Therapeutic Class Overview
Immunomodulators

INTRODUCTION

- Immunomodulators treat a wide variety of conditions, including rheumatoid arthritis (RA), juvenile idiopathic arthritis (JIA), plaque psoriasis (PsO), psoriatic arthritis (PsA), ankylosing spondylitis (AS), Crohn's disease (CD), ulcerative colitis (UC), hidradenitis suppurativa (HS), and uveitis (UV), as well as several less common conditions.
- T cells, B cells, and cytokines such as tumor necrosis factor (TNF), interleukin-1 (IL-1), and interleukin-6 (IL-6) play a key role in the inflammatory and immune process (*Choy et al 2001*). This has led to the development of biologic agents to target these areas. The Food and Drug Administration (FDA) has currently approved 5 originator TNF inhibitors: Cimzia (certolizumab), Enbrel (etanercept), Humira (adalimumab), Remicade (infliximab), and Simponi/Simponi Aria (golimumab), as well as numerous biosimilar TNF inhibitors: Amjevita (adalimumab-atto), Abrilada (adalimumab-afzb), Cyltezo (adalimumab-adbm), Hadlima (adalimumab-bwwd), Hyrimoz (adalimumab-adaz), Erelzi (etanercept-szzs), Eticovo (etanercept-ykro), Avsola (infliximab-axxq), Inflectra (infliximab-dyyb), Ixifi (infliximab-qbtx), and Renflexis (infliximab-abda). Other immunomodulators targeting different cells and cytokines in the inflammatory and immune process are also FDA-approved. These include Orencia (abatacept), which inhibits CD28-B7 mediated costimulation of the T-cell; Rituxan (rituximab), which targets CD20, a molecule that is found on the surface of B-cells; Actemra (tocilizumab) and Kevzara (sarilumab), which have activity directed against the IL-6 receptor; and Kineret (anakinra), which targets the IL-1 receptor. Of these agents, 2 biosimilar products have been approved: Truxima (rituximab-abbs) and Ruxience (rituximab-pvvr). Oral agents on the market, Xeljanz and Xeljanz XR (tofacitinib), Rinvoq (upadacitinib), and Olumiant (baricitinib) target Janus-associated kinase (JAK) pathways. By inhibiting the JAK pathway, the ability of cytokines to produce inflammation is reduced.
- Other immunomodulators include Ilaris (canakinumab), which binds to the IL-1ß receptor and is approved to treat JIA, and Entyvio (vedolizumab), which binds to the α4β7 integrin and is approved to treat CD and UC. Otezla (apremilast), an oral, small-molecule phosphodiesterase 4 (PDE-4) inhibitor, and Stelara (ustekinumab), which targets the IL-12 and IL-23 cytokines, are each approved for the treatment of PsA and PsO; Stelara is additionally indicated for the treatment of CD and UC. Cosentyx (secukinumab) and Taltz (ixekizumab) bind and neutralize IL-17A and are indicated for the treatment of PsO, PsA, and AS. Siliq (brodalumab), an IL-17 receptor antagonist, as well as Tremfya (guselkumab), Skyrizi (risankizumab), and Ilumya (tildrakizumab-asmn), IL-23 antagonists, are indicated for selected patients with PsO.
- Certain rare conditions for which immunomodulators are indicated are mentioned in this review but are not discussed in detail include:
    - Ilaris for the treatment of 1) cryopyrin-associated periodic syndromes (CAPS), specifically the subtypes familial cold autoinflammatory syndrome (FCAS) and Muckle-Wells syndrome (MWS); 2) TNF receptor associated periodic syndrome (TRAPS); 3) hyperimmunoglobulin D syndrome (HIDS)/mevalonate kinase deficiency (MKD); and 4) familial Mediterranean fever (FMF).
    - Kineret for the treatment of CAPS, specifically neonatal-onset multisystem inflammatory disease (NOMID).
    - Actemra for giant cell arteritis (GCA) and cytokine release syndrome (CRS).
    - Cimzia for non-radiographic axial spondyloarthritis (NRAS) with objective signs of inflammation.
    - Otezla for treatment of adults with oral ulcers associated with Behçet disease.
- Rituxan is also approved for non–Hodgkin's lymphoma (NHL), chronic lymphocytic leukemia (CLL), granulomatosis with polyangiitis (GPA) (Wegener's granulomatosis) and microscopic polyangiitis (MPA), and pemphigus vulgaris. These indications will not be discussed in this review.
- Tysabri (natalizumab), an integrin receptor antagonist, is indicated for multiple sclerosis and CD for patients who have had an inadequate response to, or are unable to tolerate conventional therapies and TNF inhibitors; it is not included as a drug product in this review (*Tysabri prescribing information 2019*). Arcalyst (rilonacept), an interleukin-1 blocker indicated for CAPS, is also not included in this review (*Arcalyst prescribing information 2016*).
- Although FDA-approved, the launch plans for the biosimilar drugs Abrilada (adalimumab-afzb), Amjevita (adalimumab-atto), Erelzi (etanercept-szzs), Eticovo (etanercept-ykro), Cyltezo (adalimumab-adbm), Hadlima (adalimumab-bwwd), Hyrimoz (adalimumab-adaz), Avsola (infliximab-axxq), and Ixifi (infliximab-qbtx) are pending and

may be delayed; therefore, these agents are not currently included in this review. The manufacturer of Ixifi to date does not have plans to launch Ixifi in the United States.

- Medispan Classes: Antineoplastic-Monoclonal Antibodies, Antipsoriatics, Antirheumatic-Enzyme Inhibitors, Anti-TNF-Alpha-Monoclonal Antibodies, Integrin Receptor Antagonists, Interleukin-1 Receptor Antagonists, Interleukin-1beta Receptor Inhibitors, Interleukin-6 Receptor Inhibitors, PDE-4 Inhibitors, Selective Costimulation Modulators, Soluble Tumor Necrosis Factor Receptor Agents, Tumor Necrosis Factor Alpha Blockers

Table 1. Medications Included Within Class Review

Drug	Biosimilar or Generic Availability	Type of Agent
Actemra (tocilizumab)	-	Human monoclonal antibody targeting the IL-6 receptor
Cimzia (certolizumab)	-	TNFα inhibitor
Cosentyx (secukinumab)	-	Human monoclonal antibody to IL-17A
Enbrel (etanercept)	-*	sTNFR fusion protein, TNFα inhibitor
Entyvio (vedolizumab)	-	Human monoclonal antibody binds to the α4β7 integrin
Humira (adalimumab)	-*	TNFα inhibitor
Ilaris (canakinumab)	-	Human monoclonal antibody that binds to IL-1ß
Ilumya (tildrakizumab-asmn)	-	Human monoclonal antibody to IL-23
Inflectra (infliximab-dyyb)	N/A†	TNFα inhibitor
Kevzara (sarilumab)	-	Human monoclonal antibody targeting IL-6 receptor
Kineret (anakinra)	-	IL-1 receptor antagonist
Olumiant (baricitinib)	-	Small molecule Janus kinase (JAK) inhibitor
Orencia (abatacept)	-	sCTLA-4-Ig recombinant fusion protein
Otezla (apremilast)	-	Small-molecule phosphodiesterase 4 inhibitor
Remicade (infliximab)	-†	TNFα inhibitor
Renflexis (infliximab-abda)	N/A†	TNFα inhibitor
Rinvoq (upadacitinib)	-	Small molecule Janus kinase (JAK) inhibitor
Rituxan (rituximab)	-*	Anti-CD20 monoclonal antibody
Ruxience (rituximab-pvvr)	N/A†	Anti-CD20 monoclonal antibody
Siliq (brodalumab)	-	Human monoclonal antibody directed against the IL-17 receptor A (IL-17RA)
Simponi/ Simponi Aria (golimumab)	-	TNFα inhibitor
Skyrizi (risankizumab-rzaa)	-	Human monoclonal antibody to IL-23
Stelara (ustekinumab)	-	Human monoclonal antibody targeting the IL-12 and IL-23 cytokines
Taltz (ixekizumab)	-	Human monoclonal antibody to IL-17A
Tremfya (guselkumab)	-	Human monoclonal antibody to IL-23 cytokine
Truxima (rituximab-abbs)	N/A†	Anti-CD20 monoclonal antibody
Xeljanz/Xeljanz XR (tofacitinib)	-	Small molecule Janus kinase (JAK) inhibitor

*Erelzi (etanercept-szzs) and Eticovo (etanercept-ykro) have been FDA-approved as biosimilars to Enbrel (etanercept). Abrilada (adalimumab-afzb), Amjevita (adalimumab-atto), Cyltezo (adalimumab-adbm), Hadlima (adalimumab-bwwd), and Hyrimoz (adalimumab-adaz) have been FDA-approved as biosimilars to Humira (adalimumab). Two biosimilars are FDA-approved for Rituxan (rituximab), but Truxima (rituximab-abbs) only carries indications for the treatment of adult patients

with NHL or CLL, while Ruxience (rituximab-pvvr) is approved for adult patients with NHL, CLL, and GPA/MPA. Further information on Erelzi, Eticovo, Abrilada, Amjevita, Cyltezo, Hadlima, and Hyrimoz will be included in this review after these products have launched.
†Inflectra (infliximab-dyyb), Renflexis (infliximab-abda), Avsola (infliximab-axxq), and Ixifi (infliximab-qbtx) have been FDA-approved as biosimilar agents to Remicade (infliximab) and Truxima (rituximab-abbs) and Ruxience (rituximab-pvvr) have been FDA-approved as biosimilar agents to Rituxan (rituximab). However, none of these agents is FDA-approved as an interchangeable biologic.

(Drugs@FDA, 2020; Prescribing information: Actemra, 2019; Cimzia, 2019; Cosentyx, 2020; Enbrel, 2019; Entyvio, 2019; Humira, 2019; Ilaris, 2016; Ilumya 2018; Inflectra, 2019; Kevzara, 2018; Kineret, 2018; Olumiant 2019; Orencia, 2019; Otezla, 2019; Remicade, 2018; Renflexis, 2019; Rinvoq, 2019; Rituxan, 2020; Ruxience, 2019; Siliq, 2018; Simponi, 2019; Simponi Aria, 2019; Skyrizi, 2019; Stelara, 2020; Taltz, 2019; Tremfya, 2019; Truxima, 2019; Xeljanz/Xeljanz XR, 2019)

Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

INDICATIONS

Table 2. Food and Drug Administration Approved Indications (see footnotes for less common indications: oral ulcers associated with Behçet disease, CAPS, CRS, FMF, GCA, HIDS/MKD, NRAS, and TRAPS)*******

Drug	Rheumatoid Arthritis (RA)	Crohn's Disease (CD)	Systemic Juvenile Idiopathic Arthritis (SJIA)	Polyarticular Juvenile Idiopathic Arthritis (PJIA)	Plaque Psoriasis (PsO)	Psoriatic Arthritis (PsA)	Ankylosing Spondylitis (AS)	Ulcerative Colitis (UC)	Hidradenitis Suppurativa (HS)	Uveitis (UV)
Actemra˅ (tocilizumab)	✔ *		✔ **	✔ **						
Cimzia˜˜ (certolizumab)	✔	✔			✔ ‡	✔	✔			
Cosentyx (secukinumab)					✔ ‡	✔	✔			
Enbrel (etanercept)	✔ †			✔ **	✔ ‡	✔ †	✔			
Entyvio (vedolizumab)		✔						✔		
Humira (adalimumab)	✔ ‡‡	✔ ⌐		✔ ∫	✔ ‡	✔ ∫∫	✔	✔	✔ ↑	✔ ▼

Drug	Rheumatoid Arthritis (RA)	Crohn's Disease (CD)	Systemic Juvenile Idiopathic Arthritis (SJIA)	Polyarticular Juvenile Idiopathic Arthritis (PJIA)	Plaque Psoriasis (PsO)	Psoriatic Arthritis (PsA)	Ankylosing Spondylitis (AS)	Ulcerative Colitis (UC)	Hidradenitis Suppurativa (HS)	Uveitis (UV)
Ilaris" (canakinumab)			✔ **							
Ilumya (tildrakizumab-asmn)					✔ ‡					
Inflectra (infliximab-dyyb)	✔ ⊥	✔ ⌐⌐			✔ ‡‡‡	✔	✔	✔ ⊥⊥		
Kevzara (sarilumab)	✔ *									
Kineret▼▼ (anakinra)	✔ ∞									
Olumiant (baricitinib)	✔ *									
Orencia (abatacept)	✔ ∞∞			✔ ⌂		✔				

Drug	Rheumatoid Arthritis (RA)	Crohn's Disease (CD)	Systemic Juvenile Idiopathic Arthritis (SJIA)	Polyarticular Juvenile Idiopathic Arthritis (PJIA)	Plaque Psoriasis (PsO)	Psoriatic Arthritis (PsA)	Ankylosing Spondylitis (AS)	Ulcerative Colitis (UC)	Hidradenitis Suppurativa (HS)	Uveitis (UV)
Otezla~~~ (apremilast)					✔ ‡	✔				
Remicade (infliximab)	✔ ⊥	✔ ⌐⌐			✔ ‡‡‡	✔	✔	✔ ⊥⊥		
Renflexis (infliximab-abda)	✔ ⊥	✔ ⌐⌐			✔ ‡‡‡	✔	✔	✔ ⊥⊥		
Rinvoq (upadacitinib)	✔ †									
Rituxan''' (rituximab)	✔ ⫩									
Siliq (brodalumab)					✔ ⫩					
Simponi (golimumab)	✔ ⫞					✔ ⫞⫞	✔	✔ ~		

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Simponi Aria (golimumab)	✔┤					✔	✔			
Skyrizi (risankizumab-rzaa)					✔‡					
Stelara (ustekinumab)		✔⌐⌐⌐			✔‡	✔		✔		
Taltz (ixekizumab)					✔‡	✔	✔			
Tremfya (guselkumab)					✔‡					
Xeljanz/ Xeljanz XR (tofacitinib)	✔╪					✔		✔		

ϓActemra is also indicated for treatment of giant cell arteritis in adults and chimeric antigen receptor T cell-induced severe or life-threatening cytokine release syndrome in adults and pediatric patients ≥ 2 years.
*Patients with moderately to severely active RA who have had an inadequate response (or intolerance [Kevzara]) to ≥ 1 Disease-Modifying Anti-Rheumatic Drugs (DMARDs) or [≥ 1 TNF antagonists (Olumiant)].
**Patients 2 years and older.
†In combination with methotrexate (MTX) or used alone.

