Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35
Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-2596

Drug Class Update: Targeted Immune Modulators for Autoimmune Diseases

Date of Review: October 2021

Date of Last Review: October 2020
Dates of Literature Search: 01/01/2020 – 06/09/2021

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

Purpose for Class Update: Review new comparative evidence between targeted immune modulators (TIMs) approved by the Food and Drug Administration (FDA) to manage autoimmune conditions.

Research Questions:
1. Is there new comparative evidence that TIMs differ in efficacy or effectiveness for alleviating symptoms and stabilizing disease in patients with rheumatoid arthritis (RA), ankylosing spondylitis (AS), psoriatic arthritis (PsA), plaque psoriasis (PsO), Crohn's disease (CD), or ulcerative colitis (UC)?
2. Is there new comparative evidence that TIMs differ in harms when used to treat patients with autoimmune conditions?
3. Are there specific subpopulations for which one TIM is better tolerated or more effective than other available TIMs when used for autoimmune conditions?

Conclusions:
Since the last class update, 6 high-quality systematic reviews and 5 high-quality guidelines were published.
Systematic Reviews
- In April 2020 the American Gastroenterological Association (AGA) sponsored a systematic review focused on the efficacy and safety of disease-modifying anti-rheumatic drugs (DMARDs) approved to manage moderate-to-severe UC.[1] Therapies of interest included conventional synthetic DMARDs (thiopurines, methotrexate [MTX], and cyclosporine) and TIMs (tumor necrosis factor [TNF] inhibitors, vedolizumab, tofacitinib and ustekinumab), either as monotherapy, or in combination with conventional synthetic DMARDs.[1] For induction of remission in biologic-naïve patients with moderate-to-severe UC, infliximab is probably superior to adalimumab (moderate quality of evidence) and may be superior to golimumab, vedolizumab, tofacitinib and ustekinumab (low to very low quality of evidence).[1] In biologic-naïve patients with moderate-to-severe UC, vedolizumab is probably superior to adalimumab for achieving remission (moderate quality of evidence).[1] The benefit of vedolizumab relative to golimumab, tofacitinib or ustekinumab for induction of remission remains uncertain (low to very low quality of evidence).[1] Overall risk of serious infections requiring hospitalization in patients treated with conventional synthetic DMARD monotherapy, TNF inhibitor monotherapy or combination therapy was generally rare (less than 1%).[1] Long-term safety data for serious risks of infection for vedolizumab, tofacitinib, ustekinumab in patients with UC are insufficient.[1] In population-based studies, TNF inhibitors have been variably associated with a 2-to 5-fold increased risk of lymphoid malignancy.[1]

Author: Deanna Moretz, PharmD, BCPS

- The objective of a 2020 Cochrane systematic review was to update a 2017 systematic review of the efficacy and safety of TIMs for management of moderate-to-severe PsO.[2] Three head-to-head comparisons compared 2 different biologics to assess the proportion of participants who achieved PASI 90 at 52 weeks.[2] One meta-analysis compared risankizumab versus ustekinumab. For reaching PASI 90 at 52 weeks, risankizumab was more effective than ustekinumab (RR 1.73, 95% CI 1.46 to 2.05).[2] In other analyses, secukinumab was more effective than ustekinumab to reach PASI 90 at 52 weeks (RR 1.24, 95% CI 1.11 to 1.38; 1 study) and guselkumab was more effective than adalimumab to reach PASI 90 at 52 weeks (RR 1.59, 95% CI 1.40 to 1.81; 1 study).[2] Due to the limited number of head-to-head (n=14) comparisons, the relative benefit of DMARDs in managing PsO remains unclear.[2] Differences in specific adverse effects were not evaluated.[2] No statistically significant differences were observed between any of the TIMs and placebo for the risk of serious adverse effects (SAEs).[2] However, the SAE analyses were based on a very low number of events with low to very low certainty for just under half of the treatment estimates, and moderate certainty for the others.[2]
- A 2020 systematic review conducted by the European League against Rheumatism (EULAR) evaluated recently published evidence on the safety and efficacy of TIMs for treatment of PsA.[3] The efficacy of TNF inhibition across various disease domains was confirmed; the non-inferiority of CT-P13, an infliximab biosimilar agent, to infliximab, was also confirmed.[3] Compared to placebo, the IL-23 inhibitor guselkumab demonstrated efficacy at reducing arthritis, skin, enthesitis and dactylitis symptoms.[3] Interluekin-17A inhibitors (secukinumab, ixekizumab, and brodalumab) and a Janus kinase (JAK) inhibitor, tofacitinib, were also effective compared with placebo across all PsA disease domains.[3] The clinical efficacy of phosphodiesterase 4 (PDE4) inhibition using apremilast in PsA compared to placebo was confirmed; however, radiographic outcomes have not been assessed.[3] Evaluation of treatment safety across nine cohort studies and one case–control study did not reveal new safety signals for TNF inhibitors or conventional synthetic DMARDs regarding infections, occurrence of cardiovascular events, malignancies, infusion reactions or incidence of multiple sclerosis in patients with PsA.[3] Safety data of randomized controlled trials (RCTs) and their respective long-term extensions showed patients who received ixekizumab compared with placebo had higher rates of injection site reactions (placebo, 4.7% versus ixekizumab, 24.3%, p-value not reported) and candida infections (placebo, 0 cases versus ixekizumab, 8 cases [difference: 3%, p-value not reported).[3] Rates of herpes zoster were higher in patients who received tofacitinib compared to placebo (incidence rate [IR]: 2.05; 95% CI 1.17 to 3.33, p-value not reported).[3] In JAK inhibitor-treated patients with PsA no venous thromboembolic events (VTEs) were reported in any of the RCTs or long term extension periods, but regulators issued warnings on the risk of JAK inhibitor-associated VTE based on data in other patient populations and indications.[3]
- A 2020 EULAR systematic review focused on the efficacy of TIMs in patients with RA.[4] Most of the evidence compared biologic DMARDs to placebo with or without conventional synthetic DMARD background therapy. Comparative head-to-head assessments were sparse. Adalimumab was the most frequently used as an active comparator. In one head-to-head trial, sarilumab monotherapy showed clinical and functional superiority compared with adalimumab monotherapy in patients who were intolerant or inadequately responding to MTX.[4] Another study did not show superiority of certolizumab pegol compared with adalimumab and therefore failed to meet its primary endpoint, as similar ACR20 response rates were observed at week 12.[4] Three different head-to-head trials with low risk of bias compared targeted synthetic DMARDs to adalimumab.[4] In one RCT, baricitinib 4 mg plus MTX was superior to adalimumab based on clinical endpoints (ACR20 at week 12: 70% vs. 61%, p=0.014; change in DAS28-CRP at week 12: −2.24 vs. −1.95, p<0.001) and a functional endpoint (change in HAQ at week 12: −0.66 vs. −0.56, p≤0.01).[4] In one RCT, upadacitinib plus MTX was shown to be superior to adalimumab plus MTX in both co-primary endpoints (ACR20 at week 12: 70.5% vs. 63%, p<0.05; DAS28-CRP <2.6 at week 12: 28.7% vs. 18%, p<0.001).[4] Non-inferiority was demonstrated for tofacitinib plus MTX versus adalimumab plus MTX (ACR50 at week 24: 46% vs. 44%, difference: 2%; 98% CI 6% to 11%), but not for tofacitinib monotherapy versus adalimumab plus MTX (ACR50 at week 24: 38% vs. 44%; difference: −6%; 98% CI −14% to 3%).[4] Five non-inferiority trials (low risk of bias) investigated the bioequivalence of biologic DMARDs (adalimumab, etanercept, infliximab and rituximab) to their respective biosimilar DMARDs.[4] Switching between biosimilars and bio-originators revealed no changes in efficacy in one trial of an adalimumab biosimilar (SB5); 2 trials of etanercept biosimilars (GP2015, LBEC0101); and 2 trials of infliximab biosimilars (SB2, CT-P13).[4]

- Recently published evidence on the safety of TIMs used to manage RA was summarized in a 2020 EULAR systematic review.[5] Safety outcomes of interest included infections, opportunistic infections, malignancies, mortality, major adverse cardiovascular events (MACE), VTE, change in lipid levels, elevation of creatine phosphokinase, impairment in renal function, elevation of liver enzymes, hematological abnormalities, gastrointestinal adverse effects, demyelinating disease, induction of autoimmune disease and teratogenicity.[5] Nine studies showed no difference in the risk of serious infections across biologic DMARDs.[5] Two studies with a high risk of bias showed an increased infection risk with biologic DMARDs compared with conventional synthetic DMARDs (adjusted incidence rate ratio 3.1-3.9).[5] Three studies (1 study at low risk of bias) showed no increased risk of MACE for biologic DMARDs compared with conventional synthetic DMARDs.[5] In 4 studies (1 study at low risk of bias) no differences in the risk of MACE between biologic DMARDs were found.[5] The risk of VTE was evaluated in 2 studies, both at high risk of bias.[5] One showed no increase with tofacitinib (adjusted HR 1.33, 95% CI, 0.78 to 2.24) and another study showed no increase with abatacept (adjusted HR 1.27, 95% CI 0.63 to 2.57), both compared with TNF inhibitors.[5] The risk of herpes zoster infection was similar across TIMs, but one study showed an increased risk with tofacitinib compared with abatacept (adjusted HR 2.0, 95% CI 1.40 to 2.88).[5] Five studies showed no increased risk of cancer for biologic DMARDs compared with conventional synthetic DMARDs.[5] An increased risk of lower intestinal perforation was found for tocilizumab compared with conventional synthetic DMARDs (adjusted HR 2.55, 95% CI 1.33 to 4.88) and TNF inhibitors (adjusted HR 3.24, 95% CI 1.05 to 10.04).[5] Overall, no unexpected safety outcomes were found.[5]
- JAK inhibitor therapies (tofacitinib, upadacitinib, and baricitinib) are effective treatment options for immune-mediated inflammatory diseases, but their use has been limited by VTE risk warnings from licensing authorities.[6] Interim analysis of the data results from long term extension trials resulted in an FDA advisory warning regarding the use of tofacitinib at a higher dose (10 mg twice daily) due to an increased risk of VTE.[7] A 2021 meta-analysis evaluated the risk of VTE with JAK inhibitor therapy.[6] Eligible studies were original reports of phase 2 and phase 3 RCTs of JAK inhibitor therapy, with a placebo comparator arm. Long-term, open-label extension trials were excluded from the analysis. For the 42 included RCTS, 40 (95%) studies were randomized and double-blind (with regard to participants and assessors), with 33 (79%) studies considered to have an overall low risk of bias.[6] There were 6,542 JAK inhibitor patient exposure years compared to 1,578 placebo patient exposure years. In the JAK inhibitor group 15 VTEs were reported and 4 VTEs were reported in the placebo group.[6] The pooled incidence rate ratios of VTE, pulmonary embolism (PE), and deep vein thrombosis (DVT) in patients receiving JAK inhibitors were 0.68 (95% CI 0.36–1.29), 0.44 (95% CI 0.28–0.70), and 0.59 (95% CI 0.31–1.15), respectively.[6] Overall, the pooled-effect estimates from the 42 RCTs in this meta-analysis suggest VTE risk is unlikely to be substantially increased in those receiving JAK inhibitors compared to those receiving placebo.[6] The likely explanation for the discrepancy in findings is the exclusion of long term extension trials from the meta-analysis and the pooling of results across 3 different JAK inhibitor therapies.[6] An additional study that examines long-term safety of tofacitinib in patients at increased risk for cardiovascular disease is ongoing.[6]
- In September 2021, the FDA issued a drug safety communication warning providers and patients about the increased risk of serious heart-related events, cancer, blood clots, and death for JAK inhibitors used to treat RA, PsA, and UC.[8] The communication is based on an FDA review of a large randomized, open-label, safety clinical trial which evaluated 2 doses of tofacitinib in comparison to treatment with a TNF inhibitor. There was an increased risk of death, MACE, malignancies, and thrombosis associated with both regimens of tofacitinib.[8] The data showed evidence of a dose-dependent increased risk for MACE, all-cause mortality, and thrombosis at both doses of tofacitinib when compared to treatment with TNF inhibitor.[8] Additionally, the data showed evidence of a non-dose-dependent increased risk for malignancy excluding nonmelanoma skin cancer at both doses of tofacitinib when compared to TNF inhibitors.[8] Lymphomas and lung cancers were observed at a higher rate in patients treated at both doses of tofacitinib compared to those treated with TNF inhibitors. In particular, a higher rate of lung cancers was observed in current or past smokers treated with tofacitinib.[8] Current or past smokers had an additional increased risk of overall cancers. Other JAK inhibitors have not been studied in similar large safety clinical trials, so the risk with these medicines has not been evaluated.[8] However, since they share mechanisms of action with tofacitinib, FDA considers that these medicines may have similar risks as seen in the safety clinical trial with tofacitinib.[8]

Guidelines

- In April 2020, the AGA published clinical practice guidelines on the management of moderate to severe UC.[9] The recommendations were supported by the previously described AGA systematic review.[1] Due to limited head-to-head assessments of the safety and efficacy of TIMs in UC, most of the recommendations are conditional due to low quality of evidence. The only strong recommendation based on moderate quality of evidence was a recommendation to use infliximab, adalimumab, golimumab, vedolizumab, tofacitinib, or ustekinumab in adult outpatients with moderate-to-severe UC, over no treatment.[9] (Medications are ordered based on year of approval by the FDA.)[9]
- The EULAR guidance for the management of PsA with TIMs was updated in 2019.[10] The recommendations are supported by evidence previously presented in the systematic review of TIMs for treatment of PsA.[3] In patients with polyarthritis, a conventional synthetic DMARD (i.e., MTX, sulfasalazine, leflunomide) should be initiated rapidly, with MTX preferred in those with relevant skin involvement.[10] In patients with peripheral arthritis and an inadequate response to at least one conventional synthetic DMARD, therapy with a biologic DMARD should be commenced.[10] When there is relevant skin involvement, an IL-17 inhibitor or IL-12/23 inhibitor may be preferred.[10] In patients with peripheral arthritis and an inadequate response to at least one conventional synthetic DMARD and at least one biologic DMARD, or when a biologic DMARD is not appropriate, a JAK inhibitor may be considered.[10] In patients with mild disease and an inadequate response to at least one conventional synthetic DMARD, in whom neither a biologic DMARD nor a JAK inhibitor is appropriate, a PDE4 inhibitor may be considered.[10]
- The EULAR recommendations for the management of RA with TIMs were updated in 2019.[11] The previously described systematic review focused on efficacy[4] and an additional systematic review focused on safety[5] informed the 2019 EULAR guidance for management of RA. Recommendations based on high quality evidence regarding the use of conventional synthetic DMARDs (MTX, leflunomide, sulfasalazine); glucocorticoids; biologic DMARDs (adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, abatacept, rituximab, tocilizumab, sarilumab) and targeted synthetic DMARDs (tofacitinib, baricitinib, upadacitinib) are included in the guidance. Methotrexate should be part of the first treatment strategy.[11] If the treatment target is not achieved with the first conventional synthetic DMARD strategy, and poor prognostic factors are present, a biologic DMARD or a targeted synthetic DMARD should be added.[11] Biologic DMARDs and targeted synthetic DMARDs should be combined with a conventional synthetic DMARD; in patients who cannot use conventional synthetic DMARDs as co-medication, IL-6 pathway inhibitors and targeted synthetic DMARDs may have some advantages compared with other types of TIMs.[11] When poor prognostic factors are present (presence of autoantibodies, high disease activity, early erosions or failure of two conventional synthetic DMARDs), any biologic DMARD or JAK inhibitor should be added to conventional synthetic DMARD therapy.[11]
- National Institute for Health and Care Excellence (NICE) guidance for the use of upadacitinib in treating severe RA was published in December 2020.[12] Clinical trials show that for moderate-to-severe RA that has not responded adequately to conventional synthetic DMARDs, upadacitinib with MTX is more effective than adalimumab with MTX or placebo with MTX.[12]
- NICE guidance for ustekinumab treatment of moderately to severely active UC was published June 2020.[13] The most commonly used biological treatment option for moderately to severely active UC are TNF inhibitors.[13] Clinical trial evidence shows that ustekinumab is more effective than placebo for treating moderately to severely active UC.[13] Ustekinumab is recommended when a TNF inhibitor is not appropriate or has not been effective.[13]
- Expanded indications recently approved by the FDA for the following medications include:
    - Adalimumab use in children 5 years and older with moderate-to-severe UC.[14]
    - Ozanimod for the treatment of adults with moderate-to-severe UC.[15]
    - Tofacitinib for the treatment of children and adolescents 2 years and older with active polyarticular course juvenile idiopathic arthritis.[16]
    - Golimumab indication to include patients 2 years and older for treatment of active PsA or active polyarticular juvenile idiopathic arthritis.[17]
    - Anakinra for treatment of deficiency of IL-1 receptor antagonist.[18]
    - Subcutaneous tocilizumab to curb the rate of progressive loss of lung function among adults with systemic sclerosis-associated interstitial lung disease.[19]

- Secukinumab for use in children 6 years and older for treatment of active PsO who are candidates for systemic therapy or phototherapy.[20]

Recommendations:

- After clinical review, no changes to the Preferred Drug List (PDL) are recommended.
- Rename the "Biologics for Autoimmune Disease" to "Targeted Immune Modulators" to reflect different mechanisms of action for drugs in this class.
- Modify prior authorization (PA) criteria for the "Targeted Immune Modulators" drug class to include expanded ages and indications for recent FDA-approvals as outlined in the conclusions.
- Modify PA criteria for the "Multiple Sclerosis Oral Agents" drug class to include the expanded indication for ozanimod in adults with moderate-to-severe UC.
- After review of costs in executive session secukinumab was made preferred on the PDL.

