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OHSU Drug Effectiveness Review Project Summary Report – Targeted Immune Modulators for Autoimmune Conditions

Date of Review: October 2020

Date of Last Review: February 2020
Literature Search: 1/1/20 – 6/28/20

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

Purpose: New comparative evidence for existing biologics for autoimmune conditions will be reviewed as presented in 3 Drug Effectiveness Review Project (DERP) systematic reviews focused on safety and efficacy of targeted immune modulators (TIMS) to treat ankylosing spondylitis (AS), rheumatoid arthritis (RA), plaque psoriasis (PsO), psoriatic arthritis (PsA), Crohn's disease (CD), and ulcerative colitis (UC).

Research Questions:
1. What is the comparative effectiveness of TIMs for alleviating symptoms and stabilizing disease in patients with RA, AS, PsO, PsA, CD and UC?
2. What are the comparative harms of TIMs when used to treat RA, AS, PsO, PsA, CD, and UC?
3. Do the included drugs differ in their effectiveness or harms in the following subgroups: age and racial groups, gender, patients with comorbidities, patients taking other commonly prescribed drugs, or in patients with early vs. established disease?

Conclusions:
Targeted Immune Modulators for Rheumatoid Arthritis and Ankylosing Spondylitis
- Most comparisons for the safety and efficacy of TIMs in RA are limited to single trials.[1] Moderate- or high-quality of evidence (QoE) indicates that baricitinib, sarilumab, and upadacitinib are more effective than adalimumab as first-line treatments for RA.[1] In a fair-quality, multi-center, double-blind randomized clinical trial (RCT) comparing adalimumab with baricitinib (n=1,305), adalimumab was less effective than baricitinib for achieving response American College of Rheumatology (ACR) response (ACR20, 61% vs. 70%; P=0.01) and improvements in functional capacity (Health Assessment Questionnaire-Disability Index [HAQ-DI] of ≥ 0.22, 58% vs. 68%; P<0.01; high QoE at 52 weeks).[1] In a fair-quality head-to-head comparison of adalimumab versus sarilumab (n=369), adalimumab was less effective than sarilumab for achieving response (ACR50, 30% vs. 46%; P=0.002) and improvements in functional capacity (HAQ-DI, −0.43 vs. −0.61; p<0.005) at 24 weeks (moderate QoE).[1] When adalimumab was compared to upadacitinib in a fair-quality, double-blinded RCT (n=1,629), adalimumab was less effective than upadacitinib for achieving response (ACR50, 29% vs. 45%; P<0.001), remission (28 joint Disease Activity Score [DAS-28] <2.6, 18% vs. 21%; P<0.001), and improvements in functional capacity (HAQ-DI, −0.49 vs. −0.60; P<0.01) at 12 weeks (high QoE for response and remission).[1]
- Moderate QoE shows abatacept is more effective than secukinumab as a second-line treatment for RA.[1] In a fair quality, multi-center, double-blind RCT comparing abatacept versus secukinumab (n=551), abatacept was more effective than secukinumab 150 mg or secukinumab 75 mg for achieving response (ACR50, 28% vs. 17% vs. 12%; P-value NR) and improved functional capacity (HAQ-DI, −0.6 vs. −0.4 vs. −0.3; P-value NR) at 24 weeks (moderate QoE for clinical improvement).[1]

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- One head-to-head trial provided evidence for comparative effectiveness of TIMs in AS.[1] In this trial, etanercept was less effective for clinical improvement than infliximab at 12 weeks based on the Bath Ankylosing Spondylitis Disease Activity Index [BASDI] (5.9 vs. 4.8; P<0.005; very low QoE).[1]
- Data published in 8 trials show 2 pipeline oral Janus kinase (JAK) inhibitors (filgotinib and peficitinib), have superior efficacy compared to placebo in treating RA.[1] In a phase 3 randomized controlled trial (RCT), filgotinib was more effective than placebo at 12 weeks for achieving response to therapy (ACR 20, 66% vs. 31%; p<0.001) and disease remission DAS28-Erythrocyte Sedimentation Rate (ESR), 31% vs. 12%; p<0.001; high QoE for both outcomes).[1] Another phase 3 RCT showed that at 12 weeks, peficitinib was more efficacious than placebo for achieving response in patients with moderate-to-severe RA (ACR20, 64% vs. 22%; P<0.001) and remission (DAS28-ESR < 2.6, 35% vs. 8%; p<0.001) at 12 weeks (moderate QoE for both outcomes).[1]
- One fair-quality RCT demonstrated the superior efficacy of filgotinib over placebo for the treatment of AS.[1] Participants treated with filgotinib improved based on the Ankylosing Spondylitis Disease Activity Score (ASDAS) compared to placebo (−1.47 vs.−0.57; difference between groups, -0.85; 95% Confidence Interval [CI]-1.17 to -0.53; P<0.001; moderate QoE).[1]
- High- and moderate- QoE has shown no difference in the incidence of overall adverse effects (AEs) and serious adverse effects (SAEs) with TIMs used to manage RA or AS.[1] Most observational studies reported no significant differences in mortality, malignancies, cardiovascular events or congestive heart failure between TIMs.[1] However, in most studies, infliximab was associated with a higher incidence of serious infections than other TIM agents.[1] Some studies also showed a higher incidence of opportunistic infections, tuberculosis, and varicella zoster infections with infliximab than with other tumor necrosis factor (TNF)-inhibitors.[1] Two observational studies reported a higher incidence of gastrointestinal perforations with tocilizumab than with TNF-inhibitors.[1]
- The combination of TNF-inhibitors with a TIM of a different mechanism of action substantially increased the frequency of SAEs.[1] For example, the combination of etanercept with abatacept or anakinra resulted in more SAEs compared to etanercept monotherapy (11% vs. 3%; RR, 5.93; 95% CI, 0.81 to 43.42; moderate QoE).[1] Abatacept plus another TIM (adalimumab, anakinra, etanercept, or infliximab) resulted in more SAEs compared to another TIM alone (22% vs. 13%; RR, 1.79; 95% CI, 0.85 to 3.75; low QoE).[1]

Targeted Immune Modulators for Plaque Psoriasis and Psoriatic Arthritis

- The largest body of comparative evidence for PsO with TIM agents is for etanercept and ustekinumab.[2] For disease remission outcomes, high QoE shows that etanercept is less effective than ixekizumab, secukinumab, and tildrakizumab.[2] Two fair-quality RCTs: UNCOVER-2 (n=1,224) and UNCOVER-3 (n=1,346) compared etanercept to ixekizumab and found etanercept was less effective than ixekizumab for achieving disease remission at 12 weeks (Psoriasis Area and Severity Index [PASI] 75: Absolute Risk Differences [ARDs], 31% to 48% for both RCTs; P-value not reported (NR); high QoE).[2] In a fair-quality head to head RCT comparing etanercept to secukinumab (n=1,306), etanercept was less effective than secukinumab for achieving disease remission at 12 weeks (PASI 75: 44% vs. 77% for 300 mg secukinumab; P<0.001 and 44% vs. 67% for 150 mg secukinumab; P<0.001; high QoE).[2] In a fair-quality RCT comparing etanercept versus tildrakizumab (n=934), etanercept was less effective than tildrakizumab for disease remission at 12 weeks (PASI 75: 48% vs. 66% for 200 mg tildrakizumab; P=0.001 and 48% vs. 61% for 100 mg tildrakizumab; P<0.001; high QoE).[2]
- High QoE also shows that ustekinumab is less effective than brodalumab and risankizumab; moderate QoE shows it may also be less effective than ixekizumab for disease remission outcomes.[2] High QoE shows that adalimumab is less effective than guselkumab and moderate QoE suggests that it is also less effective than risankizumab.[2] Moderate QoE suggests that guselkumab is more effective than secukinumab for maintenance therapy.[2]
- Few differences in harms among TIM agents were observed in patients with PsO, based on moderate-to-low QoE.[2]
- Limited head-to-head comparisons of TIMs for PsA are available to evaluate comparative efficacy and harm.[2] Based on low QoE, ixekizumab, tofacitinib, and remtolumab may be more effective than adalimumab with no difference in harms.[2]

Targeted Immune Modulators for Crohn's Disease and Ulcerative Colitis

- Limited evidence exists for the comparative effectiveness of TIM agents for the treatment of CD.[3] The QoE was previously rated as very low for the comparative effectiveness of adalimumab and infliximab (data from 2 RCTs showed no significant differences in QoL or clinical improvement between the 2 drugs), and no new RCTs were identified that evaluated comparative effectiveness of these agents.[3]
- One new RCT evaluated the comparative effectiveness and harms of TIMs for UC.[3] Authors of this study reported greater efficacy and no statistically significant differences in harms for vedolizumab compared to adalimumab.[3] At 1 year, more participants randomized to vedolizumab achieved clinical remission compared to participants on adalimumab (31% vs. 23%; absolute risk difference [ARD], 9%; 95% CI 3% to 15%; Number Needed to Treat ([NNT] 12) and endoscopic remission (40% vs. 28%; ARD, 12%; 95% CI 5% to 19%; all results, P<0.05; moderate quality QoE).[3]
- One new cohort study evaluating the comparative harms of adalimumab and infliximab was recently published, but indirectness and imprecision of the data provide very low QoE to compare harms.[3] No new cohort studies compared harms between adalimumab and other agents (infliximab, etanercept, certolizumab pegol); thus, the QoE on comparative harms for these agents remains very low.[3]

Targeted Immune Modulators Summary Conclusions

- No studies were identified that evaluated differences in TIM effectiveness and harms in RA, AS, PsO, PsA, CD, or UC based on specific demographic characteristics, such as age, race, gender, comorbidities, or concomitant drugs.[1-3]
- Expanded indications were recently approved by Food and Drug Administration (FDA) for the following medications:
    - secukinumab for adults with active non-radiographic axial spondyloarthritis (nr-axSpA) with objective signs of inflammation;
    - canakinumab for treatment of active Still's disease;
    - guselkumab to treat adults with active PsA;
    - ixekizumab for adults with nr-axSpA and objective signs of inflammation; and
    - ixekizumab for pediatric patients with PsO aged 6 years and older who are candidates for systemic therapy or phototherapy

Recommendations:

- After clinical review, no changes to the Preferred Drug List (PDL) are recommended.
- Modify PA criteria to reflect updated indications for the TIM agents as noted above.
- Evaluate costs in executive session.
- After executive session, secukinumab was made non-preferred on the PDL.

Summary of Prior Reviews and Current Policy

Targeted Immune Modulators (aka, biologic medications) were last reviewed by the Pharmacy and Therapeutics (P & T) Committee at the February 2020 meeting. At that time, upadacitinib and risankisumab-rzaa were added to the prior authorization (PA) criteria. Adalimumab, etanercept, and secukinumab are preferred medications on the PDL (see **Appendix 1** for PDL status of all biologics). All preferred and nonpreferred TIMs require PA to ensure appropriate utilization. Current clinical PA criteria are outlined in **Appendix 2.**

OHP FFS Utilization:

In the second quarter of 2020, there were approximately 152 pharmacy claims for biologic agents in the fee-for-service (FFS) population. Eighty-four percent of the claims were for the preferred agents secukinumab, etanercept and adalimumab. For the non-preferred agents, 4-5% of claims were for certolizumab pegol and ixekizumab, and 1-2% of claims were for tofacitinib, tocilizumab, natalizumab, and vedolizumab. There were no pharmacy claims for brodalumab,

canakinumab, guselkumab, ustekinumab, tildrakizumab, sarilumab, risankizumab, or baricitinib. The most frequent utilization for biologic drugs that are physician administered include: infliximab, vedolizumab, abatacept, golimumab, ustekinumab, rituximab and natalizumab.