‡Indicated for the treatment of adult patients (18 years or older) with chronic moderate to severe PsO who are candidates for systemic therapy or phototherapy, with the exception of Enbrel, which is indicated for the treatment of patients 4 years and older with chronic moderate to severe PsO who are candidates for systemic therapy or phototherapy, and Stelara, which is indicated for the treatment of patients 12 years and older with moderate to severe PsO.
‡‡Indicated for reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in adult patients with moderately to severely active RA. Can be used alone or in combination with MTX or other DMARDs.
‡‡‡ Indicated for the treatment of adult patients with chronic severe (ie, extensive and/or disabling) PsO who are candidates for systemic therapy and when other systemic therapies are medically less appropriate.
∫Indicated for reducing signs and symptoms of JIA for patients 2 years of age and older. Can be used alone or in combination with MTX.
∫∫Indicated for reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in adult patients with active PsA. Can be used alone or in combination with non-biologic DMARDs.
▼ Treatment of non-infectious intermediate, posterior and panuveitis in adult and pediatric patients 2 years of age or older.
↑ Treatment of moderate to severe hidrandenitis suppurative in patients 12 years of age or older.
▼▼Kineret is also indicated for the treatment of cryopyrin-associated periodic syndromes (CAPS) including neonatal-onset multisystem inflammatory disease (NOMID).
“Ilaris also indicated for the treatment of CAPS in adults and children 4 years of age and older including: familial cold autoinflammatory syndrome (FCAS) and Muckle-Wells syndrome (MWS); tumor necrosis factor receptor associated periodic syndrome (TRAPS) in adult and pediatric patients; hyperimmunoglobulin D syndrome (HIDS)/mevalonate kinase deficiency (MKD) in adult and pediatric patients; and familial Mediterranean fever (FMF) in adult and pediatric patients.
∞Indicated for the reduction in signs and symptoms and slowing the progression of structural damage in moderately to severely active RA, in patients 18 years of age or older who have failed one or more DMARDs. Can be used alone or in combination with DMARDs other than TNF blocking agents.
∞∞Indicated for reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in adult patients with moderately to severely active RA. May be used as monotherapy or concomitantly with DMARDs other than TNF antagonists.
⌂ Indicated for reducing signs and symptoms in pediatric patients 2 years and older with moderate to severely active PJIA. May be used as monotherapy or with MTX.
⌐For all patients 6 years of age and older, indicated for reducing signs and symptoms and inducing and maintaining clinical remission in patients who have had an inadequate response to conventional therapy. For adults, also indicated for reducing signs and symptoms and inducing clinical remission if patients have also lost a response to or are intolerant of infliximab.
⌐⌐Indicated for reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with moderately to severely active disease who have had an inadequate response to conventional therapy and for reducing the number of draining enterocutaneous and rectovaginal fistulas and maintaining fistula closure in adult patients with fistulizing CD. And for patients 6 years of age and older for reducing signs and symptoms and inducing and maintaining clinical remission with moderately to severely active disease who have had an inadequate response to conventional therapy.
⌐⌐⌐Indicated for treatment of adult patients with moderately to severely active CD who have: 1) failed or were intolerant to treatment with immunomodulators or corticosteroids but never failed a TNF blocker, or 2) failed or were intolerant to treatment with ≥ 1 TNF blockers
⊥In combination with MTX, is indicated for reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in patients with moderately to severely active RA.
⊥⊥For reducing signs and symptoms, inducing and maintaining clinical remission and mucosal healing, and eliminating corticosteroid use in adult patients with moderately to severely active disease who have had an inadequate response to conventional therapy. Also for reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients 6 years of age and older with moderately to severely active disease who have had an inadequate response to conventional therapy (Remicade, Inflectra, Renflexis).
'''Rituxan also indicated for Non–Hodgkin’s lymphoma (NHL), chronic lymphocytic leukemia (CLL), granulomatosis with polyangiitis (GPA) (Wegener’s Granulomatosis) and microscopic polyangiitis (MPA), and pemphigus vulgaris.
╪In combination with MTX is indicated for the treatment of adult patients with moderately- to severely- active RA who have had an inadequate response to ≥ 1TNF antagonist therapies.
╪╪Treatment of moderate to severe PsO in adult patients who are candidates for systemic therapy or phototherapy and have failed to respond or have lost response to other systemic therapies.
┤ In combination with MTX, is indicated for the treatment of adult patients with moderately to severely active RA.
┤┤ Alone or in combination with MTX, is indicated for the treatment of adult patients with active PsA.
╪╪Indicated for the treatment of adult patients with moderately to severely active RA who have had an inadequate response or intolerance to MTX. It may be used as monotherapy or in combination with MTX or other nonbiologic DMARDs. Use in combination with biologic DMARDs or with potent immunosuppressants such as azathioprine and cyclosporine is not recommended.
˜Indicated in adult patients with moderately to severely active UC who have demonstrated corticosteroid dependence or who have had an inadequate response to or failed to tolerate oral aminosalicylates, oral corticosteroids, azathioprine, or 6-mercaptopurine for: inducing and maintaining clinical response; improving endoscopic appearance of the mucosa during induction; inducing clinical remission; and achieving and sustaining clinical remission in induction responders.
¯Cimzia also indicated for treatment of adults with active non-radiographic axial spondyloarthritis (NRAS) with objective signs of inflammation.
~~~Otezla also indicated for treatment of adults with oral ulcers associated with Behçet disease.
†Indicated for treatment of adults with moderately to severely active disease who have had an inadequate response or intolerance to MTX.
***Ruxience is indicated for NHL, CLL, GPA (Wegener’s Granulomatosis) and MPA. Truxima is indicated for NHL and CLL.
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CLINICAL EFFICACY SUMMARY

Rheumatoid arthritis (RA)

- The approval of the subcutaneous (SQ) formulation of Orencia (abatacept) was based on a double-blind, double-dummy, randomized trial demonstrating noninferiority to the intravenous (IV) formulation. The trial enrolled patients with RA who had an inadequate response to methotrexate (MTX). The proportion of patients achieving American College of Rheumatology 20% improvement (ACR 20) was not significantly different between the groups (*Genovese et al 2011*).
- Orencia (abatacept), Remicade (infliximab), and placebo were compared in a Phase 3, randomized, double-blind trial (n = 431). Enrolled patients had an inadequate response to MTX, and background MTX was continued during the trial. Although efficacy was comparable between abatacept and infliximab after 6 months of treatment, some differences in favor of abatacept were evident after 1 year of treatment. After 1 year, the mean changes from baseline in disease activity score based on erythrocyte sedimentation rate (DAS28-ESR) were -2.88 and -2.25 in the abatacept and infliximab groups, respectively (estimate of difference, -0.62; 95% confidence interval [CI], -0.96 to -0.29). Abatacept demonstrated greater efficacy vs infliximab on some (but not all) secondary endpoints, including the proportion of patients with a good European League Against Rheumatism (EULAR) response (32.0% vs 18.5%), low disease activity score (LDAS) (35.3% vs 22.4%), ACR 20 responses (72.4% vs 55.8%), and improvements in the Medical Outcomes Study short-form-36 (SF-36) physical component summary (PCS) (difference of 1.93). Overall, abatacept had a relatively more acceptable safety and tolerability profile, with fewer serious adverse events (AEs) and discontinuations due to AEs than the infliximab group (*Schiff et al 2008*).
- Treatment with Orencia (abatacept) was directly compared to treatment with Humira (adalimumab), when added to MTX, in a multicenter, investigator-blind, randomized controlled trial (n = 646) of RA patients with inadequate response to MTX. After 2 years, the proportions of patients achieving ACR 20 responses were comparable between abatacept and adalimumab treatment groups (59.7 and 60.1%, respectively; difference 1.8%; 95% CI, -5.6 to 9.2%). ACR 50 and ACR 70 responses were also similar between the 2 groups after 2 years of treatment. Rates of AEs were similar between treatment groups (*Schiff et al 2014*).
- The RAPID-1 and RAPID-2 studies compared Cimzia (certolizumab) in combination with MTX to placebo plus MTX in adults with active RA despite MTX therapy (*Keystone et al 2008, Smolen et al 2009a*). A significantly greater proportion of patients on certolizumab 400 mg plus MTX at weeks 0, 2, and 4 then 200 or 400 mg every 2 weeks attained greater ACR 20, ACR 50 and ACR 70 responses compared to patients on placebo and MTX, respectively, after 24 weeks ($p \leq 0.01$). The response rates were sustained with active treatment over 52 weeks (*Keystone et al 2008*). The Modified Total Sharp Score (mTSS) was significantly lower with certolizumab in combination with MTX compared to MTX in combination with placebo (*Keystone et al 2008, Smolen et al 2009a*). A trial evaluated Cimzia (certolizumab) monotherapy vs placebo in patients with active disease who had failed at least 1 prior DMARD. After 24 weeks, ACR 20 response rates were significantly greater with active treatment (45.5%) compared to placebo (9.3%; $p < 0.001$). Significant improvements in secondary endpoints (ACR 50, ACR 70, individual ACR component scores, and patient reported outcomes) were also associated with certolizumab therapy (*Fleischmann et al 2009*).
- More Cimzia (certolizumab)-treated patients achieved clinical disease activity index (CDAI) remission than placebo-treated patients (18.8% vs 6.1%, $p \leq 0.05$) in a randomized, double-blind, placebo-controlled trial of certolizumab over 24 weeks in 194 patients with RA who were on DMARD therapy with MTX, leflunomide, sulfasalazine and/or hydroxychloroquine for at least 6 months (*Smolen et al 2015a*).
- A randomized, double-blind, placebo-controlled trial (n = 316) conducted in Japan compared Cimzia (certolizumab) plus MTX to placebo plus MTX in MTX-naïve patients with early RA (≤ 12 months persistent disease) and poor prognostic factors: high anti-cyclic citrullinated peptide (anti-CCP) antibody and either positive rheumatoid factor and/or presence of bone erosions (*Atsumi et al 2016*). The primary endpoint was inhibition of radiographic progression (change from baseline in mTSS at week 52). The certolizumab plus MTX group showed significantly greater inhibition of radiographic progression vs MTX alone (mTSS change, 0.36 vs 1.58; $p < 0.001$). Clinical remission rates were higher in patients treated with certolizumab plus MTX vs MTX alone. The authors suggest that certolizumab plus MTX could be used as possible first-line treatment in this patient population. In a long-term extension, a higher percentage of patients treated with certolizumab plus MTX experienced inhibition of radiographic progression (change from baseline in mTSS) at week 104 vs MTX alone (84.2% vs 67.5%; $p < 0.001$) (*Atsumi et al 2017*).
- The FDA approval of Simponi (golimumab) for RA was based on 3 multicenter, double-blind, randomized, controlled trials in 1,542 patients ≥ 18 years of age with moderate to severe active disease. A greater percentage of patients from all 3 trials treated with the combination of golimumab and MTX achieved ACR responses at week 14 and week

24 vs patients treated with MTX alone (*Emery et al 2009, Keystone et al 2009, Smolen et al 2009b*). Additionally, the golimumab 50 mg groups demonstrated a greater improvement compared to the control groups in the change in mean Health Assessment Questionnaire (HAQ) Disability Index (HAQ-DI) (*Keystone et al 2009, Smolen et al 2009b*). Response with golimumab + MTX was sustained for up to 5 years (*Keystone et al 2013a, Smolen et al 2015b*).

- Simponi Aria (golimumab) was studied in patients with RA. In 1 trial, 643 patients could receive golimumab 2 mg/kg or 4 mg/kg intravenously (IV) every 12 weeks with or without MTX, or placebo with MTX. The proportion of patients meeting the primary endpoint of ACR 50 response was not significantly different between the golimumab with or without MTX groups and the placebo group. However, significantly more patients receiving golimumab plus MTX achieved an ACR 20 response at week 14 compared with patients receiving placebo plus MTX (53 vs 28%; $p < 0.001$) (*Kremer et al 2010*). In the GO-FURTHER trial (n = 592), golimumab 2 mg/kg IV or placebo was given at weeks 0, 4 and then every 8 weeks. An increased percentage of patients treated with golimumab + MTX achieved ACR 20 response at week 14 (58.5% [231/395] of golimumab + MTX patients vs 24.9% [49/197] of placebo + MTX patients [$p < 0.001$]) (*Weinblatt et al 2013*). In an open-label extension period, treatment was continued through week 100, with placebo-treated patients crossing over to golimumab at week 16 (early escape) or week 24. Clinical response was maintained through week 100, with an ACR 20 response of 68.1%. There was a very low rate of radiographic progression throughout the study, and patients treated with IV golimumab plus MTX from baseline had significantly less radiographic progression to week 100 compared to patients who had initially received placebo plus MTX. No unexpected AEs occurred (*Bingham et al 2015*). In the GO-MORE trial, investigators treated patients with golimumab SQ for 6 months. If patients were not in remission, they could be randomized to receive golimumab SQ or IV. The percentages of patients who achieved DAS28-ESR remission did not differ between the combination SQ + IV group and the SQ golimumab group (*Combe et al 2014*).
- The efficacy and safety of Actemra (tocilizumab) were assessed in several randomized, double-blind, multicenter studies in patients age ≥ 18 years with active RA. Patients were diagnosed according to ACR criteria, with at least 8 tender and 6 swollen joints at baseline. Tocilizumab was given every 4 weeks as monotherapy (AMBITION), in combination with MTX (LITHE and OPTION) or other DMARDs (TOWARD) or in combination with MTX in patients with an inadequate response to TNF antagonists (RADIATE). In all studies, mild to moderate AEs were reported, occurring in similar frequencies in all study groups. The most common AEs in all studies were infections and gastrointestinal symptoms (*Emery et al 2008, Genovese et al 2008, Jones et al 2010, Kremer et al 2011, Smolen et al 2008*).
    - AMBITION evaluated the safety and efficacy of tocilizumab monotherapy vs MTX in patients with active RA for whom previous treatment with MTX or biological agents had not failed. A total of 673 patients were randomized to 1 of 3 treatment arms, tocilizumab 8 mg/kg every 4 weeks, MTX 7.5 mg/week and titrated to 20 mg/week within 8 weeks, or placebo for 8 weeks followed by tocilizumab 8 mg/kg. The primary endpoint was the proportion of patients achieving ACR 20 response at week 24. The results showed that tocilizumab monotherapy when compared to MTX monotherapy produced greater improvements in RA signs and symptoms, and a favorable benefit-risk ratio in patients who had not previously failed treatment with MTX or biological agents. Additionally, more patients treated with tocilizumab achieved remission at week 24 when compared to patients treated with MTX (*Jones et al 2010*).
    - LITHE evaluated 1,196 patients with moderate to severe RA who had an inadequate response to MTX. Patients treated with tocilizumab had 3 times less progression of joint damage, measured by Total Sharp Score, when compared to patients treated with MTX alone. Significantly more patients treated with tocilizumab 8 mg/kg were also found to achieve remission at 6 months as compared to MTX (33% vs 4%), and these rates continued to increase over time to 1 year (47% vs 8%) (*Kremer et al 2011*). These benefits were maintained or improved at 2 years with no increased side effects (*Fleishmann et al 2013*).
    - OPTION evaluated tocilizumab in 623 patients with moderate to severely active RA. Patients received tocilizumab 8 mg/kg, 4 mg/kg, or placebo IV every 4 weeks, with MTX at stable pre-study doses (10 to 25 mg/week). Rescue therapy with tocilizumab 8 mg/kg was offered at week 16 to patients with < 20% improvement in swollen and tender joint counts. The primary endpoint was ACR 20 at week 24. The findings showed that ACR 20 was seen in significantly more patients receiving tocilizumab than in those receiving placebo at week 24 ($p < 0.001$). Significantly more patients treated with tocilizumab achieved ACR 50 and ACR 70 responses at week 24 as well ($p < 0.001$). Greater improvements in physical function, as measured by the HAQ-DI, were seen with tocilizumab when compared to MTX (-0.52 vs -0.55 vs -0.34; $p < 0.0296$ for 4 mg/kg and $p < 0.0082$ for 8 mg/kg) (*Smolen et al 2008*).

  - TOWARD examined the efficacy and safety of tocilizumab combined with conventional DMARDs in 1220 patients with active RA. Patients remained on stable doses of DMARDs and received tocilizumab 8 mg/kg or placebo every 4 weeks for 24 weeks. At week 24, significantly more patients taking tocilizumab with DMARDs achieved an ACR 20 response than patients in the control group. The authors concluded that tocilizumab, combined with any of the DMARDs evaluated (MTX, chloroquine, hydroxychloroquine, parenteral gold, sulfasalazine, azathioprine, and leflunomide), was safe and effective in reducing articular and systemic symptoms in patients with an inadequate response to these agents. A greater percentage of patients treated with tocilizumab also had clinically meaningful improvements in physical function when compared to placebo (60% vs 30%; p value not reported) (*Genovese et al 2008).*
  - RADIATE evaluated the safety and efficacy of tocilizumab in patients with RA refractory to TNF antagonist therapy. A total of 499 patients with inadequate response to ≥ 1TNF antagonists were randomly assigned to 8 or 4 mg/kg tocilizumab or placebo every 4 weeks with stable MTX doses (10 to 25 mg/week) for 24 weeks. ACR 20 responses and safety endpoints were assessed. This study found that tocilizumab plus MTX is effective in achieving rapid and sustained improvements in signs and symptoms of RA in patients with inadequate response to TNF antagonists and has a manageable safety profile. The ACR 20 response in both tocilizumab groups was also found to be comparable to those seen in patients treated with Humira (adalimumab) and Remicade (infliximab), irrespective of the type or number of failed TNF antagonists (*Emery et al 2008*). In the ADACTA trial, patients with severe arthritis who could not take MTX were randomized to monotherapy with tocilizumab or adalimumab. The patients in the tocilizumab group had a significantly greater improvement in DAS28 at week 24 than patients in the adalimumab group (*Gabay et al 2013*).
- More recently, results of a randomized, double-blind trial evaluating Actemra (tocilizumab) in early RA were published (*Bijlsma et al 2016*). Patients (n = 317) had been diagnosed with RA within 1 year, were DMARD-naïve, and had a DAS28 score of ≥ 2.6. Patients were randomized to 1 of 3 groups: tocilizumab plus MTX, tocilizumab plus placebo, or MTX plus placebo. Tocilizumab was given at a dose of 8 mg/kg every 4 weeks (maximum 800 mg per dose), and MTX was given at a dose of 10 mg orally per week, increased to a maximum of 30 mg per week as tolerated. Patients not achieving remission switched from placebo to active treatments, and patients not achieving remission in the tocilizumab plus MTX group switched to a standard of care group (usually a TNF inhibitor plus MTX). The primary endpoint was the proportion of patients achieving sustained remission (defined as DAS28 < 2.6 with a swollen joint count ≤4, persisting for at least 24 weeks). The percentages of patients achieving a sustained remission on the initial regimen were 86%, 84%, and 44% in the tocilizumab plus MTX, tocilizumab monotherapy, and MTX monotherapy groups, respectively ($p < 0.0001$ for both comparisons vs MTX). The percentages of patients achieving sustained remission during the entire study were 86%, 88%, and 77% in the tocilizumab plus MTX, tocilizumab monotherapy, and MTX monotherapy groups, respectively ($p = 0.06$ for tocilizumab plus MTX vs MTX; $p = 0.0356$ for tocilizumab vs MTX). The authors concluded that immediate initiation of tocilizumab is more effective compared to initiation of MTX in early RA.
- The FDA approval of the SQ formulation of Actemra (tocilizumab) was based on 1 multicenter, double-blind, randomized, controlled trial in patients (n = 1262) with RA. Weekly tocilizumab SQ 162 mg was found to be non-inferior to tocilizumab IV 8 mg/kg every 4 weeks through 24 weeks. A higher incidence of injection-site reactions were reported with the SQ formulation (*Burmester et al 2014a*). In an open-label extension period, patients in both treatment arms were re-randomized to receive either IV or SQ tocilizumab through week 97. The proportions of patients who achieved ACR 20/50/70 responses, DAS28 remission, and improvement from baseline in HAQ-DI ≥ 0.3 were sustained through week 97 and comparable across arms. IV and SQ treatments had a comparable safety profile with the exception of higher injection-site reactions with the SQ formulation (*Burmester et al 2016*). A placebo-controlled trial in 656 patients further confirmed the efficacy of SQ Actemra administered every other week (*Kivitz et al 2014*).
- A phase 3 trial (MONARCH) evaluating the efficacy of Kevzara (sarilumab) monotherapy vs Humira (adalimumab) monotherapy for the treatment of patients with active RA with an inadequate response or intolerance to MTX reported superiority of sarilumab over adalimumab based on change from baseline in DAS28-ESR at week 24 (-3.28 vs -2.20; difference, -1.08; 95% CI, -1.36 to -0.79; $p < 0.0001$) (*Burmester et al 2017*). DAS28-ESR remission, ACR 20/50/70 response rates, and improvements in HAQ-DI scores were also more likely with sarilumab. Aside from the MONARCH trial, sarilumab has not been directly compared to any other biologic or tofacitinib. Nonetheless, 2 pivotal trials have shown the agent to be superior in achievement of ACR 50 when compared to MTX plus placebo, in both MTX inadequate responders and TNF inhibitor inadequate responder patients (*Genovese et al 2015, Fleischmann et al 2017*). Additionally, a meta-analysis of 4 randomized controlled trials (RCTs) has shown that ACR 50 response rates

were significantly higher with sarilumab 200 mg and sarilumab 200 mg plus MTX when compared to MTX plus placebo (OR, 4.05; 95% CI, 2.04 to 8.33 and OR, 3.75; 95% CI, 2.37 to 5.72, respectively). Ranking probability based on the surface under the cumulative ranking curve (SUCRA) suggested that sarilumab 200 mg was most likely to achieve ACR 50 response rate, followed by sarilumab 200 mg plus MTX, sarilumab 150 mg plus MTX, adalimumab 40 mg, and MTX plus placebo (*Bae et al 2017).*

- In a Phase 3 trial, the percentage of patients who met criteria for RA disease remission was not significantly different in the Xeljanz (tofacitinib) groups (5 mg and 10 mg twice daily) vs placebo. However, significantly more patients in the tofacitinib groups did meet criteria for decrease of disease activity. The tofacitinib groups also had significant decreases in fatigue and pain (*Fleishmann et al 2012*). In another Phase 3 study, Xeljanz (tofacitinib), when administered with background MTX, was superior to placebo with respect to all clinical outcomes. Although not directly compared to Humira (adalimumab), the clinical efficacy of tofacitinib was numerically similar to that observed with adalimumab. Safety of tofacitinib continues to be monitored for long term effects (*van Vollenhoven et al 2012*). The ORAL Scan trial showed the ACR 20 response rates at month 6 for patients receiving tofacitinib 5 mg and 10 mg twice daily were 51.5% and 61.8%, respectively, vs 25.3% for patients receiving placebo ($p < 0.0001$ for both comparisons) (*van der Heijde et al 2013*). Treatment effects were maintained through month 24 in the ORAL Scan trial, with an ACR 20 response rate of 50.5% and 58.3% for tofacitinib 5 mg and 10 mg twice daily, respectively (*van der Heijde et al 2019*). The ORAL START trial evaluated tofacitinib and MTX in 956 patients with active RA over 24 months. The primary endpoint of mean change from baseline in modified total Sharp score was significantly less with tofacitinib (0.6 for 5 mg; 0.3 for 10 mg) compared to MTX (2.1; $p < 0.001$) (*Lee et al 2014*). No radiographic progression was defined as a change from baseline in the modified total Sharp score of < 0.5 points. However, a minimal clinically important difference in modified total Sharp score is 4.6 points; this study did not meet this minimal clinical meaningful difference threshold.
- In the ORAL Step study, patients with RA who had an inadequate response to ≥ 1 TNF inhibitors were randomized to Xeljanz (tofacitinib) 5 mg or 10 mg twice daily or placebo; all patients were on MTX (*Burmester et al 2013a, Strand et al 2015a*). The primary outcome, ACR 20 response rate, was significantly higher with tofacitinib 5 mg (41.7%; 95% CI, 6.06 to 28.41; $p = 0.0024$) and 10 mg (48.1%; 95% CI, 12.45 to 34.92; $p < 0.0001$) compared to placebo (24.4%). Improvements in HAQ-DI was reported as -0.43 (95% CI, -0.36 to -0.157; $p < 0.0001$) for tofacitinib 5 mg and -0.46 (95% CI, -0.38 to -0.17; $p < 0.0001$) for tofacitinib 10 mg groups compared to -0.18 for placebo. Common AEs included diarrhea, nasopharyngitis, headache, and urinary tract infections in the tofacitinib groups.