Summary of Prior Reviews and Current Policy:

Targeted immune modulators for autoimmune conditions were last reviewed by the Pharmacy and Therapeutics (P & T) Committee at the October 2020 meeting. Evidence focused on safety and efficacy of TIMs was summarized in 3 separate Drug Effectiveness Review Project (DERP) reports and shared with committee members. The reviews evaluated the use of TIMs for: RA and AS;[21] PsO and PsA;[22] and CD and UC.[23] Prior authorization criteria were revised to reflect expanded indications for various TIMs. After executive session, secukinumab was designated as non-preferred on the PDL. Currently, adalimumab and etanercept 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. A 3 month trial and failure of adalimumab or etanercept is required for management of AS, RA, PsO or PsA before advancing to another TIM. Trial and failure of adalimumab for at least 3 months is required before advancing to another TIM for CD. Current clinical PA criteria are outlined in **Appendix 2.**

In the second quarter of 2021, there were approximately 206 pharmacy claims for TIMs from 67 patients in the fee-for-service (FFS) population. Sixty-eight percent of the claims were for the preferred agents etanercept and adalimumab. For the non-preferred agents, 4-5% of claims were for certolizumab pegol, ixekizumab, and apremilast and 1-3% of claims were for secukinumab, tofacitinib, tocilizumab, anakinra, and ustekinumab. There were pharmacy claims for brodalumab, canakinumab, guselkumab, tildrakizumab, sarilumab, risankizumab, or baricitinib. In the first quarter of 2021, there were 71 claims for physician administered TIMs (reflects increased utilization from 52 claims in the first quarter of 2020). The most frequent claims for physician administered drugs from this class included: infliximab, vedolizumab, abatacept, golimumab, tocilizumab, tildrakizumab, and rituximab.

Background:

Biologic DMARDs are large, complex, proteins that must be administered parentally. The biologic DMARDs include TNF inhibitors (e.g., adalimumab, certolizumab pegol, etanercept, golimumab, and infliximab), interleukin antagonists (e.g., anakinra, sarilumab, tocilizumab, ustekinumab, secukinumab, brodalumab, ixekizumab, secukinumab guselkumab, risankizumab and tildrakizumab), lymphocyte antagonists (e.g., rituximab and abatacept), and integrin receptor antagonists (e.g., vedolizumab and natalizumab). FDA-approved biosimilars are available for adalimumab, etanercept, infliximab, and rituximab.[24] Targeted synthetic DMARDs are small chemical molecules that can be taken orally. The JAK inhibitors (e.g., tofacitinib, baricitinib, and upadacitinib), the PDE-4 inhibitor (apremilast), and the sphingosine 1-phosphate receptor agonist (ozanimod) are classified as targeted synthetic DMARDs. **Table 1** summarizes the TIMs indicated for management of AS, RA, PsA, PsO, CD and UC discussed in this report.

Table 1. FDA-Approved Targeted Immune Modulators for Selected Auto-Immune Diseases[25,26]

Drug – Route of Administration	Molecular Target	Approved Indication(s)
Biologic DMARDs		
Adalimumab (HUMIRA) - SC	TNF	AS, RA, PsA, PsO, CD, UC
Certolizumab Pegol (CIMZIA) - SC		AS, RA PsA, PsO, CD
Etanercept (ENBREL) - SC		AS, RA, PsA, PsO
Golimumab - (SIMPONI and SIMPONI ARIA) - IV or SC		AS, RA, PsA, UC
Infliximab (REMICADE) - IV		AS, RA, PsA, PsO, CD, UC
Anakinra (KINERET) - SC	IL-1	RA
Sarilumab (KEVZARA) - SC	IL-6	RA
Tocilizumab (ACTEMRA) – IV or SC		RA
Ustekinumab (STELARA) – IV or SC	IL-12 and IL-23	PsA, PsO, CD, UC
Brodalumab (SILIQ) - SC	IL-17	PsO
Ixekizumab (TALTZ) - SC		AS, PsA, PsO
Secukinumab (COSYNTEX) - SC		AS, PsA, PsO
Guselkumab (TREMFYA) - SC	IL-23	PsA, PsO
Risankizumab (SKYRIZI) - SC		PsO
Tildrakizumab (ILUMYA) - SC		PsO
Vedolizumab (ENTYVIO) – IV	Integrin receptor	CD, UC
Natalizumab (TYSABRI) – IV		CD
Abatacept (ORENCIA) - IV or SC	T-lymphocyte	RA, PsA
Rituximab (RITUXAN) - IV	B-lymphocyte	RA
Targeted Synthetic DMARDs		
Baricitinib (OLUMIANT) - PO	JAK 1,2	RA
Tofacitinib (XELJANZ)- PO	JAK 1,2,3	RA, PsA, UC
Upadacitinib (RINVOQ) - PO	JAK 1	RA
Apremilast (OTEZLA) - PO	PDE4	PsA, PsO
Ozanimod (ZEPOSIA) – PO	S1P receptors	UC

Abbreviations: AS=ankylosing spondylitis; CD=Crohn's Disease; DMARD=Disease-Modifying Antirheumatic Drug; FDA=Food and Drug Administration; IL=interleukin; IV=intravenous; JAK=Janus Kinase; PDE=phosphodiesterase; PO=oral; PsA=psoriatic arthritis; PsO=plaque psoriasis; S1P=sphingosine 1-phosphate; RA=rheumatoid arthritis; SC=subcutaneous; TNF=tumor necrosis factor; UC=Ulcerative Colitis

Ankylosing Spondylitis

Ankylosing spondylitis is a chronic rheumatic disorder that primarily affects the sacroiliac joints and spine.[27] 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.[28] Patients who have chronic pain and other features suggestive of spondyloarthritis (SpA) without radiologic changes are classified as having non-radiographic axial SpA.[29] The goals of treatment for patients with AS are to reduce symptoms, maintain spinal flexibility, reduce functional limitations, maintain work ability, and decrease disease complications.[30] Guidelines for management of AS were updated in 2019 by the American College of Rheumatology (ACR) in conjunction with the Spondylitis Association of America (SAA).[31] Nonsteroidal anti-inflammatory drugs (NSAIDs) and exercise are recommended as first-line therapies to alleviate pain and stiffness.[31,32] Tumor necrosis factor inhibitors are recommended for patients with persistent disease activity despite conventional treatment.[31,32] All the TNF inhibitors are proven to provide sustained improvement in patient functioning and reduced disease activity as assessed by the Bath Ankylosing Spondylitis Disease Activity Index (BASDI) and Functional Index (BASFI) scores.[32] More details for these 2 outcomes are presented in **Appendix 4**. Two anti–interleukin monoclonal antibodies, secukinumab and ixekizumab, have also demonstrated efficacy in treating AS.[31] However, the ACR/SAA guidance recommends a TNF inhibitor as the first TIM for use after NSAID therapy over secukinumab or ixekizumab.[31] Co-administration of low-dose MTX with a TNF inhibitor is not recommended for AS management.[31] Some trials have measured clinical response using Assessment in Spondyloarthritis International Society (ASAS) scores, which is a composite score of 4-6 domains.[33] Percentage of responders in each improvement criteria were reported as ASAS20 (20% improvement), ASAS40 (40% improvement) ASAS5/6 (20% improvement in five of six domains) and ASAS-PR (partial remission).[33] Outcomes used to assess AS in clinical trials are summarized in **Appendix 4**.

Rheumatoid Arthritis

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.[34] Tumor necrosis factor plays a central role in the pathophysiology of RA.[34] The 2019 EULAR recommendations suggest RA treatment begin with a conventional synthetic DMARD such as MTX as soon as diagnosis of RA is established.[11] Other conventional synthetic DMARDs recommended to treat RA include sulfasalazine and leflunomide.[11] Biologic DMARDs or targeted synthetic DMARDs are recommended for patients with a suboptimal response or intolerance to conventional synthetic DMARDs.[11] Monotherapy with biologic DMARDs or targeted synthetic DMARDs or combination therapy that includes MTX can be initiated as second-line therapy, depending on the patient's response to previous therapy and any pertinent comorbidities.[11]

Primary endpoints used in RA clinical trials are ACR response, the Health Assessment Questionnaire Disability Index (HAQ-DI), and the Disease Activity Score-28 (DAS-28). The ACR response is considered a measure of efficacy and evaluates tender joint count, swollen joint count, patient's assessment of pain, patient's and physician's global assessments of disease activity, patient's assessment of physical function, and laboratory evaluation of an acute-phase reactant (erythrocyte sedimentation rate [ESR] or C-reactive protein level [CRP]).[35] The HAQ-DI is a self-reported measure of functional capacity (total score 0 to 3).[36] Scores of 0 to 1 are generally considered mild to moderate disability, 1 to 2 moderate to severe disability, and 2 to 3 severe to very severe disability.[36] A decrease of 0.22 to 0.25 is generally considered the minimum clinically important difference for this scale.[37] However, one study has also indicated that a greater decrease of -0.375 may be needed to be clinically significant.[38] The DAS-28 is another index of disease activity (similar to the ACR response) which assesses 28 joints in swelling, tenderness, ESR or CRP levels, and patient global assessment of health. A DAS-28 score greater than 5.1 corresponds to high disease activity and less than 3.2 corresponds to low disease activity.[36] A DAS-28 score of 2.6 corresponds with remission.[36] Outcomes used to assess RA in clinical trials are summarized in **Appendix 4**.

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.[39] The development of the disease is driven by multiple pathways of immune mediators, including TNF, IL-23 and IL-17 cytokines.[40] Plaque psoriasis is characterized by itchy, red, scaly, raised lesions on the skin, especially on the scalp, elbows, knees, scalp, and trunk. Typically, PsO is classified as mild, moderate or severe. Mild disease involves less than 5% of the body surface area and has little to no impact on quality of life or function. Mild PsO is not a funded condition per the Health Evidence Review Commission (HERC) Guideline Note 57.[41] Per 2017 NICE guidance, first-line agents for PsO include: topical medications including corticosteroids, vitamin D analogs (e.g., calcipotriene), retinoids (e.g., tazarotene) or calcineurin inhibitors (e.g., tacrolimus or pimecrolimus).[42] Phototherapy is an option for patients with moderate-to-severe PsO who have not responded to topical therapy.[42] Systemic non-biologic treatments are recommended for patients with moderate-to-severe PsO unresponsive to topical or phototherapy and include MTX, cyclosporine, or acitretin.[42] Biologics including TNF inhibitors, IL-12/23 antagonists, IL-23 antagonists, or IL-17 antagonists, may be added for patients with moderate-to-severe PsO not controlled by other therapies.[42]

Psoriatic arthritis is a disease with heterogeneous manifestations in patients who have manifest or latent psoriasis.[10] It comprises both musculoskeletal as well as non-musculoskeletal manifestations; the latter particularly include the skin and the nails, but also potentially the gut (inflammatory bowel disease) or the eyes (uveitis).[10] Active chronic PsA is associated with cardiovascular, psychological and metabolic comorbidities, which, together with the musculoskeletal manifestations, impose a significant patient burden with impact on quality of life and also accelerated mortality.[10] First-line treatment for PsA includes NSAIDs, although in most cases conventional synthetic DMARDs (MTX, sulfasalazine or leflunomide) are necessary.[10]

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.[43] 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.[43,44] 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.[43] 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.[44] 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.[44] Additional outcomes used to assess PsO and PsA in clinical trials are summarized in **Appendix 4.**

<u>Crohn's Disease and Ulcerative Colitis</u>

Crohn's disease and UC are classified as inflammatory bowel diseases (IBDs). 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. Clinical diagnosis of both conditions is most accurately made with colonoscopy. 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.[45] More details about the CDAI are summarized in **Appendix 4**. Practice guidelines for CD recommend taking into account the disease location, severity, complications, and extra intestinal manifestations when choosing a treatment strategy.[45,46] 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).[45] NICE guidance recommends 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.[47] 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 treatment with conventional therapy.[45] Cyclosporine, mycophenolate mofetil, and tacrolimus should not be used to treat CD due to insufficient evidence demonstrating efficacy.[45]

According to the AGA, in outpatients with moderate-severe UC, induction and maintenance of clinical remission are critical outcomes for decision-making, whereas achieving endoscopic remission, corticosteroid-free remission, serious adverse events and treatment tolerability (drug discontinuation due to adverse events) are important outcomes.[1] The risk of colectomy is also considered a critical outcome, however, clinical trials are not powered to measure this outcome, so inducing and maintaining clinical remission, outcomes strongly associated with decreasing risk of colectomy, are used as surrogates for avoidance of colectomy.[1] Predictors of an aggressive disease course and colectomy include: young age at diagnosis (age 40 years old and younger), extensive disease, severe endoscopic activity (presence of large and/or deep ulcers), presence of extra-intestinal manifestations, early need for corticosteroids and elevated inflammatory markers.[48] Clinical remission is most commonly measured using the Mayo Clinic score (MCS), an index with scores ranging from 0–12, based on measures of stool frequency, rectal bleeding, and physician global assessment, along with endoscopic disease activity.[49] Scores of 6–12 correspond to moderate to severe disease activity, whereas clinical remission is most consistently defined as MCS less than 3, with no individual sub-score greater than 1.[1] By current convention, endoscopic remission is defined as a sub-score of 0 or 1, implying that all patients in clinical remission by MCS would be in endoscopic remission too.[1] The AGA[9] and the NICE[50] 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.[51] Ozanimod, an oral sphingosine 1-phosphate receptor agonist initially approved to treat relapsing forms of multiple sclerosis, recently received FDA-approval for use in managing UC.[15]

Methods:
A Medline literature search for new systematic reviews and RCTs assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 3**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

New Systematic Reviews:
American Gastroenterological Association – Management of Ulcerative Colitis
In April 2020 the AGA published a systematic review on the safety and efficacy of TIMs to manage moderate-to-severe UC.[1] This review was conducted to inform development of 2020 AGA clinical guidance for treatment of UC, which is summarized later in this document.[9] Conventional synthetic DMARDs (thiopurines, MTX, cyclosporine, and tacrolimus) and TIMs (TNF inhibitors, vedolizumab, tofacitinib and ustekinumab), either as monotherapy, or in combination with conventional synthetic DMARDs , were included in the review.[1] The members of the technical review panel were selected based on their clinical content and guideline development methodological expertise, and were vetted for potential conflicts of interest in accordance with Institute of Medicine (IOM) guidance.[1] The literature search was conducted through October 2019.[1] For evidence synthesis, RCTs conducted in adults with moderate-severe UC were priortized.[1] If RCT-

level evidence was not available for specific outcomes, then observational studies were included to inform the review.[1] Minimum trial duration for induction and maintenance therapy was 2 weeks and 16 weeks, respectively.[1]

Efficacy

Overall, 16 RCTs provided data to support the efficacy of infliximab, adalimumab, golimumab, vedolizumab, tofacitinib, and ustekinumab for both induction and maintenance of remission in patients with moderate-to-severe UC.[1] While most trials were sponsored by industry, no significant risk of bias, inconsistency or indirectness impacted the quality of evidence.[1] The evidence was downgraded for imprecision due to the lower number of events (less than 200) for all comparisons, failing to achieve the optimal information size.[1] All drugs were superior to placebo for induction of remission, regardless of prior biologic exposure (infliximab: RR, 2.85; 95% CI, 2.11 to 3.86; adalimumab: RR, 1.62; 95% CI, 1.15 to 2.29; golimumab: RR, 2.49; 95% CI, 1.58 to 3.93; vedolizumab: RR, 2.22; 95% CI, 1.36 to 3.64; tofacitinib: RR, 3.22; 95% CI, 2.03 to 5.08; ustekinumab: RR, 2.91; 95% CI, 1.72 to 4.94; moderate quality of evidence for all comparisons).[1] In addition, all active interventions were superior to placebo for maintenance of remission (infliximab: RR, 2.25; 95% CI, 1.67 to 3.05; adalimumab: RR, 2.28; 95% CI, 1.52 to 3.42; golimumab: RR, 1.88; 95% CI, 1.32 to 2.68; vedolizumab: RR, 2.31; 95% CI, 1.63 to 3.28; tofacitinib: 5 mg twice daily RR, 3.09; 95% CI, 1.99 to 4.79; ustekinumab: RR, 1.83; 95% CI, 1.33 to 2.49; moderate quality of evidence for all comparisons).[1] Controlled trials in UC patients have shown infliximab and adalimumab can decrease the risk of hospitalization and colectomy.[1] Comparable data on the impact of golimumab, vedolizumab, ustekinumab and tofacitinib on outcomes related to healthcare utilization are currently unavailable.[1] Key AGA messages regarding comparative efficacy for TIMs in UC include:

- In TIM-naïve patients with moderate-to-severe UC, infliximab is probably superior to adalimumab (moderate quality of evidence) and may be superior to golimumab, vedolizumab, tofacitinib and ustekinumab (low to very low quality of evidence) for induction of remission.[1]
- In TIM-naïve patients with moderate-to-severe UC, vedolizumab is probably superior to adalimumab for achieving remission (moderate quality evidence). The benefit of vedolizumab over golimumab, tofacitinib and ustekinumab for induction of remission is uncertain (low to very low quality of evidence).[1]
- In TIM-naïve patients with moderate-to-severe UC, the benefit of golimumab, tofacitinib, ustekinumab or adalimumab, over other comparator medications, for induction of remission is uncertain (low to very low quality of evidence).[1]
- In patients with moderate-to-severe UC with prior TNF inhibitor exposure, both ustekinumab and tofacitinib may be superior to adalimumab and vedolizumab for induction of remission (low quality evidence). The benefit of ustekinumab over tofacitinib, for induction of remission is uncertain (very low quality of evidence*).*[1]
- In patients with moderate-to-severe UC with prior TNF inhibitor exposure, the benefit of vedolizumab over adalimumab for achieving remission is uncertain (very low quality of evidence). There is very limited evidence to inform the overall and comparative efficacy of infliximab and golimumab in patients with prior TNF inhibitor exposure.[1]
- In adult outpatients with moderate-to-severe UC, combination therapy with infliximab and conventional synthetic DMARD (i.e. azathioprine) is probably superior to infliximab monotherapy for induction of remission (moderate quality of evidence). Combination therapy with other TIMs (TNF inhibitors, vedolizumab or ustekinumab) and a conventional synthetic DMARD may be superior to TIM monotherapy for induction of remission (low quality of evidence). The benefit of combination therapy of a TIM and a conventional synthetic DMARD over TIM monotherapy for maintenance of remission is uncertain (very low quality of evidence). However, the benefit of tofacitinib with a conventional synthetic DMARD is currently unknown.[1]

Safety

Limited direct assessment exists of comparative safety between TIMs in patients with UC.[1] Overall risk of serious infections (infections requiring hospitalizations) in patients treated with conventional synthetic DMARD monotherapy, TNF inhibitor monotherapy or combination therapy was generally less than 1%.[1] Risks are higher in older patients with multiple co-morbidities.[1] Some studies demonstrate that risk of serious infections may be 1.1 to 2.0 times higher with TNF inhibitor

monotherapy versus conventional synthetic DMARD monotherapy.[1] Long-term safety data for serious infection risk for TNF inhibitors (i.e., adalimumab, infliximab, certolizumab pegol, and golimumab), vedolizumab, tofacitinib, and ustekinumab in patients with UC are lacking.[1]