Background:

Ankylosing Spondylitis and Rheumatoid Arthritis

Ankylosing spondylitis is a chronic rheumatic disorder that primarily affects the sacroiliac joints and spine.[4] 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 for age and sex.[5] Patients who have chronic pain and other features suggestive of spondyloarthritis (SpA) without radiologic changes are classified as having nr-axSpA.[6] Guidelines for management of AS were updated in 2019 by the ACR in conjunction with the Spondylitis Association of America (SAA).[7] The Assessments in Ankylosing Spondylitis International Society (ASAS) and European League against Rheumatism (EULAR) recommendations were last updated in 2016.[8] Nonsteroidal anti-inflammatory drugs (NSAIDs) and exercise are recommended as first-line therapies to alleviate pain and stiffness.[7,8] Tumor necrosis factor inhibitors are recommended for patients with persistent disease activity despite conventional treatment.[7,8] All 5 TNF-inhibitors are proven to provide sustained improvement in disease activity and patient functioning as assessed by the Bath Ankylosing Spondylitis Disease Activity Index (BASDI) and Functional Index (BASFI) scores.[8] Two anti–interleukin monoclonal antibodies, secukinumab and ixekizumab, have also demonstrated efficacy in treating AS.[7] However, the ACR/SAA guidance recommends a TNF-inhibitor as the first biologic for use after NSAID therapy over secukinumab or ixekizumab.[7] Co-administration of low-dose methotrexate (MTX) with a TNF-inhibitor is not recommended for AS management.[7] There is no evidence for the efficacy of systemic glucocorticoids or disease-modifying antirheumatic drugs (DMARDs) in the treatment of AS.[8]

The BASDI includes 6 different 10-centimeter visual analog scales (VAS) to measure the severity of fatigue, spinal and peripheral joint pain, localized tenderness and morning stiffness (both qualitative and quantitative).[1] The scale is scored on a scale from 0 to 10, with lower scores indicating less pain and tenderness.[1] The BASFI is a tool used to assess functional ability in AS patients. The score ranges from 0 to 10, with lower scores indicating better function.[1] An additional instrument used to measure AS disease activity is the ASDAS. The ASDAS categorizes the disease activity as inactive, low, high, or very high.[9] A change of 1.1 or greater in the ASDAS score is considered a significant improvement, while a change of 2.0 or greater is a major improvement.[9]

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 2015 ACR[11] and 2016 EULAR[12] recommendations suggest RA treatment begin with conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) such as MTX as soon as diagnosis of RA is established. Other csDMARDs recommended to treat RA include sulfasalazine, hydroxychloroquine, and leflunomide.[11,12] Biologic DMARDs (bDMARDs) or targeted synthetic DMARDs (tsDMARDs) are recommended for patients with a suboptimal response or intolerance to csDMARDs.[11,12] Biologic DMARDs are proteins that must be administered parentally. Targeted synthetic DMARDs are small chemical molecules that can be given orally. Monotherapy with bDMARDs or tsDMARDs 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.[11,12] **Table 1** summarizes the different TIMs FDA-approved for management of RA and AS. FDA-approved biosimilars are available for adalimumab, etanercept, and infliximab.

Table 1. FDA-Approved Targeted Immune Modulators for Rheumatoid Arthritis and Ankylosing Spondylitis[13,14]

Drug - Route of Administration	Molecular Target	Approved Indication	Warnings
Biologic DMARDs			
Adalimumab - SC (HUMIRA)	TNF	AS and RA	Infections, reactivation of TB, psoriasiform skin changes, exacerbation of demyelinating diseases, drug-induced lupus, non-melanoma skin cancer, injection site or infusion reactions
Certolizumab Pegol - SC (CIMZIA)			
Etanercept - SC (ENBREL)			
Golimumab - IV or SC (SIMPONI and SIMPONI ARIA)			
Infliximab - IV (REMICADE)			
Sarilumab - SC (KEVZARA)	IL-6	RA	Infections, reactivation of TB, bowel perforation, hypersensitivity reactions, neutropenia, injection site reactions, hyperlipidemia
Tocilizumab – IV or SC (ACTEMRA)			
Ixekizumab - SC (TALTZ)	IL-17	AS	Can worsen Crohn's disease and ulcerative colitis
Secukinumab – IV or SC (COSENTYX)			
Anakinra - SC (KINERET)	IL-1	RA	Infections, injection site pain
Rituximab - IV (RITUXAN)	B-lymphocyte	RA	Hypersensitivity reactions, reactivation of hepatitis B, leukocytopenia, PML, tumor lysis syndrome, worsening heart failure
Abatacept) - IV or SC (ORENCIA)	T-lymphocyte	RA	Infections, reactivation of TB, leukocytopenia, injection site reactions
Targeted Synthetic DMARDs			
Tofacitinib - PO (XELJANZ)	JAK 1,2,3	RA	Infections, reactivation of TB, thrombosis, malignancies
Baricitinib - PO (OLUMIANT)	JAK 1,2		
Upadacitinib - PO (RINVOQ)	JAK 1		
Abbreviations: AS=ankylosing spondylitis; CPK=creatine phosphokinase; DMARD=Disease-Modifying Antirheumatic Drug; FDA=Food and Drug Administration; IL=interleukin; IV=intravenous; JAK=Janus Kinase; LFT=liver function test; PML = progressive multifocal leukoencephalopathy; PO=oral; RA=rheumatoid arthritis; SC= subcutaneous; TB=tuberculosis; TNF=tumor necrosis factor			

Primary endpoints used in RA clinical trials include the ACR response, the HAQ-DI, and the DAS-28. The ACR response score is a composite endpoint with 7 domains used to calculate the proportion of patients achieving a target percentage of improvement from baseline and is a considered a measure of efficacy and overall disease activity.[15] Patients are said to meet ACR20 criteria when they have at least 20% reductions in tender joint counts, 20% reduction swollen joint counts and 20% improvement in at least 3 of the 5 remaining domains.[15] The additional 5 domains include patient global assessment of arthritis on a visual analog scale (VAS), physician global assessment of arthritis on a VAS, patient assessment of pain on a VAS, patient assessment of physical functioning (e.g., health assessment questionnaire), and acute phase reactant (ESR or c-reactive protein [CRP]). ACR50 and ACR70 criteria are similar, but with improvement of at least 50% and 70% in ACR criteria.[15] ACR50 and ACR70 are considered more clinically significant than ACR20.[15] The HAQ-DI is a widely used self-reported measure of functional capacity. Scores of 0 to 1 are generally considered to represent mild to moderate disability, 1 to 2 moderate to severe disability, and 2 to 3 severe to very severe disability.[16] The minimal clinically important difference (MCID) of an improvement on the HAQ-DI is a change of at least 0.20 from baseline.[17] The DAS-28 is another index of disease activity (similar to the ACR response). The DAS is a continuous composite outcome that consists of: the number of painful joints (Ritchie Articular Index, 0-78 joints), 44-joint count for swollen joints, ESR and patient global assessment of disease activity or general health using a VAS.[17] A DAS-28 score greater than 5.1 corresponds to high disease activity and less than 3.2 of low disease activity. A DAS-28 score of 2.6 is considered to correspond to remission.[18]

Plaque Psoriasis and Psoriatic Arthritis

Plaque psoriasis is a chronic, immune-mediated inflammatory disorder of the skin, scalp and joints that affects about 2 to 3% of the population. Psoriatic arthritis is a chronic inflammatory arthritis associated with psoriasis that can affect any joint in the body.[19] In all cases, symptoms include pain and stiffness in the affected joint as well as joint-line tenderness, swelling, and sometimes loss of range of motion. Typically, PsO is classified as mild, moderate or severe. Mild to moderate disease involves less than 10% of the body surface area, does not involve the hand, foot, or mucous membranes, and has little to no impact on quality of life or function. Mild to moderate PsO is not a funded condition per the Health Evidence Review Commission (HERC) Guideline Note 21.[20] Per 2017 National Institute for Health and Care Excellence (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).[21] Phototherapy is an option for patients with moderate-to-severe PsO who have not responded to topical therapy.[21] Systemic non-biologic treatments are recommended for patients with moderate-to-severe PsO unresponsive to topical or phototherapy and include MTX, cyclosporine, or acitretin.[21] Biologics may be added for patients with moderate-to-severe PsO not controlled by other therapies.[21] The first line of treatment for PsA is nonsteroidal anti-inflammatory drugs (NSAIDs), although in most cases DMARDs are necessary. The TIMS that are FDA-approved to treat PsO and PsA are presented in **Table 2.**

Table 2. FDA-Approved Targeted Immune Modulators for Plaque Psoriasis and Psoriatic Arthritis[13,14]

Drug – Route of Administration	Molecular Target	Approved Indication(s)	Approved Age Range for PsO	Warnings
Adalimumab - SC (HUMIRA)	TNF	PsA and PsO	Adults	Infections, reactivation of TB, psoriasiform skin changes, exacerbation of demyelinating diseases, drug-induced lupus, non-melanoma skin cancer, injection site or infusion reactions
Etanercept - SC (ENBREL)			Patients ≥ 4 years of age	
Infliximab - IV (REMICADE)			Adults	
Certolizumab Pegol - SC (CIMZIA)			Adults	
Golimumab (SIMPONI)		PsA	Adults	
Ustekinumab - SC (STELARA)	IL-12 and IL-23	PSA and PsO	Patients ≥ 12 years of age	Infections, malignancies
Secukinumab - SC (COSYNTEX)	IL-17	PsA and PsO	Adults	Can worsen Crohn's disease and ulcerative colitis, infections
Ixekizumab - SC (TALTZ)			Patients ≥ 6 years of age	
Brodalumab - SC (SILIQ)		PsO	Adults	REMS program for suicide ideation, infections, can exacerbate Crohn's disease and ulcerative colitis
Guselkumab - SC (TREMFYA)	IL-23	PsA and PsO	Adults	Upper respiratory infections, tinea infections, and herpes simplex infections
Tildrakizumab - SC (ILUMYA)		PsO		
Risankizumab-rzaa - SC (SKYRIZI)				
Apremilast - PO (OTEZLA)	PDE-4	PsA and PsO	Adults	Worsening depression
Tofacitinib - PO (XELJANZ)	JAK	PsA	Adults	Infections, reactivation of TB, thrombosis, malignancies
Abatacept – IV or SC (ORENCIA)	T-lymphocyte	PsA	Adults	Infections, reactivation of TB, leukocytopenia, injection site reactions

Abbreviations: FDA=Food and Drug Administration; IL=interleukin; IV= intravenous; JAK= Janus Kinase; PASI=Psoriasis Area and Severity Index; PDE=phosphodiesterase; PO=oral; PsA=psoriatic arthritis; PsO=plaque psoriasis; REMS=Risk Evaluation and Mitigation Strategy; SC=subcutaneous; TNF=tumor necrosis factor

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 Psoriasis Area and Severity Index (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.[22] The PASI

ranges from 0 to 72 points and evaluates body surface area involvement, induration, scaling, and erythema. Because the PASI only evaluates skin involvement on the trunk, head, arms and legs, the PASI has limited sensitivity in patients with mild to moderate disease or limited BSA involvement.[22,23] It does not consider symptoms affecting hands, feet, face or genitals. Because the PASI scale is not linear, small changes in BSA involvement can result in a significant improvement of the overall score without change in other symptoms.[22] In addition, though the PASI evaluates symptoms on a range of 0 to 72 points, in clinical practice, patients often do not have scores greater than 40.[23] 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.[23] The sPGA is another physician-reported symptom severity scale which evaluates symptom severity at a single point in time with higher scores indicating more severe disease (range 0 to 5). Responders to therapy are typically defined as patients with a sPGA score of 0 or 1, corresponding to clear or almost clear skin or patients with an improvement of at least 2 points. In clinical trials of patients with moderate to severe disease, the proportion of patients with a sPGA score of 0 or 1 has a strong correlation with a 75% improvement in PASI.[23] Finally, the PSI evaluates patient-reported rather than physician-assessed symptoms. Eight individual symptoms in the prior 24 hours are assessed, including itching, redness, scaling, burning, stinging, cracking, flaking and pain.[23] Individual symptoms are rated from 0 to 4 with total scores ranging from 0 to 32 points.[23] Patients with total scores of 8 or less with no single item rated greater than 1 are generally considered responders to therapy. An additional tool used to assess QoL is the DLQI. Scores on the DLQI range from 0 to 30; a score of 0 or 1 indicates no effect of psoriasis on QoL.[2]

Crohn's Disease and Ulcerative Colitis

Crohn's disease and UC are classified as inflammatory bowel diseases. Crohn's disease is characterized by inflammation involving the full thickness of the bowel wall at any point from mouth to anus, whereas UC is characterized by mucosal ulceration limited to the colon and rectum.[19] Clinical diagnosis of both conditions is most accurately made with colonoscopy.[19] The Crohn's Disease Activity Score (CDAI) is an evaluation of 8 clinical factors, including number of soft stools per day, abdominal pain, general well-being, use of medications for diarrhea, presence of abdominal mass, hematocrit, and percentage deviation from standard weight. A total score of 450 or greater indicates extremely severe disease, a score of 150 or greater indicates active disease, and a score less than 150 indicates minimal disease.[24] Practice guidelines for CD recommend taking into account the disease location, severity, complications, and extra intestinal manifestations when choosing a treatment strategy.[24,25] Treatment is largely directed at symptom relief rather than cure, and active treatment of acute disease (inducing remission) should be distinguished from preventing relapse (maintaining remission).[24] The National (NICE) guidelines recommend TNF-inhibitors for induction, but only after failure of conventional therapy with corticosteroids, aminosalicylates (i.e., sulfasalazine, mesalamine), azathioprine or mercaptopurine, and should only be used for maintenance if there is clear evidence of active disease.[25] The American College of Gastroenterology (ACG) strongly recommends induction with a TNF-inhibitor to maintain remission in patients who have moderate-to-severe CD despite standard therapies.[24] Cyclosporine, mycophenolate mofetil, and tacrolimus should not be used to treat CD due to insufficient evidence demonstrating efficacy.[24] The IL-23 inhibitor risankizumab is currently being evaluated in clinical trials for safety and efficacy in CD and UC.[16] The JAK inhibitor upadacitinib is also being studied for use in CD and UC.[3]

The ACG[26] and the NICE[27] guidelines recommend the use of TIMs for treating moderately to severely active UC in adults whose disease has responded inadequately to, or have intolerance or contraindications to conventional therapy including aminosalicylates, corticosteroids, azathioprine or mercaptopurine. Continuation of these agents is only recommended if there is clear evidence of response.[26] **Table 3** presents the TIMs that are FDA-approved to treat CD and UC.