- The approval of Olumiant (baricitinib) was based on 2 confirmatory, 24-week, phase 3 trials in patients with active RA. In RA-BEACON, enrolled patients (N = 527) had moderate to severe RA and an inadequate response or intolerance to ≥ 1 TNF antagonist(s) (*Genovese et al 2016*). Patients received baricitinib once daily or placebo along with continuing a stable dose of a conventional DMARD. The primary endpoint, ACR 20 response at week 12, was achieved by 49% and 27% of patients in the baricitinib 2 mg and placebo groups, respectively ($p \leq 0.001$). In RA-BUILD, enrolled patients (N = 684) had moderate to severe RA and an inadequate response or intolerance to ≥ 1 conventional DMARD(s) (*Dougados et al 2017*). Patients received baricitinib once daily or placebo; concomitant conventional DMARDs were permitted but not required. The primary endpoint, ACR20 response at week 12, was achieved by 66% and 39% of patients in the baricitinib 2 mg and placebo groups, respectively ($p \leq 0.001$).
- Approval of Rinvoq (upadacitinib) was based on clinical trials from the SELECT program in patients with RA. In SELECT-EARLY (n = 947), 52% of MTX-naïve patients treated with upadacitinib 15 mg daily achieved ACR 50 vs 28% treated with MTX at week 12, and at week 24, significantly more patients treated with upadacitinib 15 mg daily had no radiographic progression (87.5% vs 77.7%; $p < 0.01$) *(van Vollenhoven et al 2018)*. In SELECT-MONOTHERAPY (n = 648), 68% of patients with an inadequate response or intolerance to MTX (MTX-IR) treated with upadacitinib 15 mg daily achieved ACR 20 vs 41% treated with continued MTX at week 14 *(Smolen et al 2019)*. In SELECT-COMPARE, which evaluated MTX-IR patients (n = 1629), ACR 20 was significantly more frequent with upadacitinib 15 mg daily vs placebo and vs adalimumab at week 12 (70.5% vs 36.4% and 63%, respectively; $p < 0.001$ and $p < 0.05$) and at week 26 (67.4% vs 35.6% and 57.2%, respectively; $p <0.001$ and $p <0.01$). At week 26, significantly more patients treated with upadacitinib had no radiographic progression vs placebo (83.5% vs. 76.0%; $p < 0.001$) *(Fleischman et al 2018)*. In SELECT-BEYOND (n = 499), 65% of biologic-IR patients treated with upadacitinib 15 mg daily plus conventional DMARDs achieved ACR 20 vs 28% treated with placebo plus conventional DMARDs at week 12 ($p <0.0001$) *(Genovese et al 2018)*.
- Inflectra (infliximab-dyyb) was evaluated and compared to Remicade (infliximab; European Union formulation) in PLANETRA (N=606), a double-blind, multicenter, randomized trial (*Yoo et al 2013, Yoo et al 2016, Yoo et al 2017*). The primary endpoint, ACR 20 at week 30, was achieved by 58.6% and 60.9% of patients in the Remicade and

Inflectra groups, respectively (treatment difference [TD], 2%; 95% CI, -6% to 10%) (intention-to-treat population). Corresponding results in the per-protocol population were 69.7% and 73.4%, respectively (TD, 4%; 95% CI, -4% to 12%). Equivalence was demonstrated between the 2 products.
    - Secondary endpoints included several other disease activity scales and a quality-of-life scale; no significant differences were noted in any of these endpoints at either the 30-week or 54-week assessments.
    - In the extension study (n = 302) through 102 weeks, all patients received Inflectra. Response rates were maintained, with no differences between the Inflectra maintenance group and the group who switched from Remicade to Inflectra.
- Renflexis (infliximab-abda) was evaluated and compared to Remicade (infliximab; European Union formulation) in 584 patients in a double-blind, multicenter, randomized phase 3 trial (*Choe et al 2017*). The primary endpoint, ACR 20 at week 30, was achieved by 64.1% and 66.0% of patients in the Renflexis and Remicade groups, respectively (TD, -1.88%; 95% CI, -10.26% to 6.51%) (per-protocol population). Equivalence was demonstrated between the 2 products.
    - Secondary endpoints were also very similar between the 2 groups.
    - At week 54 of this trial, patients transitioned into the switching/extension phase, in which patients initially taking Remicade were re-randomized to continue Remicade or switch to Renflexis; patients initially taking Renflexis continued on the same treatment. Although slight numerical differences were observed, there was consistent efficacy over time across treatments and the proportions of patients achieving ACR responses were comparable between groups (*Renflexis FDA clinical review 2017*).
- Two studies, 1 double-blind and 1 open-label, evaluated Rituxan (rituximab) in patients who had failed treatment with a TNF blocker (*Cohen et al 2006, Haraoui et al 2011*). All patients continued to receive MTX. Both studies showed > 50% of patients achieving ACR 20 response. AEs were generally mild to moderate in severity.
- A Cochrane review (*Lopez-Olivo et al 2015*) examined Rituxan (rituximab) for the treatment of RA. Eight studies and a total of 2720 patients were included. Rituximab plus MTX, compared to MTX alone, resulted in more patients achieving ACR 50 at 24 weeks (29% vs 9%, respectively) and clinical remission at 52 weeks (22% vs 11%). In addition, rituximab plus MTX compared to MTX alone resulted in more patients having no radiographic progression (70% vs 59% at 24 weeks, with similar results at 52 through 56 and 104 weeks). Benefits were also shown for physical function and quality of life (QoL).
- In the open-label ORBIT study (n = 295), adults with active, seropositive RA and an inadequate response to DMARDs who were biologic-naïve were randomized to either Rituxan (rituximab) (n = 144) or a TNF inhibitor (physician/patient choice of Enbrel [etanercept] or Humira [adalimumab]; n = 151) (*Porter et al 2016*). Medication doses were generally consistent with FDA-approved recommendations. Patients were able to switch over to the alternative treatment due to side effects or lack of efficacy. The primary endpoint was the change in DAS28-ESR in the per-protocol population at 12 months.
    - The changes in DAS28-ESR were -2.6 and -2.4 in patients in the rituximab and TNF inhibitor groups, respectively. The difference of -0.19 (95% CI, -0.51 to 0.13) was within the prespecified non-inferiority margin of 0.6 units. The authors concluded that initial treatment with rituximab was non-inferior to initial TNF inhibitor treatment in this patient population. However, interpretation of these results is limited due to the open-label study design and the high percentage of patients switching to the alternative treatment (32% in the TNF inhibitor group and 19% in the rituximab group). The indication for rituximab is limited to patients with an inadequate response to TNF inhibitor(s).
- A randomized, open-label trial evaluated biologic treatments in patients with RA who had had an inadequate response to a TNF inhibitor (*Gottenberg et al 2016*). Patients (n = 300) were randomized to receive a second TNF inhibitor (n = 150) or a non-TNF-targeted biologic (n = 150) of the prescriber's choice. The second TNF inhibitors, in order of decreasing frequency, included Humira (adalimumab), Enbrel (etanercept), Cimzia (certolizumab), and Remicade (infliximab), and the non-TNF biologics included Actemra (tocilizumab), Rituxan (rituximab), and Orencia (abatacept). The primary endpoint was the proportion of patients with a good or moderate EULAR response at week 24, defined as a decrease in DAS28-ESR of > 1.2 points resulting in a score of ≤ 3.2.
    - At week 24, 52% of patients in the second anti-TNF group and 69% of patients in the non-TNF group achieved a good or moderate EULAR response (p = 0.003 or p = 0.004, depending on how missing data were handled). Secondary disease activity scores also generally supported better efficacy for the non-TNF biologics; however, HAQ scores did not differ significantly between groups. Among the non-TNF biologics, the proportion of EULAR good and moderate responders at week 24 did not significantly differ between abatacept, rituximab, and tocilizumab (67%, 61%, and 80%, respectively). There were 8 patients (5%) in the second TNF inhibitor group and 16 patients (11%) in the non-TNF biologic group that experienced serious

AEs (p = 0.10), predominantly infections and cardiovascular events. There were some limitations to this trial; notably, it had an open-label design, and adherence may have differed between groups because all non-TNF biologics were given as infusions under observation and most of the TNF inhibitor drugs were self-injected by patients. The authors concluded that among patients with RA inadequately treated with TNF inhibitors, a non-TNF biologic was more effective in achieving a good or moderate disease activity response at 24 weeks; however, a second TNF inhibitor was also often effective in producing clinical improvement.

- Another recent randomized trial (*Manders et al 2015*) evaluated the use of Orencia (abatacept) (n = 43), Rituxan (rituximab) (n = 46), or a different TNF inhibitor (n = 50) in patients (n =139) with active RA despite previous TNF inhibitor treatment. Actemra (tocilizumab) was not included. In this trial, there were no significant differences with respect to DAS28, HAQ-DI, or SF-36 over the 1-year treatment period, and AEs also appeared similar. A cost-effectiveness analysis was also included in this publication, but results are not reported in this review.
- A Cochrane review examined Orencia (abatacept) for the treatment of RA. ACR 50 response was not significantly different at 3 months but was significantly higher in the abatacept group at 6 and 12 months compared to placebo (relative risk [RR], 2.47; 95% CI, 2 to 3.07 and RR, 2.21; 95% CI, 1.73 to 2.82). Similar results were seen in ACR 20 and ACR 70 (*Maxwell et al 2009*).
- The safety and efficacy of Humira (adalimumab) for the treatment of RA were assessed in a Cochrane systematic review. Treatment with adalimumab in combination with MTX was associated with a RR of 1.52 to 4.63, 4.63 (95% CI, 3.04 to 7.05) and 5.14 (95% CI, 3.14 to 8.41) for ACR 20, ACR 50, and ACR 70 responses, respectively, at 6 months when compared to placebo in combination with MTX. Adalimumab monotherapy was also proven efficacious (*Navarro-Sarabia et al 2005*). In another study, patients received adalimumab 20 mg or 40 mg every other week for 1 year, and then could receive 40 mg every other week for an additional 9 years. At Year 10, 64.2%, 49%, and 17.6% of patients achieved ACR 50, ACR 70, and ACR 90 responses, respectively (*Keystone et al 2013b*).
- A Phase 3, open-label study evaluated the long-term efficacy of Humira (adalimumab) for RA. Patients receiving adalimumab in 1 of 4 early assessment studies could receive adalimumab for up to 10 years in the extension study. Of 846 enrolled patients, 286 (33.8%) completed 10 years of treatment. In patients completing 10 years, adalimumab led to sustained clinical and functional responses, with ACR 20, ACR 50, and ACR 70 responses being achieved by 78.6%, 55.5%, and 32.8% of patients, respectively. The authors stated that patients with shorter disease duration achieved better outcomes, highlighting the need for early treatment. No unexpected safety findings were observed. This study demonstrated that some patients with RA can be effectively treated with adalimumab on a long-term basis; however, the study is limited by its open-label design, lack of radiographic data, and the fact that only patients who continued in the study were followed (*Furst et al 2015*).
- A Cochrane review was performed to compare Kineret (anakinra) to placebo in adult patients with RA. Significant improvements in both primary (ACR 20, 38% vs 23%; RR, 1.61; 95% CI, 1.32 to 1.98) and secondary (ACR 50 and ACR 70) outcomes were detected. The only significant difference in AEs noted with anakinra use was the rate of injection site reactions (71% vs 28% for placebo) (*Mertens et al 2009*).
- In another Cochrane review, Enbrel (etanercept) was compared to MTX or placebo in adult patients with RA and found that at 6 months, 64% of individuals on etanercept 25 mg twice weekly attained an ACR 20 vs 15% of patients on either MTX alone or placebo (RR, 3.8; number needed to treat [NNT], 2). An ACR 50 and ACR 70 were achieved by 39% and 15%, respectively, in the etanercept group compared to 4% (RR, 8.89; NNT, 3) and 1% (RR, 11.31; NNT, 7) in the control groups, respectively. Etanercept 10 mg twice weekly was only associated with significant ACR 20 (51% vs 11% of controls; RR, 4.6; 95% CI, 2.4 to 8.8; NNT, 3) and ACR 50 responses (24% vs 5% of controls; RR, 4.74; 95% CI, 1.68 to 13.36; NNT, 5). Seventy-two percent of patients receiving etanercept had no increase in Sharp erosion score compared to 60% of MTX patients. Etanercept 25 mg was associated with a significantly reduced total Sharp score (weighted mean difference, -10.5; 95% CI, -13.33 to -7.67). The Sharp erosion scores and joint space narrowing were not significantly reduced by either etanercept dose (*Blumenauer et al 2003*). In a trial of 353 patients with RA, patients received a triple therapy combination of sulfasalazine, hydroxychloroquine and MTX or etanercept and MTX. Triple therapy was shown to be noninferior to etanercept + MTX (*O'Dell et al 2013*).
- A more recent Cochrane review (*Singh et al 2016a*) evaluated the benefits and harms of 10 agents for the treatment of RA in patients failing treatment with MTX or other DMARDs. Agents included Xeljanz (tofacitinib) and 9 biologics (Orencia [abatacept], Humira [adalimumab], Kineret [anakinra], Cimzia [certolizumab], Enbrel [etanercept], Simponi [golimumab], Remicade [infliximab], Rituxan [rituximab], and Actemra [tocilizumab]), each in combination with MTX or other DMARDS, compared to comparator agents such as DMARDs or placebo. Data from 79 randomized trials (total 32,874 participants) were included. Key results from this review are as follows:

  - ACR 50: Biologic plus MTX/DMARD was associated with a statistically significant and clinically meaningful improvement in ACR 50 vs comparators. TNF inhibitors did not differ significantly from non-TNF biologics. Differences between treatments in individual comparisons were small.
  - HAQ: Biologic plus MTX/DMARD was associated with a clinically and statistically significant improvement in function measured by HAQ vs comparators. TNF inhibitors did not differ significantly from non-TNF biologics.
  - Remission: Biologic plus MTX/DMARD was associated with clinically and statistically significantly greater proportion of patients achieving RA remission, defined by DAS < 1.6 or DAS28 < 2.6, vs comparators. TNF inhibitors did not differ significantly from non-TNF biologics.
  - Radiographic progression: Radiographic progression was statistically significantly reduced in those on biologic plus MTX/DMARD vs comparator. The absolute reduction was small and clinical relevance is uncertain.
  - Safety: Biologic plus MTX/DMARD was associated with a clinically significantly increased risk of serious AEs; statistical significance was borderline. TNF inhibitors did not differ significantly from non-TNF biologics.
- A similar Cochrane review focused on the use of biologic or Xeljanz (tofacitinib) monotherapy for RA in patients with traditional DMARD failure (*Singh et al 2016[b]*). A total of 41 randomized trials (n = 14,049) provided data for this review. Key results are as follows:
  - Biologic monotherapy was associated with a statistically significant and clinically meaningful improvement in ACR 50 and HAQ vs placebo and vs MTX or other DMARDs.
  - Biologic monotherapy was associated with a statistically significant and clinically meaningful greater proportion of patients with disease remission vs placebo.
  - Based on a single study, the reduction in radiographic progression was statistically significant for biologic monotherapy compared to active comparators, but the absolute reduction was small and of unclear clinical relevance.
- Another Cochrane review evaluated the use of biologics or Xeljanz (tofacitinib) in patients with RA who had been unsuccessfully treated with a previous biologic (*Singh et al 2017[a]*). The review included 12 randomized trials (n = 3,364). Key results are as follows:
  - Biologics, compared to placebo, were associated with statistically significant and clinically meaningful improvement in RA as assessed by ACR 50 and remission rates. Information was not available for HAQ or radiographic progression.
  - Biologics plus MTX, compared to MTX or other traditional DMARDs, were associated with statistically significant and clinically meaningful improvement in ACR 50, HAQ, and RA remission rates. Information was not available for radiographic progression.
  - There were no published data for tofacitinib monotherapy vs placebo.
  - Based on a single study, tofacitinib plus MTX, compared to MTX, was associated with a statistically significant and clinically meaningful improvement in ACR 50 and HAQ. RA remission rates were not statistically significantly different, and information was not available for radiographic progression.
- In another meta-analysis, ACR 20 and ACR 70 response rates for Xeljanz (tofacitinib) 5 mg and 10 mg were comparable to the other monotherapies (Orencia [abatacept], Humira [adalimumab], Kineret [anakinra], Cimzia [certolizumab], Enbrel [etanercept], Simponi [golimumab], Remicade [infliximab], Actemra [tocilizumab]) at 24 weeks (*Bergrath et al 2017*). ACR 50 response rates were also comparable for tofacitinib 10 mg and other monotherapies. At 24 weeks, ACR 20/50/70 response rates for the combination of tofacitinib 5 mg or 10 mg plus conventional DMARD were comparable to other biologic plus conventional DMARD therapies except tofacitinib 5 mg plus conventional DMARD and tofacitinib 10 mg plus conventional DMARD were both superior to certolizumab 400 mg every 4 weeks plus conventional DMARD for achieving ACR 70 response (OR, 59.16; [95% CI, 2.70 to infinity]; and OR, 77.40; [95% CI, 3.53 to infinity], respectively).
- Another recent Cochrane review (*Hazlewood et al 2016*) compared MTX and MTX-based DMARD combinations for RA in patients naïve to or with an inadequate response to MTX; DMARD combinations included both biologic and non-biologic agents. A total of 158 studies and over 37,000 patients were included. Evidence suggested that efficacy was similar for triple DMARD therapy (MTX plus sulfasalazine plus hydroxychloroquine) and MTX plus most biologic DMARDs or Xeljanz (tofacitinib). MTX plus some biologics were superior to MTX in preventing joint damage in MTX-naïve patients, but the magnitude of effect was small.
- An additional Cochrane review evaluated biologics for RA in patients naïve to MTX in 19 studies (*Singh et al 2017[b]*). Agents included in the review were Humira (adalimumab), Enbrel (etanercept), Simponi (golimumab), Remicade (infliximab), Orencia (abatacept), and Rituxan (rituximab). When combined with MTX, use of biologics showed a

benefit in ACR 50 vs comparator (MTX/MTX plus methylprednisolone) (RR, 1.40; 95% CI, 1.30 to 1.49) and in RA remission rates (RR, 1.62; 95% CI, 1.33 to 1.98), but no difference was found for radiographic progression. When used without MTX, there was no significant difference in efficacy between biologics and MTX.

- A meta-analysis evaluated the efficacy of Remicade (infliximab) in combination with MTX compared to placebo plus MTX. There was a higher proportion of patients in the infliximab group that achieved an ACR 20 at 30 weeks compared to patients in the placebo group (RR, 1.87; 95% CI, 1.43 to 2.45). These effects were similar in the proportion of patients achieving ACR 50 and ACR 70 (RR, 2.68; 95% CI, 1.79 to 3.99 and RR, 2.68; 95% CI, 1.78 to 4.03) (*Wiens et al 2009*).
- Another meta-analysis of randomized controlled trials included Humira (adalimumab), Kineret (anakinra), Enbrel (etanercept), and Remicade (infliximab) with or without MTX. The odds ratio (OR) for an ACR 20 was 3.19 (95% CI, 1.97 to 5.48) with adalimumab, 1.7 (95% CI, 0.9 to 3.29) with anakinra, 3.58 (95% CI, 2.09 to 6.91) with etanercept and 3.47 (95% CI, 1.66 to 7.14) with infliximab compared to placebo. The OR to achieve an ACR 50 with adalimumab was 3.97 (95% CI, 2.73 to 6.07), 2.13 (95% CI, 1.27 to 4.22) with anakinra, 4.21 (95% CI, 2.74 to 7.43) and with etanercept 4.14 (95% CI, 2.42 to 7.46) compared to placebo. Further analysis of each agent against another was performed, and no significant difference was determined between individual agents in obtaining an ACR 20 and ACR 50. However, the TNF-blockers as a class showed a greater ACR 20 and ACR 50 response compared to anakinra (OR, 1.96; 95% CI, 1.03 to 4.01 and OR, 1.93; 95% CI,1.05 to 3.5; $p < 0.05$) (*Nixon et al 2007*).
- The Agency for Healthcare Research and Quality published a review of drug therapy to treat adults with RA (*Donahue et al 2012*). They concluded that there is limited head-to-head data comparing the biologics. Studies that are available are generally observational in nature or mixed treatment comparison meta-analysis. At this time, there appears to be no significant differences amongst the agents. Clinical trials have shown better efficacy with combination biologics and MTX and no additional increased risk of AEs. However, combinations of 2 biologic agents showed increased rate of serious AEs with limited or no increase in efficacy.
- A meta-analysis of 6 trials (n = 1,927) evaluated the efficacy of withdrawing biologics from patients with RA who were in sustained remission or had low disease activity (*Galvao et al 2016*). The biologics in the identified trials were TNF inhibitors, most commonly Enbrel (etanercept) or Humira (adalimumab). Compared to withdrawing the medication, continuing the biologic increased the probability of having low disease activity (RR, 0.66; 95% CI, 0.51 to 0.84) and remission (RR, 0.57; 95% CI, 0.44 to 0.74). Although outcomes were worse in patients withdrawing the biologic, the investigators noted that almost half of the patients maintained a low disease activity after withdrawal. The authors suggested that further research is necessary to identify subgroups for which withdrawal may be more appropriate.

Ankylosing spondylitis (AS)

- The FDA approval of Humira (adalimumab) for the treatment of AS was based on 1 randomized, double-blind, placebo-controlled study (n = 315) in which a significantly greater proportion of patients achieved a 20% improvement in the Assessment of SpondyloArthritis International Society criteria (ASAS 20) (primary endpoint) with adalimumab (58% vs 21% with placebo; $p < 0.001$). A greater than 50% improvement in Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score, a measure of fatigue severity, spinal and peripheral joint pain, localized tenderness, and morning stiffness that is considered clinically meaningful, was detected in 45% of adalimumab-treated patients compared to 16% of placebo-treated patients ($p < 0.001$) at week 12. This response was sustained through week 24, with 42% in the adalimumab group achieving a greater than or equal to 50% improvement in BASDAI score compared to 15% in the placebo group ($p < 0.001$) (*van der Heijde et al 2006*).
- In 2 double-blind, randomized, placebo-controlled trials, the efficacy of Enbrel (etanercept) was evaluated in patients with AS (*Calin et al 2004, Gorman et al 2002*). Etanercept had a significantly greater response to treatment compared to placebo ($p < 0.001$) (*Gorman et al 2002*). More patients achieved an ASAS 20 response compared to placebo ($p < 0.001$) (*Calin et al 2004*). An open-label extension study, evaluating the long-term safety and efficacy of etanercept in patients with AS, was conducted. Safety endpoints included AEs, serious AEs, serious infection, and death while efficacy endpoints included ASAS 20 response, ASAS 5/6 response and partial remission rates. After up to 192 weeks of treatment, the most common AEs were injection site reactions, headache, and diarrhea. A total of 71% of patients were ASAS 20 responders at week 96 and 81% of patients were responders at week 192. The ASAS 5/6 response rates were 61% at week 96 and 60% at week 144, and partial remission response rates were 41% at week 96 and 44% at week 192. Placebo patients who switched to etanercept in the open-label extension trial showed similar patterns of efficacy maintenance (*Davis et al 2008*). A multicenter, randomized, double-blind trial compared etanercept and sulfasalazine in adult patients with active AS that failed treatment with nonsteroidal anti-inflammatory drugs (NSAIDs). A significantly greater proportion of patients treated with etanercept compared to patients treated with sulfasalazine achieved the primary outcome of ASAS 20 at week 16 ($p < 0.0001$). There were also significantly

more patients that achieved ASAS 40 and ASAS 5/6 in the etanercept group compared to the sulfasalazine group ($p < 0.0001$ for both) (*Braun et al 2011*).

- The FDA approval of Simponi (golimumab) for AS was based on a multicenter, randomized, double-blind, placebo-controlled trial in adult patients with active disease for at least 3 months (n = 356). Golimumab with or without a DMARD was compared to placebo with or without a DMARD and was found to significantly improve the signs and symptoms of AS as demonstrated by the percentage of patients achieving an ASAS 20 response at week 14 (*Inman et al 2008*). Sustained improvements in ASAS 20 and ASAS 40 response rates were observed for up to 5 years in an open-label extension trial (*Deodhar et al 2015*). Safety profile through 5 years was consistent with other TNF inhibitors.
- The efficacy of Remicade (infliximab) in the treatment of AS was demonstrated in 12- and 24-week double-blind, placebo-controlled trials. There were significantly more patients that achieved a 50% BASDAI score in the infliximab group compared to the placebo group at 12 weeks ($p < 0.0001$) (*Braun et al 2002*), At 24 weeks, significantly more patients in the infliximab group achieved ASAS 20 compared to the placebo group ($p < 0.001$) (*van der Heijde et al 2005*).