Several large population-based studies have identified no association between TNF inhibitor exposure and solid-organ malignancy.[1] In population-based studies, TNF inhibitors have been variably associated with a 2- to 5-fold increased risk of lymphoid malignancy.[1] Although long-term follow-up and real-world evidence is lacking, safety analyses of clinical trials and open-label extension studies have not observed any significant increase in risk of solid-organ or hematological malignancies with the integrin receptor antagonist, vedolizumab.[1] While long-term safety studies are lacking, analysis of clinical trials and open-label extension studies of the JAK inhibitor tofacitinib in UC suggest an annual incidence rate of malignancy excluding non-melanoma skin cancer of 0.5 per 100 person-years.[1] In an integrated safety analysis of phase 2 and phase 3 trials of the interleukin antagonist ustekinumab for PsO, PsA, and CD, the incidence of malignancy (excluding non-melanoma skin cancer) was low and comparable among ustekinumab-treated patients (0.4 per 100 person-years) and placebo-treated patients (0.2 per 100 person-years).[1]

Cochrane: Management of Chronic Plaque Psoriasis

The objective of a 2020 Cochrane systematic review was to update a 2017 review that compared the efficacy and safety of DMARDs for people with moderate-to-severe PsO.[2] Only medications FDA-approved for PsO will be summarized in this report. Conventional systemic DMARDs included cyclosporine, MTX, and acitretin. The only small molecule drug that has FDA-approval to treat PsO is apremilast, although the JAK inhibitor, tofacitinib, and the sphingosine 1-phosphate receptor agonist, ponesimod, were included in the Cochrane analysis. The review included the following biologic DMARDs: infliximab, adalimumab, etanercept, certolizumab pegol, ustekinumab, guselkumab, tildrakizumab, risankizumab, secukinumab, ixekizumab, and brodalumab. The literature search was conducted through January 2019. Inclusion criteria focused on RCTs of systemic treatments in adults with moderate-to-severe PsO in comparison to placebo or another active agent.[2]

One hundred forty studies (n=51,749) in patients with moderate-to-severe PsO were included in the review.[2] Thirty-one new studies were included in the update.[2] Study participants were mostly male (68%); average age was 45 years; and mean baseline PASI score was 20 (range: 9.5 to 39), indicating a high level of disease severity.[2] Most of the 140 studies (59%) were placebo-controlled, 30% were head-to-head studies, and 11% were multi-armed studies with both an active comparator and a placebo.[2] Some studies (57/140; 41%) were assessed at high risk of bias; 42 studies (30%) were at unclear risk of bias, and 41 (29%) studies at low risk of bias.[2] Most studies (107/140; 76%) declared funding by a pharmaceutical company and 22 studies did not report the source of funding.[2]

Three head-to-head comparisons compared two different biologics to assess the proportion of participants who achieved PASI 90 (clear or almost clear skin) at 52 weeks.[2] One meta-analysis compared risankizumab versus ustekinumab. For reaching PASI 90 at 52 weeks, risankizumab was more effective than ustekinumab (RR 1.73, 95% CI 1.46 to 2.05).[2] Secukinumab was more effective than ustekinumab to reach PASI 90 at 52 weeks (RR 1.24, 95% CI 1.11 to 1.38; 1 study).[2] Guselkumab was more effective than adalimumab to reach PASI 90 at 52 weeks (RR 1.59, 95% CI 1.40 to 1.81; 1 study).[2]

The 3 head-to-head comparisons also assessed the proportion of participants who achieved PASI 75 at 52 weeks.[2] For reaching PASI 75 at 52 weeks, risankizumab was more effective than ustekinumab (RR 1.26, 95% CI 1.12 to 1.41).[2] Secukinumab was more effective than ustekinumab to reach PASI 75 at 52 weeks (RR 1.17, 95%CI 1.10 to 1.26; 1 study) and guselkumab was more effective than adalimumab to reach PASI 75 at 52 weeks (RR 1.40, 95% CI 1.28 to 1.54; 1 study).[2] Due to the limited number of head-to-head (n=14) comparisons, the relative benefit of biologic DMARDs in managing PsO remains unclear.[2]

Differences in specific adverse effects were not evaluated.[2] No significant difference was observed between any of the DMARDs and placebo for the risk of SAEs.[2] However, the SAE analyses were based on a very low number of events with low to very low certainty for just under half of the treatment estimates.[2] Thus, the safety results should be viewed with caution.[2]

European League against Rheumatism: Management of Psoriatic Arthritis

A systematic review conducted by EULAR updated evidence on the safety and efficacy of TIMs for treatment of adults with PsA.[3] This review supported the 2019 update of the EULAR guidelines for the management of PsA.[10] Studies of systemic PsA therapies were reviewed, including conventional synthetic DMARDs (i.e., MTX, leflunomide, sulfasalazine, hydroxychloroquine, chloroquine, injectable gold/gold salts, azathioprine, cyclosporine, penicillamine, cyclophosphamide, mycophenolate, and chlorambucil); biologic DMARDs (i.e., anakinra, infliximab, etanercept, adalimumab, rituximab, abatacept, tocilizumab, golimumab, certolizumab pegol, ustekinumab, secukinumab, brodalumab, ixekizumab, guselkumab, and respective biosimilars); targeted synthetic DMARDs (i.e., apremilast, tofacitinib, baricitinib, and upadacitinib); systemic glucocorticoids or NSAIDs; or any combination of these treatments.[3] Efficacy was assessed in 33 RCTs. For safety, cohort studies, case–control studies and long term extensions of RCTs (n=23) were analyzed.[3] Fifty-six publications met inclusion criteria.[3] Outcomes of interest were signs and symptoms of PsA, defined as composite measures including the ACR response criteria, the Disease Activity Index for Psoriatic Arthritis or the minimal disease activity state.[3] The literature was searched from January 2015 through December 2018.[3] Most RCTs were regarded to have low risk of bias.[3] Unclear risk of bias was most commonly due to insufficient reporting on random sequence generation.[3] Open-label studies (n=3) and long term extensions (n=13) were considered to have high risk of bias.[3]

Efficacy

No recent RCTs were published to evaluate the efficacy of conventional synthetic DMARDs.[3] One trial investigated the efficacy of etanercept in conventional synthetic DMARD-naïve adults. Etanercept monotherapy and combination therapy with MTX were superior to MTX monotherapy and showed similar efficacy in both treatment groups (ACR20 response at week 24: 50.7% vs. 60.9% vs. 64% for MTX, etanercept monotherapy and etanercept plus MTX combination therapy, respectively).[3] The efficacy of another TNF inhibitor, golimumab, was studied in conventional synthetic DMARD-insufficient responders.[3] Intravenous golimumab was superior compared with placebo (ACR20 at week 14: 75.1% vs. 21.8%).[3] One non-inferiority study demonstrated the bioequivalence of infliximab and an infliximab biosimilar (CT-P13, low risk of bias).[3] Ten reports of IL-17 inhibitors (ixekizumab and secukinumab) were included in the analysis with low risk of bias of all primary study reports.[3] Ixekizumab demonstrated efficacy in conventional synthetic DMARD-insufficient responders as well as TNF inhibitor-insufficient reponders.[3] In conventional synthetic DMARD- insufficient responders, better efficacy was seen with ixekizumab at week 24 compared with placebo, with numerically similar ACR20, ACR50 and ACR70 rates as adalimumab (included as reference arm; study not powered to show non-inferiority).[3] Secukinumab continued to show efficacy in reducing signs and symptoms of arthritis as well as skin disease and extra-articular musculoskeletal manifestations (enthesitis, dactylitis) and inhibited radiographic progression when compared with placebo in NSAID-insufficient responders, conventional synthetic DMARD-insufficient responders, and TNF-insufficient responders.[3] When compared to placebo, the IL-23 inhibitor guselkumab demonstrated efficacy in reducing arthritis, skin, enthesitis and dactylitis symptoms.[3] Two RCTs (low risk of bias) investigated JAK inhibition in PsA.[3] In one trial, tofacitinib was superior to placebo in conventional synthetic DMARD-insufficient responders.[3] An additional trial investigated tofacitinib in TNF inhibitor-insufficient responders and met its co-primary efficacy endpoints (ACR20 and HAQ-DI at week 12) for 5 mg and 10 mg two times per day, compared with placebo ($p<0.001$, 95% CI not reported).[3] Clinical efficacy of PDE4 inhibition using apremilast was confirmed in 2 RCTs (one low risk of bias, one unclear risk of bias); however, radiographic outcomes have not been assessed.[3]

Safety

Safety was evaluated in 13 long term extensions, 9 cohort studies and 1 case-control study investigating malignancies, infections, infusion reactions, multiple sclerosis and major cardiovascular events, as well as efficacy and safety of vaccination.[3] Risk of bias for cohort and case–control studies were assessed using the Newcastle-Ottawa Scale.[3] Evaluation of treatment safety across nine cohort studies and one case–control study did not reveal new safety signals for TNF inhibitors and conventional synthetic DMARDs regarding infections, occurrence of cardiovascular events, malignancies, infusion reactions or incidence of multiple sclerosis in patients with PsA.[3] Safety data of RCTs and respective long term extensions showed patients receiving ixekizumab compared with placebo had higher rates of injection site reactions (placebo; 4.7% versus ixekizumab; 24.3%; p-value not reported) and candida infections (placebo; 0 cases versus ixekizumab; 8 cases [3%; p-value not reported]).[3] Herpes zoster rates were higher in patients receiving tofacitinib compared to placebo (incidence rate 2.05; 95% CI 1.17 to 3.33).[3] No VTEs or PEs were reported in any of the RCTs or long term extensions in JAK inhibitor-treated patients with PsA, but regulators issued warnings on the risk of VTE and PE based on data in other patient populations and indications, especially for patients at risk for VTE.[3]

European League against Rheumatism: Efficacy of Treatments for Rheumatoid Arthritis

A systematic review published in February 2020 investigated recent evidence supporting the efficacy of DMARD therapy in patients with RA.[4] This review and an additional safety review[5] informed the 2019 update of the EULAR guidance for management of RA.[11] Studies eligible for inclusion in the analysis were randomized, controlled, double-blind trials investigating conventional synthetic DMARDs, biologic DMARDs, targeted synthetic DMARDs or glucocorticoids in adult patients with RA.[4] The literature search was conducted from January 2016 through March 2019. One hundred thirty-six articles met inclusion criteria.[4] Most of the evidence compared biologic DMARDs to placebo with or without conventional synthetic DMARD background therapy. Risk of bias was considered low for most of the included RCTs.[4] Studies were rated as having an unclear risk of bias most commonly due to insufficient reporting of random sequence generation and/or allocation concealment.[4]

Two head-to-head studies with low risk of bias evaluated FDA-approved biologic DMARDs.[4] Sarilumab monotherapy showed clinical and functional superiority compared with adalimumab monotherapy in patients who were intolerant or inadequately responding to MTX.[4] Sarilumab was superior to adalimumab in the primary end point of change from baseline in DAS28-ESR (−3.28 vs −2.20; p<0.0001).[52] Sarilumab-treated patients achieved significantly higher ACR 20/50/70 response rates (sarilumab: 71.7%/45.7%/23.4%; adalimumab: 58.4%/29.7%/11.9%; all p≤0.0074) and had significantly greater improvement in Health Assessment Questionnaire-Disability Index (p=0.0037).[52] The EXXELERATE study did not show superiority of certolizumab pegol compared with adalimumab and therefore failed to meet its primary endpoint, showing similar ACR20% response rates at week 12.[4]

Three different head-to-head trials with low risk of bias compared targeted synthetic DMARDs to adalimumab.[4] In one RCT, baricitinib 4 mg plus MTX was superior to adalimumab based on clinical endpoints (ACR20 at week 12: 70% vs. 61%, p=0.014; change in DAS28-CRP at week 12: −2.24 vs. −1.95, p<0.001) and a functional endpoint (change in HAQ at week 12: −0.66 vs. −0.56, p≤0.01).[4] In one RCT, upadacitinib plus MTX was shown to be superior to adalimumab plus MTX in both co-primary endpoints (ACR20 at week 12: 70.5% vs. 63%, p<0.05; DAS28-CRP <2.6 at week 12: 28.7% vs. 18%, p<0.001).[4] Non-inferiority was demonstrated for tofacitinib plus MTX versus adalimumab plus MTX (ACR50 at week 24: 46% vs. 44%, difference: 2%; 98% CI 6% to 11%), but not for tofacitinib monotherapy versus adalimumab plus MTX (ACR50 at week 24: 38% vs. 44%; difference: −6%; 98% CI −14% to 3%).[4]

Five non-inferiority trials (low risk of bias) investigated the bioequivalence of biologic DMARDs (adalimumab, etanercept, infliximab and rituximab) to their respective biosimilar DMARDs.[4] Switching between biosimilars and bio-originators revealed no changes in efficacy in one trial of an adalimumab biosimilar (SB5); 2 trials of etanercept biosimilars (GP2015, LBEC0101); and 2 trials of infliximab biosimilars (SB2, CT-P13).[4]

European League against Rheumatism: Safety of Treatments for Rheumatoid Arthritis

A EULAR systematic review evaluated the safety of DMARDs approved for RA.[5] This review informed the 2019 EULAR update of recommendations for the management of RA.[11] Observational studies comparing safety outcomes of any DMARD with another intervention for the management of RA were included in the analysis.[5] For treatments without registry data (e.g., sarilumab, baricitinib, and upadacitinib), RCTs and long term extensions were used.[5] The literature search was conducted through March 2019. All interventions with a DMARD including conventional synthetic DMARDs, biologic DMARDs and targeted synthetic DMARDs were included. The comparator was another biologic DMARD, targeted synthetic DMARD, glucocorticoid, combination therapy or the general population.[5] Safety outcomes included: serious infections, opportunistic infections such as tuberculosis and herpes zoster, malignancies, mortality, MACE, VTE, change in lipid levels, elevation of creatine phosphokinase, impairment in renal function, elevation of liver enzymes, hematological abnormalities, gastrointestinal side effects, demyelinating disease, induction of autoimmune disease and teratogenicity.[5]

Forty-two observational studies fulfilled the inclusion criteria.[5] Of these, 16 studies addressed the risk of infections in patients receiving biologic DMARDs (3 also included patients on tofacitinib), 8 studies focused on malignancies, with all except one (comparing MTX to the general population), assessing patients on biologic DMARDs.[5] The risk of MACE was evaluated in 10 studies, all performed in patients treated with biologic DMARDs, with one also including patients on tofacitinib.[5] Three studies addressed the risk of lower intestinal perforations, 5 addressed the risk of withdrawal due to adverse events, and 2 addressed the risk of immunological reactions, all in patients treated with biologic DMARDs.[5] Studies were heterogeneous so data pooling was not possible.[5]

Nine studies were unable to find a difference in the risk of serious infections across biologic DMARDs; two studies (high risk of bias) found a higher associated risk with biologic DMARDs compared with conventional synthetic DMARDs (adjusted incidence rate ratio 3.1-3.9).[5] Three studies (1 study at low risk of bias) showed no increased risk of MACE for biologic DMARDs compared with conventional synthetic DMARDs.[5] In 4 studies (1 study at low risk of bias) no differences in the risk of MACE between biologic DMARDs were found.[5] The risk of VTE was evaluated in 2 studies, both at high risk of bias.[5] One showed no increase with tofacitinib (adjusted HR 1.33, 95% CI, 0.78 to 2.24) and another study showed no increase with abatacept (adjusted HR 1.27, 95% CI 0.63 to 2.57), both compared with TNF inhibitors.[5] The risk of herpes zoster infection was similar across biologic DMARDs, but one study showed an increased associated risk with tofacitinib compared with abatacept (adjusted HR 2.0, 95% CI 1.40 to 2.88).[5] Five studies increased risk of cancer for biologic DMARDs compared with conventional synthetic DMARDs.[5] An increased risk of lower intestinal perforation was found for tocilizumab compared with conventional synthetic DMARDs (adjusted HR 2.55, 95% CI 1.33 to 4.88) and TNF inhibitors (adjusted HR 3.24, 95% CI 1.05 to 10.04).[5] Overall, no unexpected safety outcomes were found.[5]
Overall, no unexpected safety outcomes were found.[5]

Venous Thromboembolism Risk with Janus Kinase Inhibitors

JAK inhibitor therapies (tofacitinib, upadacitinib, and baricitinib) are effective treatment options for immune-mediated inflammatory diseases, but their use has been limited by VTE risk warnings from licensing authorities.[6] Interim analysis of the data results from long term extension trials resulted in an FDA advisory warning regarding the use of tofacitinib at a higher dose (10 mg twice daily) due to an increased risk of VTE.[7] A 2021 meta-analysis evaluated the risk of VTE with JAK inhibitor therapy.[6] For this analysis, literature was searched through November 2019.[6] Eligible studies were original reports of phase 2 and phase 3 RCTs of JAK inhibitor therapy with a placebo comparator arm. Long-term, open-label extension trials were excluded. A total of 42 studies were included in the meta-analysis, of which 20 studies were phase 2 trials and 20 studies were phase 3 RCTs.[6] Twenty-nine studies were RCTs of patients with inflammatory arthropathies (RA, PsA, AS), 6 focused on UC and CD, and 7 focused on PsO. Of the 42 studies, 31 (74%) included patients with previous or current exposure to other immunosuppressive therapies.[6] Forty studies (95%) were randomized and double-blind (with regard to participants and assessors), with 33 studies (79%) considered to have an overall low risk of bias.[6]

There were 6,542 JAK inhibitor patient exposure years compared to 1,578 placebo patient exposure years.[6] There were 15 VTE events in the JAK inhibitor group and 4 in the placebo group.[6] The pooled incidence rate ratios (Incidence rate ratios) of VTE, PE, and DVT in patients receiving JAK inhibitors were 0.68 (95% CI 0.36–1.29), 0.44 (95% CI 0.28–0.70), and 0.59 (95% CI 0.31–1.15), respectively.[6] Overall, the pooled-effect estimates from the 42 RCTs in this meta-analysis suggest VTE risk is unlikely to be substantially increased in those receiving JAK inhibitors compared to those receiving placebo.[6] The likely explanation for the discrepancy in findings is the exclusion of long term extensions from the meta-analysis and the pooling of results across different JAK inhibitor therapies.[6] An important additional study that examines the long-term safety of tofacitinib in patients at increased risk for cardiovascular disease is ongoing.[6] Interim analysis of the data resulted in an FDA advisory warning regarding the use of tofacitinib at a higher dose (10 mg twice daily) because of an increased risk of infection and VTE.[7]