Table 3. FDA-Approved Targeted Immune Modulators for Crohn's Disease and Ulcerative Colitis[13,14]

Drug – Route of Administration	Molecular Target	Approved Indication(s)	Warnings
Adalimumab - SC (HUMIRA)	TNF	CD and UC	Infections, Malignancies including Lymphoma
Infliximab - IV (REMICADE)		CD and UC	
Certolizumab Pegol - SC (CIMZIA)		CD	
Golimumab (SIMPONI)		UC	
Ustekinumab - IV (initial dose) followed by SC (STELARA)	IL-12 and IL-23	CD	Infections, malignancies
Tofacitinib - PO (XELJANZ)	JAK	UC	Infections, reactivation of TB, thrombosis, malignancies
Vedolizumab – IV (ENTYVIO)	Integrin receptor	CD and UC	Infections, PML
Natalizumab – IV (TYSABRI)		CD	Infections, liver injury, PML, thrombocytopenia

Abbreviations: CD=Crohn's Disease; FDA=Food and Drug Administration; IL=interleukin; IV=intravenous; JAK= Janus Kinase; PASI=Psoriasis Area and Severity Index; PDE=phosphodiesterase; PML=progressive multifocal encephalopathy; PO=oral; REMS=Risk Evaluation and Mitigation Strategy; SC=subcutaneous; TNF=tumor necrosis factor; UC=Ulcerative Colitis

Methods:

The May 2020 drug class summary report on TIMS by DERP at the Center for Evidence Based Policy at the Oregon Health & Science University (OHSU) was used to inform recommendations for this drug class.[19] The DERP report summarizes findings from 3 systematic reviews recently completed by DERP. The reviews evaluated the use of TIM agents for: RA and AS;[1] PsO and PsA;[2] and CD and UC.[3]

The original report is available to Oregon Pharmacy and Therapeutics Committee members upon request. An executive summary report is publicly available in the agenda packet and on the DURM website.

The searches for standard DERP evidence sources were completed by late August or early September 2019, based on the specific systematic review.[19] Randomized controlled trials of at least 12 weeks' duration, conducted among persons with the clinical conditions of interest were included in the systematic reviews.[19] In addition, cohort studies with a sample size of at least 1,000 for the key question about harms.[19] Selected studies had to report health outcomes (e.g., clinical improvement, quality of life or harms).[19] Most studies were assessed as fair methodological quality because of extensive manufacturer involvement in study design, execution, and reporting.[19] A few studies were evaluated as poor methodological quality for having other relevant biases.[19] Poor-

quality trials with very low quality evidence are excluded from the report. Efficacy was evaluated via quality of life assessments, functional capacity, clinical improvement, and disease remission. Harms were assessed through overall AEs, withdrawals due to AEs, SAEs, specific AEs (i.e. serious infectious disease) and mortality. The DERP authors calculated absolute risk differences (ARD), risk ratios (RR), incident rate ratios (IRR), and associated 95% confidence intervals (CI) based on data provided in the study when these values were not reported by the original study authors.[19]

Of note, the DERP reviews did not include RCTs shorter than 12 weeks in duration, cohort studies with fewer than 1,000 participants, or studies published in languages other than English.[19] Only studies published in the peer-reviewed literature were included; data presented in press releases or conference abstracts was not used.[19] The current review represents a cumulative synthesis of the evidence; thus, studies included in the prior DERP review on this topic were carried forward into the update if they continued to meet eligibility criteria, but data from these studies were not rechecked against the original sources for accuracy.[19] Furthermore, DERP authors did not reevaluate the methodological study quality for the previously included studies, except for RCTs that were previously assessed as good quality.[19] The authors reassessed these good-quality RCTs to determine the influence of manufacturer involvement on study design and execution, consistent with current DERP methodology.[19] Lastly, the previous report used a modified Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach whereby the lowest quality rating was termed insufficient*;* the authors converted all previous insufficient quality of evidence ratings to very low for consistency with current GRADE methods.[19]

1. Targeted Immune Modulators for Rheumatoid Arthritis and Ankylosing Spondylitis

Comparative RCTs and cohort studies that evaluated the effectiveness and harms of TIM agents approved for the treatment of moderate-to-severe RA and AS were identified.[1] The literature search was conducted through September 2019.[1] Twenty-three new studies were identified in addition to 53 studies from the previous DERP review, for a total of 76 eligible studies in this update.[1] All RCTs except one, and all cohort studies except 2, evaluated TIM agents in patients with RA.[1] One RCT evaluated TIM agents for AS; 2 cohort studies assessed TIMs in a mixed population that included participants with RA and AS.[1]

Of the 76 eligible studies, 35 were RCTs and 41 were cohort studies.[1] Among the 35 RCTs, 6 studies were assessed as poor quality; the others were rated as fair quality.[1] Among the 41 cohort studies, 5 studies were of poor methodological quality, 11 studies were of good methodological quality, and the rest were rated as fair quality.[1] Outcomes selected for GRADE ratings ranged from very low to high QoE, but most outcomes were rated very low.[1] Generally, outcomes were downgraded for study limitations and imprecision (i.e., wide CI because of small sample size).[1] For the statistical data analysis, p-values and 95% CI are reported if available.

A. Comparative Effectiveness of Targeted Immune Modulators

First-Line Targeted Immune Modulators for Rheumatoid Arthritis

The evidence for the comparative effectiveness of TIM agents includes data for 12 comparisons of TIMs as first-line treatments for the treatment of RA.[1] Most comparisons are limited to single RCTs.[1] Fifteen RCTs provided evidence for 11 different head-to-head TIM comparisons and 2 comparisons of combination treatments with monotherapy when used to treat RA.[1] All studies enrolled participants with moderate-to-severe RA despite treatment with DMARDs.[1] 1 poor-quality, open-label RCT is excluded from this summary.

- *Abatacept vs. Adalimumab* (1 fair-quality, open-label, noninferiority RCT; n=646): No differences were observed between treatment groups in response (ACR 50 45% vs. 57%; P-value not reported [NR), remission (ACR70, 29% vs. 26%; P-value NR), or improvements in functional capacity (HAQ-DI) at 48 weeks (low QoE for response and remission).[1]

- *Abatacept vs. Infliximab* (1 fair-quality, double-blind RCT; n=431): No significant differences were noted between groups in response (ACR50, 40% vs. 37%; P-value NR), remission (ACR70, 21% vs. 24%; P-value NR), or improvements in functional capacity (HAQ-DI) at 24 weeks (low QoE for response and remission).[1]
- *Adalimumab vs. Baricitinib* (1 fair-quality, multi-center, double-blind RCT; n=1,305): Adalimumab was less effective than baricitinib for achieving response (ACR20, 61% vs. 70%; P=0.01) and improvements in functional capacity (HAQ-DI of ≥ 0.22, 58% vs. 68%; P<0.01; high QoE) at 52 weeks.[1] No differences in remission were detected (Simplified Disease Activity Index [SDAI] < 3.3; low QoE).[1]
- *Adalimumab vs. Certolizumab Pegol* (1 fair-quality RCT; n=915): No differences between groups in response (ACR20, 71% vs. 69%; P=0.47) and remission (ACR70; data NR) at 12 weeks were found (high QoE for response; data NR for remission).[1]
- *Adalimumab vs. Etanercept* (1 fair-quality, open-label, 24-week RCT [n=64]): After 24 weeks, participants in the adalimumab and the etanercept groups had similar improvements on the HAQ-DI score (0.69 vs. 0.68; *P* value NR) and the DAS28-ESR (−2.12 vs. −2.84; *P* value NR).[1]
- *Adalimumab vs. Sarilumab* (1 fair-quality, double-blinded RCT; n=369): Adalimumab was less effective than sarilumab for achieving response (ACR50, 30% vs. 46%; P=0.002), remission (Clinical Disease Activity Index: 3% vs. 7%; P=0.47), improvements in functional capacity (HAQ-DI, −0.43 vs. −0.61; p<0.005), and quality of life (QoL) (SF-36, 6.09 vs. 8.75; P<0.001) at 24 weeks (moderate QoE for QoL and response; low QoE for remission).[1]
- *Adalimumab vs. Tocilizumab* (1 fair-quality, double-blind RCT [n=326] and 1 fair-quality, open-label RCT [n=43]): In the larger trial, adalimumab was less effective than tocilizumab for achieving response (ACR50, 28% vs. 47%; P<0.001) and remission (ACR70, 18% vs. 33%; P=0.002) at 24 weeks.[1] No differences in QoL (SF-36) at 24 weeks were reported (low QoE for response, remission, and QoL).[1] Results of the small, open-label RCT showed no difference in ACR50 between participants treated with adalimumab or tocilizumab.[1] In both trials, tocilizumab was used at a higher dose than is FDA-approved (8 mg intravenous (IV) or subcutaneous (SC) once monthly), which makes dosing equivalence to adalimumab 20 to 40mg SC every 2 weeks questionable.[1]
- *Adalimumab vs. Tofacitinib* (1 fair-quality, double-blinded, noninferiority, 52-week RCT [n=1,146], 1 fair-quality, double-blind, 24-week RCT [n=717] and 1 fair-quality, 12-week, dose-ranging study [n=384]): No difference between groups in response (ACR50, 44% vs. 46% P value NR) was reported in the noninferiority trial (high QoE for response).[1] In the RCT with 717 participants, one tofacitinib arm was dosed at 10 mg orally twice daily, a higher dose than is FDA-approved.[1] In this trial, similar ACR20 response rates were observed in all 3 treatment groups (adalimumab, 47%; tofacitinib 5 mg, 52%; tofacitinib 10 mg, 53%; P-value NR; high QoE for remission).[1] The dose-ranging study reported lower ACR20 response rates after 12 weeks of treatment for participants treated with adalimumab than for those on tofacitinib 5 mg or 10 mg (36% vs. 59% vs. 71%; P-value NR; high QoE for response).[1]
- *Adalimumab vs. Upadacitinib* (1 fair-quality, double-blinded RCT; n=1,629): Adalimumab was less effective than upadacitinib for achieving response (ACR50, 29% vs. 45%; P<0.001), remission (DAS28<2.6, 18% vs. 21%; P<0.001), and improvements in functional capacity (HAQ-DI, −0.49 vs. −0.60; P<0.01) at 12 weeks (high QoE for response and remission).[1]
- *Etanercept vs. Infliximab* (1 fair-quality, open-label RCT; n=32): Etanercept was more effective than infliximab for achieving response (ACR20, 74% vs. 60%; P-value NR) and improving functional capacity (HAQ-DI, −32.30 vs. −21.60; P-value NR) at 54 weeks.[1] No dose increase was allowed for infliximab (very low QoE for response).[1]
- *Etanercept vs. Tocilizumab* (1 fair-quality, open-label RCT; n=43)*:* No differences in clinical improvement (DAS-28, -2.84 vs. -2.10; P-value NR) and improvement in functional capacity (HAQ-DI, 0.68 vs. 0.70; P-value NR) were found at 24 weeks (very low QoE).[1]
- *Combination Therapies* (1 fair-quality RCT; n=244 and 1 fair quality RCT; n=121): The larger study did not detect any benefit for treatment with a combination of etanercept (25 mg/week or 50 mg/week) and anakinra (100 mg/day) compared to monotherapy with etanercept (25 mg twice per week) over 24 weeks.[1] The second trial examined a combination of abatacept (2 mg/kg on days 1, 15, and 30 and every 4 weeks thereafter) and etanercept (25

mg twice weekly) compared to abatacept monotherapy (2 mg/kg).[1] The combination was associated with increased SAEs but limited additional efficacy (ACR50, 26% vs. 19%, respectively; P-value NR).[1]

Second-Line Targeted Immune Modulators for Rheumatoid Arthritis

Six RCTs provided evidence for 5 different head-to-head comparisons of TIMs and 1 comparison of TIM combination treatment versus TIM monotherapy as second-line agents (i.e. at least one inadequate response to a TIM) in RA.[1] Two poor-quality, open-label RCTs are excluded from this summary.