- Inflectra (infliximab-dyyb) was evaluated alongside Remicade (infliximab; European Union formulation) for the treatment of AS in PLANETAS (n = 250), a double-blind, multicenter, randomized trial (*Park et al 2013, Park et al 2016, Park et al 2017*). The primary endpoints related to pharmacokinetic equivalence. Secondary efficacy endpoints supported similar clinical activity between Inflectra and Remicade. An ASAS 20 response was achieved by 72.4% and 70.5% of patients in the Remicade and Inflectra groups, respectively, at 30 weeks, and by 69.4% and 67.0% of patients at 54 weeks. Other disease activity endpoints and a quality-of-life scale were also similar between groups.
    - In the extension study (n = 174) through 102 weeks, all patients received Inflectra. From weeks 54 to 102, the proportion of patients achieving a clinical response was maintained at a similar level to that of the main study in both the maintenance and switch groups and was comparable between groups.
- The efficacy of Cimzia (certolizumab) for the treatment of AS was established in 1 randomized, double-blind, placebo-controlled study (n = 325) in which a significantly greater proportion of patients achieved ASAS 20 response with certolizumab 200 mg every 2 weeks and certolizumab 400 mg every 4 weeks compared to placebo at 12 weeks (*Landewe et at 2014*). Patient-reported outcomes measured by the SF-36, health-related quality of life (HRQoL), and reports of pain, fatigue and sleep were significantly improved with certolizumab in both dose groups (*Sieper et al 2015a*). A Phase 3, randomized, placebo-controlled trial found that 62.5% of patients on certolizumab maintained ASAS 20 response to week 96 in a population of patients with axial spondyloarthritis, which includes AS (*Sieper et al 2015b*).
- The efficacy and safety of Cosentyx (secukinumab) were evaluated in the double-blind, placebo-controlled, randomized MEASURE 1 and 2 studies (*Baeten et al 2015*). MEASURE 1 enrolled 371 patients and MEASURE 2 enrolled 219 patients with active AS with radiologic evidence treated with NSAIDs. Patients were treated with secukinumab 75 or 150 mg SQ every 4 weeks (following IV loading doses) or placebo. The primary outcome, ASAS 20 response at week 16, was significantly higher in the secukinumab 75 mg (60%) and 150 mg (61%) groups compared to placebo (29%, $p < 0.001$ for each dose) for MEASURE 1. For MEASURE 2 at week 16, ASAS 20 responses were seen in 61% of the secukinumab 150 mg group, 41% of the 75 mg group, and 28% of the placebo group ($p < 0.001$ for secukinumab 150 mg vs placebo; $p = 0.10$ for secukinumab 75 mg vs placebo). Common AEs reported included nasopharyngitis, headache, diarrhea, and upper respiratory tract infections. Improvements were observed from week 1 and sustained through week 52. In a long-term extension of MEASURE 1, ASAS 20 response rates were 73.7% with secukinumab 150 mg and 68.0% with 75 mg at week 104 and in MEASURE 2, ASAS 20 response rates were 71.5% with both doses at week 104 (*Braun et al 2017, Marzo-Ortega et al 2017*). In a 3-year extension of MEASURE-1, ASAS 20/40 response rates were 80.2%/61.6% for secukinumab 150 mg and 75.5%/50.0% for secukinumab 75 mg at week 156 (*Baraliakos et al 2017*). Four-year results from MEASURE-1 demonstrated sustained efficacy with ASAS 20/40 response rates of 79.7%/60.8% and 71%/43.5% with secukinumab 150 mg and 75 mg, respectively, at week 208 (*Braun et al 2018*).
- The efficacy and safety of Taltz (ixekizumab) were evaluated in the phase 3 randomized, double-blind, placebo-controlled COAST-V and COAST-W trials. In total, 657 patients were studied in these trials, incuding biologic DMARD-naïve patients in COAST-V and patients with previous inadequate response or intolerance to TNF inhibitors in COAST-W. The primary endpoint in both trials, ASAS 40 response at week 16, was significantly improved with ixekizumab every 4 weeks vs placebo (48% vs 18% in COAST-V, $p < 0.0001$; 25% vs 13% in COAST-W, $p < 0.017$). Common adverse events included nasopharyngitis, upper respiratory tract infection, neutropenia, and infection *(van der Heijde et al 2018[a]; Deodhar et al 2019[a])*. The efficacy and safety of ixekizumab were also recently evaluated in

non-radiographic AS in the 52 week, randomized, double-blind, placebo-controlled, parallel-group, multicenter COAST-X trial (*Deodhar et al 2020*). In COAST-X, 303 adults with non-radiographic AS and an inadequate response or intolerance to NSAIDs were randomly assigned to ixekizumab 80 mg SQ every 4 weeks (n = 96), every 2 weeks (n = 102), or placebo (n = 105). Both primary endpoints were met with ixekizumab: ASAS 40 at week 16 (35% every 4 weeks vs 40% every 2 weeks vs 19% placebo; p = 0.0094 and p = 0.0016, respectively) and ASAS 40 at week 52 (30% every 4 weeks vs 31% every 2 weeks vs 13% placebo; p = 0.0045 and p = 0.0037, respectively). The most common treatment-emergent adverse events were nasopharyngitis and injection site reaction.

- In 2 systematic reviews of TNF blockers for the treatment of AS, patients taking Simponi (golimumab), Enbrel (etanercept), Remicade (infliximab), and Humira (adalimumab) were more likely to achieve ASAS 20 or ASAS 40 responses compared with patients from control groups. The RR of reaching ASAS 20 after 12 or 14 weeks was 2.21 (95% CI, 1.91 to 2.56) (*Machado et al 2013*). After 24 weeks, golimumab, etanercept, infliximab, and adalimumab were more likely to achieve ASAS 40 compared to placebo (*Maxwell et al 2015*). A systematic review and network meta-analysis evaluated biologic agents for the treatment of AS, including adalimumab, etanercept, golimumab, infliximab, Cosentyx (secukinumab), and Actemra (tocilizumab; not FDA-approved for AS) (*Chen et al 2016*). A total of 14 studies were included. Infliximab was ranked best and secukinumab second best for achievement of ASAS 20 response; however, differences among agents were not statistically significant with the exception of infliximab 5 mg compared to tocilizumab (OR, 4.81; 95% credible interval [CrI], 1.43 to 17.04). Safety endpoints were not included in this analysis.

Crohn's disease (CD)

- In a trial evaluating Remicade (infliximab) for induction of remission, significantly more patients achieved remission at 4 weeks with infliximab compared to placebo (p < 0.005) (*Targan et al 1997*). In a placebo-controlled trial, significantly more patients treated with infliximab 5 and 10 mg/kg had a reduction greater than or equal to 50% in the number of fistulas compared to patients treated with placebo (p = 0.002 and p = 0.02, respectively) (*Present et al 1999*). In an open-label trial evaluating the use of infliximab in pediatric CD patients, 88.4% responded to the initial induction regimen, and 58.6% were in clinical remission at week 10 (*Hyams et al 2007*). More recently, an international, randomized, double-blind, phase 3, study revealed biosimilar infliximab (Inflectra) to be non-inferior to infliximab in patients with active CD with similar response rates (*Ye et al 2019*).
- The safety and efficacy of Entyvio (vedolizumab) was demonstrated in 2 trials for CD in patients who responded inadequately to immunomodulator therapy, TNF blockers, and/or corticosteroids. In 1 trial, a higher percentage of Entyvio-treated patients achieved clinical response and remission at week 52 compared to placebo. However, in the second trial, Entyvio did not achieve a statistically significant clinical response or clinical remission over placebo at week 6 (*Sandborn et al 2013, Sands et al 2014*).
- A meta-analysis evaluating Cimzia (certolizumab) use over 12 to 26 weeks for the treatment of CD demonstrated that the agent was associated with an increased rate of induction of clinical response (RR, 1.36; p = 0.004) and remission (RR, 1.95; p < 0.0001) over placebo. However, risk of infection was higher with certolizumab use (*Shao et al 2009*).
- Additionally, Humira (adalimumab), Cimzia (certolizumab) and Remicade (infliximab) demonstrated the ability to achieve clinical response (RR, 2.69; p < 0.00001; RR, 1.74; p < 0.0001 and RR, 1.66; p = 0.0046, respectively) and maintain clinical remission (RR, 1.68; p = 0.000072 with certolizumab and RR, 2.5; p = 0.000019 with infliximab; adalimumab, data not reported) over placebo in patients with CD. Adalimumab and infliximab also had a steroid-sparing effect (*Behm et al 2008*). Other systematic reviews have further demonstrated the efficacy of these agents in CD (*Singh et al 2014, Fu et al 2017*).
- In a systematic review of patients with CD who had failed a trial with Remicade (infliximab), the administration of Humira (adalimumab) was associated with remission rates of 19 to 68% at 1 year. Serious cases of sepsis, cellulitis, and fungal pneumonia occurred in 0 to 19% of patients in up to 4 years of treatment (*Ma et al 2009*).
- A systematic review of 8 randomized clinical trials with TYSABRI (natalizumab) or Entyvio (vedolizumab) for the management of CD evaluated the rates of failure of remission induction (*Chandar et al 2015*). Fewer failures of remission induction were reported with natalizumab and vedolizumab compared to placebo (RR 0.87; 95% CI, 0.84 to 0.91; I^2=0%). The summary effect sizes were similar for both natalizumab (RR 0.86; 95% CI, 0.80 to 0.93) and vedolizumab (RR 0.87; 95% CI, 0.79 to 0.95). No significant difference was detected between the 2 active treatments (p = 0.95). No significant differences between natalizumab and vedolizumab were observed for rates of serious AEs, infections (including serious infections), and treatment discontinuation. Rates of infusion reactions in induction trials were more common with natalizumab over vedolizumab (p = 0.007). Progressive multifocal leukoencephalopathy (PML) has been reported with natalizumab but has not been reported with vedolizumab.

- The use of Stelara (ustekinumab) for the treatment of CD was evaluated in the UNITI-1, UNITI-2, and IM-UNITI studies (*Feagan et al 2016*). All were Phase 3, double-blind, placebo-controlled trials.
    - UNITI-1 (n = 741) was an 8-week induction trial that compared single IV doses of ustekinumab 130 mg IV, weight-based ustekinumab (~6 mg/kg), and placebo in patients with nonresponse or intolerance to ≥ 1 TNF inhibitors. The primary endpoint was clinical response at week 6, which was defined as a decrease from baseline in the CDAI of ≥100 points or a CDAI score of < 150. A clinical response was achieved by 34.4%, 33.7%, and 21.5% of patients in the ustekinumab 130 mg, weight-based ustekinumab, and placebo groups, respectively (p = 0.002 for 130 mg dose vs placebo; p = 0.003 for weight-based dose vs placebo). Benefits were also demonstrated on all major secondary endpoints, which included clinical response at week 8, clinical remission (CDAI < 150) at week 8, and CDAI decrease of ≥70 points at weeks 3 and 6.
    - UNITI-2 (n = 628) had a similar design to UNITI-1, but was conducted in patients with treatment failure or intolerance to immunosuppressants or glucocorticoids (with no requirement for prior TNF inhibitor use). In this trial, a clinical response was achieved by 51.7%, 55.5%, and 28.7% of patients in the ustekinumab 130 mg, weight-based ustekinumab, and placebo groups, respectively (p < 0.001 for both doses vs placebo). Benefits were also demonstrated on all major secondary endpoints.
    - IM-UNITI was a 44-week maintenance trial that enrolled patients completing UNITI-1 and UNITI-2. Of 1,281 enrolled patients, there were 397 randomized patients (primary population); these were patients who had had a clinical response to ustekinumab induction therapy and were subsequently randomized to ustekinumab 90 mg SQ every 8 or 12 weeks or placebo. The primary endpoint, clinical remission at week 44, was achieved by 53.1%, 48.8%, and 35.9% of patients in the ustekinumab every 8 week, ustekinumab every 12 week, and placebo groups, respectively (p = 0.005 for every 8 week regimen vs placebo; p = 0.04 for every 12 week regimen vs placebo). Numerical and/or statistically significant differences for ustekinumab vs placebo were observed on key secondary endpoints including clinical response, maintenance of remission, and glucocorticoid-free remission.

Hidradenitis suppurativa (HS)

- Two 36-week, Phase 3, double-blind, multicenter, placebo-controlled, randomized trials, PIONEER I and II, evaluated Humira (adalimumab) for the treatment of HS (*Kimball et al 2016*). A total of 633 adults (307 in PIONEER I and 326 in PIONEER II) with moderate to severe HS were enrolled. The study consisted of 2 treatment periods; in the first period, patients were randomized to placebo or weekly adalimumab for 12 weeks; in the second period, patients initially assigned to placebo received weekly adalimumab (PIONEER I) or placebo (PIONEER II) for 24 weeks and patients initially assigned to adalimumab were re-randomized to placebo, weekly adalimumab, or every-other-week adalimumab. The adalimumab dosage regimen was 160 mg at week 0, followed by 80 mg at week 2, followed by 40 mg doses starting at week 4.
    - The primary endpoint was HS clinical response (HiSCR) at week 12, defined as at least 50% reduction in total abscess and inflammatory nodule count with no increase in abscess count and no increase in draining fistula count compared to baseline. HiSCR rates at week 12 were significantly higher for the groups receiving adalimumab than for the placebo groups: 41.8% vs 26.0% in PIONEER I (p = 0.003) and 58.9% vs 27.6% in PIONEER II (p < 0.001).
    - Among patients with a clinical response at week 12, response rates in all treatment groups subsequently declined over time. During period 2, there were no significant differences in clinical response rates in either trial between patients randomly assigned to adalimumab at either a weekly dose or an every-other-week dose and those assigned to placebo, regardless of whether the patients had a response at week 12. For patients who received placebo in period 1, 41.4% of those assigned to adalimumab weekly in period 2 (PIONEER I) and 15.9% of those reassigned to placebo in period 2 (PIONEER II) had a clinical response at week 36.
    - The authors noted that the magnitude of improvement with adalimumab treatment was modest compared with adalimumab treatment in other disease states, and patients were unlikely to achieve complete symptom resolution.

Juvenile idiopathic arthritis (JIA)

- In a trial of pediatric patients (6 to 17 years of age) with JIA (extended oligoarticular, polyarticular, or systemic without systemic manifestations), the patients treated with placebo had significantly more flares than the patients treated with Orencia (abatacept) (p = 0.0003). The time to flare was significantly different favoring abatacept (p = 0.0002) (*Ruperto et al 2008*).
- Humira (adalimumab) was studied in a group of patients (4 to 17 years of age) with active polyarticular JIA who had previously received treatment with NSAIDs. Patients were stratified according to MTX use and received 24 mg/m^2

(maximum of 40 mg) of adalimumab every other week for 16 weeks. The patients with an American College of Rheumatology Pediatric 30 (ACR Pedi 30) response at week 16 were randomly assigned to receive adalimumab or placebo in a double-blind method every other week for up to 32 weeks. The authors found that 74% of patients not receiving MTX and 94% of those receiving MTX had an ACR Pedi 30 at week 16. Among those not receiving MTX, flares occurred in 43% receiving adalimumab and 71% receiving placebo (p = 0.03). In the patients receiving MTX, flares occurred in 37 and 65% in the adalimumab and placebo groups, respectively (p = 0.02). ACR Pedi scores were significantly greater with adalimumab than placebo and were sustained after 104 weeks of treatment (*Lovell et al 2008*).

- A double-blind, multicenter, randomized controlled trial compared Humira (adalimumab) and placebo in 46 children ages 6 to 18 years with enthesitis-related arthritis (*Burgos-Vargas et al 2015*). Patients were TNF inhibitor naïve. At week 12, the percentage change from baseline in the number of active joints with arthritis was significantly reduced with adalimumab compared to placebo (-62.6% vs -11.6%, p = 0.039). A total of 7 patients (3 placebo; 4 adalimumab) escaped the study early during the double-blind phase and moved to open-label adalimumab therapy. Analysis excluding these patients produced similar results (adalimumab, -83.3 vs placebo -32.1; p = 0.018). At week 52, adalimumab-treated patients had a mean reduction in active joint count from baseline of 88.7%. A total of 93.5% of patients achieved complete resolution of their swollen joints with a mean of 41 days of adalimumab therapy.
- In a trial involving 69 pediatric patients with active polyarticular JIA despite treatment with NSAIDs and MTX, Enbrel (etanercept) was associated with a significant reduction in flares compared to placebo (28% vs 81%; p = 0.003) (*Lovell et al 2000*). Ninety-four percent of patients who remained in an open-label 4 year extension trial met ACR Pedi 30; C-reactive protein (CRP) levels, articular severity scores, and patient pain assessment scores all decreased. There were 5 cases of serious AEs related to etanercept therapy after 4 years (*Lovell et al 2006*).
- The approval of Actemra (tocilizumab) for the indication of SJIA was based on a randomized, placebo-controlled trial (n = 112). Children age 2 to 17 years of age with active SJIA and inadequate response to NSAIDs and corticosteroids were included in the study. The primary endpoint was ACR 30 and absence of fever at week 12. At week 12, the proportion of patients achieving ACR 30 and absence of fever was significantly greater in the tocilizumab-treated patients compared to the placebo treated patients (85% vs 24%; p < 0.0001) (*De Benedetti et al 2012*). The double-blind, randomized CHERISH study evaluated tocilizumab for JIA flares in patients ages 2 to 17 years with JIA with an inadequate response or intolerance to MTX (*Brunner et al 2015*). Tocilizumab-treated patients experienced significantly fewer JIA flares at week 40 compared to patients treated with placebo (25.6% vs 48.1%; p < 0.0024).
- In 2 trials in patients with SJIA, Ilaris (canakinumab) was more effective at reducing flares than placebo. It also allowed for glucocorticoid dose tapering or discontinuation. More patients treated with canakinumab experienced infections than patients treated with placebo (*Ruperto et al 2012*). Patients enrolled in these trials were eligible for an open-label extension and were followed for 5 years. At 3 years, aJIA-ACR 50/70/90 response rates were 54.8%, 53.7%, and 49.7%, respectively (*Ruperto et al 2018*).
- A meta-analysis of trials evaluating biologics for the treatment of SJIA included 5 trials; 1 each for Kineret (anakinra), Ilaris (canakinumab), and Actemra (tocilizumab), and 2 for rilonacept (not FDA-approved for JIA and not included in this review) (*Tarp et al 2016*). The primary endpoint, the proportion of patients achieving a modified ACR Pedi 30 response, was superior to placebo for all agents, but did not differ significantly among anakinra, canakinumab, and tocilizumab. However, comparisons were based on low-quality, indirect evidence and no firm conclusions can be drawn on their relative efficacy. No differences among drugs for serious AEs were demonstrated.

Plaque psoriasis (PsO)

- In a randomized, double-blind, double-dummy trial, Humira (adalimumab) was compared to MTX and placebo in patients with moderate to severe PsO despite treatment with topical agents. The primary outcome was the proportion of patients that achieved Psoriasis Area and Severity Index (PASI) 75 at 16 weeks. Significantly more patients in the adalimumab group achieved the primary endpoint compared to patients in the MTX (p < 0.001) and placebo (p < 0.001) groups, respectively (*Saurat et al 2008*).
- More than 2,200 patients were enrolled in 2 published, pivotal, phase III trials that served as the primary basis for the FDA approval of Stelara (ustekinumab) in PsO. PHOENIX 1 and PHOENIX 2 enrolled patients with moderate to severe PsO to randomly receive ustekinumab 45 mg, 90 mg or placebo at weeks 0, 4, and every 12 weeks thereafter (*Leonardi et al 2008, Papp et al 2008, Langley et al 2015*). In PHOENIX 1, patients who were initially randomized to ustekinumab at week 0 and achieved long-term response (at least PASI 75 at weeks 28 and 40) were re-randomized at week 40 to maintenance ustekinumab or withdrawal from treatment. Patients in the 45 mg ustekinumab and 90 mg ustekinumab groups had higher proportion of patients achieving PASI 75 compared to patients in the placebo group at week 12 (p < 0.0001 for both). PASI 75 response was better maintained to at least 1 year in those receiving

maintenance ustekinumab than in those withdrawn from treatment at week 40 ($p < 0.0001$) (*Leonardi et al 2008*). In PHOENIX 2, the primary endpoint (the proportion of patients achieving a PASI 75 response at week 12) was achieved in significantly more patients receiving ustekinumab 45 and 90 mg compared to patients receiving placebo ($p < 0.0001$). Partial responders were re-randomized at week 28 to continue dosing every 12 weeks or escalate to dosing every 8 weeks. More partial responders at week 28 who received 90 mg every 8 weeks achieved PASI 75 at week 52 than did those who continued to receive the same dose every 12 weeks. There was no such response to changes in dosing intensity in partial responders treated with 45 mg. AEs were similar between groups (*Papp et al 2008*). A total of 70% (849 of 1212) of ustekinumab-treated patients completed therapy through week 244. At week 244, the proportions of patients initially randomized to ustekinumab 45 mg and 90 mg who achieved PASI 75 were 76.5% and 78.6%, respectively. A total of 50.0% and 55.5% of patients, respectively, achieved PASI 90 (*Langley et al 2015*).

- In a study comparing Enbrel (etanercept) and Stelara (ustekinumab), a greater proportion of PsO patients achieved the primary outcome (PASI 75 at week 12) with ustekinumab 45 (67.5%) and 90 mg (73.8%) compared to etanercept 50 mg (56.8%; $p = 0.01$ vs ustekinumab 45 mg; $p < 0.001$ vs ustekinumab 90 mg). In this trial, etanercept therapy was associated with a greater risk of injection site erythema (14.7% vs 0.7% of all ustekinumab patients) (*Griffiths et al 2010).*
- Approval of Otezla (apremilast) for moderate to severe PsO was based on results from the ESTEEM trials. In the trials, 1,257 patients with moderate to severe PsO were randomized 2:1 to apremilast 30 mg twice daily (with a titration period) or placebo. The primary endpoint was the number of patients with a 75% improvement on the PASI 75. In ESTEEM 1, significantly more patients receiving apremilast achieved PASI 75 compared to placebo (33.1% vs 5.3%; $p < 0.0001$) at 16 weeks. In ESTEEM 2, significantly more patients receiving apremilast also achieved PASI 75 compared to placebo (28.8% vs 5.8%; $p < 0.0001$) at 16 weeks (*Papp et al 2015, Paul et al 2015a*).
    - Additional analyses of the ESTEEM trials have been published. In 1 analysis (*Thaçi et al 2016*), the impact of apremilast on HRQoL, general function, and mental health was evaluated using patient-reported outcome assessments. The study demonstrated improvement with apremilast vs placebo, including improvements on the dermatology life quality index (DLQI) and SF-36 mental component summary (MCS) that exceeded minimal clinically important differences. In another analysis (*Rich et al 2016*), effects of apremilast on difficult-to-treat nail and scalp psoriasis were evaluated. At baseline in ESTEEM 1 and ESTEEM 2, respectively, 66.1% and 64.7% of patients had nail psoriasis and 66.7% and 65.5% had moderate to very severe scalp psoriasis. At week 16, apremilast produced greater improvements in Nail Psoriasis Severity Index (NAPSI) score vs placebo; greater NAPSI-50 response (50% reduction from baseline in target nail NAPSI score) vs placebo; and greater response on the Scalp Physician Global Assessment (ScPGA) vs placebo. Improvements were generally maintained over 52 weeks in patients with a PASI response at week 32.
- Cosentyx (secukinumab) was evaluated in 2 large, phase 3, double-blind trials in patients with moderate to severe PsO. The co-primary endpoints were the proportions of patients achieving PASI 75 and the proportions of patients with clear or almost clear skin (score 0 or 1) on the modified investigator's global assessment (IGA) at 12 weeks.
    - In ERASURE (n = 738), 81.6%, 71.6%, and 4.5% of patients achieved PASI 75 with secukinumab 300 mg, secukinumab 150 mg, and placebo, respectively, and 65.3%, 51.2%, and 2.4% achieved a score of 0 or 1 on the IGA (*Langley et al 2014*).
    - In FIXTURE (n = 1306), 77.1%, 67%, 44%, and 4.9% of patients achieved PASI 75 with secukinumab 300 mg, secukinumab 150 mg, Enbrel (etanercept) at FDA-recommended dosing, and placebo, respectively, and 62.5%, 51.1%, 27.2%, and 2.8% achieved a score of 0 or 1 on the IGA (*Langley et al 2014*).
- Two smaller, phase 3, double-blind, placebo-controlled trials evaluated Cosentyx (secukinumab) given by prefilled syringe (FEATURE) or auto-injector/pen (JUNCTURE). Again, co-primary endpoints were the proportions of patients achieving PASI 75 and obtaining a score of 0 or 1 on the modified IGA at 12 weeks.
    - In FEATURE (n = 177), 75.9%, 69.5%, and 0% of patients achieved PASI 75 with secukinumab 300 mg, secukinumab 150 mg, and placebo, respectively, and 69%, 52.5%, and 0% achieved a score of 0 or 1 on the IGA (*Blauvelt et al 2015*).
    - In JUNCTURE (n = 182), 86.7%, 71.7%, and 3.3% of patients achieved PASI 75 with secukinumab 300 mg, secukinumab 150 mg, and placebo, respectively, and 73.3%, 53.3%, and 0% achieved a score of 0 or 1 on the IGA (*Paul et al 2015b*).