After further review, 22 systematic reviews were excluded due to poor quality (e.g., indirect network-meta analyses or failure to meet AMSTAR criteria),[53-69] wrong study design of included trials (e.g., observational),[70-74] comparator (e.g., no control or placebo-controlled),[75] or outcome studied (e.g., non-clinical).[76]

New Guidelines

High Quality Guidelines:

American Gastroenterological Association – Ulcerative Colitis

In April 2020, the AGA published clinical practice guidelines on the management of moderate to severe UC.[9] The recommendations were supported by a systematic review funded by the AGA.[1] Most of the evidence supporting the recommendations was derived from 16 moderate-quality RCTs in which the DMARD of interest was compared to placebo, as previously described in this update. Members of the guideline panel included specialists and patients. The guideline and accompanying technical review underwent independent peer review, and a 30-day open public comment period.[9] The AGA process for developing clinical practice guidelines incorporate GRADE methodology and best practices as outlined by the Institute of Medicine.[9] Due to limited head-to-head assessments of the safety and efficacy of DMARDs in UC, most of the recommendations are conditional due to low quality of evidence. The recommendations for outpatient treatment are as follows:

- In adult outpatients with moderate to severe UC, the AGA recommends using infliximab, adalimumab, golimumab, vedolizumab, tofacitinib, or ustekinumab over no treatment. Medications are ordered based on year of approval by the FDA. (Strong recommendation: moderate Quality of evidence)[9]
- In adult outpatients with moderate to severe UC who are naïve to biologic agents, the AGA suggests using infliximab or vedolizumab rather than adalimumab, for induction of remission. Patients, particularly those with less severe disease, who place higher value on the convenience of self-administered subcutaneous injection, and a lower value on the relative efficacy of medications, may reasonably chose adalimumab as an alternative. (Conditional recommendation: moderate Quality of evidence)[9]
- In adult outpatients with moderate to severe UC who are naïve to biologic agents, the AGA recommends that tofacitinib only be used in the setting of a clinical or registry study*. Comment: Updated FDA recommendations (July 26, 2019) on indications for use of tofacitinib in UC recommends its use only after failure of or intolerance to TNF inhibitors*. (No recommendation, knowledge gap)[9]
- In adult outpatients with active moderate to severe UC, the AGA suggests against using thiopurine monotherapy for induction of remission. (Conditional recommendation, very low Quality of evidence)[9]
- In adult outpatients with moderate to severe UC in remission, the AGA suggests using thiopurine monotherapy, rather than no treatment, for maintenance of remission. (Conditional recommendation low Quality of evidence)[9]
- In adult outpatients with moderate to severe UC, the AGA suggests against using MTX monotherapy for induction or maintenance of remission. (Conditional recommendation, low quality evidence)[9]

- In adult outpatients with active moderate to severe UC, the AGA suggests using biologic monotherapy (TNF inhibitor, vedolizumab, ustekinumab) rather than thiopurine monotherapy for induction of remission. (Conditional recommendation, low Quality of evidence).[9]
- In adult outpatients with moderate to severe UC who have previously been exposed to infliximab, particularly those with primary non-response, the AGA suggests using ustekinumab or tofacitinib rather than vedolizumab or adalimumab for induction of remission. (Conditional recommendation: low Quality of evidence)[9]
- In adult outpatients with active moderate to severe UC, the AGA suggests using biologic monotherapy (TNF inhibitor, vedolizumab, or ustekinumab) or tofacitinib rather than thiopurine monotherapy for induction of remission. (Conditional recommendation: low Quality of evidence.)[9]
- In adult outpatients with moderate to severe UC, the AGA suggests combining TNF inhibitor, vedolizumab or ustekinumab with thiopurines or MTX rather than initiating biologic monotherapy. *Comment: Patients, particularly those with less severe disease, who place higher value on the safety of biologic monotherapy and lower value on the efficacy of combination therapy may reasonably chose biologic monotherapy.* (Conditional recommendation: low Quality of evidence).[9]
- In adult outpatients with moderate to severe UC, the AGA suggests combining a TNF inhibitor, vedolizumab, or ustekinumab with thiopurines or MTX rather than thiopurine monotherapy. (Conditional recommendation: low Quality of evidence.)[9]
- In adult outpatients with moderate to severe UC, the AGA suggests early use of biologic agents with or without immunomodulator therapy rather than gradual step up after failure of 5-aminosalicylate (ASA). *Comment: Patients, particularly those with less severe disease, who place higher value on the safety of 5-ASA therapy and lower value on the efficacy of biologic agents or tofacitinib may reasonably chose gradual step therapy with 5-ASA therapy.* (Conditional recommendation: very low Quality of evidence.)[9]
- In adult outpatients with moderate to severe ulcerative colitis who have achieved remission with biologic agents and/or immunomodulators, or tofacitinib, the AGA suggests against continuing 5-ASA for induction and maintenance of remission. (Conditional recommendation, very low Quality of evidence).[9]

European League against Rheumatism: Psoriatic Arthritis

The EULAR recommendations for the management of PsA with pharmacological therapies were updated in 2019.[10] A systematic literature review was followed by a consensus meeting involving 28 international taskforce members.[10] The taskforce consisted of people from 15 European countries: 21 rheumatologists, 2 people affected with PsA, 1 health professional, 1 dermatologist and 3 rheumatology fellows/trainees.[10] Standardized EULAR operating procedures guided the formulation of recommendations.[77] Grade 1A evidence is based on meta-analyses of RCTs, while grade 1B evidence is derived from at least one RCT.[77] Only Grade A and B grades are summarized in this report. Pharmacologic recommendations based on high quality evidence include:

- NSAIDs may be used to relieve musculoskeletal signs and symptoms. (Recommendation Grade A; Level of Evidence 1b)[10]
- In patients with polyarthritis, a conventional synthetic DMARD should be initiated rapidly, with methotrexate preferred in those with relevant skin involvement. (Recommendation Grade B; Level of Evidence 1b)[10]
- In patients with peripheral arthritis and an inadequate response to at least one conventional synthetic DMARD, therapy with a biologic DMARD should be commenced; when there is relevant skin involvement, an IL-17 inhibitor or IL-12/23 inhibitor may be preferred. (Recommendation Grade B; Level of Evidence 1b)[10]
- In patients with peripheral arthritis and an inadequate response to at least one conventional synthetic DMARD and at least one biologic DMARD, or when a biologic DMARD is not appropriate, a JAK inhibitor may be considered. (Recommendation Grade B; Level of Evidence 1b).[10]
- In patients with mild disease and an inadequate response to at least one conventional synthetic DMARD, in whom neither a biologic DMARD nor a JAK inhibitor is appropriate, a PDE4 inhibitor may be considered. Recommendation Grade B; Level of Evidence 1b).[10]

- In patients with unequivocal enthesitis and insufficient response to NSAIDs or local glucocorticoid injections, therapy with a biologic DMARD should be considered. (Recommendation Grade B; Level of Evidence 1b).[10]
- In patients with predominantly axial disease which is active and has insufficient response to NSAIDs, therapy with a biologic DMARD should be considered, which according to current practice is a TNF inhibitor; when there is relevant skin involvement, IL-17 inhibitor may be preferred. (Recommendation Grade B; Level of Evidence 1b).[10]

European League against Rheumatism: Rheumatoid Arthritis

The EULAR recommendations for the management of RA were updated in 2019 to account for recent treatment developments.[11] Two systematic reviews (one focused on efficacy and the other on safety) informed the task force recommendations and are previously described in this class update.[4,5] The steering committee included 8 rheumatologists, one patient representative, and 2 fellows who performed the systematic reviews. The task force consisted of 47 individuals, including the steering committee members.[11] Among the task force members were 3 patients, 2 health professionals and 2 delegates of the EULAR young rheumatologists' network.[11] Recommendations based on high quality evidence regarding the use of conventional synthetic DMARDs (MTX, leflunomide, sulfasalazine); glucocorticoids; biologic DMARDs (adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, abatacept, rituximab, tocilizumab, sarilumab) and targeted synthetic DMARDs (tofacitinib, baricitinib, upadacitinib) are summarized as follows:

- Therapy with DMARDs should be started as soon as the diagnosis of RA is made. (Recommendation Grade A; Level of Evidence 1a).[11]
- Treatment should be aimed at reaching a target of sustained remission or low disease activity in every patient. (Recommendation Grade A; Level of Evidence 1a).[11]
- Monitoring should be frequent in active disease (every 1–3 months); if there is no improvement by at most 3 months after the start of treatment or the target has not been reached by 6 months, therapy should be adjusted. (Recommendation Grade B; Level of Evidence 2b).[11]
- Methotrexate should be part of the first treatment strategy. (Recommendation Grade A; Level of Evidence 1a).[11]
- In patients with a contraindication to MTX (or early intolerance), leflunomide or sulfasalazine should be considered as part of the first treatment strategy. (Recommendation Grade A; Level of Evidence 1a).[11]
- Short-term glucocorticoids should be considered when initiating or changing conventional synthetic DMARDs, in different dose regimens and routes of administration, but should be tapered as rapidly as clinically feasible. (Recommendation Grade A; Level of Evidence 1a).[11]
- If the treatment target is not achieved with the first conventional synthetic DMARD strategy, and when poor prognostic factors are present, a biologic DMARD or a targeted synthetic DMARD should be added. (Recommendation Grade A; Level of Evidence 1a).[11]
- Biologic DMARDs and targeted synthetic DMARDs should be combined with a conventional synthetic DMARD; in patients who cannot use conventional synthetic DMARDs as co-medication, IL-6 pathway inhibitors and targeted synthetic DMARDs may have some advantages compared with other biologic DMARDs. (Recommendation Grade A; Level of Evidence 1a).[11]
- If a patient is in persistent remission after having tapered glucocorticoids, one can consider tapering biologic DMARDs or targeted synthetic DMARDs, especially if this treatment is combined with a conventional synthetic DMARD. (Recommendation Grade A; Level of Evidence 1b).[11]

National Institute for Health and Care Excellence

<u>Upadacitinib in Severe Rheumatoid Arthritis</u>

NICE guidance for the use of upadacitinib in treating severe RA was published in December 2020.[12] Clinical trials show that upadacitinib with MTX or conventional synthetic DMARDs is more effective than MTX or conventional synthetic DMARDs for treating moderate to severe active RA that has not responded

adequately to conventional synthetic DMARDs.[12] The trials also show that for moderate to severe active RA that has not responded adequately to conventional synthetic DMARDs, upadacitinib with MTX is more effective than adalimumab with MTX or placebo with MTX.[12] The specific recommendations include:

1. Upadacitinib, with MTX, is recommended as an option for treating active RA in adults whose disease has responded inadequately to intensive therapy with a combination of conventional synthetic DMARDs only if disease is severe (a DAS28 of more than 5.1).[12]
2. Upadacitinib, with MTX, is recommended as an option for treating active RA in adults whose disease has responded inadequately to or who cannot have other DMARDs, including at least 1 biological DMARD, only if:
    - disease is severe (a DAS28 of more than 5.1) and
    - they cannot have rituximab.[12]
3. Upadacitinib, with MTX, is recommended as an option for treating active RA in adults whose disease has responded inadequately to rituximab and at least 1 biologic DMARDs, only if disease is severe (a DAS28 of more than 5.1).[12]
4. Upadacitinib can be used as monotherapy for people who cannot take MTX because it is contraindicated or because of intolerance, when criteria in sections 1, 2 and 3 have been met.[12]
5. Continue treatment only if there is a moderate response measured using EULAR criteria at 6 months after starting therapy. After an initial response within 6 months, stop treatment if at least a moderate EULAR response is not maintained.[12]

Ustekinumab in Moderate-to-Severe Ulcerative Colitis

NICE guidance for ustekinumab for treating moderately to severely active UC was published June 2020. Tumor necrosis factor inhibitors are the most commonly used biological treatment option for moderately to severely active UC.[78] People who cannot have TNF inhibitors are usually offered vedolizumab, so this is the most relevant comparator for ustekinumab.[78] Both drugs have similar safety profiles and work differently than TNF inhibitors.[78] Clinical trial evidence shows that ustekinumab is more effective than placebo for treating moderately to severely active UC.[78] Ustekinumab is recommended as an option for treating moderately to severely active UC in adults when conventional therapy or a biological agent cannot be tolerated, or the disease has responded inadequately or lost response to treatment, only if:

- a TNF inhibitor has failed (that is the disease has responded inadequately or has lost response to treatment) or
- a TNF inhibitor cannot be tolerated or is not suitable.[78]

After review, no guidelines were excluded due to poor quality.

New Formulations or Indications:

Adalimumab

February 2020: The FDA expanded the approved age range for the use of adalimumab (HUMIRA) in children 5 years and older with moderate-to-severe UC.[14]

Ozanimod

May 2020: The FDA approved an expanded indication for ozanimod (ZEPOSIA), an sphingosine 1-phosphate (S1P) receptor modulator, for the treatment of adults with moderate-to-severe UC.[15] Ozanimod received initial approval to treat relapsing forms of multiple sclerosis in March 2020.[15] The expanded indication is based on results from True North, a phase 3 trial that assessed ozanimod as an induction[79] and maintenance[80] therapy compared with placebo in patients with moderate- to-severe UC. In the induction period, 645 patients were randomized 2:1 to either ozanimod 0.92 mg given orally once daily or placebo for 10 weeks, beginning with an ozanimod dosing titration to minimize adverse cardiovascular effects.[79] The trial included adult patients with moderately to severely active UC who had an inadequate response or were intolerant conventional synthetic DMARDs or biologic DMARDs. A total of 30% of patients had previously failed or

were intolerant to TNF inhibitors.[79] Of these patients, 63% received at least two biologics including TNF inhibitors.[79] Concomitant immunomodulators or biologic therapies were not permitted during the study. The primary endpoint in the induction period was the proportion of patients in clinical remission at week 10 using the 3-component Mayo score (rectal bleeding score = 0, stool frequency score ≤1 and decrease from baseline ≥1, and endoscopy subscore ≤1) at week 10.[79] At week 10, 18.4% and 6.0% of patients in the ozanimod and placebo groups, respectively, achieved clinical remission (difference, 12.4% [95% CI, 7.5-17.2]; P<0.0001).[79] In patients with prior TNF inhibitor exposure, the proportion of patients achieving clinical remission at week 10 favored ozanimod but was not significant versus placebo (10.0% vs 4.6%, P=0.195).[79] The most common treatment-emergent adverse events (TEAEs) for patients who received ozanimod vs placebo, respectively, were anemia (4.2% vs 5.6%), nasopharyngitis (3.5% vs 1.4%), and headache (3.3% vs 1.9%).[79] Cardiovascular events were infrequent and included bradycardia (0.5% vs 0%) and hypertension (1.4% vs 0%) for ozanimod vs placebo.[79] Serious TEAEs occurred in 4.0% of ozanimod vs 3.2% of placebo-treated patients.[79] Serious infections occurred in less than 1% per group.[79]

Tofacitinib

September 2020: The FDA approved an expanded indication of tofacitinib (XELJANZ) for the treatment of children and adolescents 2 years and older with active polyarticular course juvenile idiopathic arthritis.[16] Tofacitinib was previously approved for the treatment of adult patients with RA, PsA and UC who had failed other therapies. Two formulations were approved, a tablet and an oral solution, both are dosed based on weight.[16]

Golimumab

September 2020: The FDA expanded the golimumab (SIMPONI ARIA) indication to include patients 2 years and older for treatment of active PsA or active polyarticular juvenile idiopathic arthritis.[81] In addition to the new indications, golimumab is approved for the treatment of adults with moderately to severely active RA (in combination with MTX), active PsA, or active AS.[81] The FDA based its approval on results from the phase 3 GO-VIVA trial, a 52-week open-label study among children with JIA (n=127) with active polyarthritis aged two to 17 years who had active arthritis in five or more joints, despite receiving treatment with MTX for at least two months.[82]

Anakinra

December 2020: The FDA approved an expanded indication for anakinra (KINERET) to treat deficiency of IL-1 receptor antagonist.[18] Previously anakinra was approved for RA and cryopyrin-associated periodic syndrome.[18] The recommended starting dose of anakinra is 1-2 mg/kg daily for patients with deficiency of IL-1 receptor antagonist.[18] The dose can be individually adjusted to a maximum of 8 mg/kg daily to control active inflammation.[18]

Tocilizumab

March 2021: The FDA approved an expanded indication for subcutaneous tocilizumab (ACTEMRA) to curb the rate of progressive loss of lung function among adults with systemic sclerosis-associated interstitial lung disease.[19] Previously, tocilizumab was FDA approved for RA, sJIA, pJIA, giant cell arteritis (GCA) and cytokine release syndrome (CRS). The FDA based its approval on results from a phase 3, randomized, placebo-controlled, double-blind, multi-center 48-week study.[83] A total of 212 adults with systemic sclerosis were randomized 1:1 to receive either weekly subcutaneous injections of 162 mg of tocilizumab or placebo.[83] The primary endpoint was the change in modified Rodnan skin score (mRSS), a measure of biopsied skin thickness,[84] from baseline to 48 weeks.[83] In the intention-to-treat population, least squares mean [LSM] change from baseline to week 48 in mRSS was −6.14 for tocilizumab and −4.41 for placebo (adjusted difference −1.73 [95% CI −3.78 to 0.32]; P=0.10).[83] The primary skin fibrosis endpoint was not met.[83] However, findings for the secondary endpoint of percentage of predicted forced vital capacity (%FVC predicted) indicate that tocilizumab might preserve lung function in people with early systemic sclerosis-associated interstitial lung disease and elevated acute-phase reactants.[83] The shift in distribution of change from baseline in %FVC predicted at week 48 favored

tocilizumab with a difference in LSM of 4.2 (95% CI 2.0–6.4; nominal P=0.0002), as did time to treatment failure (HR 0.63 [95% CI 0.37–1.06]; P=0.08).[83] Safety was consistent with the known profile of tocilizumab.[83]

Secukinumab

May 2021: The FDA expanded the secukinumab (COSENTYX) indication to include patients 6 years and older for treatment of active PsO who are candidates for systemic therapy or phototherapy.[20] Secukinumab dosing in pediatrics is weight based. For children who weigh less than 50 kg, the initial loading dose is 75 mg SC once a week, every week for 4 weeks, followed by 75 mg SC every 4 weeks.[20] For children who weigh 50 kg or more, the secukinumab dose is 150 mg SC once a week, every week for 4 weeks, followed by 150 mg SC every 4 weeks.[20] All age-appropriate vaccinations as recommended by current guidelines should be administered prior to starting secukinumab treatment.[20] Previously, secukinumab was approved for the treatment of adult patients with PsO, PsA, AS, and non-radiographic axial spondyloarthritis. For adults, dosing varies by indication as described in the manufacturer's prescribing information.