- *Abatacept vs. Secukinumab* (1 fair-quality, multi-center, double-blind RCT; n=551): Abatacept was more effective than secukinumab 150 mg or secukinumab 75 mg for achieving response (ACR50, 28% vs. 17% vs. 12%; P-value NR) and improved functional capacity (HAQ-DI, −0.6 vs. −0.4 vs. −0.3; P-value NR) at 24 weeks (moderate QoE for clinical improvement).[1]
- *TNF-Inhibitors (adalimumab, certolizumab pegol, etanercept, golimumab, infliximab) vs. other TIMs* (*abatacept, rituximab, tocilizumab)* (1 fair-quality, open-label RCT; n=300): Non-TNF-inhibitors were more effective than TNF-inhibitors for achieving response (odds ratio (OR), 2.06; 95% CI, 1.27 to 3.37) and remission (DAS28 < 2.6, 27% vs. 14%; p<0.01) at 52 weeks (low QoE for both assessments).[1]
- *Combination therapies* (1 fair-quality, double-blind RCT; n=54): Combination treatment (rituximab when given in combination with methotrexate and etanercept or methotrexate and adalimumab) was more effective than TNF-inhibitor maintenance treatment (methotrexate in combination with etanercept or adalimumab) for achieving response (ACR50, 12% vs. 6%; P value NR) and remission (DAS28 < 2.6, 18% vs. 6%; P value NR) at 24 weeks (low QoE for both).[1]

Pipeline Targeted Immune Modulators for Rheumatoid Arthritis

Nine fair-quality RCTs evaluating effectiveness of 3 pipeline (not yet FDA-approved) drugs for the treatment of RA were included in the DERP review.[1] These studies provided evidence on filgotinib compared to placebo, peficitinib compared to placebo, peficitinib compared to etanercept, and one combination treatment of certolizumab pegol plus bimekizumab compared to certolizumab pegol monotherapy.[1] Filgotinib and peficitinib are oral Janus kinase (JAK) inhibitors and bimekizumab is an IV interleukin (IL)-17 receptor inhibitor.

- *Filgotinib vs. Placebo* (1 fair-quality, multi-center, phase 3 RCT [n=449]; 2 fair-quality phase 2 RCTs [n=594 and n=283])*:* Enrolled subjects in all 3 RCTs had moderate-to-severe RA and were naïve to TIM agents (phase 2 trials) or had an inadequate response or intolerance to at least 1 prior TIM agent (phase 3 RCT).[1] In the phase 3 RCT, filgotinib was more effective than placebo for achieving response (ACR20, 66% vs. 31%; p<0.001), remission (DAS28-erythrocyte sedimentation rate (ESR), 31% vs. 12%; p<0.001, and improvement of QoL (SF-36: 7.6 vs. 3.6; p<0.001) at 12 weeks (high QoE for all outcomes).[1] The 2 phase 2 RCTs reported similar results as the phase 3 RCT for response, remission, and functional capacity.[1]
- *Peficitinib vs. Placebo* (3 fair-quality phase 2 RCTs [n=379, n=289 and n=281] and 2 fair-quality phase 3 RCTs [RAJ 3; n=509 and RAJ 4; n=519]): All 5 studies were rated as fair-quality because of extensive manufacturer involvement in study design, execution, and reporting.[1] All studies included participants with moderate-to-severe RA for at least 6 months.[1] Two studies included participants with inadequate response to, or intolerance of, at least one DMARD agent; in the other 3 studies, participants had an inadequate response to methotrexate.[1] Both phase 3 RCTs reported similar results.[1] After 12 weeks, more participants in the intervention group achieved an ACR20 response compared to participants in the placebo group (peficitinib 100 mg, 59% and 58%; peficitinib 150 mg, 64% and 75%; placebo, 22% and 31%; P<0.001 for all comparisons with placebo).[1] Higher proportions of remission as defined by DAS28-CRP less than 2.6 were achieved with peficitinib than placebo (peficitinib 100 mg, 25% and 31%; peficitinib 150 mg, 35% and 35%; placebo, 8% and 5%; P<0.001 for all comparisons with placebo; high QoE for response and remission).[1] Two of the phase 2 studies reported similar results for response, remission, and functional capacity as the phase 3 trials.[1] The third phase 2 study did not identify statistically significant clinical improvements for peficitinib 100 mg and 150 mg compared to placebo.[1]

- *Peficitinib vs. Etanercept* (1 fair-quality RCT; n=509): The double-blinded, multicenter, RAJ 3 trial assessed the efficacy of peficitinib compared to open-label etanercept in participants with RA.[1] Participants were randomized to peficitinib 100 mg, peficitinib 150 mg, etanercept 50 mg, or placebo for 52 weeks.[1] At 12 weeks, a lower proportion of participants in peficitinib groups achieved an ACR20 response compared to participants in the etanercept group (peficitinib 100 mg, 58%; peficitinib 150 mg, 75%; etanercept 50 mg, 84%; P-value NR; moderate QoE).[1]
- *Certolizumab Pegol vs. Certolizumab Pegol + Bimekizumab* (1 fair-quality RCT; n=79): At 12 weeks, combination treatment with bimekizumab was more effective than certolizumab pegol monotherapy for achieving response (DAS28-CRP < 3.2, 46% vs. 29%; P value NR) and remission (DAS28-CRP < 2.6, 26% vs. 8%; P-value NR; low QoE for both outcomes).[1]

Targeted Immune Modulators for Ankylosing Spondylitis

One poor-quality, open-label RCT compared etanercept to infliximab in a head-to-head trial, but since the results are based on very low QoE (insufficient evidence) it was excluded from this summary.

Pipeline Targeted Immune Modulators for Ankylosing Spondylitis

One placebo-controlled RCT evaluated filgotinib for the treatment of AS.[1]

- *Filgotinib vs. Placebo* (1 fair-quality RCT; n=116): Participants with active AS and an inadequate response or intolerance to 2 or more NSAIDs were enrolled in this study.[1] The study randomized participants to filgotinib 200 mg daily or placebo, with the main outcome being the change from baseline to week 12 in ASDAS.[1] Participants treated with filgotinib improved on the ASDAS compared to placebo (−1.47 vs.−0.57; difference between groups, -0.85; 95% CI -1.17 to -0.53; P < 0.001; moderate QoE).[1] More participants reported major improvement (decrease of ASDAS from baseline ≥ 2.0) and clinically significant improvement (decrease of ASDAS from baseline of at least 1.1) in the filgotinib group compared to the placebo group (33% vs. 2%, and 66% vs. 26%; P < 0.001 for both comparisons; moderate QoE).[1] Participants in the filgotinib group also had greater improvements on the Ankylosing Spondylitis Quality of Life score than participants treated with placebo (filgotinib 200 mg, –4.76; placebo, –2.24; P=0.004; moderate QoE).[1]

B. Comparative Harms of Targeted Immune Modulators

Targeted Immune Modulators for Rheumatoid Arthritis

Twenty-one RCTs provided evidence for comparative harms of TIMs in 18 different head-to-head comparisons and 40 different cohort studies in patients with RA.[1] The pharmaceutical industry funded the majority of RCTs that assessed comparative harms of TIM agents.[1] Moderate and high QoE indicates no differences in the incidence of overall AEs and SAEs.[1] Significant differences in AEs and SAEs for the incidence of some comparisons were rated as very low or low QoE, and should be interpreted with caution.[1] However, large observational studies suggest differences in some specific SAEs.[1] In the majority of studies, for example, infliximab was associated with a higher incidence of serious infections than other TIM agents.[1] Some studies also indicated a higher incidence of opportunistic infections, tuberculosis, and varicella zoster infections with infliximab than with other TNF-inhibitors.[1] Two observational studies reported a higher incidence of gastrointestinal perforations with tocilizumab than with TNF-inhibitors.[1] Even in these large observational studies, however, the number of events was generally low and findings need to be interpreted cautiously.[1] The majority of observational studies reported no significant differences in mortality, malignancies, and cardiovascular events or congestive heart failure.[1] Overall, few differences in harms were observed in head-to-head RCT comparisons of TIM agents.[1] Statistically significant differences observed in included studies are highlighted below.[1]

- *Abatacept vs. Infliximab* (1 fair-quality RCT; n=321): Fewer SAEs with abatacept than infliximab (5% vs. 12%; P-value NR; RR=0.45; 95% CI, 0.20 to 0.99) were found at 24 weeks.[1] No differences in overall AE were found (low QoE for SAEs and moderate QoE for overall AEs).[1]
- *Adalimumab vs. Baricitinib* (1 fair-quality RCT; n=817): Fewer SAEs with adalimumab than baricitinib (4% vs. 8%; RR, 0.50; 95% CI 0.27 to 0.93) were found at 52 weeks.[1] No differences in overall AEs were found (low QoE for SAEs and high QoE for overall AEs).[1]

- *Combination therapies* (4 fair-quality RCTs; n=586): The combination of TNF-inhibitors with a TIM of a different mechanism of action substantially increased the frequency of SAEs.[1] For example, the combination of etanercept with abatacept or anakinra resulted in more SAEs compared to etanercept monotherapy (11% vs. 3%; RR, 5.93; 95% CI, 0.81 to 43.42; moderate QoE).[1] Abatacept plus another TIM (adalimumab, anakinra, etanercept, or infliximab) resulted in more SAEs compared to another TIM alone (22% vs. 13%; RR, 1.79; 95% CI, 0.85 to 3.75; low QoE).[1]

Pipeline Targeted Immune Modulators for Rheumatoid Arthritis

- *Filgotinib vs. Placebo* (1 fair-quality, phase 3 RCT [n=449]; 2 fair-quality phase 2 RCTs [n=594 and n=283]): Two RCTs assessed AEs at 24 weeks and 1 RCT assessed AEs at 12 weeks. Findings related to any AE or SAE were consistent across the 3 studies.[1] No differences were found between filgotinib and placebo groups in overall AEs or SAEs (moderate QoE for both).[1]
- *Peficitinib vs. Placebo* (3 fair-quality phase 2 RCTs [n=379, n=28 and n=281]; 2 fair-quality phase 3 RCTs [RAJ 3; n=509 and RAJ 4; n=519]): All 5 RCTs assessed AEs at 12 weeks.[1] Findings related to any AE or SAE were consistent across the 5 studies.[1] No differences were found between peficitinib and placebo groups in overall AEs or SAEs (moderate QoE for both).[1]
- *Peficitinib vs. Etanercept* (1 fair-quality, open-label, double-blinded RCT; n=509): No difference in overall AEs and SAEs was reported (low QoE for both).[1]
- *Certolizumab Pegol vs. Certolizumab Pegol + Bimekizumab* (1 fair-quality RCT; n=79): More participants experienced treatment-emergent AEs in the combination group compared to the certolizumab pegol monotherapy group (79% vs. 59%; P-value NR; low QoE).[1]

Pipeline Targeted Immune Modulators for Ankylosing Spondylitis

- *Filgotinib vs. Placebo* (1 fair-quality RCT; n=116): No differences in any treatment-emergent AEs were reported between filgotinib and placebo.[1] The incidence of treatment-emergent SAEs was higher in filgotinib group compared to placebo (2% vs. 0%; P-value NR; low QoE).[1]

C. Differences in Effectiveness or Harms in Specific Populations

No studies were identified that evaluated differences in TIM effectiveness and harms in specific subgroups based on age and racial groups, gender, patients with comorbidities, patients taking other commonly prescribed drugs, or in patients with early versus established disease.[1]

D. Conclusions:

Most comparisons for the safety and efficacy of TIMs in RA and AS are limited to single trials and the QoE for many outcomes is very low or low.[1] Drug manufacturers sponsored nearly all the RCTs, and although the extent to which the manufacturer's involvement influenced study execution or reporting is not definitively known, findings from a Cochrane systematic review suggest that industry sponsorship is associated with more favorable results than sponsorship by other sources.[1] Most observational studies addressing harms were of retrospective design and based on national registries; the quality and completeness of these databases cannot be determined.[1]

Moderate or high QoE indicates that baricitinib, sarilumab, and upadacitinib are more effective than adalimumab as first-line treatments for RA.[1] Based on moderate-quality evidence, abatacept is more effective than secukinumab as a second-line treatment for RA.[1] High and moderate quality evidence indicates no differences in the incidence of AEs and SAEs for TIMs.[1] Statistically significant differences in the incidence of AEs or SAEs of some comparisons are rated as very low- or low QoE and need to be interpreted with caution.[1] Only 1 poor quality head-to-head RCT was identified for AS, which does not allow for conclusions about the comparative effectiveness or safety of etanercept versus infliximab.[1] Twenty-four studies of head-to-head comparisons of TIM agents for the treatment of RA and AS are currently in progress; 10 will be completed before 2021.[1]