- Secondary endpoints, including the proportions of patients demonstrating a reduction of 90% or more on the PASI (PASI 90), a reduction of 100% (PASI 100), and change in the DLQI further support the efficacy of Cosentyx (secukinumab) (*Blauvelt et al 2015, Langley et al 2014, Paul et al 2015b*).

- In the CLEAR study, Cosentyx (secukinumab) 300 mg SQ every 4 weeks and Stelara (ustekinumab) 45 mg or 90 mg SQ (based on body weight) every 12 weeks were compared for safety and efficacy in a double-blind, randomized controlled trial in 676 patients with moderate to severe PsO (*Thaçi et al 2015*). The primary endpoint, proportion of patients achieving PASI 90 at week 16, was significantly higher with secukinumab compared to ustekinumab (79% vs 57.6%; $p < 0.0001$). Achievement of PASI 100 response at week 16 was also significantly higher with secukinumab over ustekinumab (44.3% vs 28.4%; $p < 0.0001$). Infections and infestations were reported in 29.3% of secukinumab- and 25.3% of ustekinumab-treated patients. Most infections were not serious and were managed without discontinuation. The most commonly reported AEs included headache and nasopharyngitis. Serious AEs were reported in 3% of each group.
- Cosentyx (secukinumab) and Stelara (ustekinumab) were also compared in the 16-week randomized, double-blind CLARITY trial, which included 1102 patients with moderate to severe PsO. The co-primary endpoints were proportion of patients achieving PASI 90 response at week 12 and modified IGA score of 0/1 at week 12. Secukinumab was found be to superior to ustekinumab for both PASI 90 response (66.5% vs 47.9%; $p < 0.0001$) and modified IGA score of 0/1 (72.3% vs 55.3%; $p < 0.0001$) (*Bagel et al 2018*).
- A meta-analysis of 7 Phase 3 clinical trials demonstrated the efficacy of Cosentyx (secukinumab) vs placebo and vs Enbrel (etanercept) in patients with PsO (*Ryoo et al 2016*). The ORs for achieving PASI 75 and for achieving IGA 0 or 1 were both 3.7 for secukinumab vs etanercept. Secukinumab 300 mg was significantly more effective than 150 mg. Secukinumab was well-tolerated throughout the 1-year trials.
- The use of Taltz (ixekizumab) for the treatment of PsO was evaluated in the UNCOVER-1, UNCOVER-2, and UNCOVER-3 trials. All were Phase 3, double-blind, randomized trials.
    - UNCOVER-1 (n = 1296) compared ixekizumab 160 mg loading dose then 80 mg every 2 weeks, ixekizumab 160 mg loading dose then 80 mg every 4 weeks, and placebo (*Gordon et al 2016, Taltz product dossier 2016*). Co-primary endpoints were the proportion of patients achieving PASI 75 and the proportion of patients achieving a physician's global assessment (PGA) score of 0 or 1 (clear or almost clear) at week 12. In the ixekizumab every 2 week, ixekizumab every 4 week, and placebo groups, PASI 75 was achieved by 89.1%, 82.6%, and 3.9% of patients, respectively ($p < 0.001$ for both doses vs placebo), and PGA 0 or 1 was achieved by 81.8%, 76.4%, and 3.2% of patients, respectively ($p < 0.001$ for both doses vs placebo). Improvements for ixekizumab vs placebo were also seen in secondary endpoints including PASI 90, PASI 100, PGA 0, and change in DLQI.
    - UNCOVER-2 (n = 1224) compared ixekizumab 160 mg loading dose then 80 mg every 2 weeks, ixekizumab 160 mg then 80 mg every 4 weeks, etanercept 50 mg twice weekly, and placebo (*Griffiths et al 2015*). Co-primary endpoints were the proportion of patients achieving PASI 75 and the proportion of patients achieving a PGA 0 or 1 at week 12. The proportions of patients achieving PASI 75 were 89.7%, 77.5%, 41.6%, and 2.4% in the ixekizumab every 2 week, ixekizumab every 4 week, etanercept, and placebo groups, respectively ($p < 0.0001$ for all active treatments vs placebo and for both ixekizumab arms vs etanercept). The proportions of patients achieving PGA 0 or 1 were 83.2%, 72.9%, 36%, and 2.4% in the ixekizumab every 2 week, ixekizumab every 4 week, etanercept, and placebo groups, respectively ($p < 0.0001$ for all active treatments vs placebo and for both ixekizumab arms vs etanercept). Improvements were also greater for ixekizumab vs placebo, etanercept vs placebo, and ixekizumab vs etanercept for all secondary endpoints including PGA 0, PASI 90, PASI 100, and DLQI.
    - UNCOVER-3 (n = 1346) had the same treatment groups and primary and secondary endpoints as UNCOVER-2 (*Griffiths et al 2015*). The proportions of patients achieving PASI 75 were 87.3%, 84.2%, 53.4%, and 7.3% in the ixekizumab every 2 week, ixekizumab every 4 week, etanercept, and placebo groups, respectively ($p < 0.0001$ for all active treatments vs placebo and for both ixekizumab arms vs etanercept). The proportions of patients achieving PGA 0 or 1 were 80.5%, 75.4%, 41.6%, and 6.7% in the ixekizumab every 2 week, ixekizumab every 4 week, etanercept, and placebo groups, respectively ($p < 0.0001$ for all active treatments vs placebo and for both ixekizumab arms vs etanercept). Improvements were also greater for ixekizumab vs placebo, etanercept vs placebo, and ixekizumab vs etanercept for all secondary endpoints including PGA 0, PASI 90, PASI 100, and DLQI.
    - Results through week 60 for UNCOVER-1, UNCOVER-2, and UNCOVER-3 have been reported (*Gordon et al 2016*). At week 12 in UNCOVER-1 and UNCOVER-2, patients responding to ixekizumab (PGA 0 or 1) were re-randomized to receive ixekizumab 80 mg every 4 weeks, ixekizumab 80 mg every 12 weeks, or placebo through week 60. Among the patients who were randomly reassigned at week 12 to receive 80 mg of ixekizumab every 4 weeks (the approved maintenance dosing), 80 mg of ixekizumab every 12 weeks, or

placebo, a PGA score of 0 or 1 was maintained by 73.8%, 39.0%, and 7.0% of the patients, respectively, and high rates were maintained or attained for additional measures such as PASI 75, PASI 90, and PASI 100 (pooled data for UNCOVER-1 and UNCOVER-2). At week 12 in UNCOVER-3, patients entered a long-term extension period in which they received ixekizumab 80 mg every 4 weeks through week 60. At week 60, at least 73% had a PGA score of 0 or 1 and at least 80% had a PASI 75 response. In addition, most patients had maintained or attained PASI 90 or PASI 100 at week 60.

- The IXORA-Q study (n = 149) evaluated the efficacy of Taltz (ixekizumab) to placebo in patients with moderate-to-severe genital psoriasis. At week 12, ixekizumab was superior to placebo for the primary endpoint of the proportion of patients achieving a score of 0 or 1 on the static PGA of genitalia (73% vs 8%, p < 0.001) (*Ryan et al 2018*).
- The IXORA-S study (n = 676) was a head-to-head study that compared Taltz (ixekizumab) (160 mg LD, then 80 mg every 2 weeks for 12 weeks, then 80 mg every 4 weeks) to Stelara (ustekinumab) (45 mg or 90 mg weight-based dosing per label) (*Reich et al 2017[b]).* The primary endpoint, PASI 90 response at week 12, was achieved by 72.8% and 42.2% of patients in the ixekizumab and ustekinumab groups, respectively (p < 0.001); superior efficacy of ixekizumab was maintained through week 24. Response rates for PASI 75, PASI 100, and PGA 0 or 1 also favored ixekizumab over ustekinumab (adjusted p < 0.05).
- The use of Siliq (brodalumab) for the treatment of PsO was evaluated in the AMAGINE-1, AMAGINE-2, and AMAGINE-3 trials. All were Phase 3, double-blind, randomized trials.
    - AMAGINE-1 (n = 661) compared brodalumab 210 mg, brodalumab 140 mg, and placebo; each treatment was given at weeks 0, 1, and 2, followed by every 2 weeks to week 12 (*Papp et al 2016*). This 12-week induction phase was followed by a withdrawal/retreatment phase through week 52: patients receiving brodalumab who achieved PGA 0 or 1 (PGA success) were re-randomized to the placebo or induction dose, and patients randomized to brodalumab with PGA ≥ 2 and those initially receiving placebo received brodalumab 210 mg every 2 weeks. Patients in the withdrawal phase who had disease recurrence (PGA ≥ 3) between weeks 16 and 52 were retreated with their induction doses of brodalumab. Co-primary endpoints were the proportion of patients achieving PASI 75 and the proportion of patients achieving PGA success at week 12. PASI 75 was achieved by 83% (95% CI, 78 to 88), 60% (95% CI, 54 to 67), and 3% (95% CI, 1 to 6) of patients in the brodalumab 210 mg, brodalumab 140 mg, and placebo groups, respectively; PGA success was achieved by 76% (95% CI, 70 to 81), 54% (95% CI, 47 to 61), and 1% (95% CI, 0 to 4), respectively (p < 0.001 for all comparisons of brodalumab vs placebo). Differences in key secondary endpoints at week 12 also favored brodalumab vs placebo, including PASI 90, PASI 100, and PGA 0. In the randomized withdrawal phase, high response rates were maintained in those who continued brodalumab, while most patients re-randomized to placebo experienced return of disease (but were able to recapture disease control with retreatment).
    - AMAGINE-2 (n = 1831) and AMAGINE-3 (n = 1881) were identical in design and compared brodalumab 210 mg, brodalumab 140 mg, Stelara (ustekinumab), and placebo (*Lebwohl et al 2015*). Brodalumab was given at weeks 0, 1, and 2, followed by every 2 weeks to week 12. Ustekinumab was given in weight-based doses per its FDA-approved labeling. At week 12, patients receiving brodalumab were re-randomized to receive brodalumab at a dose of 210 mg every 2 weeks or 140 mg every 2, 4, or 8 weeks; patients receiving ustekinumab continued ustekinumab; and patients receiving placebo were switched to brodalumab 210 mg every 2 weeks; maintenance continued though week 52. The primary endpoints included a comparison of both brodalumab doses vs placebo with regard to the proportion of patients achieving PASI 75 and the proportion of patients achieving PGA success (PGA 0 or 1) at week 12, as well as a comparison of brodalumab 210 mg vs ustekinumab with regard to the proportion of patients achieving PASI 100 at week 12.
        - In AMAGINE-2, the proportion of patients achieving PASI 75 was 86% (95% CI, 83 to 89), 67% (95% CI, 63 to 70), 70% (95% CI, 65 to 75), and 8% (95% CI, 5 to 12) in the brodalumab 210 mg, brodalumab 140 mg, ustekinumab, and placebo groups, respectively, and the proportion of patients achieving PGA success was 79% (95% CI, 75 to 82), 58% (95% CI, 54 to 62), 61% (95% CI, 55 to 67), and 4% (95% CI, 2 to 7), respectively (p < 0.001 for all comparisons of brodalumab vs placebo). The proportion of patients achieving PASI 100 was 44% (95% CI, 41 to 49), 26% (95% CI, 22 to 29), 22% (95% CI, 17 to 27), and 1% (95% CI, 0 to 2), respectively (p < 0.001 for both brodalumab doses vs placebo and for brodalumab 210 mg vs ustekinumab; p = 0.08 for brodalumab 140 mg vs ustekinumab).
        - In AMAGINE-3, the proportion of patients achieving PASI 75 was 85% (95% CI, 82 to 88), 69% (95% CI, 65 to 73), 69% (95% CI, 64 to 74), and 6% (95% CI, 4 to 9) in the brodalumab 210 mg, brodalumab 140 mg, ustekinumab, and placebo groups, respectively, and the proportion of patients

achieving PGA success was 80% (95% CI, 76 to 83), 60% (95% CI, 56 to 64), 57% (95% CI, 52 to 63), and 4% (95% CI, 2 to 7), respectively ($p < 0.001$ for all comparisons of brodalumab vs placebo). The proportion of patients achieving PASI 100 was 37% (95% CI, 33 to 41), 27% (95% CI, 24 to 31), 19% (95% CI, 14 to 23), and 0.3% (95% CI, 0 to 2), respectively ($p < 0.001$ for both brodalumab doses vs placebo and for brodalumab 210 mg vs ustekinumab; $p = 0.007$ for brodalumab 140 mg vs ustekinumab).

- In both studies, the 2 brodalumab doses were superior to placebo with regard to all key secondary endpoints. Patients receiving brodalumab 210 mg throughout the induction and maintenance phases demonstrated an increase in PASI response rates through week 12 and a stabilization during weeks 16 to 52. Based on PGA success rates, maintenance with brodalumab 210 mg or 140 mg every 2 weeks was superior to the use of the less frequent maintenance regimens, and the 210 mg regimen was superior to the 140 mg regimen.

- The use of Tremfya (guselkumab) for the treatment of moderate to severe PsO was evaluated in the VOYAGE 1, VOYAGE 2, NAVIGATE, and ECLIPSE trials. All were phase 3, double-blind, randomized trials.
  - Patients in both VOYAGE 1 and VOYAGE 2 were initially assigned to receive guselkumab (100 mg at weeks 0 and 4, then every 8 weeks), placebo, or Humira (adalimumab) (80 mg at week 0, 40 mg at week 1, then every 2 weeks). Patients in the placebo group were switched to guselkumab at week 16. The coprimary endpoints included the proportion of patients achieving an IGA score of 0 or 1 at week 16 as well as the proportion of patients achieving a PASI 90 response at week 16 in the guselkumab group compared with placebo. Comparisons between guselkumab and adalimumab were assessed as secondary endpoints at weeks 16, 24, and 48. To evaluate maintenance and durability of response in VOYAGE 2, subjects randomized to guselkumab at week 0 and who were PASI 90 responders at week 28 were re-randomized to either continue treatment with guselkumab every 8 weeks or be withdrawn from therapy (ie, receive placebo).
    - In VOYAGE 1 (n = 837), IGA 0 or 1 was achieved in more patients treated with guselkumab (85.1%) compared to placebo (6.9%) at week 16 ($p < 0.001$), and a higher percentage of patients achieved PASI 90 with guselkumab (73.3%) compared to placebo (2.9%; $p<0.001$) (*Blauvelt et al 2017*). Additionally, IGA 0 or 1 was achieved in more patients with guselkumab vs adalimumab at week 16 (85.1% vs 65.9%), week 24 (84.2% vs. 61.7%), and week 48 (80.5% vs 55.4%; $p < 0.001$). PASI 90 score was also achieved in a higher percentage of patients with guselkumab vs adalimumab at week 16 (73.3% vs 49.7%), week 24 (80.2% vs 53%), and week 48 (76.3% vs 47.9%; $p < 0.001$).
    - In VOYAGE 2 (n = 992), IGA 0 or 1 and PASI 90 were achieved by a higher proportion of patients who received guselkumab (84.1% and 70%) vs placebo (8.5% and 2.4%) ($p < 0.001$ for both comparisons). At week 16, IGA score of 0 or 1 and PASI 90 were achieved in more patients with guselkumab (84.1% and 70%) vs adalimumab (67.7% and 46.8%) ($p < 0.001$). PASI 90 was achieved in 88.6% of patients who continued on guselkumab vs 36.8% of patients who were rerandomized to placebo at week 48. In patients who were nonresponders to adalimumab and switched to guselkumab, PASI 90 was achieved by 66.1% of patients.
  - In NAVIGATE (n = 871), patients were assigned to open-label ustekinumab 45 or 90 mg at weeks 0 and 4 (*Langley et al 2017*). Patients with IGA 0 or 1 at week 16 were continued on ustekinumab, while patients with an inadequate response to ustekinumab at week 16 (IGA ≥ 2) were randomized to blinded guselkumab 100 mg or ustekinumab. Patients treated with guselkumab had a higher mean number of visits with IGA of 0 or 1 and ≥ 2-grade improvement (relative to week 16) compared to randomized ustekinumab from week 28 to 40 (1.5 vs 0.7; $p < 0.001$). A higher proportion of patients achieved IGA of 0 or 1 with ≥ 2 grade improvement at week 28 with guselkumab (31.1%) vs randomized ustekinumab (14.3%; $p = 0.001$); at week 52, 36.2% of guselkumab-treated patients achieved this response vs 17.3% of the ustekinumab-treated patients. The proportion of patients with PASI 90 response at week 28 was 48.1% for the guselkumab group vs 22.6% for the ustekinumab group ($p \leq 0.001$).
  - In ECLIPSE (n = 1048), patients with moderate-to-severe plaque PsO were randomly assigned to Tremfya (guselkumab) 100 mg SQ at weeks 0 and 4 and then every 8 weeks (n = 534) or Cosentyx (secukinumab) 300 mg SQ at weeks 0, 1, 2, 3, and 4, and then every 4 weeks (n = 514) (*Reich et al 2019[a]*). Results revealed that the proportion of patients with a PASI 90 response at week 48 was greater in the guselkumab group as compared to the secukinumab group (84% vs 70%; $p < 0.0001$). The proportion of patients with adverse events, infections, and serious adverse events were similar between the treatments.

- The approval of Ilumya (tildrakizumab-asmn) was based on 2 randomized, double-blind, multicenter, phase 3 trials: reSURFACE1 (772 patients) and reSURFACE2 (1,090 patients). Enrolled adult patients with moderate-to-severe chronic PsO received tildrakizumab-asmn 200 mg, tildrakizumab-asmn 100 mg, or placebo in both studies; reSURFACE 2 also included an Enbrel (etanercept) arm. Only the tildrakizumab-asmn 100 mg dose was approved by the FDA. The coprimary endpoints included the proportion of patients achieving PASI 75 and PGA response (score of 0 or 1 with ≥ 2 reduction from baseline) at week 12 (*Reich et al 2017[a]*).
    - In reSURFACE 1, PASI 75 response was achieved by 64% and 6% of the tildrakizumab-asmn 100 mg and placebo arms at week 12, respectively; a PGA response was achieved by 58% vs 7% of the tildrakizumab-asmn 100 mg and placebo groups, respectively ($p < 0.0001$ for both comparisons).
    - In reSURFACE 2, PASI 75 response was achieved by 61% and 6% of the tildrakizumab-asmn 100 mg and placebo arms, respectively; a PGA response was achieved by 55% vs 4% of the tildrakizumab-asmn 100 mg and placebo groups, respectively ($p < 0.0001$ for both comparisons). A higher proportion of patients in the tildrakizumaz 100 mg group achieved PASI 75 vs etanercept (61% vs 48%, respectively; $p = 0.001$), but the rates of PGA responses did not differ significantly between groups (55% vs 48%, respectively; $p = 0.0663$).
- The approval of Skyrizi (risankizumab-rzaa) was based on 4 randomized, double-blind, multicenter trials. In two replicate placebo- and active-controlled trials (UltIMMa-1 and -2), patients with moderate to severe chronic PsO (n = 997) assigned to risankizumab 150 mg every 12 weeks experienced significantly higher rates of PASI 90 response at week 16 (75.3% and 74.8% in UltIMMa-1 and -2, respectively) vs patients assigned to placebo (4.9% and 2.0% in UltIMMa-1 and -2, respectively) and Stelara (ustekinumab) 45 or 90 mg (42.0% and 47.5% in UltIMMa-1 and -2, respectively; $p < 0.0001$ for both comparisons from both trials) *(Gordon et al 2018)*. In an active controlled trial (IMMvent) in patients with moderate-to-severe chronic PsO (n = 605), PASI 90 was achieved by 72% of patients receiving risankizumab-rzaa vs 47% receiving Humira (adalimumab) ($p < 0.0001$) at week 16 (*Reich et al 2019[b]*). In a trial with a randomized withdrawal and retreatment design (IMMhance) (n = 507), PASI 90 was achieved by 73.2% of risankizumab-rzaa-treated patients vs 2.0% of placebo-treated patients ($p < 0.001$) at week 16 (*Langley et al 2019)*
- For most immunomodulators that are FDA-approved for the treatment of PsO, the indication is limited to adults. In 2016, Enbrel (etanercept) received FDA approval for treatment of PsO in pediatric patients age ≥ 4 years. Limited information from published trials is also available on the use of Stelara (ustekinumab) in adolescent patients (age 12 to 17 years).
    - A 48-week, double-blind, placebo-controlled trial (n = 211) evaluated the use of etanercept in patients 4 to 17 years of age with moderate-to-severe PsO (*Paller et al 2008*). Patients received etanercept 0.8 mg SQ once weekly or placebo for 12 weeks, followed by 24 weeks of open-label etanercept; 138 patients underwent a second randomization to placebo or etanercept at week 36 to investigate effects of withdrawal and retreatment. The primary endpoint, PASI 75 at week 12, was achieved by 57% and 11% of patients receiving etanercept and placebo, respectively. A significantly higher proportion of patients in the etanercept group than in the placebo group achieved PASI 90 (27% vs 7%) and a PGA of 0 or 1 (53% vs 13%) at week 12 ($p < 0.001$). During the withdrawal period from week 36 to week 48, response was lost by 29 of 69 patients (42%) assigned to placebo at the second randomization. Four serious AEs (including 3 infections) occurred in 3 patients during treatment with open-label etanercept; all resolved without sequelae. The authors concluded that etanercept significantly reduced disease severity in this population. Results of a 5-year, open-label extension study (n = 182) demonstrated that etanercept was generally well tolerated and efficacy was maintained in those who remained in the study for up to 264 weeks (69 of 181 patients) (*Paller et al 2016*).
    - A 52-week, double-blind, placebo-controlled trial (n = 110) evaluated the use of ustekinumab in patients 12 to 17 years of age with moderate-to-severe PsO (*Landells et al 2015*). Patients received a weight-based standard dose (SD), a half-strength dose (HSD), or placebo. The primary endpoint, the proportion of patients achieving a PGA 0 or 1 at week 12, was significantly greater in the SD (69.4%) and HSD (67.6%) groups vs placebo (5.4%) ($p < 0.001$ for both doses vs placebo). The proportions of patients achieving PASI 75 at this time point were 80.6%, 78.4%, and 10.8% in the SD, HSD, and placebo groups, respectively ($p < 0.001$ for both doses vs placebo), and the proportions of patients achieving PASI 90 were 61.1%, 54.1%, and 5.4% in the SD, HSD, and placebo groups, respectively ($p < 0.001$ for both doses vs placebo). In both groups, the proportions of patients achieving these endpoints were maintained from week 12 through week 52. The authors concluded that ustekinumab appears to be a viable treatment option for moderate-to-severe PsO in the adolescent population. The standard dose provided a response comparable to that in adults with no unexpected AEs through 1 year of treatment.

- Combination therapy is commonly utilized, such as with different topical therapies, systemic plus topical therapies, and combinations of certain systemic therapies with phototherapy (*Feldman 2015*). Combinations of different systemic therapies have not been adequately studied; however, there are some data to show that combined therapy with Enbrel (etanercept) plus MTX may be beneficial for therapy-resistant patients (*Busard et al 2014; Gottlieb et al 2012*).
- In a meta-analysis evaluating the efficacy and tolerability of biologic and nonbiologic systemic treatments for moderate to severe PsO, Humira (adalimumab) use was associated with a risk difference of 64% compared to placebo in achieving a PASI 75 response ($p < 0.00001$) while Enbrel (etanercept) 25 and 50 mg twice weekly were associated with a risk difference of 30 and 44% compared to placebo ($p < 0.00001$ for both strengths vs placebo). The Remicade (infliximab) group had the greatest response with a risk difference of 77% compared to the placebo group ($p < 0.0001$). The withdrawal rate was 0.5% with adalimumab, 0.4 to 0.5% with etanercept and 1.3% with infliximab (*Schmitt et al 2008*).
- Another meta-analysis evaluated the efficacy and safety of long-term treatments (≥24 weeks) for moderate-to-severe PsO (*Nast et al 2015a*). A total of 25 randomized trials (n = 11,279) were included. Compared to placebo, RRs for achievement of PASI 75 were 13.07 (95% CI, 8.60 to 19.87) for Remicade (infliximab), 11.97 (95% CI, 8.83 to 16.23) for Cosentyx (secukinumab), 11.39 (95% CI, 8.94 to 14.51) for Stelara (ustekinumab), 8.92 (95% CI, 6.33 to 12.57) for Humira (adalimumab), 8.39 (95% CI, 6.74 to 10.45) for Enbrel (etanercept), and 5.83 (95% CI, 2.58 to 13.17) for Otezla (apremilast). Head-to-head studies demonstrated better efficacy for secukinumab and infliximab vs etanercept, and for infliximab vs MTX. The biologics and apremilast also had superior efficacy vs placebo for endpoints of PASI 90 and PGA 0 or 1. The investigators stated that based on available evidence, infliximab, secukinumab, and ustekinumab are the most efficacious long-term treatments, but noted that additional head-to-head comparisons and studies on safety and patient-related outcomes are desirable.
- In a meta-analysis of 41 RCTs that used hierarchical clustering to rate efficacy and tolerability, Humira (adalimumab), Cosentyx (secukinumab), and Stelara (ustekinumab) were characterized by high efficacy and tolerability, Remicade (infliximab) and Taltz (ixekizumab) were characterized by high efficacy and poorer tolerability, and Enbrel (etanercept), MTX, and placebo were characterized by poorer efficacy and moderate tolerability in patients with PsO (*Jabbar-Lopez et al 2017*).
- A Cochrane review evaluated biologics in patients with moderate to severe PsO in 140 studies (*Sbidian E et al 2020*). The network meta-analysis showed that compared to placebo, the biologics infliximab, ixekizumab, risankizumab, guselkumab, secukinumab, and brodalumab were the best choices for achieving PASI 90 in patients with moderate-to-severe PsO on the basis of moderate- to high-certainty evidence.

Psoriatic arthritis (PsA)

- In 2 trials, PsA patients receiving Humira (adalimumab) 40 mg every other week achieved an ACR 20 at a higher rate than with placebo. Thirty-nine percent in the active treatment group vs 16% in the placebo group achieved this endpoint by week 12 ($p = 0.012$) in a trial (n = 100); while 58 and 14% of patients, respectively, achieved this endpoint in a second trial ($p < 0.001$) (*Genovese et al 2007, Mease et al 2005*). Adalimumab use was also associated with an improvement in structural damage, as measured by the mTSS, compared to those receiving placebo (-0.2 vs 1; $p < 0.001$) (*Mease et al 2005*).
- In a 12-week trial in adult patients with PsA despite NSAID therapy, 87% of Enbrel (etanercept) treated patients met PsA response criteria, compared to 23% of those on placebo ($p < 0.0001$). A PASI 75 improvement and ACR 20 response were detected in 26 and 73% of etanercept-treated patients vs 0 ($p = 0.0154$) and 13% ($p < 0.0001$) of placebo-treated patients (*Mease et al 2000*). In a second trial, the mean annualized rate of change in the mTSS with Enbrel (etanercept) was -0.03 unit, compared to 1 unit with placebo ($p < 0.0001$). At 24 weeks, 23% of etanercept patients eligible for PsO evaluation achieved at least a PASI 75, compared to 3% of placebo patients ($p = 0.001$). Additionally, HAQ scores were significantly improved with etanercept (54%) over placebo (6%; $p < 0.0001$). Injection site reaction occurred at a greater rate with etanercept than placebo (36% vs 9%; $p < 0.001$) (*Mease et al 2004*).