New FDA Safety Alerts:

Table 1. Description of new FDA Safety Alerts

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Tofacitinib Baricitinib Upadacitinib	XELJANZ, XEJANZ XR OLUMIANT RINVOQ	9/2021	Drug Safety Communication[8]	FDA is requiring new and updated warnings about an increased risk of major adverse cardiovascular events, malignancy, thrombosis, and mortality with the Janus kinase (JAK) inhibitors XELJANZ, XELJANZ XR (tofacitinib), OLUMIANT (baricitinib), and RINVOQ (upadacitinib). These warnings are based on FDA review of a large randomized, open-label safety clinical trial.[8] The multicenter, randomized, open-label trial evaluated two doses of XELJANZ (5 mg twice daily (N=1455), which is the approved dosage for RA, and a higher 10 mg twice daily dosage (N=1456)) in comparison to treatment with a TNF blocker (N=1451). Patients in the trial were required to be 50 years of age or older and have at least one cardiovascular risk factor. The co-primary endpoints were major adverse cardiovascular events (MACE), defined as cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke; and malignancy, excluding nonmelanoma skin cancer (NMSC). The trial was designed to exclude a prespecified risk margin of 1.8 for the hazard ratio of combined XELJANZ regimens when compared to the TNF blocker control for

				each co-primary endpoint. The median on-study follow-up time was 4 years.[8] The mean age of the population was 61 years and the median age was 60 (range 50-88 years). Most patients were female (78 percent) and Caucasian (77 percent). The noninferiority criterion was not met for the comparison of the combined XELJANZ regimens to TNF blockers for the endpoints of MACE and malignancies since the upper limit of the 95% CI for these hazard ratios exceeded the prespecified noninferiority criterion of 1.8. For MACE, the estimated hazard ratio and 95% CI associated with the combined XELJANZ regimens relative to TNF blockers were 1.33 (0.91, 1.94). For malignancies excluding NMSC, the estimated hazard ratio and 95% CI associated with the combined XELJANZ regimens relative to TNF blockers were 1.48 (1.04, 2.09).[8] There was an increased risk of death, MACE, malignancies, and thrombosis associated with both regimens of XELJANZ. The data showed evidence of a dose-dependent increased risk for MACE, all-cause mortality, and thrombosis at both doses of XELJANZ when compared to treatment with TNF blockers. Additionally, the data showed evidence of a non-dose-dependent increased risk for malignancy excluding NMSC at both doses of XELJANZ when compared to TNF blockers. Lymphomas and lung cancers were observed at a higher rate in patients treated at both doses of XELJANZ compared to those treated with TNF blockers. In particular, a higher rate of lung cancers was observed in current or past smokers treated with XELJANZ. Current or past smokers had an additional increased risk of overall cancers.[8] Other JAK inhibitors have not been studied in similar large safety clinical trials, so the risk with these medicines has not been evaluated. However, since they share mechanisms of action with XELJANZ, FDA considers that these medicines

				may have similar risks as seen in the safety clinical trial with Xeljanz.[8]
Guselkumab	TREMFYA	7/2020	Warnings and Precautions	Serious hypersensitivity reactions, including anaphylaxis, have been reported with post-market use of guselkumab.[85]
Abatacept	ORENCIA	6/2020	Warnings and Precautions	New section added to Warning and Precautions section regarding the risk of immunosuppression. The possibility exists for drugs inhibiting T cell activation, including abatacept, to affect host defenses against infections and malignancies since T cells mediate cellular immune responses. In clinical trials in patients with adult RA, a higher rate of infections was seen in abatacept-treated patients compared to placebo-treated patients. The impact of treatment with abatacept on the development and course of malignancies is not fully understood. There have been reports of malignancies, including skin cancer in patients receiving abatacept. Periodic skin examinations are recommended for all abatacept-treated patients, particularly those with risk factors for skin cancer.[86]
Baricitinib	OLUMIANT	7/2020	Warnings and Precautions	New subsection added to Warning and Precautions section regarding hypersensitivity. Reactions such as angioedema, urticaria, and rash that may reflect drug hypersensitivity have been observed in patients receiving baricitinib, including serious reactions. If a serious hypersensitivity reaction occurs, promptly discontinue baricitinib while evaluating the potential causes of the reaction.[87]
Secukinumab	COSENTYX	5/2021	Warnings and Precautions	In the post marketing setting, serious and some fatal infections have been reported in patients receiving secukinumab.[20]

Randomized Controlled Trials:

A total of 337 citations were manually reviewed from the initial literature search. After further review, 332 citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical). The remaining 5 trials are summarized in the table below. Full abstracts are included in **Appendix 2**.

Table 2. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results
McInnes IB, et al.[88] PG, DB, AC, MC, Phase 3 RCT Duration: 52 weeks	1. Secukinumab 300 mg SC at baseline, weeks 1, 2, 3 & 4, and then every 4 weeks x 48 weeks (n=426) 2. Adalimumab 40 mg SC every 2 weeks x 50 weeks (n=427) Both drugs were used as monotherapy	Adults ≥ 18 yo with active PsA naïve to biologic DMARDs and who were intolerant or had an inadequate response to conventional synthetic DMARDs n=853	Proportion of patients with at least 20% improvement in the ACR response criteria (ACR20) at week 52 Attrition 1. 16 (14%) 2. 101 (24%)	1. 67% 2. 62% OR 1.30, 95% CI 0.98–1.2; p=0.0719. The primary endpoint of superiority was not met.
Rubbert-Roth A, et al.[89] AC, DB, MC Phase 3 RCT Duration: 24 weeks	1. Upadacitinib 15 mg PO once daily (n=303) 2. Abatacept 500 to 1000 mg (weight based) IV on day 1 and weeks 2, 4, 8, 12, 16, and 20 (n=309) Both drugs were used in combination with conventional synthetic DMARDs	Adults ≥ 18 yo with moderate- to severe active RA despite treatment with a biologic DMARD or unacceptable side effects from at least 1 biologic DMARD n=612	Change from baseline in the composite Disease Activity Score for 28 joints based on the C-reactive protein level (DAS28-CRP) (range, 0 to 9.4, with higher scores indicating more disease activity) at week 12, assessed for non-inferiority)	1. 5.70 (mean change at week 12 = −2.52) 2. 5.88 mean change at week 12 = −2.00) Mean (difference, −0.52 points; 95% CI, −0.69 to −0.35; P<0.001 for noninferiority; P<0.001 for superiority
McInnes IB et al.[90] AC, DB, MC Phase 3 RCT Duration: 24 weeks	1. Upadacitinib 15 mg once daily (n=429) 2. Upadacitinib 30 mg once daily (n=423) 3. Adalimumab 40 mg every other week (n=429)	Adults ≥ 18 yo with active PsA naïve to biologic DMARDs and who were intolerant or had an inadequate response to at least 1 DMARD	Proportion of patients with at least 20% improvement in the ACR response criteria (ACR20 at week 12	The percentage of patients who had an ACR20 response at week 12 was 1. 70.6% 2. 78.5% 3. 65.0% 4. 36.2% Between-group differences were as follows: • 1 vs. 4: 34.5% (95% CI, 28.2 to 40.7; P<0.001);

	4. Placebo (n=423)	n=1705		• 2 vs. 4: 42.3% (95% CI, 36.3 to 48.3; P<0.001); • 1 vs. 3: 5.6% (95% CI, −0.6 to 11.8; the hierarchical analysis failed at this point, so no P-value is given); and • 2 vs. 3: 13.5% (95% CI, 7.5 to 19.4; P<0.001). Both upadacitinib doses were noninferior to adalimumab based on ACR20 at week 12; the 30-mg dose but not the 15-mg dose was superior to adalimumab.
Blauvelt A, et al.[91] MC, DB, PG Phase 4 RCT	1. Ixekizuamb 160 mg SC at week 0, followed by 80 mg every weeks x 12 weeks (n=520) 2. Guselkumab 100 mg SC at weeks 0, 4, and 12 x 12 weeks (n=507)	Adults ≥ 18 yo with chronic PsO for at least 6 months and a candidate for phototherapy and/or systemic therapy n=1027	Percentage of patients reaching PASI 100 (complete skin clearance) at week 12	1. 41% 2. 25% OR 2.14; 95% CI 1.63 to 2.81; p<0.001 Ixekizumab was superior to guselkumab based on PASI 100 at 12 weeks.
Mease PJ, et al.[92] MC, OL, Phase 3b/4 RCT	1.Ixekizumab 160 mg SC at week 0, followed by 80 mg every 4 weeks beginning week 4 up to week 24 (7 doses total unless criteria met for moderate-to-severe disease, then 10 doses were given in a modified dosing regimen) (n=283) 2.Adalimumab 40 mg SC at week 0, followed by 40 mg every 2 weeks beginning week 2 up to week 24 (14	Adults ≥ 18 yo in bDMARD -naïve patients with active PsA and inadequate response to csDMARDs 18% of patients met criteria for moderate to severe PsA n=566	Percentage of patients reaching ACR50 and PASI 100 response at week 24	1. 36% 2. 27.9% Treatment difference: 8.1%; 95% CI 0.5 to 15.8; p=0.036 Ixekizumab was superior to adalimumab based on ACR50 and PASI 100 at 24 weeks in 82% of patients with mild PsA and 18% with moderate-to-severe PsA

	doses total unless criteria met for moderate-to-severe disease, then 15 doses were given in a modified dosing regimen) (n=283)			

Abbreviations: AC = active comparator; ACR = American College of Rheumatology; bDMARDs = biologic disease-modifying anti-rhematic drugs; csDMARDs = conventional synthetic disease-modifying anti-rhematic drugs; CI = confidence interval; DB = double-blind; IV = intravenous; MC = multi-center; OL = open label; OR = odds ratio; PASI = Psoriasis Area and Severity Index; PG = parallel group; PO = oral; PSA = psoriatic arthritis; PsO = plaque psoriasis; RA = rheumatoid arthritis; RCT = randomized clinical trial; SC = subcutaneous; yo = years old

References:

1. Singh S, Allegretti JR, Siddique SM, Terdiman JP. AGA Technical Review on the Management of Moderate to Severe Ulcerative Colitis. *Gastroenterology.* 2020;158(5):1465-1496.e1417.
2. Sbidian E, Chaimani A, Afach S, et al. Systemic pharmacological treatments for chronic plaque psoriasis: a network meta-analysis. *Cochrane Database Syst Rev.* 2020;1:CD011535.
3. Kerschbaumer A, Smolen JS, Dougados M, et al. Pharmacological treatment of psoriatic arthritis: a systematic literature research for the 2019 update of the EULAR recommendations for the management of psoriatic arthritis. *Ann Rheum Dis.* 2020;79(6):778-786.
4. Kerschbaumer A, Sepriano A, Smolen JS, et al. Efficacy of pharmacological treatment in rheumatoid arthritis: a systematic literature research informing the 2019 update of the EULAR recommendations for management of rheumatoid arthritis. *Ann Rheum Dis.* 2020;79(6):744-759.
5. Sepriano A, Kerschbaumer A, Smolen JS, et al. Safety of synthetic and biological DMARDs: a systematic literature review informing the 2019 update of the EULAR recommendations for the management of rheumatoid arthritis. *Ann Rheum Dis.* 2020;79(6):760-770.
6. Yates M, Mootoo A, Adas M, et al. Venous Thromboembolism Risk With JAK Inhibitors: A Meta-Analysis. *Arthritis rheumatol.* 2021;73(5):779-788.
7. Nikoo Z, Badihian S, Shaygannejad V, Asgari N, Ashtari F. Comparison of the efficacy of azathioprine and rituximab in neuromyelitis optica spectrum disorder: a randomized clinical trial. *J Neurol.* 2017;264(9):2003-2009.
8. Food & Drug Administration Update. FDA requires warnings about increased risk of serious heart-related events, cancer, blood clots, and death for JAK inhibitors that treat certain chronic inflammatory conditions. 9/1/2021. https://www.fda.gov/media/151936/download Accessed 9/1/2021.
9. Feuerstein JD, Isaacs KL, Schneider Y, Siddique SM, Falck-Ytter Y, Singh S. AGA Clinical Practice Guidelines on the Management of Moderate to Severe Ulcerative Colitis. *Gastroenterology.* 2020;158(5):1450-1461.
10. Gossec L, Baraliakos X, Kerschbaumer A, et al. EULAR recommendations for the management of psoriatic arthritis with pharmacological therapies: 2019 update. *Ann Rheum Dis.* 2020;79(6):700-712.

11. Smolen JS, Landewe RBM, Bijlsma JWJ, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update. *Ann Rheum Dis.* 2020;79(6):685-699.
12. Gaubitz M, Gottl KH, Behmer O, Lippe R, Meng T, Loschmann PA. Etanercept is effective as monotherapy or in combination with methotrexate in rheumatoid arthritis: subanalysis of an observational study. *Clin Rheumatol.*36(9):1989-1996.
13. National Institute for Health and Care Excellence. Ustekinumab for treating moderately to severely active ulcerative colitis. June 2020. https://www.nice.org.uk/guidance/TA633/Resources. Accessed June 16, 2021.
14. HUMIRA (adalimumab) Injection Prescribing Information. North Chicago, IL: AbbVie Inc., February 2020.
15. ZEPOSIA (ozanimod) capsule Prescribing Information. Summit, NJ: Celgene Corporation. May 2020.
16. XELJANZ (tofacitinib) Oral Tablet Prescribing Information. New York, NY; Pfizer, Inc. September 2020.
17. SIMPONI ARIA (golimumab) intravenous infusion Prescribing Information. Horsham, PA: Janssen Biotech, Inc. February 2021.
18. KINERET (anakinra) SC injection. Stockhol, Sweden; Swedish Orphan Biovitrum AB. December 2020.
19. ACTEMRA (tocilizumab) SC or IV injection Prescribing Information. South San Francisco, CA; Genentech, Inc. March 2021.
20. COSENTYX (Secukinumab) Injection Prescribing Information. East Hanover, NJ: Novartis Pharmaceuticals Corporation. May 2021.
21. Gartlehner G WG, Dobrescu A, et al. Targeted immune modulators: rheumatoid arthritis and ankylosing spondylitis. Portland, OR: Center for Evidence-based Policy, Oregon Health & Science University; 2020.
22. Kahwati L GK, Ali R, Gartlehner G. Targeted Immune Modulators: Plaque Psoriasis and Psoriatic Arthritis. Portland, OR: Center for Evidence-based Policy, Oregon Health & Science University; March 2020.
23. Kahwati L, et al. Targeted Immune Modulators: Crohn's disease and Ulcerative Colitis. Portland, OR: Center for Evidence-based Policy, Oregon Health & Science University; February 2020.
24. Food and Drug Administration. List of Licensed Biological Products with Reference Product Exclusivity and Biosimilarity or Interchangeability Evaluations (Purple Book). https://www.fda.gov/drugs/biosimilars/background-information-list-licensed-biological-products-reference-product-exclusivity Accessed August 9. 2021.
25. Micromedex [internet database]. Truven Health Analytics, Greenwood Village, Colorado, USA. Available at http://www.micromedexsolutions.com. Accessed May 1, 2020.
26. Lexicomp Online [internet database]. Wolters Kluwer Health, Hudson, Ohio, USA. Available at http://online.lexi.com. Accessed May 18, 2020.
27. McVeigh CM, Cairns AP. Diagnosis and management of ankylosing spondylitis. *Bmj.* 2006;333(7568):581-585.
28. Corbett M, Soares M, Jhuti G, et al. Tumour necrosis factor-alpha inhibitors for ankylosing spondylitis and non-radiographic axial spondyloarthritis: a systematic review and economic evaluation. *Health Technol Assess.* 2016;20(9):1-334, v-vi.
29. Ward MM, Deodhar A, Akl EA, et al. American College of Rheumatology/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network 2015 Recommendations for the Treatment of Ankylosing Spondylitis and Nonradiographic Axial Spondyloarthritis. *Arthritis Rheumatol.* 2016;68(2):282-298.
30. Bell Gorrod H, Latimer NR, Damian D, Hettle R, Harty GT, Wong SL. Assessing the Long-Term Effectiveness of Cladribine vs. Placebo in the Relapsing-Remitting Multiple Sclerosis CLARITY Randomized Controlled Trial and CLARITY Extension Using Treatment Switching Adjustment Methods. *Advances in therapy.* 2020;37(1):225-239.