2. Targeted Immune Modulators for Plaque Psoriasis and Psoriatic Arthritis

The literature search for the DERP systematic review focused on TIMs for PsO and PsA was conducted from January 1, 2017 through August 20, 2019, with active surveillance of the literature through January 31, 2020.[2] The quality of the body of evidence for each drug comparison and indication (PsO or PsA) was evaluated for up to 5 selected outcomes (i.e., disease remission, clinical improvement, quality of life, AEs, and SAEs) using the GRADE approach.[2]

Twenty new studies were identified and 18 studies from the previous report were carried forward for a total of 38 eligible studies included in this update.[2] Thirty studies evaluated TIM agents for PsO, and 8 studies evaluated TIMs for PsA.[2] Of the 38 eligible studies, 31 were RCTs and 7 studies were cohort studies.[2] Among the 31 RCTs, 3 studies were rated as poor methodological quality and the rest as fair methodological quality.[2] Among the 7 cohort studies, 1 study was rated as poor methodological quality and the rest as fair methodological quality.[2] Outcomes selected for GRADE ratings ranged from low to high quality of evidence for most efficacy outcomes, and very low to moderate for most harm outcomes[2]. Generally, outcomes were downgraded for serious or very serious imprecision (i.e., wide confidence interval because of small sample size).[2]

A. Comparative Effectiveness of Targeted Immune Modulators

Targeted Immune Modulators for Plaque Psoriasis

Twenty-one RCTs provided direct evidence for 14 head-to-head TIM agent comparisons in patients with moderate-to-severe PsO.[2] One RCT was rated as poor-quality because of insufficient blinding and switching treatments.[2] The rest of the RCTs were rated as fair-quality, primarily because of industry sponsorship of studies and extensive manufacturer involvement in study design, execution, and reporting, and sponsorship of studies.[2] All studies reported disease remission outcomes as a primary study endpoint; the most commonly reported outcomes were the PASI 90 and PASI 75.[2] A score of 0 (no impact) or 1 (very minimal impact) on the PGA or investigator's global assessment (IGA) measure was also commonly used as either a primary or secondary outcome for disease remission.[2] Seventeen RCTs reported QoL; the Dermatology Life Quality Index (DLQI) was the mostly commonly reported QoL outcome.[2] One poor-quality RCT comparing etanercept to infliximab is excluded from this summary due to insufficient evidence demonstrating a difference in efficacy between the 2 drugs.

- *Apremilast vs. Etanercept* (1 fair-quality RCT; n=250): No difference in disease remission between apremilast and etanercept (PASI 75, 40% vs. 48%; P=0.26) or QoL was reported (change in DLQI; data and P-value NR; low QoE for remission and QoL) at 16 weeks. The dosage of etanercept used in this RCT (50 mg once per week) is the standard labeled dose in Europe; however, it is less than the FDA-approved dosage in the United States (50 mg twice weekly for 3 months, followed by 50 mg once a week).[2]
- *Brodalumab vs. Ustekinumab* (2 fair-quality, multi-center RCTs: AMAGINE-2 [n=1,883] and AMAGINE-3 [n=1,881]): Brodalumab was more effective compared to ustekinumab for achieving disease remission at 12 weeks (PASI 100: AMAGINE-2, 44% vs. 22%; P <0.001; AMAGINE-3, 37% vs. 19%; P <0.001; high QoE).[2] Those treated with brodalumab had greater response when compared to those receiving ustekinumab (AMAGINE-2: 79% vs. 61%; P <0.001; AMAGINE-3: 80% vs. 57%; P<0.001; high QoE) for achieving a 0 or 1 on the PGA.[2]
- *Etanercept vs. Ixekizumab* (2 fair-quality RCTs: UNCOVER-2 [n=1,224] and UNCOVER-3 [n=1,346]): Etanercept was less effective than ixekizumab for achieving disease remission at 12 weeks (PASI 75: ARDs, 31% to 48% for both RCTs; P-value NR) and for improving QoL (DLQI 0 or 1: ARDs, 20 to 30 percentage points for both RCTs; P-value NR); high QoE for both remission and QoL.[2]
- *Etanercept vs. Secukinumab* (1 fair-quality RCT; n=1,306): Etanercept was less effective than secukinumab for achieving disease remission at 12 weeks (PASI 75: 44% vs. 77% for 300 mg secukinumab; P<0.001 and 44% vs. 67% for 150 mg secukinumab; P<0.001; high QoE).[2] Etanercept was also less effective at improving QoL (mean change DLQI: -7.9 vs. -10.4 for 300 mg secukinumab; P-value NR and -7.9 vs. -9.7 for 150 mg secukinumab; P-value NR; moderate QoE).[2] Etanercept was also less effective at maintaining remission at 52 weeks (PASI 75: 73% vs. 84% for 300 mg secukinumab; and 73% vs. 82%; for 150 mg secukinumab; high QoE).[2]

- *Etanercept vs. Tildrakizumab* (1 fair-quality RCT; n=934): Etanercept was less effective than tildrakizumab for disease remission at 12 weeks (PASI 75: 48% vs. 66% for 200 mg tildrakizumab; P=0.001 and 48% vs. 61% for 100 mg tildrakizumab; P<0.001; high QoE).[2] Etanercept was also less effective than both doses of tildrakizumab for improving QoL at both 12 weeks (PGA 0 or 1: 36% vs. 47% for 200 mg tildrakizumab; p=0.003; moderate QoE) and 28 weeks (PGA 0 or 1: 39% for etanercept vs. 54% for 100 mg tildrakizumab vs. 65% for 200 mg tildrakizumab; P<0.001 for both tildrakizumab doses compared to etanercept; high QoE).[2]
- *Etanercept vs. Tofacitinib (not FDA-approved for psoriasis)* (1 fair-quality RCT; n=1,106): Etanercept was more effective than 5 mg tofacitinib at achieving disease remission at 12 weeks (PASI 75: 59% vs. 40%; P<0.001) but no differences compared to tofacitinib 10 mg was detected (PASI 75: 59% vs. 64%; P=0.20; moderate QoE).[2] Etanercept was more effective than 5 mg tofacitinib for improving QoL (DLQI 0 or 1: 75% vs. 66%, P=0.03; moderate QoE) but no differences compared to 10 mg tofacitinib were found (DLQI 0 or 1: 75% vs. 78%; P=0.31; low QoE).[2]
- *Etanercept vs. Ustekinumab* (1 fair-quality RCT; n=251): Etanercept was less effective compared to ustekinumab at 12 weeks (PASI 75: 57% vs. 74% for ustekinumab 90 mg; P<0.001, and 57% vs. 68% for ustekinumab 45 mg; P=0.01; low QoE).[2]
- *Guselkumab vs. Adalimumab* (3 fair-quality RCTs: X-PLORE [n=25]; VOYAGE-1 [n= 663]; and VOYAGE-2 [n=744]): Guselkumab was more effective than adalimumab for disease remission at 16 weeks (PGA 0 or 1: ARD range 16% to 28%; P-value NR; high QoE).[2] Guselkumab was also more effective at improving QoL (DLQI 0 or 1: ARD range 13% to 15%; P-value NR; moderate QoE).[2]
- *Guselkumab vs. Secukinumab* (1 fair-quality RCT; n=251): Guselkumab was more effective than secukinumab for disease remission at 48 weeks (PASI 90: 84% vs. 70%; P<0.001; moderate QoE).[2] Guselkumab was noninferior to secukinumab for disease remission at both 12 and 48 weeks (PASI 75: 85% vs. 80%; P<0.001 for non-inferiority; P=0.06 for superiority; moderate QoE).[2] A higher PASI 90 response was observed for secukinumab compared to guselkumab (69% vs. 76%), but no statistical testing was performed to control for type I error.[2]
- *Ixekizumab vs. Ustekinumab* (1 fair-quality RCT; n=302): Ixekizumab was more effective than ustekinumab for disease remission at 12 weeks (PASI 90: 73% vs. 42%; P<0.001; moderate QoE) and at 52 weeks (PASI 90: 77% vs. 59%; P-value NR; moderate QoE).[2] Ixekizumab was also more effective for improving QoL at 12 weeks (DLQI 0 or 1: 61% vs. 45%; P=0.01; moderate QoE).[2]
- *Risankizumab vs. Adalimumab* (1 fair-quality RCT; n= 605) Risankizumab was more effective than adalimumab for disease remission at 16 weeks (PASI 90: 72% vs. 47%; P-value NR; ARD 25%; 95% CI 18 to 32; P<0.001; moderate QoE).[2] Risankizumab was also more effective at improving QoL at 16 weeks (DLQI 0 or 1: 66% vs. 49%; P<0.001; moderate QoE).[2]
- *Risankizumab vs. Ustekinumab* (3 fair-quality RCTs: UltIMMA-1 [n= 506]; UltIMMA-2 [n=393]; and Papp, et al. [n=166]): At 16 weeks, more participants randomized to risankizumab in UltIMMA-1 and UltIMMA-2 had disease remission compared to ustekinumab (PASI 90 75% vs. 42%; P <0.001 in UltIMMA-1; 75% vs. 48%; P <0.001 in UltIMMA-2; moderate QoE).[2] Risankizumab was more effective than ustekinumab for disease remission at 12 to 16 weeks (PASI 90: ARD range 28% to 37%, P-value NR; moderate QoE). Risankizumab was also more effective at improving QoL at 12 to 16 weeks (DLQI 0 or 1: ARD range 19% to 23%; P-value NR; moderate QoE). In the Papp, et al. RCT, risankizumab (data pooled for 90-mg and 180-mg dosages) was more effective than ustekinumab for the PASI 90 response (77% vs. 40%; P <0.001; moderate QoE).[2]
- *Secukinumab vs. Ustekinumab* (2 RCTs: CLEAR [n=676] and CLARITY [n=1,102]): For the primary study outcome in CLEAR, participants randomized to secukinumab had a higher PASI 90 response (79%) compared to those randomized to ustekinumab (58%; P<0.001; high QoE) at 16 weeks.[2] For the primary study outcome in CLARITY, participants randomized to secukinumab had a higher PASI 90 response (67%) compared to those randomized to ustekinumab (48%; P<0.001; high QoE).[2] Secukinumab was more effective than ustekinumab for disease remission at 16 weeks (PASI 90: ARDs 21% and 22%; P-value NR; high QoE).[2] Secukinumab was also more effective at improving QoL at 16 weeks (DLQI 0 or 1: ARDs 13% and 15%; P-value NR; high QoE).[2]

Pipeline Targeted Immune Modulators for Plaque Psoriasis

Three pipeline drugs, bimekizumab, BMS-986165, and mirikizumab, have been studied for effectiveness in managing PsO compared to placebo in 4 fair-quality RCTs.[2] Bimekizumab is an IL-17 inhibitor administered via SC and IV routes to patients with PsO in clinical trials. BMS-986165 is a novel oral tyrosine kinase 2 inhibitor. Mirikizumab is an IL-23 inhibitor administered via the SC route.