- A 24-week trial of adult patients with PsA randomized 851 patients to oral methotrexate monotherapy, etanercept monotherapy, or combination therapy. At week 24, ACR 20 response rates were significantly greater with etanercept monotherapy (60.9%) compared to methotrexate monotherapy (50.7%), but combination therapy (65%) did not provide any significant improvement over etanercept monotherapy (*Mease et al 2019*).
- The FDA approval of Simponi (golimumab) for PsA was based on the GO-REVEAL study, a multicenter, randomized, double-blind, placebo-controlled trial in adult patients with moderate to severely active PsA despite NSAID or DMARD therapy (n = 405). Golimumab with or without MTX compared to placebo with or without MTX, resulted in significant improvement in signs and symptoms as demonstrated by the percentage of patients achieving a ACR 20 response at

week 14. The ACR responses observed in the golimumab-treated groups were similar in patients receiving and not receiving concomitant MTX therapy (*Kavanaugh et al 2009*).
    - Subcutaneous golimumab for patients with active PsA demonstrated safety and efficacy over 5 years in the long-term extension of the GO-REVEAL study. Approximately one-half of patients took MTX concurrently. ACR 20 response rates at year 5 were 62.8 to 69.9% for golimumab SQ 50 or 100 mg every 4 weeks (*Kavanaugh et al 2014b*).
    - Post-hoc analyses of the 5-year GO-REVEAL results evaluated the relationship between achieving minimal disease activity (MDA; defined as the presence of ≥5 of 7 PsA outcomes measures [≤1 swollen joint, ≤1 tender joint, PASI ≤1, patient pain score ≤15, patient global disease activity score ≤20, HAQ disability index [HAQ DI] ≤0.5, and ≤1 tender enthesis point]) and long-term radiographic outcomes including radiographic progression. Among golimumab-treated patients, achieving long-term MDA was associated with better long-term functional improvement, patient global assessment, and radiographic outcomes. Radiographic benefit was more pronounced in patients using MTX at baseline. The authors conclude that in patients with active PsA, aiming for MDA as part of a treat-to-target strategy may provide long-term functional and radiographic benefits (*Kavanaugh et al 2016*).
- In another trial, more Remicade (infliximab) treated patients achieved ACR 20 at weeks 12 and 24 compared to placebo treated patients ($p < 0.001$) (*Antoni et al 2005*).
- The efficacy of Cimzia (certolizumab) in the treatment of PsA was established in 1 multicenter, double-blind, placebo controlled trial (n = 409). Patients were randomized to receive placebo, Cimzia 200 mg every 2 weeks, or Cimzia 400 mg every 4 weeks. At week 12, ACR 20 response was significantly greater in both active treatment groups compared to placebo (*Mease et al 2014*).
- The FDA-approval of Stelara (ustekinumab) for PsA was based on the results of 2 randomized, double-blind, placebo-controlled trials in adult patients with active PsA despite NSAID or DMARD therapy (PSUMMIT 1 and PSUMMIT 2). In PSUMMIT 1 (n = 615), a greater proportion of patients treated with ustekinumab 45 mg or 90 mg alone or in combination with MTX achieved ACR 20 response at week 24 compared to placebo (42.4% and 49.5% vs 22.8%; $p < 0.0001$ for both comparisons); responses were maintained at week 52 (*McInnes et al 2013*). Similar results were observed in the PSUMMIT 2 trial (n = 312) with 43.8% of ustekinumab-treated patients and 20.2% of placebo-treated patients achieving an ACR 20 response ($p < 0.001$) (*Ritchlin et al 2014*).
    - In PSUMMIT-1, patients taking placebo or ustekinumab 45 mg could adjust therapy at week 16 if they had an inadequate response, and all remaining patients in the placebo group at week 24 were crossed over to receive treatment with ustekinumab 45 mg (*McInnes et al 2013*). At week 100 (*Kavanaugh et al 2015a*), the ACR 20 responses were 63.6%, 56.7%, and 62.7% in the 90 mg, 45 mg, and placebo crossover groups, respectively. ACR 50 and ACR 70 responses followed a similar pattern and ranged from 37.3% to 46% and 18.6% to 24.7%, respectively. At week 100, the proportions of patients achieving PASI 75 were 71.3%, 72.5%, and 63.9% in the 90 mg, 45 mg, and placebo crossover groups, respectively. Improvements in physical function and HRQoL were sustained over time, with median decreases in HAQ-DI scores from baseline to week 100 of 0.38, 0.25, and 0.38 in the 90 mg, 45 mg, and placebo crossover groups, respectively.
- Cosentyx (secukinumab) gained FDA approval for the treatment of PsA based on 2 multicenter, double-blind, placebo-controlled randomized controlled trials – FUTURE 1 and FUTURE 2 *(Mease et al 2015, McInnes et al 2015*). The FUTURE 1 study randomized patients to secukinumab 75 mg or 150 mg every 4 weeks (following IV loading doses) or placebo and evaluated ACR 20 at week 24. In the FUTURE 2 study, patients were randomized to secukinumab 75 mg, 150 mg, or 300 mg SQ every 4 weeks (following SQ loading doses given at weeks 0, 1, 2, 3, and 4) or placebo and evaluated at week 24 for ACR 20 response.
    - In FUTURE 1 at week 24, both the secukinumab 75 mg and 150 mg doses demonstrated significantly higher ACR 20 responses vs placebo (50.5% and 50.0% vs 17.3%, respectively; $p < 0.0001$ vs placebo).
    - All pre-specified endpoints including dactylitis, enthesitis, SF-36 PCS, HAQ-DI, DAS28-CRP, ACR 50, PASI 75, PASI 90, and mTSS score were achieved by week 24 and reached statistical significance.
    - At week 104 in a long-term extension study of FUTURE 1, ACR 20 was achieved in 66.8% of patients with secukinumab 150 mg and 58.6% of patients with secukinumab 75 mg (*Kavanaugh et al 2017*).
    - In FUTURE 2 at week 24, ACR 20 response rates were significantly greater with secukinumab than with placebo: 54.0%, 51.0%, and 29.3% vs 15.3% with secukinumab 300 mg, 150 mg, and 75 mg vs placebo, respectively ($p < 0.0001$ for secukinumab 300 mg and 150 mg; $p < 0.05$ for 75 mg vs placebo).

  - Improvements were seen with secukinumab 300 mg and 150 mg with regard to PASI 75/90 scores, DAS28-CRP, SF-36 PCS, HAQ-DI, dactylitis, and enthesitis. Efficacy was observed in both TNF-naïve patients and in patients with prior TNF inadequate response or intolerance.
- The efficacy of Otezla (apremilast) was demonstrated in 3 placebo-controlled trials in patients with PsA. At week 16, significantly more patients in the Otezla groups had ≥ 20% improvement in symptoms, as defined by ACR response criteria (*Cutolo et al 2013, Edwards et al 2016, Kavanaugh et al 2014a*). Clinical improvements observed at 16 weeks were sustained at 52 weeks (*Edwards et al 2016, Kavanaugh et al 2015b*).
- Orencia (abatacept) gained FDA approval for the treatment of PsA based on 2 double-blind, placebo-controlled clinical trials in patients with an inadequate response or intolerance to DMARD therapy (*Mease et al 2011, Mease et al 2017[a]*). In a phase 2 dose-finding trial (n = 170), patients received abatacept 3 mg/kg, 10 mg/kg, or 30/10 mg/kg (2 doses of 30 mg/kg then 10 mg/kg) on days 1, 15, 29 and then every 28 days (*Mease et al 2011*). Compared to placebo (19%), the proportion of patients achieving ACR 20 was significantly higher with abatacept 10 mg/kg (48%; p = 0.006) and 30/10 mg/kg (42%; p = 0.022) but not 3 mg/kg (33%). A phase 3 trial (n = 424) randomized patients to abatacept 125 mg weekly or placebo (*Mease et al 2017[a]*). At week 24, the proportion of patients with ACR 20 response was significantly higher with abatacept (39.4%) vs placebo (22.3%; p < 0.001).
- Taltz (ixekizumab) received FDA approval for the treatment of PsA based on 2 double-blind clinical trials, SPIRIT-P1 and SPIRIT-P2 (*Mease et al 2017[b], Nash et al 2017*). SPIRIT-P1 randomized 417 biologic naïve patients to placebo, adalimumab 40 mg every 2 weeks, ixekizumab 80 mg every 2 weeks, or ixekizumab 80 mg every 4 weeks. At week 24, ACR 20 response rates for ixekizumab every 2 weeks and every 4 weeks were 62.1% and 57.9%, respectively, which was significantly greater than the ACR 20 reponse rate with placebo (30.2%; p ≤ 0.001). The active reference treatment, adalimumab, had an ACR 20 at week 24 of 57.4% (*Mease et al 2017[b]*). SPIRIT-P2 randomized 363 patients who had a previous inadequate response to a TNF inhibitor to placebo, ixekizumab 80 mg every 2 weeks, or ixekizumab 80 mg every 4 weeks. At week 24, ACR 20 response rates for ixekizumab every 2 weeks and every 4 weeks were 48% and 53%, respectively, which was significantly greater than the ACR 20 reponse rate with placebo (20%; p < 0.0001) (*Nash et al 2017*).
  - An open-label extension of the SPIRIT-P1 trial followed patients through week 52, demonstrating sustained efficacy with ixekizumab. The ACR 20, ACR 50, and ACR 70 reponse rates for the every 4 week and every 2 weeks groups were 69.1% and 68.8%, 54.6% and 53.1%, and 39.2% and 39.6% at week 52, respectively (*van der Heijde et al 2018[b]*).
- Xeljanz (tofacitinib) received FDA approval for the treatment of PsA based on 2 double-blind, placebo-controlled clinical trials in patients with an inadequate response or intolerance to DMARD therapy (*Mease et al 2017[c], Gladman et al 2017*). The OPAL Broaden trial randomized 422 patients to tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, adalimumab 40 mg every 2 weeks, placebo with a blinded switch to tofacitinib 5 mg after 3 months, or placebo with a blinded switch to tofacitinib 10 mg after 3 months. The primary endpoint of the proportion of patients achieving ACR 20 at month 3 occurred in 50% in the tofacitinib 5 mg group, 61% in the tofacitinib 10 mg group, 33% in the placebo group (p = 0.01 vs 5 mg; p < 0.001 vs 10 mg), and 52% in the adalimumab group (*Mease et al 2017[c]*). The OPAL Beyond trial randomized 395 patients to tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, placebo with a blinded switch to tofacitinib 5 mg after 3 months, or placebo with a blinded switch to tofacitinib 10 mg after 3 months. The primary endpoint of the proportion of patients achieving ACR 20 at month 3 occurred in 50% in the tofacitinib 5 mg group, 47% in the tofacitinib 10 mg group, and 24% in the placebo group (p < 0.001 for both comparisons) (*Gladman et al 2017*).
- A small, single-center randomized trial (N = 100) compared Remicade (infliximab), Enbrel (etanercept), and Humira (adalimumab) in patients with PsA who had had an inadequate response to DMARDs (*Atteno et al 2010*). The investigators found that each of the agents effectively controlled the signs and symptoms of PsA, and ACR response rates were similar among agents. Patients receiving infliximab and adalimumab showed the greatest improvement in PASI scores, whereas patients receiving etanercept showed the greatest improvement on the tender joint count and HAQ. Limitations of this trial were lack of blinding and lack of a placebo group.
- A meta-analysis based on both direct and indirect comparisons evaluated the efficacy and safety of Humira (adalimumab), Enbrel (etanercept), Remicade (infliximab), and Simponi (golimumab) over 24 weeks for the treatment of PsA (*Fénix et al 2013*). The investigators found no differences among products for the primary endpoint of ACR 50 or secondary endpoints of ACR 20 and ACR 70, except that etanercept was associated with a lower ACR 70 response. However, low sample sizes limited the power of the analysis.
- A meta-analysis of 9 randomized controlled trials and 6 observational studies evaluated Humira (adalimumab), Enbrel (etanercept), Simponi (golimumab), or placebo in the achievement of ACR 20, ACR 50, and ACR 70 endpoints in

patients with moderate to severe PsA (*Lemos et al 2014*). Patients who used adalimumab, etanercept and golimumab were more likely to achieve ACR 20 and ACR 50 after 12 or 24 weeks of treatment. In long-term analysis (after all participants used anti-TNF for at least 24 weeks), there was no difference in ACR 20 and ACR 50 between the anti-TNF and control groups, but patients originally randomized to anti-TNF were more likely to achieve ACR 70.

- A meta-analysis of 8 studies evaluated Cosentyx (secukinumab), Taltz (ixekizumab), Siliq (brodalumab), and Stelara (ustekinumab) in the achievement of ACR 20, ACR 50, and ACR 70 endpoints in patients with PsA (*Bilal et al 2018*). Patients who used these agents were more likely to achieve ACR 20, ACR 50, and ACR70 after 24 weeks of treatment. Another network meta-analysis of 6 studies evaluated Cosentyx (secukinumab), Taltz (ixekizumab), and Stelara (ustekinumab) over 24 weeks in patients with active PsA (*Wu et al 2018*). The investigators found that all agents improved ACR20 and ACR50 at week 24 compared to placebo. A different network meta-analysis of 8 studies evaluated Orencia (abatacept), Otezla (apremilast), Stelara (ustekinumab), and Cosentyx (secukinumab) in the achievement of ACR 20 and ACR 50 in adults with moderate to severe PsA (*Kawalec et al 2018*). The investigators found a significant difference in ACR20 response rate between Cosentyx (secukinumab) 150 mg and Otezla (apremilast) 20 mg (RR, 2.55; 95% CI, 1.24 to 5.23) and Cosentyx (secukinumab) 300 mg and Otezla (apremilast) 20 mg (RR, 3.57; 95% CI, 1.48 to 8.64) or Otezla (apremilast) 30 mg (RR, 2.84; 95% CI, 1.18 to 6.86).
- Two indirect comparison meta-analyses sought to compare the efficacy of biologics for the treatment of PsA in patients with an inadequate response to prior therapies.
    - An analysis of 12 randomized trials compared various biologics in patients having an inadequate response to NSAIDs or traditional DMARDs (*Ungprasert et al 2016a*). The investigators determined that patients receiving older TNF inhibitors (evaluated as a group: Enbrel [etanercept], Remicade [infliximab], Humira [adalimumab], and Simponi [golimumab]) had a statistically significantly higher chance of achieving ACR 20 compared to patients receiving Cimzia (certolizumab), Otezla (apremilast), or Stelara (ustekinumab). Patients receiving Cosentyx (secukinumab) also had a higher chance of achieving ACR 20 compared to certolizumab, ustekinumab, and apremilast, but the relative risk did not always reach statistical significance. There was no statistically significant difference in this endpoint between secukinumab and the older TNF inhibitors, or between apremilast, ustekinumab, and certolizumab.
    - An analysis of 5 randomized trials compared various non-TNF inhibitor biologics (Orencia [abatacept], secukinumab, ustekinumab, and apremilast) in patients having an inadequate response or intolerance to TNF inhibitors (*Ungprasert et al 2016[bj*]). The investigators found no difference for any between-agent comparison in the likelihood of achieving an ACR 20 response.
    - These meta-analyses had limitations, notably being based on a small number of trials, and should be interpreted with caution.
- In a network meta-analysis of 8 randomized trials (N = 3086), the efficacy and safety of apremilast were compared with tofacitinib in patients with active PsA, including treatment with tofacitinib 10 mg or 5 mg, apremilast 20 or 30 mg, and placebo *(Song et al 2019)*. Tofacitinib 10 mg and apremilast 30 mg were among the most effective treatments, followed by tofacitinib 5 mg and apremilast 20 mg. Tofacitinib 10 mg was most likely to be most effective in ACR 20 response (SUCRA = 0.785), followed by apremilast 30 mg (SUCRA = 0.670), tofacitinib 5 mg (SUCRA = 0.596), and apremilast 20 mg (SUCRA = 0.448). There were no significant differences in adverse event rates.

Ulcerative colitis (UC)

- Two trials (ACT 1 and ACT 2) evaluated Remicade (infliximab) compared to placebo for the treatment of UC. In both trials, clinical response at week 8 was significantly higher in infliximab 5 and 10 mg/kg treated patients compared to placebo treated patients (all $p < 0.001$). A significantly higher clinical response rate in both infliximab groups was maintained throughout the duration of the studies (*Rutgeerts et al 2005*). A randomized open-label trial evaluated infliximab at different dosing intervals for the treatment of pediatric UC. At week 8, 73.3% of patients met the primary endpoint of clinical response (95% CI, 62.1 to 84.5%) (*Hyams et al 2012*).
- In the ULTRA 2 study, significantly more patients taking Humira (adalimumab) 160 mg at week 0, 80 mg at week 2, and then 40 mg every other week for 52 weeks achieved clinical remission and clinical response vs patients taking placebo (*Sandborn et al 2012*). These long term results confirm the findings of ULTRA 1. This 8-week induction trial demonstrated that adalimumab in same dosage as ULTRA 2 was effective for inducing clinical remission (*Reinisch et al 2011*). In ULTRA 1, significant differences between the adalimumab and placebo groups were only achieved for 2 of the secondary end points at week 8, i.e., rectal bleeding and PGA subscores. Conversely, in ULTRA 2, significantly greater proportions of adalimumab-treated patients achieved almost all secondary end points at week 8. This may have been because of the high placebo response rates in ULTRA 1. A meta-analysis of 3 randomized trials

comparing adalimumab to placebo demonstrated that adalimumab increased the proportion of patients with clinical responses, clinical remission, mucosal healing, and inflammatory bowel disease questionnaire responses in the induction and maintenance phases. It also increased the proportion of patients with steroid-free remission in the maintenance phase (*Zhang et al 2016*).

- Simponi (golimumab) was studied in 1,064 patients with moderate to severe UC. Patients receiving golimumab 200 mg then 100 mg or golimumab 400 mg then 200 mg at weeks 0 and 2 were compared to patients receiving placebo. At week 6, significantly greater proportions of patients in the golimumab 200/100 mg and golimumab 400/200 mg groups (51.8%, and 55%, respectively) were in clinical response than patients assigned to placebo (29.7%; $p < 0.0001$ for both comparisons) (*Sandborn et al 2014b*). In a study enrolling patients who responded in a prior study with golimumab, the proportion of patients who maintained a clinical response through week 54 was greater for patients treated with golimumab 100 mg and 50 mg compared to placebo (49.7 and 47 vs 31.2%; $p < 0.001$ and $p = 0.01$, respectively) (*Sandborn et al 2014a*).
- The safety and efficacy of Entyvio (vedolizumab) was evaluated in a trial for UC in patients who responded inadequately to previous therapy. A higher percentage of Entyvio-treated patients achieved or maintained clinical response and remission over placebo at weeks 6 and 52, as measured by stool frequency, rectal bleeding, endoscopic findings, and PGA (*Feagan et al 2013*). A systematic review and meta-analysis (n = 606; 4 trials) demonstrated that vedolizumab was superior to placebo for clinical response (RR, 0.82; 95% CI, 0.75 to 0.91), induction of remission (RR, 0.86; 95% CI, 0.80 to 0.91), and endoscopic remission (RR, 0.82; 95% CI, 0.75 to 0.91) (*Bickston et al 2014, Mosli et al 2015*).
- Entyvio (vedolizumab) was directly compared to Humira (adalimumab) in the double-blind, double-dummy, randomized, multicenter, VARSITY trial (*Sands et al 2019[a]*). VARSITY enrolled 769 adults with moderate-to-severe UC and randomized them to vedolizumab (n = 383) 300 mg IV on day 1 and at weeks 2, 6, 14, 22, 30, 38, and 46 (plus placebo injections) or adalimumab (n = 386) 160 mg SQ at week 1, 80 mg at week 2, and 40 mg every 2 weeks thereafter (plus placebo infusions) until week 50. Results revealed that clinical remission at week 52 occurred in significantly more patients in the vedolizumab group (31.3% vs 22.5%; difference, 8.8%; 95% CI, 2.5 to 15; $p = 0.0006$). Endoscopic improvement was also significantly improved with vedolizumab (39.7% vs 27.7%; difference, 11.9%; 95% CI, 5.3 to 18.5; $p < 0.001$). However, corticosteroid-free clinical remission was better with adalimumab (12.6% vs 21.8%; difference, -9.3%; 95%, -18.9 to 0.4).
- The efficacy of Xeljanz (tofacitinib) for UC was evaluated in two 8-week induction trials followed by a 52-week maintance trial. In the induction trials, patients were assigned to tofacitinib 10 mg twice daily or placebo. At week 8, remission occurred in 18.5% vs 8.2% of patients in the tofacitinib and placebo groups, respectively, in the OCTAVE 1 trial and 16.6% vs 3.6% of patients of patients in the tofacitinib and placebo groups, respectively, in the OCTAVE 2 trial. In the OCTAVE Sustain maintenance trial, patients who achieved a clinical response were continued on either tofacitinib 5 mg, tofacitinib 10 mg, or placebo. At week 52, remission occurred in 34.3%, 40.6%, and 11.1% of patients in the tofacitinib 5 mg, tofacitinib 10 mg, and placebo groups, respectively (*Sandborn et al 2017*).
- The efficacy of Stelara (ustekinumab) as induction and maintenance therapy in 961 patients with moderate-to-severe UC was evaluated in the UNIFI study (*Sands et al 2019[b]*). The study involved 8 week induction and 44 week maintenance phases. Patients were randomly assigned to receive an IV induction dose of either ustekinumab 130 mg (n = 320), a weight-range-based ustekinumab dose that approximated 6 mg/kg (n = 322), or placebo (n = 319). Patients with an induction response were then randomly assigned to ustekinumab 90 mg SQ every 12 weeks (n = 172), every 8 weeks (n = 176), or placebo (n = 175) for maintenance. Results revealed a significantly higher clinical remission at week 8 with ustekinumab 130 mg (15.6%) or 6 mg/kg (15.5%) as compared to placebo (5.3%; $p < 0.001$ for both comparisons). At the end of maintenance, the percentage of patients who had clinical remission was also significantly increased in both ustekinumab groups (38.4% every 12 weeks vs 43.8% every 8 weeks vs 24% placebo; $p = 0.002$ and $p < 0.001$, respectively).
- A network meta-analysis of 12 trials of biologic-naïve patients with moderate-severe UC ranked infliximab and vedolizumab highest for induction of clinical remission and mucosal healing among tofacitinib, vedolizumab, golimumab, adalimumab, and infliximab (*Singh et al 2018*). Among patients with prior exposure to anti-TNF agents (4 trials), the results ranked tofacitinib the highest for induction of clinical remission and mucosal healing.

Uveitis (UV)

- The safety and efficacy of Humira (adalimumab) were assessed in adult patients with non-infectious intermediate, posterior, and panuveitis in 2 randomized, double-masked, placebo-controlled studies, VISUAL I and VISUAL II.
    - VISUAL I (n = 217) enrolled adults with active noninfectious intermediate UV, posterior UV, or panuveitis despite having received prednisone treatment for ≥2 weeks (*Jaffe et al 2016*). Patients were randomized to

adalimumab (80 mg loading dose then 40 mg every 2 weeks) or placebo; all patients also received a prednisone burst followed by tapering of prednisone over 15 weeks. The primary endpoint was the time to treatment failure (TTF) at or after week 6. TTF was a multicomponent outcome that was based on assessment of new inflammatory lesions, visual acuity, anterior chamber cell grade, and vitreous haze grade. The median TTF was 24 weeks in the adalimumab group and 13 weeks in the placebo group. Patients receiving adalimumab were less likely than those in the placebo group to have treatment failure (hazard ratio, 0.50; 95% CI, 0.36 to 0.70; p < 0.001).

  - VISUAL II (n = 226) had a similar design to VISUAL I; however, VISUAL II enrolled patients with inactive UV on corticosteroids rather than active disease (*Nguyen et al 2016a*). Patients were randomized to adalimumab (80 mg loading dose then 40 mg every 2 weeks) or placebo; all patients tapered prednisone by week 19. TTF was significantly improved in the adalimumab group compared with the placebo group (median not estimable [>18 months] vs 8.3 months; hazard ratio, 0.57, 95% CI, 0.39 to 0.84; p = 0.004). Treatment failure occurred in 61 (55%) of 111 patients in the placebo group compared with 45 (39%) of 115 patients in the adalimumab group.

- The SYCAMORE study established the efficacy and safety of Humira (adalimumab) in pediatric patients with JIA-associated UV. The double-blind trial evaluated 90 children and adolescents ≥ 2 years of age and randomized them to adalimumab or placebo until treatment failure or 18 months had elapsed. The primary endpoint was the time to treatment failure. Sixteen treatment failures (27% of patients) occurred with adalimumab compared to 18 failures (60% of patients) with placebo (HR, 0.25; 95% CI, 0.12 to 0.90). Adverse events occurred more frequently with adalimumab (10.07 events per patient year [PY] vs 6.51 events per PY with placebo) (*Ramanan et al 2017*).

Multiple indications

- The efficacy of infliximab-dyyb (European Union formulation) in patients (n = 481) with CD, UC, RA, PsA, spondyloarthritis, and PsO who were treated with the originator infliximab (European Union formulation) for ≥ 6 months was assessed in the NOR-SWITCH trial (*Jørgensen et al 2017*). Twenty-five percent of patients in the infliximab originator group experienced disease worsening compared to 30% of patients in the infliximab-dyyb group (TD, -4.4%; 95% CI, -12.7% to 3.9%; noninferiority margin, 15%). The authors concluded that infliximab-dyyb was noninferior to originator infliximab.

Behçet disease, CAPS, CRS, FMF, GCA, HIDS/MKD, NOMID, NRAS, and TRAPs

- The efficacy of Otezla (apremilast) for Behçet disease was evaluated in a randomized, double-blind, placebo-controlled trial in 207 adults with Behçet disease with active oral ulcers who were previously treated with at least one nonbiologic therapy (*Hatemi et al 2019*). At week 12, apremilast 30 mg twice daily was associated with a 42.7 point mean reduction from baseline in oral ulcer pain on a visual analog scale (VAS), compared with an 18.7 point reduction with placebo. The area under the curve (AUC) of the total mean number of ulcers during the 12 week period was 129.5 in the apremilast vs 222.1 in the placebo group ; p < 0.001). The proportion of patients who were oral ulcer-free at week 12 was 53% and 22% with apremilast vs placebo, respectively. Adverse events with apremilast included diarrhea, nausea, and headache.