31. Ward MM, Deodhar A, Gensler LS, et al. 2019 Update of the American College of Rheumatology/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network Recommendations for the Treatment of Ankylosing Spondylitis and Nonradiographic Axial Spondyloarthritis. *Arthritis rheumatol.* 2019;71(10):1599-1613.
32. van der Heijde D, Ramiro S, Landewé R, et al. 2016 update of the ASAS-EULAR management recommendations for axial spondyloarthritis. *Ann Rheum Dis.* 2017;76(6):978-991.
33. Katzberg HD, Barnett C, Merkies IS, Bril V. Minimal clinically important difference in myasthenia gravis: outcomes from a randomized trial. *Muscle & nerve.* 2014;49(5):661-665.
34. Aletaha D, Smolen JS. Diagnosis and Management of Rheumatoid Arthritis: A Review. *Jama.* 2018;320(13):1360-1372.
35. Wei JC, Baeten D, Sieper J, et al. Efficacy and safety of secukinumab in Asian patients with active ankylosing spondylitis: 52-week pooled results from two phase 3 studies.[Erratum appears in Int J Rheum Dis. 2017 Jul;20(7):911; PMID: 28736967]. *International Journal of Rheumatic Diseases.*20(5):589-596.
36. Edler RJ. Dental and skeletal ages in hypopituitary patients. *Journal of Dental Research.*56(10):1145-1153.
37. Orbai AM, Bingham CO, 3rd. Patient reported outcomes in rheumatoid arthritis clinical trials. *Curr Rheumatol Rep.* 2015;17(4):28.
38. Ward MM, Guthrie LC, Alba MI. Clinically important changes in individual and composite measures of rheumatoid arthritis activity: thresholds applicable in clinical trials. *Ann Rheum Dis.* 2015;74(9):1691-1696.
39. Parisi R, Symmons DP, Griffiths CE, Ashcroft DM. Global epidemiology of psoriasis: a systematic review of incidence and prevalence. *The Journal of investigative dermatology.* 2013;133(2):377-385.
40. Wolinsky JS, Arnold DL, Brochet B, et al. Long-term follow-up from the ORATORIO trial of ocrelizumab for primary progressive multiple sclerosis: a post-hoc analysis from the ongoing open-label extension of the randomised, placebo-controlled, phase 3 trial. *Lancet Neurology.* 2020;19(12):998-1009.
41. Corrado A, Di Bello V, d'Onofrio F, Maruotti N, Cantatore FP. Anti-TNF-alpha effects on anemia in rheumatoid and psoriatic arthritis. *International Journal of Immunopathology & Pharmacology.*30(3):302-307.
42. National Institute for Health and Care Excellence. Psoriasis: Assessment and Management. September 1, 2017. https://www.nice.org.uk/guidance/cg153/chapter/1-Recommendations Accessed November July 20, 2020.
43. Robinson A, Kardos M, Kimball AB. Physician Global Assessment (PGA) and Psoriasis Area and Severity Index (PASI): why do both? A systematic analysis of randomized controlled trials of biologic agents for moderate to severe plaque psoriasis. *J Am Acad Dermatol.* 2012;66(3):369-375.
44. Ashcroft DM, Wan Po AL, Williams HC, Griffiths CE. Clinical measures of disease severity and outcome in psoriasis: a critical appraisal of their quality. *The British journal of dermatology.* 1999;141(2):185-191.
45. Lichtenstein GR, Loftus EV, Isaacs KL, Regueiro MD, Gerson LB, Sands BE. ACG Clinical Guideline: Management of Crohn's Disease in Adults. *Official journal of the American College of Gastroenterology | ACG.* 2018;113(4):481-517.
46. Nevitt SJ, Marson AG, Weston J, Tudur Smith C. Sodium valproate versus phenytoin monotherapy for epilepsy: an individual participant data review. *Cochrane Database Syst Rev.*8:CD001769.
47. National Institute for Health and Care Excellence (NICE) Crohn's Disease: Management. May 3, 2019. https://www.nice.org.uk/guidance/ng130 Accessed July 20, 2020.
48. Dassopoulos T, Cohen RD, Scherl EJ, Schwartz RM, Kosinski L, Regueiro MD. Ulcerative Colitis Care Pathway. *Gastroenterology.* 2015;149(1):238-245.

49. Schroeder KW, Tremaine WJ, Ilstrup DM. Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. A randomized study. *N Engl J Med.* 1987;317(26):1625-1629.
50. National Institute for Health and Care Excellence (NICE) Ulcerative Colitis: Management. May 2019. https://www.nice.org.uk/guidance/ng130 Accessed July 20, 2020.
51. Rubin DT, Ananthakrishnan AN, Siegel CA, Sauer BG, Long MD. ACG Clinical Guideline: Ulcerative Colitis in Adults. *The American journal of gastroenterology.* 2019;114(3):384-413.
52. Burmester GR, Lin Y, Patel R, et al. Efficacy and safety of sarilumab monotherapy versus adalimumab monotherapy for the treatment of patients with active rheumatoid arthritis (MONARCH): a randomised, double-blind, parallel-group phase III trial. *Ann Rheum Dis.* 2017;76(5):840-847.
53. Khoo JK, Barnes H, Key S, Glaspole IN, Östör AJ. Pulmonary adverse events of small molecule JAK inhibitors in autoimmune disease: systematic review and meta-analysis. *Rheumatology (Oxford, England).* 2020;59(9):2217-2225.
54. Olivera PA, Lasa JS, Bonovas S, Danese S, Peyrin-Biroulet L. Safety of Janus Kinase Inhibitors in Patients With Inflammatory Bowel Diseases or Other Immune-mediated Diseases: A Systematic Review and Meta-Analysis. *Gastroenterology.* 2020;158(6):1554-1573.e1512.
55. Janke K, Biester K, Krause D, et al. Comparative effectiveness of biological medicines in rheumatoid arthritis: systematic review and network meta-analysis including aggregate results from reanalysed individual patient data. *Bmj.* 2020;370:m2288.
56. Cantini F, Blandizzi C, Niccoli L, Petrone L, Goletti D. Systematic review on tuberculosis risk in patients with rheumatoid arthritis receiving inhibitors of Janus Kinases. *Expert Opinion on Drug Safety.* 2020;19(7):861-872.
57. Chessa E, Piga M, Floris A, et al. Biologics and Targeted Synthetic Drugs Can Induce Immune-Mediated Glomerular Disorders in Patients with Rheumatic Diseases: An Updated Systematic Literature Review. *BioDrugs.* 2021;35(2):175-186.
58. Deodhar A, Chakravarty SD, Cameron C, et al. A systematic review and network meta-analysis of current and investigational treatments for active ankylosing spondylitis. *Clin Rheumatol.* 2020;39(8):2307-2315.
59. Li W, Ghamrawi R, Haidari W, Feldman SR. Risankizumab for the Treatment of Moderate to Severe Plaque Psoriasis. *Ann Pharmacother.* 2020;54(4):380-387.
60. Tada Y, Watanabe R, Noma H, Kanai Y, Nomura T, Kaneko K. Short-term effectiveness of biologics in patients with moderate-to-severe plaque psoriasis: A systematic review and network meta-analysis. *Journal of Dermatological Science.* 2020;99(1):53-61.
61. Lee YH, Song GG. Comparison of the efficacy and safety of tofacitinib and filgotinib in patients with active rheumatoid arthritis: a Bayesian network meta-analysis of randomized controlled trials. *Z Rheumatol.* 2020;79(6):590-603.
62. Lee YH, Song GG. Comparative efficacy and safety of tofacitinib, baricitinib, upadacitinib, and filgotinib in active rheumatoid arthritis refractory to biologic disease-modifying antirheumatic drugs. *Z Rheumatol.* 2021;80(4):379-392.
63. Song GG, Lee YH. Comparison of the efficacy and safety of biological agents in patients with systemic juvenile idiopathic arthritis: A Bayesian network meta-analysis of randomized controlled trials. *Int J Clin Pharmacol Ther.* 2021;59(3):239-246.
64. Pope J, Sawant R, Tundia N, et al. Comparative Efficacy of JAK Inhibitors for Moderate-To-Severe Rheumatoid Arthritis: A Network Meta-Analysis. *Advances in therapy.* 2020;37(5):2356-2372.
65. Shi J, Xu J, Chen Y. A network meta-analysis for the comparison of efficacy and safety of interleukin (IL)-23 targeted drugs in the treatment of moderate to severe psoriasis. *Dermatologic Therapy.* 2020;33(4):e13802.
66. Ho Lee Y, Gyu Song G. Comparative efficacy and safety of tofacitinib, baricitinib, upadacitinib, filgotinib and peficitinib as monotherapy for active rheumatoid arthritis. *Journal of Clinical Pharmacy & Therapeutics.* 2020;45(4):674-681.

67. Loft ND, Vaengebjerg S, Halling AS, Skov L, Egeberg A. Adverse events with IL-17 and IL-23 inhibitors for psoriasis and psoriatic arthritis: a systematic review and meta-analysis of phase III studies. *Journal of the European Academy of Dermatology & Venereology.* 2020;34(6):1151-1160.
68. Armstrong AW, Puig L, Joshi A, et al. Comparison of Biologics and Oral Treatments for Plaque Psoriasis: A Meta-analysis. *JAMA dermatology.* 2020;156(3):258-269.
69. Xu Y, Li Y, Dong M, et al. Association of previous treatment with anti-tumour necrosis factor inhibitors with the effectiveness of secukinumab in the treatment of psoriatic arthritis: systematic review and meta-analysis. *Rheumatology.* 2020;59(12):3657-3665.
70. Salvador-Rodriguez L, Montero-Vilchez T, Arias-Santiago S, Molina-Leyva A. Paradoxical Hidradenitis Suppurativa in Patients Receiving TNF-alpha Inhibitors: Case Series, Systematic Review, and Case Meta-Analysis. *Dermatology (Basel, Switzerland).* 2020;236(4):307-313.
71. Bellinato F, Gisondi P, Maurelli M, Girolomoni G. IL-17A inhibitors in patients with chronic plaque psoriasis and history of malignancy: A case series with systematic literature review. *Dermatologic Therapy.* 2021;34(2):e14889.
72. Little DHW, Tabatabavakili S, Shaffer SR, Nguyen GC, Weizman AV, Targownik LE. Effectiveness of Dose De-escalation of Biologic Therapy in Inflammatory Bowel Disease: A Systematic Review. *American Journal of Gastroenterology.* 2020;115(11):1768-1774.
73. Sandhu VK, Ighani A, Fleming P, Lynde CW. Biologic Treatment in Elderly Patients With Psoriasis: A Systematic Review. *J Cutan Med Surg.* 2020;24(2):174-186.
74. Singh S, Fumery M, Singh AG, et al. Comparative Risk of Cardiovascular Events With Biologic and Synthetic Disease-Modifying Antirheumatic Drugs in Patients With Rheumatoid Arthritis: A Systematic Review and Meta-Analysis. *Arthritis care & research.* 2020;72(4):561-576.
75. Egeberg A, Andersen YMF, Halling-Overgaard AS, et al. Systematic review on rapidity of onset of action for interleukin-17 and interleukin-23 inhibitors for psoriasis. *Journal of the European Academy of Dermatology & Venereology.* 2020;34(1):39-46.
76. Schlueter M, Rouse P, Pitcher A, Graham-Clarke PL, Nicolay C, Fakhouri W. A modeling framework for the economic evaluation of baricitinib in moderate-to-severe rheumatoid arthritis. *Expert Review of Pharmacoeconomics & Outcomes Research.* 2020;20(2):221-228.
77. van der Heijde D, Aletaha D, Carmona L, et al. 2014 Update of the EULAR standardised operating procedures for EULAR-endorsed recommendations. *Ann Rheum Dis.* 2015;74(1):8-13.
78. Soliris (eculizumab) Solution for Intravenous Infusion Prescribing Information. Boston, MA; Alexion Pharmaceuticals, Inc. 11/2020.
79. William S, Geert DH, Doug W, et al. P025 Ozanimod Efficacy, Safety, and Histology in Patients with Moderate-to-Severe Ulcerative Colitis During Induction in the Phase 3 True North Study. *Official journal of the American College of Gastroenterology | ACG.* 2020;115:S6-S7.
80. Silvio D, Brian F, Stephen H, et al. P030 Ozanimod Efficacy, Safety, and Histology in Patients with Moderate-to-Severe Ulcerative Colitis During Maintenance in the Phase 3 True North Study. *The American journal of gastroenterology.* 2020;115(Suppl 1):S8.
81. Sanders DB, Wolfe GI, Benatar M, et al. International consensus guidance for management of myasthenia gravis. *Executive summary.* 2016;87(4):419-425.
82. Brunner HI, Ruperto N, Tzaribachev N, et al. Subcutaneous golimumab for children with active polyarticular-course juvenile idiopathic arthritis: results of a multicentre, double-blind, randomised-withdrawal trial. *Ann Rheum Dis.* 2018;77(1):21-29.
83. Khanna D, Lin CJF, Furst DE, et al. Tocilizumab in systemic sclerosis: a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Respir Med.* 2020;8(10):963-974.

84. Khanna D, Furst DE, Clements PJ, et al. Standardization of the modified Rodnan skin score for use in clinical trials of systemic sclerosis. *J Scleroderma Relat Disord.* 2017;2(1):11-18.
85. TREMFYA (guselkumab) for injection. Prescribing Information. Horsham, PA: Janssen Biotech, Inc. July 2020.
86. Orencia (abatacept) SC or IV infusion Prescribing Information. Princeton, NJ; Bristol-Myers Squibb Company, June 2020. In.
87. Olumiant (baricitinib) Prescribing Information. Indianapolis, IN; Eli Lilly and Company. June 2020.
88. McInnes IB, Behrens F, Mease PJ, et al. Secukinumab versus adalimumab for treatment of active psoriatic arthritis (EXCEED): a double-blind, parallel-group, randomised, active-controlled, phase 3b trial. *Lancet (London, England).* 2020;395(10235):1496-1505.
89. Rubbert-Roth A, Enejosa J, Pangan AL, et al. Trial of Upadacitinib or Abatacept in Rheumatoid Arthritis. *N Engl J Med.* 2020;383(16):1511-1521.
90. McInnes IB, Anderson JK, Magrey M, et al. Trial of Upadacitinib and Adalimumab for Psoriatic Arthritis. *N Engl J Med.* 2021;384(13):1227-1239.
91. Blauvelt A, Papp K, Gottlieb A, et al. A head-to-head comparison of ixekizumab vs. guselkumab in patients with moderate-to-severe plaque psoriasis: 12-week efficacy, safety and speed of response from a randomized, double-blinded trial. *British Journal of Dermatology.* 2020;182(6):1348-1358.
92. Mease PJ, Smolen JS, Behrens F, et al. A head-to-head comparison of the efficacy and safety of ixekizumab and adalimumab in biological-naive patients with active psoriatic arthritis: 24-week results of a randomised, open-label, blinded-assessor trial. *Ann Rheum Dis.* 2020;79(1):123-131.
93. Lewis JD, Chuai S, Nessel L, Lichtenstein GR, Aberra FN, Ellenberg JH. Use of the noninvasive components of the Mayo score to assess clinical response in ulcerative colitis. *Inflamm Bowel Dis.* 2008;14(12):1660-1666.

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 PEDIATRIC UC	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
abatacept	ORENCIA CLICKJECT	SUB-Q	AUTO INJCT	N

abatacept	ORENCIA	SUB-Q	SYRINGE	N
abatacept/maltose	ORENCIA	INTRAVEN	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	INTRAVEN	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	INTRAVEN	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	INTRAVEN	VIAL	N
infliximab-abda	RENFLEXIS	INTRAVEN	VIAL	N
infliximab-axxq	AVSOLA	INTRAVEN	VIAL	N
infliximab-dyyb	INFLECTRA	INTRAVEN	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	INTRAVEN	VIAL	N
risankizumab-rzaa	SKYRIZI	SUB-Q	SYRINGE	N
risankizumab-rzaa	SKYRIZI (2 SYRINGES) KIT	SUB-Q	SYRINGEKIT	N
rituximab	RITUXAN	INTRAVEN	VIAL	N
rituximab-abbs	TRUXIMA	INTRAVEN	VIAL	N
rituximab-arrx	RIABNI	INTRAVEN	VIAL	N
rituximab-pvvr	RUXIENCE	INTRAVEN	VIAL	N
sarilumab	KEVZARA	SUB-Q	PEN INJCTR	N
sarilumab	KEVZARA	SUB-Q	SYRINGE	N
secukinumab	COSENTYX PEN	SUB-Q	PEN INJCTR	N
secukinumab	COSENTYX PEN (2 PENS)	SUB-Q	PEN INJCTR	N
secukinumab	COSENTYX (2 SYRINGES)	SUB-Q	SYRINGE	N

secukinumab	COSENTYX SYRINGE	SUB-Q	SYRINGE	N
tildrakizumab-asmn	ILUMYA	SUB-Q	SYRINGE	N
tocilizumab	ACTEMRA	INTRAVEN	VIAL	N
tocilizumab	ACTEMRA ACTPEN	SUB-Q	PEN INJCTR	N
tocilizumab	ACTEMRA	SUB-Q	SYRINGE	N
tofacitinib citrate	XELJANZ	ORAL	SOLUTION	N
tofacitinib citrate	XELJANZ XR	ORAL	TAB ER 24H	N
tofacitinib citrate	XELJANZ	ORAL	TABLET	N
upadacitinib	RINVOQ	ORAL	TAB ER 24H	N
ustekinumab	STELARA	INTRAVEN	VIAL	N
ustekinumab	STELARA	SUB-Q	SYRINGE	N
ustekinumab	STELARA	SUB-Q	VIAL	N
vedolizumab	ENTYVIO	INTRAVEN	VIAL	N
risankizumab-rzaa	SKYRIZI PEN	SUB-Q	PEN INJCTR	
risankizumab-rzaa	SKYRIZI	SUB-Q	SYRINGE	

Appendix 2: Abstracts of Comparative Clinical Trials

1. Secukinumab versus adalimumab for treatment of active psoriatic arthritis (EXCEED): a double-blind, parallel-group, randomised, active-controlled, phase 3b trial[88]

Background: Head-to-head trials in psoriatic arthritis are helpful in guiding clinical decision making. The EXCEED study evaluated the efficacy and safety of secukinumab versus adalimumab as first-line biological monotherapy for 52 weeks in patients with active psoriatic arthritis, with a musculoskeletal primary endpoint of ACR 20 response.

Methods: This parallel-group, double-blind, active-controlled, phase-3b, multicentre (168 sites in 26 countries) trial enrolled patients aged at least 18 years with active psoriatic arthritis. Eligible patients were randomly assigned (1:1) by means of interactive response technology to receive secukinumab or adalimumab. Patients, investigators, site personnel, and those doing the assessments (except independent study drug administrators) were masked to study assignment. 300 mg secukinumab was administered subcutaneously at baseline, weeks 1, 2, 3, and 4, and then every 4 weeks until week 48 as a pre-filled syringe. Adalimumab was administered every 2 weeks from baseline until week 50 as 40 mg per 0·4 mL citrate free subcutaneous injection. The primary outcome was the proportion of patients with at least 20% improvement in the ACR response criteria (ACR20) at week 52. Patients were analysed according to the treatment to which they were randomly assigned. Safety analyses included all safety data reported up to and including the week 52 visit for each patient who received at least one dose of study drug. The trial is registered at ClinicalTrials.gov, NCT02745080.

Findings: Between April 3, 2017 and Aug 23, 2018, we randomly assigned 853 patients to receive secukinumab (n=426) or adalimumab (n=427). 709 (83%) of 853 patients completed week 52 of the study, of whom 691 (81%) received the last study treatment at week 50. 61 (14%) of 426 patients in the secukinumab group discontinued treatment by week 52 versus 101 (24%) of 427 patients in the adalimumab group. The primary endpoint of superiority of secukinumab versus

adalimumab for ACR20 response at week 52 was not met. 67% of patients in the secukinumab group achieved an ACR20 response at week 52 versus 62% of patients in the adalimumab group (OR 1·30, 95% CI 0·98-1·72; p=0·0719). The safety profiles of secukinumab and adalimumab were consistent with previous reports. Seven (2%) of 426 patients in the secukinumab group and six (1%) of 427 patients in the adalimumab group had serious infections. One death was reported in the secukinumab group due to colon cancer and was assessed as not related to the study drug by the investigator.
Interpretation: Secukinumab did not meet statistical significance for superiority versus adalimumab in the primary endpoint of ACR20 response at week 52. However, secukinumab was associated with a higher treatment retention rate than adalimumab. This study provides comparative data on two biological agents with different mechanisms of action, which could help guide clinical decision making in the management of patients with psoriatic arthritis. Funding: Novartis Pharma.