- *Bimekizumab vs. Placebo* (2 fair-quality RCTs; BE-ABLE [n=250] and Glatt, et al. [n=39]): The BE-ABLE trial evaluated various bimekizumab (64 mg, 160 mg, 320 mg, and 480 mg) doses administered SC every 4 weeks and reported outcomes at 12 weeks.[2] Glatt et al. administered various bimekizumab doses between 8 mg and 640 mg as a single infusion and reported outcomes over 20 weeks.[2] In the BE-ABLE trial, the proportion of participants achieving PASI 90 response varied from 46% to 79% across all bimekizumab doses and was 0% in the placebo group (P<0.001 for all dose comparisons to placebo; moderate QoE for remission).[2] The Glatt et al. trial was a first in-human study with AEs designated as the primary study endpoints.[2] However, clinical efficacy was evaluated and statistically significant differences between placebo and all doses evaluated were observed at all timepoints for the lesion severity score, and for the higher doses evaluated (160 mg, 480 mg, 640 mg) at nearly all timepoints for percent change from baseline for PASI and PGA.[2]
- *BMS-986165 vs. Placebo* (1 fair-quality RCT; n=268): One trial evaluated various dosages (3 mg daily, 3 mg every other day, 6 mg twice daily, and 12 mg once daily) of BMS-98165, compared to placebo, over 12 weeks among adults with moderate-to-severe PsO for at least 6 months.[2] Except for the lowest dose (3 mg every other day), all doses were more effective than placebo for the primary study endpoint (PASI 75: ARD range 36% to 72%; moderate QoE) and nearly all secondary remission, clinical improvement, and QoL outcomes.[2]
- *Mirikizumab vs. Placebo* (1 fair-quality RCT, n=205): This phase 2 RCT compared multiple doses of mirikizumab (30 mg, 100 mg, and 300 mg) to placebo among participants with at least moderate PsO for at least 6 months.[2] The primary study endpoint was PASI 90 response at 16 weeks.[2] For the PASI 90 response, all doses of mirikizumab were superior to placebo (300 mg, 67%; 100 mg, 59%; 30 mg, 29%; 0%, placebo; P< 0.001 for 300 mg and 100 mg vs. placebo; P=0.009 for 30 mg vs. placebo; moderate QoE).[2] For QoL, 47% of participants randomized to the 300-mg dosage achieved a 0 or 1 response on the DLQI compared with 49% (100-mg dosage), 35% (30-mg dosage), and 4% (placebo, P<0.001 for all comparisons with placebo; moderate QoE).[2]

Targeted Immune Modulators for Psoriatic Arthritis

Four RCTs evaluated the comparative effectiveness of TIMs in the management of PsA; of these, 1 RCT is new to this update.[2] All studies enrolled participants with active PsA; 1 study specifically required active enthesitis (i.e., a common symptom in PsA involving inflammation of the sites where tendon or ligaments attach to bones).[2] Two RCTs were rated as poor-quality for various critical methodological flaws and are excluded from this summary. The other 2 RCTs were rated as fair-quality because of industry sponsorship and extensive manufacturer involvement in study design, execution, and reporting.[2] Nearly all studies reported clinical improvement as primary study endpoints; the most commonly reported outcomes were the ACR20 response.[2] Only 2 of the RCTs reported QoL outcomes.[2]

- *Adalimumab vs. Ixekizumab* (1 fair-quality RCT; n=417): Lower rates of clinical improvement was reported at 24 weeks with adalimumab compared to ixekizumab every 2 weeks or every 4 weeks (ACR20: 57% vs. 62% vs. 58%, respectively; low QoE); no statistical significance testing was performed as the primary study aim was to compare ixekizumab to placebo.[2] Lower skin disease remission response was also observed with adalimumab compared to ixekizumab every 2 weeks or every 4 weeks (PASI 75: 54% vs. 80% vs. 71%; low QoE).[2]
- *Adalimumab vs. Tofacitinib* (1 fair-quality RCT; n=422): This trial was designed to evaluate superiority of tofacitinib compared to placebo; it was not designed to show superiority or non-inferiority between the active drug groups and no statistical testing was conducted among active treatment groups.[2] Subjects treated with adalimumab had lower rates of clinical improvement at 12 months compared to participants treated with tofacitinib 10 mg, but not compared to participants treated with tofacitinib 5 mg (ACR20: 60% vs. 70% vs. 68%, respectively; low QoE).[2] Numerically lower skin disease remission was observed with adalimumab at 12 months compared to tofacitinib 10 mg, but not 5 mg (PASI 75: 56% vs. 67% vs. 56%; low QoE).[2] Higher

improvement in QoL (SF-36 Physical Health Component Score [PCS]) was reported with adalimumab compared to tofacitinib 10 mg or tofacitinib 5 mg (6.2 vs. 5.7 vs. 5.5, respectively; low QoE).[2]

Pipeline Targeted Immune Modulators for Psoriatic Arthritis

Two RCTs, both new to the DERP update, reported on the efficacy of 2 pipeline TIM agents for PsA: filgotinib and remtolumab.[2] Remtolumab is a dual TNF-inhibitor and IL-17 inhibitor administered via the SC route.[2]

- *Remtolumab vs. Placebo and Adalimumab* (1 fair-quality, phase 2 RCT; n=240): This study was primarily designed to evaluate remtolumab compared to placebo; however, findings for the adalimumab versus remtolumab comparison were also reported.[2] With respect to clinical improvement, a higher percentage of participants achieved an ACR50 response with both doses of remtolumab (37% and 53% for the 120 mg and 240 mg dosages, respectively) compared to placebo (13%; P<0.05 and P<0.001 respectively; moderate QoE).[2] With respect to remission, the percentage of participants achieving an ACR70 response was higher in both doses of remtolumab (23% for 120 mg dosage, 32% for 240 mg dosage) compared to placebo (4%; P<0.05 for 120 mg dosage and P<0.01 for 240 mg dosage; moderate QoE).[2] No difference in clinical improvement (ACR50) with adalimumab at 12 weeks compared to 120 mg remtolumab dose was reported; low QoE).[2] A lower proportion of adalimumab-treated patients had disease remission compared to patients who received the 240 mg remtolumab dose (ACR70: ARD, 16.2%; 95% CI, 2.7% to 29.7%), but no difference in disease remission was observed when compared to the 120 mg remtolumab dose (low QoE).[2]
- *Filgotinib vs. Placebo* (1 fair-quality, phase 2 RCT; n=131): A higher proportion of participants randomized to filgotinib (80%) had an ACR20 response compared to placebo (33%; P<0.001; low QoE) at 16 weeks.[2] Filgotinib was also superior to placebo on all secondary remission and clinical improvement outcomes.[2]

B. Comparative Harms of Targeted Immune Modulators

Targeted Immune Modulators for Plaque Psoriasis

Overall, few differences in harms were observed in 21 head-to-head RCT comparisons of TIM agents in patients with PsO.[2] In the RCT body of evidence, between-agent differences were typically in just one of several harm outcomes reported when differences were present.[2] Five cohort studies provided evidence on the comparative harms for various TIMs.[2] Two cohort studies were conducted with participants identified based on insurance claims for biologic therapy and diagnosis codes for psoriasis.[2] One study was conducted by academic researchers among 107,707 participants who were new users of adalimumab, apremilast, etanercept, infliximab, ustekinumab, and other nonbiological DMARD agents.[2] In the second cohort study (n=650), insurance claims were used to identify participants; analyses were restricted to patients on monotherapy.[2] This analysis, supported by the manufacturer, found no statistically significant differences in "adverse medical conditions" between adalimumab and the other biological agents that were included in the analysis (etanercept, ustekinumab, and infliximab).[2] Two additional cohort studies were conducted with participants identified from the British Association of Dermatologists Biologic Interventions Register (BADBIR), a prospective registry of patients from 157 dermatology centers in the U.K. and Ireland supported by multiple drug manufacturers for pharmacovigilance activities.[2] One trial analyzed 7,136 patients with psoriasis recruited within 6 months of initiating or switching to a biologic or conventional systemic therapy.[2] The primary goal of this study was to compare the incidence of SAEs among participants in the registry who would meet criteria for typical clinical trials with those participants not meeting trial eligibility criteria.[2] Another study included 3,523 patients and the data were analyzed using the BADBIR to evaluate discontinuations due to AEs.[2] The final cohort study was conducted among 10,065 participants with PsO identified from 3 Italian referral centers between 2007 and 2011 and was supported by an unrestricted grant from the manufacturer.[2] Findings where a statistically significant difference was observed in AEs, SAEs, or other serious harms are reported below.

- *Apremilast vs. Adalimumab* (1 fair-quality cohort; n=107,707): Lower incidence of serious infection requiring hospitalization for apremilast compared to adalimumab (hazard ratio [HR], 0.31; 95% CI, 0.15 to 0.65; very low QoE).[2]

- *Apremilast vs. Etanercept* (1 fair-quality RCT; n=250)*:* A lower proportion of overall AEs was observed for apremilast compared to etanercept (53% vs. 71%; RR, 0.75; 95% CI, 0.58 to 0.95; low QoE).[2]
- *Etanercept vs. Adalimumab* (2 fair-quality cohorts; [n=650 and n=7,136])*:* Lower incidence of serious infection requiring hospitalization for etanercept (HR, 0.76; 95% CI, 0.61 to 0.94; very low QoE) in 1 study; lower incidence rate of SAEs (incidence rate ratio [IRR], 0.75; 95% CI, 0.66 to 0.86; very low QoE) in other study.[2]
- *Etanercept vs. Secukinumab* (1 fair-quality RCT; n=1306): In the RCT comparing etanercept to secukinumab over 12 weeks, a higher risk of injection site reactions was observed for etanercept (11%) compared to secukinumab (1%; RR, 14.9; 95% CI, 6.7 to 33.2).[2]
- *Etanercept vs. Tildrakizumab* (1 fair-quality RCT; n=1090): Fewer overall AEs for tildrakizumab 200 mg compared with etanercept during weeks 13 to 28 (RR, 0.80; 95% CI, 0.68 to 0.93), but no difference in incidence of AE during weeks 0 to 12 (moderate QoE).[2] No difference in incidence of SAEs during both time periods was observed (low QoE).[2]
- *Etanercept vs. Ustekinumab* (1 fair-quality RCT; n=903 and 1 fair-quality cohort; n=3,523): In the RCT comparing etanercept to ustekinumab, injection site reactions were more frequent with etanercept compared to ustekinumab over 12 weeks (RR, 4.0; 95% CI, 4.0 to 9.8; moderate QoE); however, participants in the etanercept group received more injections than participants receiving ustekinumab.[2] In the cohort study ustekinumab had a statistically significantly higher incidence of SAEs compared to etanercept (IRR, 2.4; 95% CI, 1.8 to 3.1; very low QoE).[2]
- *Infliximab vs. Adalimumab* (1 fair-quality cohort; n=3,523)*:* A higher incidence of serious infection requiring hospitalization for infliximab was observed compared to adalimumab (HR, 1.9; 95% CI, 1.01 to 3.6; very low QoE).[2]
- *Risankizumab vs. Ustekinumab* (3 fair quality RCTs UltlMMA-1 [n=506]; UltlMMA-2 [n=393]; Papp, et al. [n=166])*:* One RCT (Papp, et al.) reported no statistically significant differences in AEs or SAEs between risankizumab and ustekinumab.[2] Two RCTs (UltlMMA-1 and UltlMMA-2) reported some differences but not across all time periods evaluated.[2] For overall AEs, fewer AEs were observed for risankizumab in the later time period (weeks 17 to 52) of one study (RR, 0.75; 95% CI, 0.11 to 0.77; UltlMMA-2) and fewer SAEs were observed with risankizumab compared to ustekinumab in the early time period (weeks 0 to 16) of the other study (RR, 0.29; 95% CI, 011 to 0.77: UltlMAA-1).[2]
- *Ustekinumab vs. Adalimumab* (1 fair-quality cohort; n=10,065): No difference in serious infection requiring hospitalization was observed with ustekinumab versus adalimumab (HR, 0.70; 95% CI, 0.49 to 1.0; very low QoE); however, a higher incidence of SAEs for ustekinumab was observed (IRR, 1.2; 95% CI, 1.1 to 1.4, very low QoE).[2]

Pipeline Targeted Immune Modulators for Plaque Psoriasis

Four RCTs reported on the harms versus placebo of 3 pipeline TIM agents.[2]

- *Bimekizumab vs. Placebo* (2 fair-quality RCTs; BE-ABLE [n=250] and Glatt, et al. [n=39]): In the BE-ABLE trial, an increased risk of AEs was observed with bimekizumab (all dosages pooled) compared to placebo (RR, 1.7; 95% CI, 1.1 to 2.6).[2] No differences in SAEs or withdrawals due to AEs were observed. With respect to harms in the Glatt, et al. trial, no differences were observed in AEs compared to placebo (all dosages were pooled).[2] Only 1 SAE occurred overall in the bimekizumab group. No withdrawals due to AE were observed in either the bimekizumab or placebo group.[2]
- *BMS-986165 vs. Placebo* (1 fair-quality RCT; n=268): AEs were more common at higher doses of BMS-986165 compared to placebo over 12 weeks but no differences in SAEs or withdrawals due to AEs for observed for any doses. Injection site reactions were not reported.
- *Mirikizumab vs. Placebo* (1 fair-quality RCT; n=205): No differences in AEs, SAEs, or injection site reactions were observed with mirikizumab versus placebo.[2]

Targeted Immune Modulators for Psoriatic Arthritis

Four of 5 RCTs that evaluated efficacy also reported harms associated with TIMs used to treat PsA.[2] Few differences in harms were observed in head-to-head comparisons of TIM agents for overall AEs, SAEs, and withdrawals due to AEs.[2] One new fair-quality cohort study was identified for the DERP update.[2] In this study, insurance claims were used to identify adults with PsA or PsO who initiated therapy with ustekinumab or a TNF-inhibitor between 2009 and 2015.[2] No differences were observed for incident atrial fibrillation or major cardiovascular events between the included TIMs.[2] The previous review included 1 poor-methodological-quality cohort study which identified patients with various rheumatologic conditions, including PsA, from a Turkish patient registry is excluded from this summary.[2]

Pipeline Targeted Immune Modulators for Psoriatic Arthritis

Two placebo-controlled RCTs reported on the harms of 2 pipeline TIM agents when used to manage PsA.[2]