- The efficacy of Kineret (anakinra) for NOMID was evaluated in a prospective, open-label, uncontrolled study in 43 patients treated for up to 60 months. The study demonstrated improvements in all disease symptoms comprising the disease-specific Diary Symptom Sum Score (DSSS), as well as in serum markers of inflammation. A subset of patients (n = 11) who went through a withdrawal phase experienced worsening of disease symptoms and inflammatory markers, which promptly responded to reinstitution of treatment (*Kineret prescribing information 2016*). A cohort study of 26 patients followed for 3 to 5 years demonstrated sustained improvement in disease activity and inflammatory markers (*Sibley et al 2012*).
- The efficacy of Cimzia (certolizumab) was evaluated in a phase 3, randomized, double-blind, placebo-controlled trial in 317 patients with NRAS. Patients were randomized to certolizumab (400 mg at weeks 0, 2, and 4, followed by 200 mg every 2 weeks) or placebo in addition to nonbiologic background medication. At week 52, treatment with certolizumab was associated with a significantly higher proportion of patients achieving major improvement (≥ 2 point decrease in Ankylosing Spondylitis Disease Activity Score; 47.2% vs 7.0%; p < 0.0001) *(Deodhar et al 2019[b]).*
- The efficacy and safety of Ilaris (canakinumab) has been evaluated for the treatment of CAPS, TRAPS, HIDS/MKD, and FMF.
  - Efficacy and safety in CAPS were evaluated in a trial in patients aged 9 to 74 years with the MWS phenotype and in a trial in patients aged 4 to 74 years with both MWS and FCAS phenotypes. Most of the trial periods were open-label. Trials demonstrated improvements based on physician's assessments of disease activity and assessments of skin disease, CRP, and serum amyloid A (*Ilaris prescribing information 2016*). Published

data supports the use of canakinumab for these various CAPS phenotypes (*Koné-Paut et al 2011, Kuemmerle-Deschner et al 2011, Lachmann et al 2009*).
    - Efficacy and safety in TRAPS, HIDS/MKD, and FMF were evaluated in a study in which patients having a disease flare during a screening period were randomized into a 16-week double-blind, placebo-controlled period. For the primary efficacy endpoint, canakinumab was superior to placebo in the proportion of TRAPS, HIDS/MKD, and FMF patients who resolved their index disease flare at day 15 and had no new flare for the duration of the double-blind period (45% vs 8%, 35% vs 6%, and 61% vs. 6%, respectively). Resolution of the flare was defined as a PGA score <2 (minimal or no disease) and CRP within normal range (or reduction ≥70% from baseline) (*De Benedetti et al 2018*).
- The efficacy and safety of Actemra (tocilizumab) has been evaluated for treatment of GCA and CRS.
    - Efficacy and safety of tocilizumab in GCA were evaluated in a double-blind, placebo-controlled phase 3 trial (GiACTA) in patients ≥ 50 years old with active GCA and a history of elevated ESR (*Stone et al 2017*). Patients received tocilizumab every week or every other week with a 26-week prednisone taper, or received placebo with a 26-week or 52-week prednisone taper. Patients who received tocilizumab every week and every other week experienced higher sustained remission rates at week 52 compared to placebo ($p < 0.01$).
    - The efficacy of tocilizumab in CRS was based on the result of a retrospective analysis of pooled outcome data from clinical trials of chimeric antigen receptor (CAR) T-cell therapies for hematological cancers (*Actemra prescribing information 2017*). Patients aged 3 to 23 years received tocilizumab with or without high-dose corticosteroids for severe or life-threatening CRS. Sixty-nine percent of patients treated with tocilizumab achieved a response. In a second study using a separate study population, CRS resolution within 14 days was confirmed.

Treatment Guidelines

- RA:
    - In patients with moderate or high disease activity despite DMARD monotherapy, the ACR recommends the use of combination DMARDs, a TNF inhibitor, or a non-TNF inhibitor biologic (tocilizumab, abatacept, or rituximab); tofacitinib is another option in patients with established RA, mainly in patients failing or intolerant to biologic DMARDs. If disease activity remains moderate or high despite use of a TNF inhibitor, a non-TNF biologic is recommended over another TNF inhibitor or tofacitinib. Anakinra was excluded from the ACR guideline because of its low use and lack of new data (*Singh et al 2016c*). The ACR updated guideline on RA management is currently underway with final publication anticipated in early 2020.
    - EULAR guidelines for RA management were recently updated (*Smolen et al 2020*). EULAR recommends that therapy with DMARDs should be initiated as soon as the RA diagnosis is made with treatment aimed at reaching a target of sustained remission or low disease activity in every patient. If the treatment target is not achieved with the first conventional synthetic DMARD strategy, in the absence of poor prognostic factors, others should be considered. If poor prognostic factors are present with treatment failure, a biological or targeted synthetic DMARD should be added. If a biological or targeted synthetic DMARD has failed, treatment with another should be considered. If one TNF inhibitor therapy has failed, patients may receive an agent with another mode of action or a second TNF inhibitor.
    - The ACR released a position statement on biosimilars, which stated that the decision to substitute a biosimilar product for a reference drug should only be made by the prescriber. The ACR does not endorse switching stable patients to a different medication (including a biosimilar) of the same class for cost saving reasons without advance consent from the prescriber and knowledge of the patient (*ACR 2018*). Similarly, the Task Force on the Use of Biosimilars to Treat Rheumatological Disorders recommends that both healthcare providers and patients should take part in the decision-making process for switching amongst biosimilars (*Kay et al 2018*).
    - EULAR has released guidelines for use of antirheumatic drugs in pregnancy, which state that etanercept and certolizumab are among possible treatment options for patients requiring therapy (*Götestam Skorpen et al 2016*).
- JIA:
    - According to the American College of Rheumatology (ACR) JIA guidelines focusing on the management of SJIA, the inflammatory process in SJIA is likely different from that of other JIA categories, with IL-1 and IL-6 playing a central role. In patients with SJIA and active systemic features, recommendations vary based on the active joint count and the physician global assessment. Anakinra is 1 of the recommended first-line therapies;

canakinumab, tocilizumab, and TNF-inhibitors are among the second-line therapies. In patients with SJIA and no active systemic features, treatments vary based on the active joint count. Abatacept, anakinra, tocilizumab, and TNF inhibitors are among the second-line treatments for these patients (*Ringold et al 2013*).
    - The ACR and Arthritis Foundation published a guideline for the treatment of JIA in 2019 focusing on therapy for non-systemic polyarthritis, sacroiliitis, and enthesitis. In children and adolescents with JIA and polyarthritis with moderate to high disease activity, addition of a biologic (TNF inhibitor, abatacept, or tocilizumab) is conditionally recommended. Patients with continued disease activity and primary TNF inhibitor failure are conditionally recommended to receive abatacept or tocilizumab over a second TNF inhibitor. Children and adolescents with JIA and active sacroiliitis despite treatment with NSAIDs are strongly recommended to add TNF inhibitor therapy over continuing NSAID monotherapy. In children and adolescents with JIA and active enthesitis, TNF inhibitor therapy is conditionally recommended over methotrexate or sulfasalazine *(Ringold et al 2019)*. The ACR is developing a new clinical practice guideline for the management of JIA, specifically covering pharmacologic and non-pharmacologic treatments that were not addressed in the 2019 guidelines; final publication is anticipated in early 2021.
- UC:
    - For the treatment of UC, 2019 guidelines from the American College of Gastroenterology (ACG) recommend 5-aminosalicylate (5-ASA) therapy for induction of remission in mildly active UC, and budesonide, systemic corticosteroids, TNF inhibitor therapy (adalimumab, golimumab, or infliximab), vedolizumab, and tofacitinib for induction of remission in moderately to severely active disease. Vedolizumab and tofacitinib are recommended for induction of remission in patients who have failed previous TNF inhibitor therapy. For maintenance of remission in patients with previously mildly active disease, 5-ASA therapy is recommended, and in patients with previously moderately to severely active disease, continuation of anti-TNF therapy, vedolizumab, or tofacitinib is recommended after induction of remission with these agents (*Rubin et al 2019*).
    - The American Gastroenterological Association (AGA) recommends standard-dose mesalamine or diazo-bonded 5-aminosalicylates (balsalazide, olsalazine) as first-line options for most patients with mild to moderate disease (*Ko et al 2019*). For adult outpatients with moderate to severe UC, the AGA strongly recommends using infliximab, adalimumab, golimumab, vedolizumab, tofacitinib, or ustekinumab over no treatment (*Feuerstein et al 2020*).
    - The European Crohn's and Colitis Organisation (ECCO) recommends thiopurine, anti-TNF drugs, vedolizumab, or methotrexate for patients with UC who have active steroid-dependent disease. In the case of further treatment failure, an alternative anti-TNF agent, vedolizumab, or colectomy can be considered. Anti-TNF agents and vedolizumab are also treatment options for patients who have steroid- or immunomodulator-refractory disease (*Harbord et al 2017*).
- CD:
    - The ACG states that the anti-TNF monoclonal antibodies adalimumab, certolizumab, and infliximab are effective in the treatment of moderate to severely active CD in patients who are resistant to corticosteroids or are refractory to thiopurines or methotrexate. These agents can be considered for treating perianal fistulas, and infliximab can also treat enterocutaneous and rectovaginal fistulas in CD. Adalimumab, certolizumab, and infliximab are effective for the maintenance of anti-TNF induced remission; due to the potential for immunogenicity and loss of response, combination with azathioprine/6-mercaptopurine or methotrexate should be considered. The combination of infliximab with an immunomodulator (thiopurine) is more effective than monotherapy with individual agents in patients with moderate to severe CD and who are naïve to both agents. Infliximab can also treat fuliminant CD. Vedolizumab with or without an immunomodulator can be used for induction and maintenance of remission in patients with moderate to severe CD. Patients are candidates for ustekinumab therapy, including for the maintenance of remission, if they have moderate to severe CD and have failed corticosteroids, thiopurines, methotrexate, or anti-TNF inhibitors. The guideline acknowledges the effectiveness of biosimilar infliximab and biosimilar adalimumab for the management of moderate to severe CD (*Lichtenstein et al 2018*).
    - The AGA recommends using anti-TNF drugs to induce remission in patients with moderately severe CD (*Terdiman et al 2013*). The AGA supports the use of TNF inhibitors and/or thiopurines as pharmacologic prophylaxis in patients with surgically-induced CD remission (*Nguyen et al 2017*).
    - An AGA Institute clinical decision tool for CD notes the importance of controlling both symptoms and the underlying inflammation, and makes recommendations for treatments (budesonide, azathioprine, 6-

mercaptopurine, prednisone, MTX, a TNF inhibitor, or certain combinations) based on the patient's risk level (*Sandborn 2014*).
    - In 2020, ECCO released a guideline on medical treatment in CD (*Torres et al 2020*). Regarding immunomodulators, these guidelines recommend the use of TNF inhibitors (infliximab, adalimumab, and certolizumab pegol) to induce remission in patients with moderate-to-severe CD who have not responded to conventional therapy. Other immunomodulator-related recommendations within the guideline include:
        - Suggesting against the combination of adalimumab and thiopurines over adalimumab alone to achieve clinical remission and response.
        - Recommending combination therapy with a thiopurine when starting infliximab to induce remission in patients with moderate-to-severe CD, who have had an inadequate response to conventional therapy.
        - Recommending ustekinumab for induction of remission in patients with moderate-to-severe CD with inadequate response to conventional therapy and/or to anti-TNF therapy.
        - Recommending vedolizumab for induction of response and remission in patients with moderate-to-severe CD with inadequate response to conventional therapy and/or to anti-TNF therapy.
        - Equally suggesting the use of either ustekinumab or vedolizumab for the treatment of moderate-to-severe active luminal CD in patients who have previously failed anti-TNF therapy.
- Pregnancy in inflammatory bowel disease:
    - Consensus statements for the management of inflammatory bowel disease in pregnancy, coordinated by the Canadian Association of Gastroenterology, state that TNF inhibitor treatment does not appear to be associated with unfavorable pregnancy outcomes and should generally be continued during pregnancy. Because of the low risk of transfer across the placenta, certolizumab may be preferred in women who initiate TNF inhibitor therapy during pregnancy (*Nguyen et al 2016[b]*).
    - The AGA pregnancy care pathway for inflammatory bowel disease also recommends that biologics can be continued during pregnancy and delivery as the benefits of maintaining disease remission outweigh any risks associated with biologic maintenance therapy. The pathway does note that infliximab and adalimumab have the greatest amount of safety data (*Mahadevan et al 2019*).
- PsO and PsA:
    - Consensus guidelines from the National Psoriasis Foundation Medical Board state that treatment of PsO includes topical agents; oral therapies such as acitretin, cyclosporine, and MTX; and biologic therapies (*Hsu et al 2012*).
    - Guidelines from the American Academy of Dermatology state that for the management of PsO, topical agents including corticosteroids are used adjunctively to either ultraviolet light or systemic medications for resistant lesions in patients with more severe disease (*Elmets et al 2019, Menter et al 2008, Menter et al 2009a, Menter et al 2009b, Menter et al 2011*). Biologic agents are routinely used when ≥ 1 traditional systemic agents are not tolerated, fail to produce an adequate response, or are unable to be used due to patient comorbidities. First-line agents for PsO (> 5% BSA) with concurrent PsA include adalimumab, etanercept, golimumab, infliximab, MTX, or a combination of a TNF blocker and MTX.
    - Joint guidelines from the American Academy of Dermatology/National Psoriasis Foundation on the treatment of psoriasis with biologics address the effectiveness of these drugs as monotherapy or in combination to treat moderate-to-severe disease in adults. The guideline does not provide relevant ranking for preferences of individual biologics, but does recommend that etanercept, infliximab, adalimumab, ustekinumab, secukinumab, ixekizumab, brodalumab, guselkumab, risankizumab, and tildrakizumab can all be recommended as a monotherapy option for patients. Further recommendations on specific presentations of the disease, combination therapy, and dosing recommendations are included in the guidance (*Menter et al 2019*).
    - Guidelines for PsO from the European Dermatology Forum, European Association for Dermatology and Venereology, and International Psoriasis Council (European S3 guidelines) state that adalimumab, etanercept, infliximab, and ustekinumab are recommended as second-line medications for induction and long-term treatment if phototherapy and conventional systemic agents were inadequate, contraindicated, or not tolerated (*Nast et al 2015b*). In patients with PsA and active joint involvement despite use of NSAIDs and a potential poor prognosis due to polyarthritis, increased inflammatory markers and erosive changes, it is recommended to start synthetic DMARDs early to prevent progression of disease and erosive joint destruction. For inadequately responding patients with PsA after at least 1 synthetic DMARD, biologic DMARDS are recommended in combination with synthetic DMARDs or as monotherapy.

- The American Academy of Dermatology recommends that moderate to severe PsA that is more extensive or aggressive in nature or that significantly impacts QoL should be treated with MTX, TNF-blockers, or both (*Gottleib et al 2008, Menter et al 2009b, Menter et al 2011*).
- EULAR 2015 PsA guidelines recommend TNF inhibitors in patients with peripheral arthritis and an inadequate response to at least 1 synthetic DMARD, such as MTX. For patients with peripheral arthritis and an inadequate response to at least 1 synthetic DMARD, in whom a TNF inhibitor is not appropriate, biologics targeting IL-12/23 or IL-17 pathways may be considered. Apremilast is considered a treatment option in patients with peripheral arthritis and an inadequate response to at least 1 synthetic DMARD, in whom biologics are not appropriate (*Gossec et al 2016, Ramiro et al 2016*).
- The Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) recommendations for PsA vary based on whether the arthritis is peripheral or axial and based on prior therapies, and may include DMARDS, NSAIDs, simple analgesics, a TNF inhibitor, an IL-12/23 inhibitor, or a PDE-4 inhibitor (*Coates et al 2016).*
- The American College of Rheumatology/National Psoriasis Foundation guideline on PsA recommends that a TNF inhibitor is preferred in treatment-naïve patients with active PsA, although an oral therapy (MTX, sulfasalazine, leflunomide, cyclosporine, or apremilast) can be a first-line option in patients without severe PsA and without severe psoriasis, or if a patient has another compelling reason to avoid a TNF inhibitor. In patients who fail oral therapy, a switch to a TNF inhibitor is preferred and placed ahead of IL-17 biologics (secukinumab, ixekizumab, brodalumab), IL-12/23 biologics (ustekinumab), abatacept, and tofacitinib (*Singh et al 2019*).

- AS:
  - The American College of Rheumatology/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network joint recommendations for treatment of AS and NRAS were updated in 2019. Patients with active AS or NRAS who do not respond to initial NSAID therapy are conditionally recommended to be treated with sulfasalazine, MTX, or tofacitinib; sulfasalazine or methotrexate should be considered only in patients with prominent peripheral arthritis or when TNF inhibitors are not available. Patients who do not respond to NSAID therapy are strongly recommended to receive treatment with a TNF inhibitor, although no particular TNF inhibitor is preferred. Treatment with a TNF inhibitor is conditionally recommended over tofacitinib, secukinumab, and ixekizumab in these patients. In patients with active disease who have primary nonresponse with a TNF inhibitor, treatment with secukinumab or ixekizumab is strongly recommended, and treatment with tofacitinib is conditionally recommended. Patients with secondary nonresponse to treatment with a TNF inhibitor are conditionally recommended to receive treatment with an alternative TNF inhibitor. In patients with AS and inflammatory bowel disease or recurrent iritis, TNF inhibitors are conditionally recommended over treatment with other biologics. In patients with stable disease who are treated with an originator TNF inhibitor, the guideline strongly recommends continuing the originator TNF inhibitor over mandated switching to its biosimilar *(Ward et al 2019).*
  - Joint recommendations for the management of axial spondyloarthritis are available from ASAS and EULAR. (AS is synonymous with radiographic axial spondyloarthritis; these guidelines also include non-radiographic axial spondyloarthritis). The guidelines state that NSAIDs should be used first-line in patients with pain and stiffness; other analgesics might be considered if NSAIDs have failed or are contraindicated or poorly tolerated. Glucocorticoid injections may be considered but patients with axial disease should not receive long-term systemic glucocorticoids. Sulfasalazine may be considered in patients with peripheral arthritis, but patients with purely axial disease should normally not be treated with conventional DMARDs. Biologic DMARDs should be considered in patients with persistently high disease activity despite conventional treatments, and current practice is to start with a TNF inhibitor. If a TNF inhibitor fails, switching to another TNF inhibitor or to an IL-17 inhibitor should be considered (*van der Heijde et al 2017[b]*).
- Ocular inflammatory disorders:
  - Expert panel recommendations for the use of TNF inhibitors in patients with ocular inflammatory disorders are available from the American Uveitis Society (*Levy-Clarke et al 2014*). Infliximab and adalimumab can be considered as first-line immunomodulatory agents for the treatment of ocular manifestations of Behçet's disease and as second-line immunomodulatory agents for the treatment of UV associated with juvenile arthritis. They also can be considered as potential second-line immunomodulatory agents for the treatment of severe ocular inflammatory conditions including posterior UV, panuveitis, severe UV associated with

seronegative spondyloarthropathy, and selected patients with scleritis. Etanercept seems to be associated with lower rates of treatment success in these conditions.
    - A 2019 guideline by the ACR and Arthritis foundation focusing on children with JIA-associated UV conditionally recommended starting a monoclonal antibody TNF inhibitor over etanercept in children and adolescents with chronic anterior UV. Children and adolescents with inadequate response to one monoclonal TNF inhibitor are conditionally recommended to be treated with an escalated dose and/or frequency of the TNF inhibitor over switching to another TNF inhibitor; patients failing dose escalation are conditionally recommended to switch to another monoclonal TNF inhibitor. Children and adolescents failing MTX and 2 monoclonal TNF inhibitors are conditionally recommended to receive abatacept or tocilizumab as biologic DMARD options *(Angeles-Han et al 2019).*
- Additional indications:
    - Based upon guidelines from the European Dermatology Forum, adalimumab is recommended among first-line therapies for HS, and infliximab may be considered a second-line option (*Gulliver et al 2016, Zouboulis et al 2015*).
    - For the treatment of FMF, EULAR recommendations state that treatment with colchicine should begin as soon as FMF is diagnosed. Biologic treatment, such as anti-IL-1 therapy, is indicated in patients not responding to the maximum tolerated dose of colchicine. TNF inhibitors have also been used in colchicine-resistant patients, with good responses seen in observational studies (*Ozen et al 2016*).
    - For the management of HS, the US and Canadian Hidradenitis Suppurativa Foundation recommend adalimumab to improve disease severity and QoL in patients with moderate-to-severe disease (*Alikhan et al, 2019*). Additionally, infliximab is recommended for moderate-to-severe disease; however, the optimal dose is not currently known. Anakinra and ustekinumab may be effective agents for HS as well.
    - No recent guidelines were identified for CAPS, CRS, GCA, HIDS/MKD, or TRAPS.

SAFETY SUMMARY

- Contraindications:
    - Actemra (tocilizumab), Cimzia (certolizumab), Cosentyx (secukinumab), Entyvio (vedolizumab), Ilaris (canakinumab), Ilumya (tildrakizumab-asmn), Inflectra (infliximab-dyyb), Kevzara (sarilumab), Kineret (anakinra), Otezla (apremilast), Remicade (infliximab), Renflexis (infliximab-abda), Stelara (ustekinumab), and Taltz (ixekizumab) use in patients with hypersensitivity to any component of the product.
    - Siliq in patients with CD because Siliq may cause worsening of disease.
    - Enbrel (etanercept) in patients with sepsis.
    - Kineret (anakinra) in patients with hypersensitivity to *E coli*-derived proteins.
    - Remicade (infliximab), Inflectra (infliximab-dyyb), and Renflexis (infliximab-abda) in patients with hypersensitivity to murine proteins; and doses >5 mg/kg in patients with moderate to severe heart failure.
- Boxed Warnings:
    - Actemra (tocilizumab), Cimzia (certolizumab), Enbrel (etanercept), Humira (adalimumab), Inflectra (infliximab-dyyb), Kevzara (sarilumab), Olumiant (baricitinib), Remicade (infliximab), Renflexis (infliximab-abda), Rinvoq (upadacitinib), Simponi / Simponi Aria (golimumab), and Xeljanz / Xeljanz XR (tofacitinib) all have warnings for serious infections such as active tuberculosis, which may present with pulmonary or extrapulmonary disease; invasive fungal infections; and bacterial, viral, and other infections due to opportunistic pathogens.
    - In addition, Cimzia (certolizumab), Enbrel (etanercept), Humira (adalimumab), Inflectra (infliximab-dyyb), Olumiant (baricitinib), Remicade (infliximab), Renflexis (infliximab-abda), Rinvoq (upadacitinib), Simponi / Simponi Aria (golimumab), and Xeljanz (tofacitinib) all have warnings for increased risk of malignancies.
    - Xeljanz and Xeljanz XR (tofacitinib) have warnings for increased risk of thrombosis and death with the 10 mg twice daily dose, which is used in patients with UC. Rinvoq (upadacitinib) and Olumiant (baricitinib), other JAK inhibitors, also carry a boxed warning for this risk.
    - Rituxan (rituximab) can cause fatal infusion reactions, hepatitis B activation, severe mucocutaneous reactions, and progressive multifocal leukoencephalopathy (PML).
    - Siliq has a boxed warning that suicidal ideation and behavior, including completed suicides, have occurred in patients treated with Siliq. The prescriber should weigh potential risks and benefits in patients with a history of depression and/or suicidal ideation or behavior, and patients should seek medical attention if these conditions arise or worsen during treatment.