2. Trial of Upadacitinib or Abatacept in Rheumatoid Arthritis[89]
Background: Upadacitinib is an oral selective Janus kinase inhibitor to treat rheumatoid arthritis. The efficacy and safety of upadacitinib as compared with abatacept, a T-cell co-stimulation modulator, in patients with rheumatoid arthritis refractory to biologic disease-modifying antirheumatic drugs (DMARDs) are unclear.
Methods: In this 24-week, phase 3, double-blind, controlled trial, we randomly assigned patients in a 1:1 ratio to receive oral upadacitinib (15 mg once daily) or intravenous abatacept, each in combination with stable synthetic DMARDs. The primary end point was the change from baseline in the composite Disease Activity Score for 28 joints based on the C-reactive protein level (DAS28-CRP; range, 0 to 9.4, with higher scores indicating more disease activity) at week 12, assessed for noninferiority. Key secondary end points at week 12 were the superiority of upadacitinib over abatacept in the change from baseline in the DAS28-CRP and the percentage of patients having clinical remission according to a DAS28-CRP of less than 2.6.
Results: A total of 303 patients received upadacitinib, and 309 patients received abatacept. From baseline DAS28-CRP values of 5.70 in the upadacitinib group and 5.88 in the abatacept group, the mean change at week 12 was -2.52 and -2.00, respectively (difference, -0.52 points; 95% confidence interval [CI], -0.69 to -0.35; P<0.001 for noninferiority; P<0.001 for superiority). The percentage of patients having remission was 30.0% with upadacitinib and 13.3% with abatacept (difference, 16.8 percentage points; 95% CI, 10.4 to 23.2; P<0.001 for superiority). During the treatment period, one death, one nonfatal stroke, and two venous thromboembolic events occurred in the upadacitinib group, and more patients in the upadacitinib group than in the abatacept group had elevated hepatic aminotransferase levels.

Conclusions: In patients with rheumatoid arthritis refractory to biologic DMARDs, upadacitinib was superior to abatacept in the change from baseline in the DAS28-CRP and the achievement of remission at week 12 but was associated with more serious adverse events. Longer and larger trials are required in order to determine the effect and safety of upadacitinib in patients with rheumatoid arthritis. (Funded by AbbVie; SELECT-CHOICE Clinicaltrials.gov number, NCT03086343.).

3. Trial of Upadacitinib and Adalimumab for Psoriatic Arthritis[90]
Background: The Janus kinase inhibitor upadacitinib is a potential treatment for psoriatic arthritis. The efficacy and safety of upadacitinib as compared with adalimumab, a tumor necrosis factor α inhibitor, in patients who have an inadequate response to nonbiologic disease-modifying antirheumatic drugs are unclear.
Methods: In a 24-week, phase 3 trial, we randomly assigned patients in a 1:1:1:1 ratio to receive oral upadacitinib at a dose of 15 mg or 30 mg once daily, placebo, or subcutaneous adalimumab (40 mg every other week). The primary end point was an American College of Rheumatology 20 (ACR20) response (≥20% decrease in the number of tender and swollen joints and ≥20% improvement in at least three of five other domains) at week 12 with upadacitinib as compared with placebo. Secondary end points included comparisons of upadacitinib with adalimumab.

Results: A total of 1704 patients received an active drug or placebo. The percentage of patients who had an ACR20 response at week 12 was 70.6% with 15-mg upadacitinib, 78.5% with 30-mg upadacitinib, 36.2% with placebo (P<0.001 for both upadacitinib doses vs. placebo), and 65.0% with adalimumab. The difference between groups for 15-mg upadacitinib as compared with adalimumab was 5.6 percentage points (95% confidence interval [CI], −0.6 to 11.8) and for 30-mg upadacitinib as compared with adalimumab was 13.5 percentage points (95% CI, 7.5 to 19.4). Both upadacitinib doses were noninferior to adalimumab for the ACR20 response at week 12; the 30-mg dose but not the 15-mg dose was superior to adalimumab. The incidence of adverse events through week 24 was 66.9% with 15-mg upadacitinib, 72.3% with 30-mg upadacitinib, 59.6% with placebo, and 64.8% with adalimumab. There were serious infections in 1.2%, 2.6%, 0.9%, and 0.7% of the patients, respectively. Hepatic disorders occurred in 9.1% of patients in the 15-mg upadacitinib group and 12.3% in the 30-mg upadacitinib group, but grade 3 increases in aminotransferase levels occurred in 2% of patients or fewer in all groups.
Conclusions: The percentage of patients with psoriatic arthritis who had an ACR20 response at week 12 was significantly higher with 15-mg or 30-mg upadacitinib than with placebo. The 30-mg dose but not the 15-mg dose was superior to adalimumab. Adverse events were more frequent with upadacitinib than with placebo. (Funded by AbbVie; SELECT-PsA 1 ClinicalTrials.gov number, NCT03104400. opens in new tab.)

4. A head-to-head comparison of ixekizumab vs. guselkumab in patients with moderate-to-severe plaque psoriasis: 12-week efficacy, safety and speed of response from a randomized, double-blinded trial.[91]
Background: Patients with psoriasis value rapid and complete skin clearance. No head-to-head studies have focused on early responses to interleukin (IL)-17 vs. IL-23 inhibitors.
Objectives: To compare early and complete skin clearance by the IL-17A inhibitor ixekizumab vs. the IL-23 inhibitor guselkumab.
Methods: IXORA-R, a 24-week, randomized, double-blinded study, enrolled adults with moderate-to-severe plaque psoriasis [static Physician's Global Assessment of Disease (sPGA) score of ≥ 3, Psoriasis Area and Severity Index (PASI) ≥ 12, and ≥ 10% body surface area]. Patients were randomized (1 : 1) to receive the approved dose of subcutaneous ixekizumab or guselkumab. Primary end point was 100% improvement in PASI (PASI 100) at week 12. Major secondary end points included other levels of improved PASI and sPGA at different time points. Comparisons were made using the Cochran-Mantel-Haenszel test with a multiple testing strategy. Non-responder imputation was used for missing data. After the completion of the study, the final secondary end point (PASI 100 at 24 weeks) and safety data through week 24 will be reported.
Results: In total, 1027 patients were randomized. The primary end point PASI 100 at week 12 was met [215/520 ixekizumab (41%); 126/507 guselkumab (25%); P < 0·001]. All major secondary end points measured up to week 12 were met, including PASI 50 at week 1 and PASI 75 at week 2. Serious adverse event frequency was 3% for each group; no new safety signals were identified.
Conclusions: Ixekizumab was superior to guselkumab for rapidly improving signs and symptoms in patients with moderate-to-severe plaque psoriasis by week 12. Adverse events were similar to previous ixekizumab and guselkumab studies. Compared with the IL-23 inhibitor guselkumab, ixekizumab can offer complete skin clearance more rapidly to patients with moderate-to-severe plaque psoriasis. What's already known about this topic? Patients with plaque psoriasis desire both high levels of clearance and rapid onset of treatment effects. Ixekizumab, a high-affinity monoclonal antibody that selectively targets interleukin (IL)-17A, has demonstrated greater and faster skin clearance than etanercept and ustekinumab, with consistent long-term efficacy, safety and durability of response. Clinical trial data and systematic reviews have suggested that IL-17 inhibitors can improve a patient's psoriasis more rapidly than IL-23 inhibitors. What does this study add? The head-to-head study design directly compares the efficacy and speed of response of ixekizumab and the IL-23 inhibitor guselkumab in moderate-to-severe plaque psoriasis. The primary end point was met, showing superiority of ixekizumab over guselkumab for achieving complete skin clearance at week 12. The safety profile of ixekizumab was consistent with previous studies. Ixekizumab can deliver patients complete skin clearance and improved quality of life more rapidly than guselkumab.

5. **A head-to-head comparison of the efficacy and safety of ixekizumab and adalimumab in biological-naive patients with active psoriatic arthritis: 24-week results of a randomised, open-label, blinded-assessor trial**[92]

Objectives: To compare efficacy and safety of ixekizumab (IXE) to adalimumab (ADA) in biological disease-modifying antirheumatic drug-naive patients with both active psoriatic arthritis (PsA) and skin disease and inadequate response to conventional synthetic disease-modifying antirheumatic drug (csDMARDs).
Methods: Patients with active PsA were randomised (1:1) to approved dosing of IXE or ADA in an open-label, head-to-head, blinded assessor clinical trial. The primary objective was to evaluate whether IXE was superior to ADA at week 24 for simultaneous achievement of a >=50% improvement from baseline in the American College of Rheumatology criteria (ACR50) and a 100% improvement from baseline in the Psoriasis Area and Severity Index (PASI100). Major secondary objectives, also at week 24, were to evaluate whether IXE was: (1) non-inferior to ADA for achievement of ACR50 and (2) superior to ADA for PASI100 response. Additional PsA, skin, treat-to-target and quality-of-life outcome measures were assessed at week 24.
Results: The primary efficacy endpoint was met (IXE: 36%, ADA: 28%; p=0.036). IXE was non-inferior for ACR50 response (IXE: 51%, ADA: 47%; treatment difference: 3.9%) and superior for PASI100 response (IXE: 60%, ADA: 47%; p=0.001). IXE had greater response versus ADA in additional PsA, skin, nail, treat-to-target and quality-of-life outcomes. Serious adverse events were reported in 8.5% (ADA) and 3.5% (IXE) of patients.
Conclusions: IXE was superior to ADA in achievement of simultaneous improvement of joint and skin disease (ACR50 and PASI100) in patients with PsA and inadequate response to csDMARDs. Safety and tolerability for both biologicals were aligned with established safety profiles.

Appendix 3: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to June Week 1 2021, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations 1946 to June 9, 2021

1 Adalimumab/	5754
2 Etanercept/	6048
3 tocilizumab.mp.	3704
4 Abatacept/	2867
5 Infliximab/	10702
6 Rituximab/	15831
7 golimumab.mp.	1163
8 apremilast.mp.	608
9 tofacitinib.mp.	1457
10 certolizumab.mp.	1169
11 Certolizumab Pegol/	654
12 secukinumab.mp.	1049
13 Abatacept/	2867
14 ixekizumab.mp.	523
15 Ustekinumab/	1229
16 Natalizumab/	1678
17 vedolizumab.mp.	937
18 brodalumab.mp.	310
19 guselkumab.mp.	245
20 anakinra reporteda.mp.	1721
21 canakinumab.mp.	687
22 sarilumab.mp.	159
23 baricitinib.mp	408
24 guselkumab.mp	245
25 upadacitinib.mp	134
26 risankizumab.mp	142
27 tildrakizumab.mp	124
23 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27	47879
24 Arthritis, Psoriatic/or Arthritis, Rheumatoid/or Arthritis/ or Arthritis, Juvenile	78515
25 Psoriasis/	22688
27 Spondylitis, Ankylosing/	8189
28 Crohn Disease/	26938
29 Colitis, Ulcerative/	21349
30 24 or 25 or 26 or 27 or 28 or 29	145319
32 23 and 30	18364
33 limit 32 to (yr="2018-current" and (clinical trial, all or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or guideline or meta-analysis or practice guideline or pragmatic clinical trial or randomized controlled trial or systematic reviews))	337

Appendix 4. Selected Outcomes Used for Assessment of Disease Progression in Clinical Trials[21-23,93]

Ankylosing Spondylitis		
Outcome Measure	**Domains**	**Scale and Scoring**
Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)	Level of symptoms: 1. Fatigue 2. Pain in hips, back and neck 3. Pain in joints other than hips, back or neck 4. Discomfort in areas tender to touch or pressure Mean measurements of: 5. Intensity of morning stiffness 6. Duration of morning stiffness (0 to 2 hours scored on a 0-10 scale)	VAS scale 0-10: 0 is no symptoms, 10 is very severe BASADI score calculation: 1.Add scores for first 4 questions 2. Add one half of the sum of question 5 and 6 3. Divide the result by 5 A BASDI score ≥ 4 (on a scale of 0-10) indicates active disease that warrants consideration of therapy
BASDI 50	• ≥ 50% improvement in BASDAI	
Bath Ankylosing Spondylitis Functional Index (BASFI)	Severity of 10 functional abilities: 1. Putting on socks 2. Bend from the waist to pick up a pen from the floor 3. Reaching up to a high shelf 4. Getting up from an armless chair 5. Getting up off the floor 6. Standing unsupported 7. Climbing 12-15 steps unaided 8. Looking over shoulder 9. Doing physically demanding activities 10. Doing a full day's activities	VAS scale 0-10: easy (0) to impossible (10) BASFI score calculation: Total all 10 items and divide by 10 for final score Reported as change in score from baseline
Assessment of Spondyloarthritis International Society (ASAS) Response	Combines measures of symptoms and disability in 4 disease measures: 1. Spinal inflammation (BASDI questions 5 and 6) 2. Spinal pain 3. Patient global assessment of spondylitis 4. Functional impairment (BASFI score)	Scale of 0-10: 0 is no symptoms, 10 is very severe
ASAS20	• Improvement of ≥ 20% and ≥ 1 unit in ≥ 3 of disease measures above • No worsening of ≥ 20% and ≥ 1 unit in remaining unimproved measure	Assessment of response to therapy by percent in symptom improvement
ASAS40	• Improvement of ≥ 40% and ≥ 2 units in ≥ 3 of disease measures above	
ASAS Partial Remission	• No worsening at all in remaining measure	Value of ≤ 2 in each of the 4 domains

	• Reflects low disease activity	
Ankylosing Spondylitis Disease Activity Score (ASDAS) ASDAS Calculator: http://www.asas-group.org/clinical-instruments/asdas_calculator/asdas.html	Measures severity of symptoms and signs of inflammation including: 1. Back pain 2. Patient global assessment of spondylitis 3. Peripheral pain and swelling (BASDAI score) 4. Duration of morning stiffness (BASDI score) 5. CRP or ESR	Scale of 0-10: 0 is no symptoms, 10 is very severe ASDAS scores: < 1.3 – Inactive Disease 1.4 to 2.1 – Moderate Disease Activity 2.2 to 3.4 – High Disease Activity >3.5 – Very High Disease Activity Improvement Criteria: Change ≥ 1.1 – Clinically Important Improvement Change ≥ 2.0 – Major Improvement
Rheumatoid Arthritis		
Outcome Measure	**Domains**	**Scale and Scoring**
Disease Activity Score(DAS)-28 DAS-28 calculator https://www.das-score.nl/das28/DAScalculators/dasculators.html	Clinical assessment of disease activity in combination with an acute phase reactant level 1. Assessment of 28 joints for swelling and tenderness - swollen joint count (SJC) - tender joint count (TJC) 2. General health (GH) - patient assessment of disease on a 0-100 scale where 100 means maximal disease activity 3. Either ESR or CRP adjusted with SJC and TJC scores	DAS-28 scoring ranges from 0 to 9.4: <2.6: Remission ≥2.6 and ≤3.2: Low Disease Activity >3.2 and ≤5.1: Moderate Disease Activity >5.1: High disease activity • DAS-28 reduction by 0.6 represents a moderate improvement. • DAS-28 reduction more than 1.2 represents a major improvement.
Health Assessment Questionnaire Disability Index (HAQ-DI)	Assess 8 domains of daily activity – patient self-reported 1. Dressing and Grooming 2. Arising 3. Eating 4. Walking 5. Hygiene 6. Reach 7. Grip 8. Chores or Activities	Scored 0 to 3: 0 - no difficulty 1 - with some difficulty 2- with much difficulty 3 - unable to do HAQ-DI calculation: Sum of all domains then divided by 8 to give total score ranging from 0 (best) to 3 (worst)

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

Plaque Psoriasis and Psoriatic Arthritis		
Outcome Measure	**Domains**	**Scale and Scoring**
Static Physician's Global Assessment Scale (sPGA)	The static PGA is a 0-5 ordinal rating ranging from "clear" to "very severe psoriasis" as evaluated by the provider	Scale of 0 – 5: 0 = clear; scores 1–5 = increasing severity Response to therapy indicated by a score of 0 or 1
Psoriasis Symptom Inventory (PSI)	Patient reported outcome in 8 areas: 1. Itch 2. Redness 3. Scaling 4. Burning 5. Cracking 6. Stinging 7. Flaking 8. Pain of Lesions	Scale of 0-4: 0 = not at all severe, 1 = mild, 2 = moderate, 3 = severe, and 4 = very severe Score ranges from 0 – 32 Response to therapy indicated by scores < 8 with no single item rated higher than 1
Psoriasis Area and Severity Index (PASI) PASI-75 PASI-90	Measure of overall psoriasis severity and coverage on Head, Upper Extremities, Trunk and Lower Extremities • Erythema • Induration • Scaling 75% Improvement in PASI score 90% Improvement in PASI score – clear or almost clear skin	Scale of 0-4: 0 is clear, 1-4 increasing severity PASI score: 1. Sum rows 1, 2, and 3 for each area of the body using 0-4 scale 2. Add an area score based on percentage involvement from 0 (clear) to 6 (≥90% coverage) 3. Multiply score as rated for each body area (0.1, 0.2, 0.3, 0.4 for head, arms, trunk, and legs, respectively) 4. Add all the scores together