- *Filgotinib Compared to Placebo* (1 fair-quality RCT; n=131): For harms, no statistically significant difference was observed for overall AEs (low QoE), SAEs, or withdrawals due to AEs, though findings were imprecise for the latter 2 outcomes (very low QoE).[2]
- *Remtolumab vs. Placebo and Adalimumab* (1 fair-quality, phase 2 RCT; n=240): No statistically significant differences were observed for either dose for treatment-emergent AEs (low QoE), SAEs, or withdrawals due to AEs, though findings for the latter 2 outcomes were very imprecise (very low QoE).[2]

C. Differences in Effectiveness or Harms in Specific Populations

No studies were identified to evaluate differences in TIM effectiveness and harms in PsO or PsA based on age and racial groups, gender, patients with comorbidities, patients taking other commonly prescribed drugs, or in patients with early, compared to established, disease for this report.[2]

D. Conclusions:

The largest body of comparative evidence is for etanercept and ustekinumab versus other TIM agents in patients with PsO.[2] For disease remission outcomes, high-quality evidence suggests that etanercept is less effective than ixekizumab, secukinumab, and tildrakizumab.[2] High-quality evidence also suggests that ustekinumab is less effective than brodalumab and risankizumab and moderate quality evidence suggests it may also be less effective than ixekizumab for disease remission outcomes.[2] High-quality evidence suggests that adalimumab is less effective than guselkumab and moderate-quality evidence suggests that it is also less effective than risankizumab[2]. Finally, moderate-quality evidence suggests that guselkumab is more effective than secukinumab for maintenance therapy.[2] Few differences in harms among TIM agents were observed, based on very low- to moderate-quality evidence.[2] For PsA, limited head-to-head comparisons were available.[2] Based on low-quality evidence, ixekizumab, tofacitinib, and remtolumab may be more effective than adalimumab with no difference in harms.[2]

Thirty ongoing studies are evaluating the comparative effectiveness or harms of TIM agents.[2] Twenty-three of these studies are RCTs and 7 are observational studies.[2] Seventeen RCTs are in participants with PsO and 6 are in participants with PsA.[2] Two observational studies are in participants with PsO, 3 are in participants with PsA, and 2 studies include participants with either condition.[2] Drug manufacturers are funding 27 studies, hospitals are funding 2 studies, and the NIH is funding 1 study.[2]

3. Targeted Immune Modulators for Crohn's Disease and Ulcerative Colitis

The literature search for the DERP systematic review focused on TIMs for management of CD and UC was conducted from January 1, 2017 through August 2019, with active surveillance of the literature through December 31, 2019. Three new studies were identified and 6 studies were carried forward from the previous

report for a total of 9 eligible studies in this update.[3] Four studies evaluated TIM agents exclusively among participants with CD, 2 studies evaluated TIM agents exclusively among participants with UC and 3 studies evaluated TIMs among mixed populations that included participants with CD or UC.[3]

Of the 9 eligible studies, 4 were RCTs and 5 were cohort studies. Among the 4 RCTs, 1 study was rated as poor-quality and the rest were rated as fair-quality.[3] Among the 5 cohort studies, 1 was rated as poor-quality and the rest were rated as fair-quality.[3] Outcomes selected for GRADE ratings ranged from very low to moderate QoE, with most rated as very low QoE.[3] Generally, outcomes were downgraded for indirectness (i.e., applicability) and serious imprecision (i.e., wide confidence interval because of small sample size).[3]

A. Comparative Effectiveness of Targeted Immune Modulators

One fair-quality RCT evaluated comparative effectiveness of adalimumab compared with infliximab in CD; 1 poor-quality study is excluded from this summary.

Targeted Immune Modulators for Crohn's Disease

- *Adalimumab vs. Infliximab* (1 fair-quality, open-label RCT, n=73): No difference between adalimumab and infliximab in changes in quality of life and clinical improvement were reported after 12 months of therapy (low QoE).[3]

Pipeline Targeted Immune Modulators for Crohn's Disease

One placebo-controlled RCT evaluated the efficacy of an investigational agent, PF-04236921 which is an IL-6 inhibitor administered via the SC route.

- *PF-04236921 vs. Placebo* (1 fair-quality RCT; n=249): Pfizer funded this study, and 5 authors were Pfizer employees who were involved in study design, data collection, data analysis, and data interpretation.[3] The study enrolled adults with moderate-to-severe CD who had failed or were intolerant to 1 or more TNF-inhibitors, and compared 3 doses of PF-04236921 (10 mg, 50 mg or 200 mg SC on days 1 and 28) with placebo. The 200-mg dosage was not included in the analysis because this study arm was stopped early due to fatalities seen in patients with lupus who were treated with this dose in a separate trial.[3] The primary outcome was the proportion of patients achieving a 70-point or greater reduction in the Crohn's Disease Activity Index score (CDAI-70). Compared to placebo, the 50-mg dose produced a greater CDAI-70 response at both 8 weeks (49% vs. 31%; P <0.05) and at 12 weeks (47% vs. 29%; P <0 .05; moderate QoE for both time points).[3] In contrast, no difference was found with the 10-mg dose at either 8 weeks (35% vs. 31%; P>0.05) or 12 weeks (35% vs. 29%; P >0.05; low QoE for both time points) compared to placebo.[3] No differences in QoL were noted between the 50-mg and 10-mg dosages and placebo (low QoE).[3]

Targeted Immune Modulators for Ulcerative Colitis

One head-to-head RCT evaluated comparative efficacy of 2 TIMs approved to treat UC.

- *Vedolizumab vs. Adalimumab* (1 fair-quality RCT; n=769): One RCT compared IV vedolizumab to SC adalimumab for 1 year in patients with moderate-to-severe UC. This study was sponsored by the manufacturer, and was rated as fair quality primarily because of extensive manufacturer involvement in study design and execution.[3] Compared to the adalimumab arm , participants who received vedolizumab had a higher incidence of achieving clinical remission (31% vs. 23%; ARD, 9%; 95% CI, 3% to 15%) and endoscopic remission (40% vs. 28%; ARD, 12%; 95% CI, 5% to 19%) at 1 year.[3] In addition, larger improvements in QoL at (ARD 9.6%; 95% CI, 2.8% to 16.5%) were observed at 1 year with vedolizumab compared to adalimumab (all results, P<0.05; moderate quality QoE).[3] No difference in incidence of corticosteroid-free remission (among those taking steroids at baseline) were observed between the vedolizumab and adalimumab arms (low QoE).[3]

B. Comparative Harms of Targeted Immune Modulators

Targeted Immune Modulators for Crohn's Disease

Two cohort studies compared adalimumab with etanercept and infliximab. Both studies were conducted among mixed populations with CD as well as other autoimmune disease for which TIMs are indicated. One study was rated as fair-quality and the other was rated as poor-quality and is excluded from this summary. The fair-quality study (n=8,421) used data from the Health Insurance Review and Assessment Service in South Korea.[3] This study reported a statistically significant higher risk of tuberculosis with adalimumab (IRR 3.45; 95% CI, 1.82 to 6.55) or infliximab IRR 6.80; 95% CI, 3.74 to 12.37) compared to etanercept.[3] The results of 1 head-to-head RCT and 4 observational, cohort studies evaluating the comparative harms of TIMs when used to manage CD are summarized below.

- *Adalimumab vs. Infliximab* (1 fair-quality, open-label RCT; n=73): No difference in incidence of AEs between adalimumab and infliximab were observed, but results were too imprecise to draw definitive conclusions about SAEs, withdrawals due to AEs, and infection (very low QoE).[3]
- *Adalimumab vs. Certolizumab Pegol vs. Infliximab* (1 fair-quality cohort; n=3,025): The American College of Gastroenterology sponsored this study, with additional investigator support from the National Institutes of Health.[3] This study was conducted using administrative and claims data obtained from OptumLabs, which includes privately insured and Medicare beneficiaries in the United States.[3] No difference in the incidence of serious infection was observed between the 3 TIMs agents, however results were imprecise (very low QoE).[3]
- *Adalimumab vs. Infliximab vs. Etanercept* (2 fair-quality cohorts and 1 poor-quality cohort): One fair-quality cohort study used administrative and registry data from 1,400 patients in Italy that compared infliximab with adalimumab in a population with either CD or UC.[3] Among the population with CD (n=872), a higher incidence of infections with infliximab compared to adalimumab was reported (adjusted hazard ratio [aHR], 1.63; 95% CI, 0.61 to 4.34), but this result was not statistically significant and the estimate was very imprecise (low QoE).[3]

Pipeline Targeted Immune Modulators for Crohn's Disease

One placebo-controlled RCT evaluated the harms associated with administration of the investigational agent PF-04236921.

- *PF-04236921 compared to Placebo* (1 fair-quality RCT; n=249): PF-0236921 10 mg and 50 mg compared to placebo. No difference in incidence of overall AEs between placebo and the investigational agent was reported (moderate QoE).[3] No difference in SAEs, withdrawals due to AEs, or injection site reactions was noted, but results were too imprecise to draw a definitive conclusion (low QoE).[3] Common AEs included worsening of CD, abdominal pain, headache, and nasopharyngitis.[28] One death occurred in the 50-mg dosage group.[3]

Targeted Immune Modulators for Ulcerative Colitis

One head-to-head RCT and 3 observational, cohort studies evaluated the comparative harms of TIMs when used to manage UC. One poor-quality cohort trial is excluded from this summary.

- *Vedolizumab vs. Adalimumab* (1 fair-quality RCT; n=769): marginally lower incidence of AEs at 1 year was observed for vedolizumab compared to adalimumab (RR 0.91; 95% CI 0.82 to 1.00; moderate QoE).[3] No difference in incidence of SAEs, withdrawals due to AEs, or infections at 1 year was observed between vedolizumab and adalimumab, but results were too imprecise to draw a definitive conclusion (low QoE).[3]
- *Infliximab vs. Adalimumab* (2 fair-quality cohorts): Both observational studies (1 conducted in the U.S (n=1400) and 1 conducted in Italy (n=560) were based on administrative and claims data.[3] No differences in risk of serious infection and overall infections were observed when infliximab was compared to adalimumab, but results were too imprecise to draw a definitive conclusion (very low QoE).[3]
- *Adalimumab vs. Infliximab vs. Etanercept* (1 fair-quality cohort, n=10,021)A higher incidence of tuberculosis was observed with adalimumab (IRR 5.6; 95% CI 3.3 to 9.2) or infliximab (IRR 5.8; 95% CI 3.0 to 8.5 compared to etanercept in participants with UC.[3]

C. Differences in Effectiveness or Harms in Specific Populations

No studies were identified to evaluate differences in TIM agents for effectiveness and harms in CD or UC based on age and racial groups, gender, patients with comorbidities, patients taking other commonly prescribed drugs, or in patients with early, compared to established, disease.[3]

D. Conclusions:

The evidence for comparative effectiveness and harms of TIM agents in CD is limited to comparisons between adalimumab and certolizumab pegol, etanercept, or infliximab, and nearly all outcomes were rated as low or very low QoE precluding any definitive conclusions.[3] For UC, vedolizumab is more effective compared to adalimumab (moderate QoE) with no differences in AEs (moderate to low QoE).[3] Other evidence for comparative harms in UC is limited to comparisons between adalimumab and infliximab or etanercept, and all outcomes were rated as very low QoE precluding any definitive conclusions.[3] One pipeline drug (PF-0423691) is more effective at the 50-mg dosage compared to placebo in managing CD (moderate QoE for clinical improvement and remission, low QoE for quality of life) with no difference in incidence of AE (low QoE).[3] Thirteen studies of head-to-head comparisons of TIM agents for either CD or UC are currently in progress.[3] Seven RCTs are in participants with CD, 5 RCTs are in participants with UC and 1 cohort study is in participants with both conditions. The earliest estimated completion date for any of these studies is March 2021.[3]

New Formulations and Indications:

- Hulio™, a sixth biosimilar for Humira® (adalimumab), received FDA approval July 2020. This biosimilar is approved for all the indications of Humira® including RA, AS, PsA, PsO (age 4 and older), hidradenitis suppurativa (age 12 and older), CD (age 6 and older), UC, uveitis (age 2 and older), and juvenile idiopathic arthritis (age 2 and older). The product will not be available in the U.S. until 2023 due to a patent agreement with AbbVie, the manufacturer of Humira®.

- Cosentyx® (secukinumab) received an expanded indication for treatment of adults with active non-radiographic axial spondyloarthritis (nr-axSpA) with objective signs of inflammation in June 2020.[29] Previously approved indications for secukinumab include PsO, PsA, and AS.

- Taltz® (ixekizumab) received an expanded indication for treating nr-axSpA in adults with objectives signs of inflammation in May 2020.[30] Previously approved indications include PsO, PsA and AS.

