yes:** Go to #23	**No:** Pass to RPh. Deny; medical appropriateness.
23. Is the request for risankizumab?	**Yes:** Go to #24	**No:** Go to # 25
24. Have baseline liver enzymes and bilirubin been obtained?	**Yes:** Go to #25 Document Labs and Date Obtained: LFTs: _____ Bilirubin:_____	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
25. Is the request for a preferred product or has the patient tried and failed a 3-month trial of a Humira® product?	**Yes:** Approve for up to 12 months. Document each therapy with dates. If applicable, document intolerance or contraindication(s).	**No:** Pass to RPh. Deny; medical appropriateness.
26. Is the diagnosis for an FDA approved diagnosis and age as outlined in Table 1, and is the requested drug rituximab for *induction or maintenance* of remission?	**Yes:** Approve for length of treatment.	**No:** Pass to RPh. Deny; medical appropriateness.

Renewal Criteria		
1. Is the request for treatment of psoriatic arthritis, plaque psoriasis, ulcerative colitis, Crohn's disease, or rheumatoid arthritis?	**Yes:** Go to # 6	**No:** Go to # 2
2. Is the request to renew therapy for atopic dermatitis?	**Yes:** Go to #3	**No:** Go to #4

Renewal Criteria		
3. Have the patient's symptoms improved with upadacitinib therapy? • at least a 50% reduction in the Eczema Area and Severity Index score (EASI 50) from when treatment started, OR • at least a 4-point reduction in the Dermatology Life Quality Index (DLQI) from when treatment started, OR • at least a 2-point improvement on the Investigators Global Assessment (IGA) score?	**Yes:** Approve for 12 months	**No:** Pass to RPh. Deny; medical appropriateness.
4. Is the request for continuation of adalimumab to treat moderate-to-severe Hidradenitis Suppurativa in an adult?	**Yes:** Go to # 5	**No:** Go to # 6
5. Has the patient had clear evidence of response to adalimumab therapy as evidenced by: • a reduction of 25% or more in the total abscess and inflammatory nodule count, AND • no increase in abscesses and draining fistulas.	**Yes:** Approve for an additional 12 weeks of therapy	**No:** Pass to RPh. Deny; medical appropriateness.
6. Has the patient been adherent to both biologic and DMARD therapy (if DMARD therapy has been prescribed in conjunction with the biologic therapy)?	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical appropriateness.
7. Has the patient's condition improved as assessed by the prescribing provider and provider attests to patient's improvement.	**Yes:** Approve for 6 months. Document baseline assessment and provider attestation received.	**No:** Pass to RPh; Deny; medical appropriateness.

Implementation: *1/1/23; 7/1/22; 1/1/22; 1/1/2021; 7/1/2019; 3/1/19; 3/1/18; 9/1/17; 1/1/17; 9/27/14; 2/2*