		Composite score ranges from 0 -72: 0 = normal 72 = maximal disease
PsA Response Criteria (PsARC)	Used by the National Institute of Health Care Excellence (NICE) to continue TNF inhibitor therapy with an assessment at baseline and 12 weeks 1. 66 swollen joint score 2. 68 tender joint score 3. Patient global assessment 4. Physician global assessment	**Response** = improvement in ≥ 2 of the 4 tests: -One of which must be the joint tenderness or swelling score -No worsening in any of the four measures • **Improvement** is defined as a decrease ≥ 30% in the swollen or tender joint score and ≥1 in either of the global assessments
Dermatology Quality of Life (DQLI)	10 question patient self-reported assessment 1. How itchy has your skin been? 2. How embarrassed are because of your skin? 3. Has your skin interfered with activities? 4. Has your skin influenced the clothes you wear/ 5. Has your skin affected social activities? 6. How your skin impacted your ability to participate in a sport? 7. Has your skin prevented you from working? 8. Has your skin caused any problems with friends? 9. Has your skin impacted sexual activities? 10. How much has the treatment for your skin affected your daily activities?	Scale of 0-3: 0 not at all, 1 a little, 2 a lot, and 3 very much Interpretation of DQLI score: 0 – 1 no effect at all on patient's life 2 – 5 small effect on patient's life 6 – 10 moderate effect on patient's life 11 – 20 very large effect on patient's life 21 – 30 extremely large effect on patient's life
Crohn's Disease and Ulcerative Colitis		
Outcome Measure	**Domains**	**Scale and Scoring**
Crohn's Disease Activity Score (CDAI)	Evaluation of 8 clinical factors (each weighted and summed to reach a total score) 1. Number of liquid or soft stools each day for 1 week (weight x 2) 2. Abdominal pain (graded on a severity scale of 0-3) for 1 week (weight x 5) 3. General Well-being (subjective score of 0-4) for 1 week (weight x 7) 4. Presence of complications (weight x 20) 5. Use of diphenoxylate/atropine or opiates for diarrhea (weight x 30) 6. Presence of abdominal mass (graded as 0 [none], 2 [questionable] or 5 [definite]) (weight x 10) 7. Absolute deviation of Hematocrit from 47% (men) or 42% (women) (weight x 6)	Each factor is weighted and summed to achieve a total score • Scores ≤150 indicate minimal disease • Scores >150 indicate active disease • Scores >450 indicate extremely severe disease

	8. Percentage deviation from standard weight (weight x 1)	
Mayo Clinic score (MCS) for grading activity of ulcerative colitis	Assessment Points **1.Stool Frequency** -Patient reporting a normal number of daily stools -3-4 more stools than normal 2 -≥ 5 more stools than normal 3 **2. Rectal Bleeding** -None 0 -Blood streaks seen with stool less than half the time 1 -Blood with most stools 2 -Pure blood passed 3 **3.Endoscopic Findings** -Normal or inactive colitis 0 -Mild friability, erythema, decreased vascularity 1 -Friability, marked erythema, absent vascular pattern, erosions 2 -Ulcerations and spontaneous bleeding 3 **4. Physician Global Assessment** -Normal 0 -Mild colitis 1 -Moderate colitis 2 -Severe colitis 3	The score can range from 0-12 with higher scores indicating worse severity. A critical component of this score are the endoscopic findings. Patients with lower scores but with an endoscopic score of 2 or greater are considered more severe regardless of the final score.
Abbreviations: CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; VAS = visual analog scale		

Targeted Immune Modulators

Goal(s):

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

Length of Authorization:

- Up to 12 months

Requires PA:

- All targeted immune modulators 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 Targeted Immune Modulators

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	≥5 yo (Humira) ≥18 yo (biosimilars)	Uveitis (non-infectious) ≥2 yo (Humira) HS ≥ 12 yo
Anakinra (KINERET)						≥18 yo		NOMID DIRA
Apremilast (OTEZLA)				≥18 yo	≥18 yo			Oral Ulcers associated with BD ≥ 18 yo
Baricitinib (OLUMIANT)						≥18 yo		
Brodalumab (SILIQ)				≥18 yo				
Canakinumab (ILARIS)			≥2 yo					FCAS ≥4 yo MWS ≥4 yo TRAPS ≥ 4 yo HIDS ≥ 4 yo

Drug Name	Ankylosing Spondylitis	Crohn's Disease	Juvenile Idiopathic Arthritis	Plaque Psoriasis	Psoriatic Arthritis	Rheumatoid Arthritis	Ulcerative Colitis	Other
								MKD ≥ 4 yo FMF ≥ 4 yo Stills Disease
Certolizumab (CIMZIA)	≥18 yo	≥18 yo		≥18 yo	≥18 yo	≥18 yo		Nr-axSpA ≥ 18 yo
Etanercept (ENBREL) and biosimilars	≥18 yo		≥2 yo	≥4 yo (Enbrel) ≥4 yo (biosimilars)	≥18 yo	≥18 yo		
Golimumab (SIMPONI and SIMPONI ARIA)	≥18 yo		≥2 yo active polyarticular course		≥2 yo	≥18 yo	≥18 yo (Simponi)	
Guselkumab (TREMFYA)				≥18 yo	≥18 yo			
Infliximab (REMICADE) and biosimilars	≥18 yo	≥6 yo		≥18 yo	≥18 yo	≥18 yo	≥6 yo	
Ixekizumab (TALTZ)	≥ 18 yo			≥6 yo	≥18 yo			Nr-axSpA ≥ 18 yo
Risankizumab-rzaa (SKYRIZI)				≥18 yo				
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			≥6 yo	≥18 yo			Nr-AxSpA ≥18 yo
Tildrakizumab-asmn (ILUMYA)				≥18 yo				
Tocilizumab (ACTEMRA)			≥2 yo			≥18 yo		CRS ≥2 yo GCA ≥18 yo SSc-ILD ≥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		≥6 yo	≥18 yo		≥18 yo	
Vedolizumab (ENTYVIO)		≥18 yo					≥18 yo	

Abbreviations: BD = Behcet's Disease; CLL = Chronic Lymphocytic Leukemia; CRS = Cytokine Release Syndrome; DIRA = Deficiency of Interleukin-1 Receptor Antagonist; 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; SSc-ILD = Systemic Sclerosis-Associated Interstitial Lung Disease; TRAPS = Tumor Necrosis Factor Receptor Associated Periodic Syndrome; yo = years old.

Approval Criteria		
1. What diagnosis is being treated?	Record ICD-10 code.	
2. Is the diagnosis funded by OHP? Notes: A. Mild-to-moderate psoriasis is unfunded, severe psoriasis is funded. B. Mild Hidradenitis Suppurativa (HS) is unfunded, moderate-to-severe HS (e.g., Hurley Stage II or III) is funded.	**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

Approval Criteria		
5. Has the patient been annually screened for latent or active tuberculosis and if positive, started tuberculosis treatment?* *(Note: this requirement does not apply to requests for apremilast.)	**Yes:** Go to # 6	**No:** Pass to RPh. Deny; medical appropriateness. May approve for up to 3 months to allow time for screening.
6. Is the request for a medication and corresponding diagnosis indicated according to the "Other" column of table 1? 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. Is this a request for a preferred agent OR if the request is for a non-preferred agent, has the patient failed to respond or had inadequate response to a Humira® branded product or an Enbrel® branded product after a trial of at least 3 months?	**Yes:** Approve for up to 6 months. Document therapy with dates.	**No:** Pass to RPh. Deny; medical appropriateness.
9. Is the diagnosis plaque psoriasis and the request for a drug FDA-approved for this condition as defined in Table 1? Note: Only treatment for *severe* plaque psoriasis is funded by the OHP.	**Yes:** Go to # 10	**No**: Go to #12

Approval Criteria		
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.
12. Is the diagnosis rheumatoid arthritis, juvenile idiopathic arthritis, or psoriatic arthritis and the request for a drug FDA-approved for these conditions as defined in Table 1?	**Yes:** Go to # 13	**No:** Go to # 16

Approval Criteria		
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® branded product or an Enbrel® branded product for at least 3 months? • AND • Is the patient on concurrent DMARD therapy with plans to continue concomitant use?	**Yes:** Go to # 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
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

Approval Criteria		
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 OHA Prioritized List	**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 # 21
19. Will the prescriber switch to a preferred product?	**Yes:** Approve for up to 6 months of therapy.	**No:** Go to # 20
20. 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.

Approval Criteria		
21. 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
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: *10/21 (DM); 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: *1/1/22; 1/1/2021; 7/1/2019; 3/1/19; 3/1/18; 9/1/17; 1/1/17; 9/27/14; 2/2*

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 John 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.

Approval Criteria		
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**.**
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: *10/21 (DM); 10/20; 11/17*
Implementation: *1/1/18*

Oral Multiple Sclerosis Drugs

Goal(s):
- Promote safe and effective use of oral disease-modifying drugs for multiple sclerosis or ulcerative colitis.
- Promote use of preferred multiple sclerosis drugs.

Length of Authorization:
- Up to 6 months

Requires PA:

- All oral MS therapy including:
  - Sphingosine 1-phosphate receptor modulators (e.g. fingolimod, ozanimod, ponesimod, siponimod, etc.)
  - Teriflunomide
  - Fumarate salts (e.g., dimethyl fumarate, monomethyl fumarate, diroximel fumarate, etc.)
  - Cladribine

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/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the request for ozanimod to treat moderate-to-severe ulcerative colitis?	**Yes:** Go to #3	**No:** Go to #4
3. Has the patient failed to respond or had an 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 these conventional therapies? AND • Has the patient tried and failed a 3-month trial of a Humira® product?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness.
4. Is the request for an FDA-approved form of multiple sclerosis in the appropriate age range? (see Table 1)	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness.

Approval Criteria		
5. Will the prescriber consider a change to a preferred product? Message: • Preferred products are reviewed for comparative effectiveness and safety by the Pharmacy and Therapeutics Committee and do not require PA.	**Yes:** Inform prescriber of covered alternatives in class.	**No:** Go to #6
6. Is the medication being prescribed by or in consultation with a neurologist or gastroenterologist (if the diagnosis is ulcerative colitis)?	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical appropriateness.
7. Is the patient on concurrent treatment with a disease modifying drug (i.e. interferon beta-1b, glatiramer acetate, interferon beta-1a, natalizumab, ofatumumab, ocrelizumab, or mitoxantrone)?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #8
8. Is this a request for continuation of therapy?	**Yes**: Go to **Renewal Criteria**	**No:** Go to #9
9. Is there documentation of recommended baseline testing to mitigate safety concerns (Table 2)?	**Yes:** Go to #10	**No:** Pass to RPh. Deny; medical appropriateness.
10. Is the prescription for teriflunomide?	**Yes:** Go to #11	**No:** Go to #14
11. Is the patient of childbearing potential?	**Yes:** Go to #12	**No:** Approve for up to 6 months.
12. Is the patient pregnant or actively trying to conceive?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #13
13. Is there documentation that the provider and patient have discussed the teratogenic risks of the drug if the patient were to become pregnant?	**Yes:** Go to #14	**No:** Pass to RPh. Deny; medical appropriateness.

Approval Criteria		
14. Is the prescription for a sphingosine 1-phosphate receptor modulator (Table 1)?	**Yes:** Go to #15	**No:** Go to #18
15. Does the patient have evidence of macular edema?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #16
16. Does the patient have preexisting cardiac disease, risk factors for bradycardia, or is on an anti-arrhythmic, beta-blocker, or calcium channel blocker?	**Yes:** Go to #17	**No:** Go to #21
17. Has the patient had a cardiology consultation before initiation (see clinical notes)?	**Yes:** Go to #21	**No:** Pass to RPh. Deny; medical appropriateness.
18. Is the prescription for a fumarate product?	**Yes:** Go to # 19	**No:** Go to #20
19. Does patient have a baseline CBC with lymphocyte count greater than 500/µL?	**Yes:** Approve for up to 6 months.	**No:** Pass to RPh. Deny; medical appropriateness.
20. Is the request for cladribine?	**Yes:** Go to #21	**No:** Go to #24
21. Is the patient of child bearing potential?	**Yes:** Go to #22	**No:** Go to #24
22. Is the patient pregnant or actively trying to conceive?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #23
23. Is there documentation that the provider and patient have discussed the teratogenic risks of the drug if the patient were to become pregnant?	**Yes:** Go to #24	**No:** Pass to RPh. Deny; medical appropriateness.
24. Has the patient had an inadequate response to or they are unable to tolerate alternative MS (or alternative UC treatment if the request is for ozanimod) treatment?	**Yes:** Approve for 6 months	**No:** Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
1. Has the patient's condition improved as assessed by the prescribing physician and physician attests to patient's improvement?	**Yes:** Approve for 12 months. Document baseline assessment and physician attestation received.	**No:** Pass to RPh; Deny; medical appropriateness.

Table 1. Dosing And FDA-Approved Indications for Oral MS Drugs

Generic Name	**FDA Indication (Adults unless otherwise indicated)**			
	CIS	**RRMS**	**SPMS**	**Ulcerative Colitis**
Cladribine		X	X	
Fingolimod	X *(≥ 10 years)*	X *(≥ 10 years)*	X *(≥ 10 years)*	
Siponimod	X	X	X	
Ozanimod	X	X	X	X
Ponesimod	X	X	X	
Teriflunomide	X	X	X	
Dimethyl Fumarate	X	X	X	
Monomethyl Fumarate	X	X	X	
Diroximel Fumarate	X	X	X	
Abbreviations: CIS = clinically isolated syndrome; RRMS = relapsing-remitting multiple sclerosis; SPMS = secondary progressive multiple sclerosis				

Table 2. FDA-recommended Baseline Safety Assessments (see clinical notes for details)

	Negative Pregnancy Test	LFTs	CBC with lymphocyte count	Ophthalmic Exam	Varicella Zoster Antibodies	CYP2C9 genotype	Other Screening
Fumarate salts		X	X (>500)				
Fingolimod*	X	X	X	X	X		
Ozanimod*	X	X	X	X	X		
Ponesimod*	X	X	X	X	X		
Siponimod*	X	X	X	X	X	X	

Teriflunomide	X (box warning)	X (box warning)	X				
Cladribine	X (box warning)	X	X (WNL)		X		TB; HBV; HIV; HCV; MRI for PML
Abbreviations: HBV = hepatitis B; HCV = hepatitis C; HIV = human immunodeficiency virus; MRI = magnetic resonance imaging; PML = progressive multifocal leukoencephalopathy; TB = tuberculosis; WNL = within normal limits							

* sphingosine 1-phosphate receptor modulators

Sphingosine 1-Phosphate Receptor Modulators (fingolimod, ozanimod, ponesimod, siponimod) Clinical Notes:

- Because of bradycardia and atrioventricular conduction, patients must be observed for 4 to 6 hours after initial dose in a clinically appropriate area (fingolimod, ponesimod, siponimod).
- Patients on antiarrhythmics, beta-blockers or calcium channel blockers or with risk factors for bradycardia (h/o MI, age >70 yrs., electrolyte disorder, hypothyroidism) may be more prone to development of symptomatic bradycardia and should be initiated on fingolimod, ozanimod, ponesimod, or siponimod with caution. A cardiology evaluation should be performed before considering treatment.
- An ophthalmology evaluation should be repeated 3-4 months after fingolimod, ozanimod, ponesimod, or siponimod initiation with subsequent evaluations based on clinical symptoms.
- Patients starting on siponimod therapy must be tested for CYP2C9 variants to determine CYP2C9 genotype before starting siponimod. Siponimod is contraindicated in patients with a CYP2C9*3/*3 genotype. The recommended maintenance dosage in patients with a CYP2C9*1/*3 or *2/*3 genotype is 1 mg. The recommended maintenance dosage in all other patients is 2 mg.

Teriflunomide Clinical Notes:

- Before starting teriflunomide, screen patients for latent tuberculosis infection with a TB skin test, exclude pregnancy, confirm use of reliable contraception in individuals of childbearing potential, check blood pressure, and obtain a complete blood cell count within the 6 months prior to starting therapy. Instruct patients to report symptoms of infection and obtain serum transaminase and bilirubin levels within the 6 months prior to starting therapy.
- After starting teriflunomide, monitor ALT levels at least monthly for 6 months. Consider additional ALT monitoring when teriflunomide is given with other potentially hepatotoxic drugs. Consider stopping teriflunomide if serum transaminase levels increase (>3-times the upper limit of normal). Monitor serum transaminase and bilirubin particularly in patients who develop symptoms suggestive of hepatic dysfunction. Discontinue teriflunomide and start accelerated elimination in those with suspected teriflunomide-induced liver injury and monitor liver tests weekly until normalized. Check blood pressure periodically and manage hypertension. Check serum potassium level in teriflunomide-treated patients with hyperkalemia symptoms or acute renal failure. Monitor for signs and symptoms of infection.
- Monitor for hematologic toxicity when switching from teriflunomide to another agent with a known potential for hematologic suppression because systemic exposure to both agents will overlap.

Fumarate Salts (Dimethyl Fumarate, Monomethyl Fumarate, Diroximel Fumarate) Clinical Notes:

- Fumarate salts may decrease a patient's white blood cell count. In the clinical trials the mean lymphocyte counts decreased by approximately 30% during the first year of treatment with dimethyl fumarate and then remained stable. The incidence of infections (60% vs. 58%) and serious infections (2% vs. 2%) was similar in patients treated with dimethyl fumarate or placebo, respectively. There was no increased incidence of serious infections observed in patients with lymphocyte counts <0.8 x10^3 cells/mm^3 (equivalent to <0.8 cells/µL). A transient increase in mean eosinophil counts was seen during the first 2 months of therapy.

- Fumarate salts should be held if the WBC falls below 2 $x10^3$ cells/mm^3 or the lymphocyte count is below 0.5 $x10^3$ cells/mm^3 (cells/µL) and permanently discontinued if the WBC did not increase to over 2 $x10^3$ cells/mm^3 or lymphocyte count increased to over 0.5 $x10^3$ cells/mm^3 after 4 weeks of withholding therapy.
- Patients should have a CBC with differential monitored every 6 to 12 months.

Cladribine Clinical Notes:

- Cladribine is not recommended for use in patients with clinically isolated syndrome (CIS) because of its safety profile.
- Prior to initiating cladribine follow standard cancer screening guidelines because of the risk of malignancies.
- Obtain a CBC with differential including lymphocyte count. Lymphocytes must be: within normal limits before initiating the first treatment course and at least 800 cells per microliter before initiating the second treatment course. If necessary, delay the second treatment course for up to 6 months to allow for recovery of lymphocytes to at least 800 cells per microliter. If this recovery takes more than 6 months, the patient should not receive further treatment with cladribine.
- Infection screening: exclude HIV infection, perform TB and hepatitis screening. Evaluate for active infection; consider a delay in cladribine treatment until any acute infection is fully controlled.
- Administer all immunizations according to immunization guidelines prior to starting cladribine. Administer live-attenuated or live vaccines at least 4 to 6 weeks prior to starting cladribine.
- Obtain a baseline (within 3 months) magnetic resonance imaging prior to the first treatment course because of the risk of progressive multifocal leukoencephalopathy (PML).

P&T/DUR Review: *10/21 (DM); 8/21 (DM); 6/21 (DM); 8/20 (DM); 6/20; 11/17; 11/16; 9/15; 9/13; 5/13; 3/12*
Implementation: *1/1/2022, 9/1/20; 1/1/18; 1/1/17; 1/1/14; 6/21/2012*