- In March 2020, Taltz (ixekizumab) received an expanded approval for use in pediatric patients with moderate-to-severe PsO aged 6 years and older who are candidates for systemic therapy or phototherapy.[30]

- The FDA expanded the approved indication for canakinumab (Ilaris®) in June 2020 to include treatment of active Still's disease.[31] Canakinumab had previously been approved for systemic juvenile idiopathic arthritis (JIA) in patients aged 2 years and older. According to the FDA, adult onset Still's disease shares considerable overlap with systemic JIA, which are both characterized by fever, arthritis, rash and elevated inflammation markers.

- Guselkumab (Tremfya) received FDA approval to treat adults with active PsA.[32]

Safety:

Table 4. Description of New FDA Safety Alerts

Generic Name	Brand Name	Month / Year of Change	Labeling Addition or Change	Description
Vedolizumab	Entyvio	March 2020	Warnings and Precautions	PML, a rare and often fatal opportunistic infection of the central nervous system (CNS), has been reported with systemic immunosuppressants, including another integrin receptor antagonist. PML is caused by the John Cunningham (JC) virus and typically only occurs in patients who are immunocompromised. One case of PML in a vedolizumab-treated patient with multiple contributory factors has been reported in the post marketing setting (e.g., human immunodeficiency virus [HIV] infection with a CD4 count of 300 cells/mm3 and prior and concomitant immunosuppression). Although unlikely, a risk of PML cannot be ruled out. Infusion-related reactions and hypersensitivity reactions have been reported, including anaphylaxis, dyspnea, bronchospasm, urticaria, flushing, rash, and increased blood pressure and heart rate. These reactions may occur with the first or subsequent infusions of vedolizumab and may vary in their time of onset from during infusion or up to several hours post-infusion. If anaphylaxis or other serious infusion-related or hypersensitivity reactions occur.
Infliximab	Remicade	May 2020	Warnings and Precautions	The use of infliximab at doses >5 mg/kg is contraindicated in patients with moderate or severe heart failure. A randomized, double-blind, placebo-controlled study evaluated the use of infliximab (5 mg/kg or 10 mg/kg at Weeks 0, 2, and 6) in patients with moderate or severe heart failure [New York Heart Association (NYHA) Functional Class III/IV]. Compared to patients who received placebo, there was a higher rate of mortality and a higher risk of hospitalization at Week 28 due to heart failure in patients who received the 10 mg/kg infliximab dose, and higher rates of cardiovascular adverse events in patients who received REMICADE doses of 5 mg/kg and 10 mg/kg. There have been post-marketing reports of new onset and worsening heart failure, with and without identifiable precipitating factors (e.g., pre-existing cardiovascular disease), in infliximab-treated patients. Some of these patients have been under 50 years of age. If a decision is made to administer infliximab (≤ 5 mg/kg) to patients with moderate or severe heart failure or to administer infliximab (any approved dose) to patients with mild heart failure, they should be closely monitored during therapy, and infliximab should be discontinued if new or worsening symptoms of heart failure appear.

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30. Taltz® (ixekizumab) injection. Prescribing Information. Indianapolis, IN: Eli Lilly and Company. May 2020.
31. Ilaris® (canakinumab) for injection. Prescribing information. East Hanover, NJ: Novartis. June 2020.
32. Tremfya® (guselkumab) for injection. Prescribing Information. Horsham, PA: Janssen. July 2020.

Appendix 1: Current Preferred Drug List

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

guselkumab	TREMFYA	SUB-Q	AUTO INJCT	N
guselkumab	TREMFYA	SUB-Q	SYRINGE	N
infliximab	REMICADE	IV	VIAL	N
infliximab-abda	RENFLEXIS	IV	VIAL	N
infliximab-dyyb	INFLECTRA	IV	VIAL	N
ixekizumab	TALTZ AUTOINJECTOR	SUB-Q	AUTO INJCT	N
ixekizumab	TALTZ AUTOINJECTOR (2 PACK)	SUB-Q	AUTO INJCT	N
ixekizumab	TALTZ AUTOINJECTOR (3 PACK)	SUB-Q	AUTO INJCT	N
ixekizumab	TALTZ SYRINGE	SUB-Q	SYRINGE	N
natalizumab	TYSABRI	IV	VIAL	N
risankizumab-rzaa	SKYRIZI	SUB-Q	SYRINGE	N
risankizumab-rzaa	SKYRIZI (2 SYRINGES) KIT	SUB-Q	SYRINGEKIT	N
rituximab	RITUXAN	IV	VIAL	N
rituximab-abbs	TRUXIMA	IV	VIAL	N
rituximab-pvvr	RUXIENCE	IV	VIAL	N
sarilumab	KEVZARA	SUB-Q	PEN INJCTR	N
sarilumab	KEVZARA	SUB-Q	SYRINGE	N
tildrakizumab-asmn	ILUMYA	SUB-Q	SYRINGE	N
tocilizumab	ACTEMRA	IV	VIAL	N
tocilizumab	ACTEMRA ACTPEN	SUB-Q	PEN INJCTR	N
tocilizumab	ACTEMRA	SUB-Q	SYRINGE	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	IV	VIAL	N
ustekinumab	STELARA	SUB-Q	SYRINGE	N
vedolizumab	ENTYVIO	IV	VIAL	N

Biologics for Autoimmune Diseases

Goal(s):

- Restrict use of biologics 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 high value products.

Length of Authorization:

- Up to 12 months

Requires PA:

- All biologics for autoimmune diseases (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 Biologic Immunosuppressants.

Drug Name	Ankylosing Spondylitis	Crohn's Disease	Juvenile Idiopathic Arthritis	Plaque Psoriasis	Psoriatic Arthritis	Rheumatoid Arthritis	Ulcerative Colitis	Other
Abatacept (ORENCIA)			≥2 yo		≥18 yo	≥18 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	≥18 yo	Uveitis (non-infectious) ≥2 yo (Humira) HS ≥ 12 yo
Anakinra (KINERET)						≥18 yo		NOMID
Apremilast (OTEZLA)				≥18 yo	≥18 yo			Oral Ulcers associated with BD ≥ 18 yo
Baricitinib (OLUMIANT)						≥18 yo		
Brodalumab (SILIQ)				≥18 yo				
Canakinumab (ILARIS)			≥2 yo					FCAS ≥4 yo MWS ≥4 yo TRAPS ≥ 4 yo

Drug Name	Ankylosing Spondylitis	Crohn's Disease	Juvenile Idiopathic Arthritis	Plaque Psoriasis	Psoriatic Arthritis	Rheumatoid Arthritis	Ulcerative Colitis	Other
								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) ≥18 yo (biosimilars)	≥18 yo	≥18 yo		
Golimumab (SIMPONI and SIMPONI ARIA)	≥18 yo				≥18 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				
Rituximab (RITUXAN) and biosimilars						≥18 yo		CLL ≥18 yo NHL ≥18 yo GPA ≥2yo MPA ≥ 2 yo Pemphigus Vulgaris ≥18 yo (Rituxan only)
Sarilumab (KEVZARA)						≥18 yo		
Secukinumab (COSENTYX)	≥18 yo			≥18 yo	≥18 yo			Nr-AxSpA ≥18 yo
Tildrakizumab-asmn (ILUMYA)				≥18 yo				
Tocilizumab (ACTEMRA)			≥2 yo			≥18 yo		CRS ≥2 yo GCA ≥18 yo
Tofacitinib (XELJANZ)			≥2 yo active polyarticular course		≥18 yo	≥18 yo	≥18 yo	
Upadacitinib (RINVOQ)						≥18 yo		

Drug Name	Ankylosing Spondylitis	Crohn's Disease	Juvenile Idiopathic Arthritis	Plaque Psoriasis	Psoriatic Arthritis	Rheumatoid Arthritis	Ulcerative Colitis	Other
Ustekinumab (STELARA)		≥ 18 yo		≥12 yo	≥18 yo		≥18 yo	
Vedolizumab (ENTYVIO)		≥18 yo					≥18 yo	

Abbreviations: BD = Bechet's Disease; CLL = Chronic Lymphocytic Leukemia; CRS = Cytokine Release Syndrome; 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; 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; 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?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; not funded by the OHP.
3. Is this a request for continuation of therapy?	**Yes**: Go to **Renewal Criteria**	**No:** Go to #4
4. 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.	**No:** Go to #5
5. Has the patient been annually screened for latent or active tuberculosis and if positive, started tuberculosis treatment?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness. May approve for up to 3 months to allow time for screening.

Approval Criteria		
6. Is the diagnosis Juvenile Idiopathic Arthritis, non-Hodgkin Lymphoma, Chronic Lymphocytic Leukemia, Non-infectious Posterior Uveitis, or one of the following syndromes: • Familial Cold Autoinflammatory Syndrome • Muckel-Wells Syndrome • Neonatal Onset Multi-Systemic Inflammatory Disease • Tumor Necrosis Factor Receptor Associated Periodic Syndrome • Hyperimmunoglobulin D Syndrome • Mevalonate Kinase Deficiency • Familial Mediterranean Fever • Giant Cell Arteritis • Cytokine Release Syndrome • Non-radiographic axial spondyloarthritis • Oral ulcers associated with Behcet's Disease • Still's disease AND Is the request for a drug FDA-approved for one of these conditions as defined in 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
8. If the request is for a non-preferred agent, has the patient failed to respond or had inadequate response to a Humira® product or an Enbrel® 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.

Approval Criteria		
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 or mucous membrane involvement?	**Yes:** Go to #11	**No:** Pass to RPh. Deny; not funded by the OHP.
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.

Approval Criteria		
12. Is the diagnosis rheumatoid arthritis or psoriatic arthritis and the request for a drug FDA-approved for these conditions as defined in Table 1?	**Yes:** Go to #13	**No:** Go to #16
13. 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® product or an Enbrel® product for at least 3 months? • AND • Is the patient on concurrent DMARD therapy with plans to continue concomitant use?	**Yes:** Go to #14 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.
14. Is the request for tofacitinib, baricitinib, or upadacitinib?	**Yes:** Go to #15	**No:** Approve for up to 6 months

Approval Criteria		
15. 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
16. Is the request for adalimumab in an adult with moderate-to-severe Hidradenitis Suppurativa (HS)?	**Yes:** Go to # 17	**No:** Go to # 18
17. 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**.**
18. 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 # 19	**No:** Go to # 20

Approval Criteria		
19. 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? AND • 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.
20. 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 or rheumatoid arthritis?	**Yes:** Go to # 4	**No:** Go to # 2
2. Is the request for continuation of adalimumab to treat moderate-to-severe Hidradenitis Suppurativa in an adult?	**Yes:** Go to # 3	**No:** Go to # 5

Renewal Criteria		
3. Has the patient had clear evidence of response to adalimumab therapy as evidenced by: A) a reduction of 25% or more in the total abscess and inflammatory nodule count, AND B) no increase in abscesses and draining fistulas.	**Yes:** Approve for an additional 12 weeks of therapy	**No:** Pass to RPh. Deny; medical appropriateness.
4. 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 #5	**No:** Pass to RPh. Deny; medical appropriateness.
5. 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.

P&T/DUR Review: *10/20 (DM); 2/20; 5/19; 1/19; 1/18; 7/17; 11/16; 9/16; 3/16; 7/15; 9/14; 8/12*
Implementation: *7/1/2019; 3/1/19; 3/1/18; 9/1/17; 1/1/17; 9/27/14; 2/2*

Natalizumab (Tysabri®)

Goal(s):
- Approve therapy for covered diagnosis which are supported by the medical literature.

Length of Authorization:
- Up to 12 months

Requires PA:
- Natalizumab (Tysabri®)

Covered Alternatives:
- Preferred alternatives listed at www.orpdl.org

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Has the patient been screened for Jason Cunningham (JC) Virus?	**Yes:** Go to #3	**No:** Pass to RPH; Deny for medical appropriateness
3. Does the patient have a diagnosis of relapsing multiple sclerosis (CIS, RRMS, or SPMS)?	**Yes:** Go to #4	**No:** Go to #6
4. Has the patient failed trials for at least 2 drugs indicated for the treatment of RRMS?	**Yes:** Document drug and dates trialed: 1._____(dates) 2._____(dates) Go to #5	**No:** Pass to RPh. Deny; medical appropriateness.
5. Is the medication being prescribed by or in consultation with a neurologist?	**Yes:** Approve for 12 months	**No:** Pass to RPH; Deny for medical appropriateness.
6. Does the patient have Crohn's Disease?	**Yes:** Go to #7	No: Pass to RPH; Deny for medical appropriateness.
7. Has the patient been screened for latent or active tuberculosis and if positive, started tuberculosis treatment?	**Yes:** Go to #8	**No:** Pass to RPH; Deny for medical appropriateness**.**

Approval Criteria		
8. Has the patient failed to respond 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? • AND • Has the patient tried and failed a 3 month trial of Humira?	**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.

P&T / DUR Action: *10/20 (DM); 11/17*
Implementation: *1/1/18*