  - Olumiant (baricitinib) has a boxed warning for thrombosis, including deep venous thrombosis, pulmonary embolism, and arterial thrombosis.
- Warnings/Precautions (applying to some or all of the agents in the class):
  - Reactivation of HBV or other viral infections
  - Serious infections including tuberculosis
  - New onset or exacerbation of central nervous system demyelinating disease and peripheral demyelinating disease
  - Pancytopenia
  - Worsening and new onset congestive heart failure
  - Hypersensitivity reactions
  - Lupus-like syndrome
  - Malignancy and lymphoproliferative disorders
  - Avoiding live vaccinations
  - Noninfectious pneumonia with Stelara (ustekinumab)
  - Increased lipid parameters and liver function tests with Actemra (tocilizumab), Xeljanz/Xeljanz XR (tofacitinib) and Kevzara (sarilumab)
  - Increased incidence of CD and UC with Cosentyx (secukinumab) and Taltz (ixekizumab); risk of new-onset CD or exacerbation of CD with Siliq (brodalumab)
  - Diarrhea, nausea, and vomiting with Otezla (apremilast)
  - Depression with Otezla (apremilast)
  - Gastrointestinal perforations with Xeljanz/Xeljanz XR (tofacitinib), Olumiant (baricitinib), Actemra (tocilizumab), Kevzara (sarilumab), and Rituxan (rituximab)
  - PML with Entyvio (vedolizumab)
  - Thrombosis with Olumiant (baricitinib)
  - Embryo-fetal toxicity with Rinvoq (upadacitinib)
  - Hepatotoxicity with Actemra (tocilizumab)
  - Cardiovascular and cerebrovascular reactions during and after infusion (infliximab)
  - Consult prescribing information for other drug-specific warnings/precautions
- Adverse Reactions:
  - Infusion site reactions, diarrhea, nausea/vomiting, abdominal pain, infections, hypertension, and headache.
  - Consult prescribing information for other drug-specific AEs
- Risks of Long-Term Treatment: As it becomes accepted practice to treat patients with these conditions for long-term, it is imperative to assess the long-term safety of these products. Because these agents suppress the immune system, serious infections and malignancies are a concern. Several long-term efficacy and safety studies support several agents in this class. The extension studies were performed in an open-label manner and were subject to attrition bias.
  - Rheumatoid Arthritis
    - Safety of adalimumab for RA has been supported in a 5-year study in RA and a 10-year study in patients with early RA (*Keystone et al 2014a, Burmester et al 2014b*). In the 5-year extension study, overall rates of serious AEs and serious infections were 13.8 events per 100 PY and 2.8 events per 100 PY, respectively. The rate of serious events was highest in the first 6 months and then declined. No new safety signals were reported in the 10-year study.
    - Certolizumab plus MTX had a consistent safety profile over 5 years in patients with RA (*Keystone et al 2014b*). The most frequently reported AEs included urinary tract infections (rate of 7.9 per 100 patient-years), nasopharyngitis (rate of 7.3 per 100 PY), and upper respiratory infections (rate of 7.3 per 100 PY). Serious AE rates were 5.9 events per 100 patient-years for serious infections and 1.2 events per 100 PY for malignancies.
    - Abatacept has been evaluated in 2 long-term extension studies. Abatacept IV plus MTX demonstrated a similar safety profile between the 7 year follow-up and a 52-week double-blind study (*Westhovens et al 2014*). Serious AEs reported in both the double-blind and long-term follow-up studies were the following: serious infections (17.6 events per 100 PY), malignancies (3.2 events per 100 PY), and autoimmune events (1.2 events per 100 PY). In a 5-year extension trial, rates of serious infections, malignancies, and autoimmune events were 2.8, 1.5, and 0.99 events per 100 patient-years exposure, respectively. Efficacy was demonstrated by ACR 20 with response rates of 82.3% and 83.6% of patients at year 1 and year 5, respectively.

- Data from 5 RCTs of Actemra (tocilizumab), their open-label extension trials, and a drug interaction study were analyzed for measures of safety. A total of 4,009 patients with moderate to severe RA received at least 1 dose of tocilizumab. Mean duration of tocilizumab treatment was 3.07 years (up to 4.6 years); total duration of observation was 12,293 PY. The most common AEs and serious AEs were infections. A longer-term safety profile from this analysis matches previous observations. No new safety signals were identified (*Genovese et al 2013*).
- A Cochrane review showed no evidence of a statistically significant difference in the rate of withdrawal because of AEs in the Enbrel (etanercept) plus DMARD group and the DMARD alone group at 6 months, 12 months, and 2 years. At 3 years, withdrawals were significantly reduced in the etanercept 25 mg plus DMARD group compared with the DMARD alone group (RR, 0.7; 95% CI, 0.5 to 1). There was no evidence of statistically significant differences in the rates of breast cancer at 12 months, fever at 6 months, flu-like syndrome at 6 months and 2 years, infection at 6 months and 2 years, malignancy at 12 months and 2 years, pneumonia at 12 months, and serious infection at 12 months and 2 years between the etanercept plus DMARD group and the DMARD group (*Lethaby et al 2013*).
- A systematic review analyzed 66 randomized controlled trials and 22 long-term extension studies evaluating biologics and tofacitinib for the rate of serious infections in patients with moderate to severe active RA (*Strand et al 2015b*). The estimated incidence rates (unique patients with events/100 patient-years) of serious infections were 3.04 (95% CI, 2.49 to 3.72) for abatacept, 3.72 (95% CI, 2.99 to 4.62) for rituximab, 5.45 (95% CI, 4.26 to 6.96) for tocilizumab, 4.90 (95% CI, 4.41 to 5.44) for TNF inhibitors, and 3.02 (95% CI, 2.25 to 4.05) for tofacitinib 5 mg and 3.00 (95% CI, 2.24 to 4.02) for tofacitinib 10 mg. Authors concluded that the rates of serious infections with tofacitinib in RA patients are within the range of those reported for biologic DMARDs.
- A meta-analysis analyzed 50 randomized controlled trials and long-term extension studies evaluating biologic DMARDs and tofacitinib to compare the risks of malignancies in patients with RA (*Maneiro et al 2017*). The overall risk of malignancies was 1.01 (95% CI, 0.72 to 1.42) for all TNF antagonists, 1.12 (95% CI, 0.33 to 3.81) for abatacept, 0.54 (95% CI, 0.20 to 1.50) for rituximab, 0.70 (95% CI, 0.20 to 2.41) for tocilizumab, and 2.39 (95% CI, 0.50 to 11.5) for tofacitinib. The authors concluded that treatment with biologic DMARDs or tofacitinib does not increase the risk of malignancies.
- A pooled analysis of 9 RA trials evaluating baricitinib included 3492 patients (7860 PY exposure). The incidence rate for major adverse cardiovascular events was comparable between placebo (0.5 per 100 PY) and baricitinib 4 mg (0.8 per 100 PY). Incidence rates for arterial thrombotic events and congestive heart failure were also similar between baricitinib and placebo. The occurrence of a deep vein thrombosis or pulmonary embolism occurred more frequently in the baricinitib 4 mg group (6 events in 997 patients) versus placebo (0 events in 1070 patients) (*Taylor et al 2019*).

o PsO

- A total of 3,117 patients treated with at least 1 dose of Stelara (ustekinumab) for moderate to severe PsO were evaluated for long-term safety. At least 4 years of ustekinumab exposure was seen in 1,482 patients (including 838 patients with ≥ 5 years of exposure). The most commonly reported AEs were nasopharyngitis, upper respiratory tract infection, headache and arthralgia. Infections, malignancies and cardiac disorders were the most commonly reported serious AEs. Twenty deaths were reported through year 5. The causes of death were considered related to cardiovascular events (n = 5), malignancy (n = 5), infection (n = 3) and other causes (n = 7). The observed mortality rate among ustekinumab-treated patients was consistent with that expected in the general U.S. population (SMR = 0.36; 95% CI, 0.22 to 0.55). From year 1 to year 5, rates of overall AEs, and AEs leading to discontinuation generally decreased. Serious AE rates demonstrated year-to-year variability with no increasing trend. The results of this long-term study of AEs are similar to reports of shorter-term studies (*Papp et al 2013*).
- In a 5-year extension study, a total of 2510 patients on etanercept for the treatment of PsO were evaluated for long-term safety and efficacy (*Kimball et al 2015*). Serious AEs were reported as a cumulative incidence of the entire 5-year observation period. The following incidences were reported: serious infections (6.5%, 95% CI, 5.4 to 7.7%); malignancies excluding nonmelanoma skin cancer (3.2%, 95% CI, 2.3 to 4.1%); nonmelanoma skin cancer (3.6%, 95% CI, 2.7 to 4.1%); coronary artery disease (2.8%, 95% CI, 2 to 3.6%); PsO worsening (0.7%, 95% CI, 0.3 to 1.2%); CNS demyelinating

disorder (0.2%, 95%CI, 0 to 0.4%); lymphoma and tuberculosis each (0.1%, 95% CI, 0 to 0.3%); and opportunistic infection and lupus each (0.1%, 95%CI, 0 to 0.2%). A total of 51% of patients reported clear/almost clear rating at month 6 and remained stable through 5 years.

- In a ≥ 156-week extension study, a total of 1,184 patients treated with apremilast in ESTEEM 1 and 2 were evaluated for long-term safety and tolerability (*Crowley et al 2017*). Serious AEs (≥ 2 patients) were coronary artery disease (n = 6), acute myocardial infarction (n = 4), osteoarthritis (n = 4), and nephrolithiasis (n = 4). The exposure-adjusted incidence rate for major cardiac events was 0.5/100 patients years, for malignancies was 1.2/100 patient years, for serious infections was 0.9/100 patient-years, and for suicide attempts was 0.1/100 patient-years.
- A multicenter registry called Psoriasis Longitudinal Assessment and Registry (PSOLAR) evaluated the risk of serious infections in patients with PsO (*Kalb et al 2015*). Patients were followed for up to 8 years with a total of 11,466 patients with PsO enrolled, 74.3% of whom were from the U.S. A total of 22,311 patient-years of data were collected. Ustekinumab, infliximab, adalimumab, and etanercept as well as traditional DMARDs were included in the data analysis. During the follow-up period, 323 serious infections were reported. The rates of serious infections per 100 patient-years were 0.83 (secukinumab), 1.47 (etanercept), 1.97 (adalimumab), and 2.49 (infliximab). The most commonly reported serious infection was cellulitis. Risk factors for serious infections were increasing age, diabetes mellitus, smoking, and history of significant infections prior to registry entry. Exposure to infliximab (hazard ratio, 2.51; 95% CI, 1.45 to 4.33; p < 0.001) and adalimumab (hazard ratio, 2.13; 95% CI, 1.33 to 3.41; p = 0.002) during the registry were independently associated with the risk of serious infections whereas use of ustekinumab or etanercept were not.

o PsA
- Subcutaneous golimumab for patients with active PsA demonstrated safety and efficacy over 5 years in the long-term extension of the randomized, placebo-controlled GO-REVEAL study (*Kavanaugh et al 2014b*). Approximately one-half of patients also took MTX concurrently. No new safety signals were observed.

o AS
- A meta-analysis of 25 randomized controlled studies with 2,403 patients with AS or non-radiographic axial spondyloarthritis treated with agents such as adalimumab, certolizumab, etanercept, golimumab, infliximab, sarilumab, tocilizumab, and secukinumab showed no significant increase in the risk of serious infections with biologic agents compared to controls (OR, 1.42; 95% CI, 0.58 to 3.47) (*Wang et al 2018*).
- Another meta-analysis of 14 randomized controlled trials with 2,032 patients with AS that were treated with adalimumab, certolizumab, etanercept, golimumab, or infliximab revealed no significant difference between TNF inhibitors and placebo for overall serious adverse events (OR, 1.34; 95% CI, 0.87 to 2.05), risk of serious infections (OR, 1.59; 95% CI, 0.63 to 4.01), risk of malignancy (OR, 0.98; 95% CI, 0.25 to 3.85), and discontinuation due to adverse events (OR, 1.55; 95% CI, 0.95 to 2.54) (*Hou et al 2018*).

o Multiple indications
- One study looked at 23,458 patients who were treated with Humira (adalimumab) for RA, JIA, AS, PsA, PsO and CD. Patients received adalimumab for up to 12 years. No new safety signals were observed from this analysis. Rates of malignancies and infections were similar to the general population and also similar to rates reported in other shorter-term trials for anti-TNF therapies (*Burmester et al 2013b*).
- Pooled data from 5 Phase 3 trials of SQ golimumab over at least 3 years demonstrated a safety profile consistent with other TNF inhibitors (*Kay et al 2015*). A total of 1,179 patients with RA, PsA or AS were treated for at least 156 weeks. Rates of AEs up to week 160 for placebo, golimumab 50 mg and golimumab 100 mg, respectively, were as follows: 0.28, 0.30, 0.41 for death; 5.31, 3.03, 5.09 for serious infection; 0, 0.17, 0.35 for tuberculosis; 0, 0.13, 0.24 for opportunistic infection; 0, 0, 0.12 for demyelination; and 0, 0.04, 0.18 for lymphoma.
- A total of 18 multicenter, placebo-controlled, randomized controlled trials evaluated the safety profile of certolizumab pegol monotherapy or in combination with DMARDs in RA, CD, AS, PsA and PsO (*Capogrosso Sansone et al 2015).* All but 1 trial was conducted in a double-blind manner. The overall pooled risk ratios for all doses of certolizumab pegol were reported as follows: AEs (defined as AE

reported but not evaluated for causality) 1.09 (95% CI, 1.04 to 1.14), serious AEs 1.50 (95% CI, 1.21 to 1.86), ADRs (defined as an AE possibly related to drug treatment by investigators) 1.20 (95% CI, 1.13 to 1.45), infectious AEs 1.28 (95% CI, 1.13 to 1.45), infectious serious AEs 2.17 (95% CI, 1.36 to 3.47), upper respiratory tract infections 1.34 (95% CI, 1.15 to 1.57), neoplasms 1.04 (95% CI, 0.49 to 2.22), and tuberculosis 2.47 (95% CI, 0.64 to 9.56). Rare AEs may not have been captured by the studies due to limiting the reporting of most AEs to those occurring in > 3 to 5%.

- The safety of ustekinumab was examined in a pooled analysis of 12 trials in patients with PsO, PsA, and CD. A total of 5584 patients were evaluated, equating to 4521 PYs. Respective incidences per 100 PY of infections (125.4 vs 129.4), major cardiovascular adverse events (0.5 vs 0.3), malignancies (0.4 vs 0.2), and death (0.1 vs 0.0) were similar between ustekinumab and placebo, respectively (*Ghosh et al 2019*).
- Several meta-analyses evaluated the safety of TNF inhibitors.
    - An analysis of TNF inhibitors in RA, PsA, and AS included data from 71 randomized trials (follow-up 1 to 36 months) and 7 open-label extension studies (follow-up 6 to 48 months) (*Minozzi et al 2016*). The data demonstrated that use of TNF inhibitors increases the risk of infectious AEs. Overall, there was a 20% increase of any infections, a 40% increase of serious infections, and a 250% increase of tuberculosis. The tuberculosis incidence rate was higher with infliximab and adalimumab compared to etanercept. There was little data on the incidence of opportunistic infections.
    - An analysis of TNF inhibitors in RA, PsA, and AS included data from 32 randomized trials (follow-up 2 to 36 months) and 6 open-label extension trials (follow-up 6 to 48 months) (*Bonovas et al 2016*). Synthesis of the data did not demonstrate that the use of TNF inhibitors significantly affects cancer risk during this length of treatment. However, few malignancy events were observed and evidence may be insufficient to make definitive conclusions, particularly regarding longer-term risks.

- Drug interactions
    - Do not give with live (including attenuated) vaccines; additionally, non-live vaccines may not elicit a sufficient immune response.
    - Do not give 2 immunomodulators together.
    - For Xeljanz/Xeljanz XR (tofacitinib), adjust dose with potent inhibitors of cytochrome P450 (CYP) 3A4 and medications that result in both moderate inhibition of CYP3A4 and potent inhibition of CYP2C19. Coadministration with potent CYP3A4 inducers and potent immunosuppressive drugs is not recommended.
- Risk Evaluation and Mitigation Strategy (REMS)
    - Siliq (brodalumab) is available only through the Siliq REMS program. The goal of the program is to mitigate the risk of suicidal ideation and behavior, including completed suicides, which occurred in clinical trials. Key requirements of the REMS program include:
        - Prescribers must be certified with the program.
        - Patients must sign a patient-prescriber agreement form.
        - Pharmacies must be certified with the program and must only dispense to patients who are authorized to receive the product.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
Actemra (tocilizumab)	Vials: 80 mg/4 mL; 200 mg/10 mL; 400 mg/20 mL Prefilled syringe or autoinjector: 162 mg/0.9 mL	**RA:** IV: 4 mg/kg IV every 4 weeks. May increase to 8 mg/kg IV every 4 weeks. Maximum dose = 800 mg. SQ: <100 kg, administer 162 mg SQ every other week, followed by an increase	**RA:** Can give with MTX or other DMARDs. **PJIA and SJIA:** Can give with MTX. **GCA:** Can use alone after discontinuation of	Give as a single 60-minute intravenous infusion. <30 kg, use a 50 mL infusion bag. ≥30 kg, use a 100 mL infusion bag. Before infusion, allow bag to come to room

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
		to every week based on clinical response; ≥100 kg, 162 mg administered SQ every week. **PJIA:** <30 kg, 10 mg/kg IV every 4 weeks; ≥30 kg, 8 mg/kg IV every 4 weeks. <30 kg, 162 mg SQ every 3 weeks; ≥30 kg, 162 mg SQ every 2 weeks. **SJIA:** <30 kg, 12 mg/kg IV every 2 weeks; ≥30 kg, 8 mg/kg IV every 2 weeks; <30 kg, 162 mg SQ every 2 weeks; ≥30 kg, 162 mg SQ once weekly. **GCA:** 162 mg SQ every week with tapering glucocorticoids. May give every other week depending on clinical considerations. **CRS:** <30 kg, 12 mg/kg IV; ≥30 kg, 8 mg/kg IV; maximum, 800 mg per infusion.	glucocorticoids. **CRS:** Can give with corticosteroids. May repeat up to 3 additional doses if no clinical improvement, with at least 8 hours between doses. **RA, PJIA, and SJIA, and GCA**: Adjust dose for liver enzyme abnormalities, low platelet count, infection, and low ANC.	temperature. Do not administer with other drugs. Patients can self-inject with the prefilled syringe or autoinjector. Rotate injection sites.
Cimzia (certolizumab)	Powder for reconstitution: 200 mg Prefilled syringe: 200 mg/mL	**CD:** 400 mg SQ initially and at weeks 2 and 4. Maintenance dose is 400 mg every 4 weeks. **RA, PsA:** 400 mg SQ initially and at weeks 2 and 4. Then 200 mg every 2 weeks. Can consider a maintenance dose of 400 mg every 4 weeks. **PsO:** 400 mg SQ every other week or 400 mg SQ initially and at weeks 2 and 4, followed by 200 mg every other week (for body weight ≤ 90 kg) **AS, NRAS:** 400 mg SQ initially and at weeks 2 and 4. Maintenance	Patients can self-inject with the prefilled syringe.	When a 400 mg dose is required, give as 2 200 mg SQ injections in separate sites in the thigh or abdomen.

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
		dose is 200 mg every 2 weeks or 400 mg every 4 weeks.		
Cosentyx (secukinumab)	Sensoready pen: 150 mg/1 mL Prefilled syringe: 150 mg/1 mL Vial: 150 mg lyophilized powder	**PsO:** 300 mg by SQ injection at weeks 0, 1, 2, 3 and 4, followed by 300 mg every 4 weeks. **PsA, AS:** With a loading dose (not required): 150 mg at weeks 0, 1, 2, 3, and 4, followed by 150 mg every 4 weeks; without loading dose: 150 mg every 4 weeks.	**PsO:** For some patients, a dose of 150 mg may be acceptable. **PsA:** For PsA patients with coexistent moderate to severe PsO, dosing for PsO should be followed. If active PsA or AS continues, consider 300 mg dose every 4 weeks.	Each 300 mg dose is given as 2 subcutaneous injections of 150 mg. Patients may self-administer with the pen or prefilled syringe. The vial is for healthcare professional use only.
Enbrel (etanercept)	Prefilled syringe: 25 mg/0.5 mL and 50 mg/mL Prefilled SureClick autoinjector: 50 mg/mL Multiple-use vial: 25 mg lyophilized powder Solution: 50 mg/mL in Enbrel Mini® cartridge for use with reusable autoinjector only	**RA, AS, PsA:** 50 mg SQ weekly. **PsO (adults):** 50 mg SQ twice weekly for 3 months, then 50 mg weekly. **PJIA and PsO (pediatrics):** ≥63 kg, 50 mg SQ weekly; <63 kg, 0.8 mg/kg SQ weekly.	**RA, AS, PsA:** MTX, NSAIDs, glucocorticoids, salicylates, or analgesics may be continued. **JIA:** NSAIDs glucocorticoids, or analgesics may be continued.	Patients may be taught to self-inject. May bring to room temperature prior to injecting.
Entyvio (vedolizumab)	Lyophilized cake for injection in 300 mg single-dose vial	**CD and UC:** 300 mg administered by IV infusion at time 0, 2, and 6 weeks, and then every 8 weeks thereafter. Discontinue therapy if there is no evidence of therapeutic benefit by week 14.	All immunizations should be to date according to current guidelines prior to initial dose.	Entyvio should be reconstituted at room temperature and prepared by a trained medical professional. It should be used as soon as possible after reconstitution and dilution.
Humira (adalimumab)	Prefilled syringe: 10 mg/0.1 mL 10 mg/0.2 mL 20 mg/0.2 mL 20 mg/0.4 mL 40 mg/0.4 mL 40 mg/0.8 mL	**RA, AS, PsA**: 40 mg SQ every other week. For RA, may increase to 40 mg every week if not on MTX. **PJIA or pediatric uveitis:** 10 kg to <15	**RA, AS, PsA:** MTX, other non-biologic DMARDS, glucocorticoids, NSAIDs, and/or analgesics may be continued.	Patients may be taught to self-inject. Injections should occur at separate sites in the thigh or abdomen. Rotate injection sites. May bring to room

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
	80 mg/0.8 mL Single-use pen: 80 mg/0.8 mL 40 mg/0.8 mL 40 mg/0.4 mL Single-use vial: 40 mg/0.8 mL	kg: 10 mg SQ every other week; 15 kg to <30 kg: 20 mg SQ every other week; ≥30 kg, 40 mg SQ every other week **CD, HS and UC:** 160 mg SQ on Day 1 (given in 1 day or split over 2 consecutive days), followed by 80 mg SQ 2 weeks later (Day 15). Two weeks later (Day 29) begin a maintenance dose of 40 mg SQ every other week. **PsO and UV:** initial dose of 80 mg SQ, followed by 40 mg SQ every other week starting 1 week after the initial dose. **CD in pediatric patients ≥ 6 years and older:** 17 kg to < 40 kg: 80 mg on day 1 (given as two 40 mg injections) and 40 mg 2 weeks later (on day 15); maintenance dose is 20 mg every other week starting at week 4. ≥40 kg: 160 mg on day (given in 1 day or split over 2 consecutive days) and 80 mg 2 weeks later (on day 15); maintenance dose is 40 mg every other week starting at week 4. **HS in adolescent patients ≥12 years and older:** 30 kg to <60 kg: 80 mg on day 1, 40 mg on day 8; maintenance dose is 40 mg every other week. ≥60 kg: 160 mg on day 1, 80 mg on day 15, 40 mg on day 29;	**JIA:** NSAIDs, MTX, analgesics, and/or glucocorticoids, may be continued. **CD and UC:** aminosalicylates and/or corticosteroids may be continued. Azathioprine, 6-MP or MTX may be continued if necessary. Needle cover of the syringe contains dry rubber (latex).	temperature prior to injecting.

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
		maintenance dose is 40 mg every week.		
Ilaris (canakinumab)	Vial: 150 mg (lyophilized powder and injection solution formulations)	**SJIA:** ≥7.5 kg, 4 mg/kg SQ every 4 weeks (maximum dose of 300 mg). **CAPS**: ≥15 to ≤40 kg, 2 mg/kg SQ; >40 kg, 150 mg SQ; frequency every 8 weeks. **TRAPS, HIDS/MKD, and FMF**: ≤40 kg, 2 mg/kg SQ; >40 kg, 150 mg SQ; frequency every 4 weeks.	For CAPS: children 15 to 40 kg with an inadequate response can be increased to 3 mg/kg. For TRAPS, HIDS/MKD, and FMF: If the clinical response is inadequate, the dose may be increased to 4 mg/kg (weight ≤40 kg) or 300 mg (weight >40 kg).	Do not inject into scar tissue.
Ilumya (tildrakizumab-asmn)	Prefilled syringe: 100 mg/mL	**PsO:** 100 mg SQ at weeks 0 and 4, and then every 12 weeks.		Should be administered only by a healthcare provider. Bring to room temperature (30 minutes) prior to injecting.
Inflectra (infliximab-dyyb)	Vial: 100 mg	**CD (≥6 years old), PsA, PsO and UC (≥6 years old)**: 5 mg/kg IV at 0, 2 and 6 weeks followed by a maintenance regimen of 5 mg/kg every 8 weeks. In adults with CD who lose response, can increase dose to 10 mg/kg. **RA:** 3 mg/kg IV at 0, 2 and 6 weeks followed by a maintenance regimen of 3 mg/kg every 8 weeks. Can increase to 10 mg/kg or give every 4 weeks. **AS:** 5 mg/kg IV at 0, 2 and 6 weeks followed by a maintenance regimen of 5 mg/kg every 6	**RA:** give with MTX. **CD:** If no response by week 14, consider discontinuation.	Premedication to help stop infusion reactions can include antihistamines (anti-H1 ± anti-H2), acetaminophen and/or corticosteroids. Use 250 mL 0.9% sodium chloride for infusion. Infuse over 2 hours. Do not administer with other drugs.

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
		weeks.		
Kevzara (sarilumab)	Prefilled syringe: 150 mg/1.14 mL 200 mg/1.14 mL Prefilled pen: 150 mg/1.14 mL 200 mg/1.14 mL	**RA:** 200 mg SQ every 2 weeks.	**RA:** give with or without MTX or other conventional DMARDs Reduce dose for neutropenia, thrombocytopenia, and elevated liver enzymes.	Patients may be taught to self-inject. Bring to room temperature (30 minutes [pre-filled syringe] or 60 minutes [pre-filled pen]) prior to injecting. Rotate injection sites.
Kineret (anakinra)	Prefilled syringe: 100 mg/0.67 mL	**RA:** 100 mg SQ once daily. **CAPS (NOMID):** 1 to 2 mg/kg SQ once daily. Maximum dose is 8 mg/kg/day.	**NOMID**: dose can be given once or twice daily.	Patients may be taught to self-inject. A new syringe must be used for each dose.
Olumiant (baricitinib)	Tablet: 1 mg, 2 mg	**RA:** 2 mg once daily.	Avoid use in combination with other JAK inhibitiors, biologic DMARDs, or potent immunosuppressants such as azathioprine and cyclosporine.	May be taken with or without food.
Orencia (abatacept)	Vial: 250 mg Prefilled syringe: 50 mg/0.4 mL 87.5 mg/0.7 mL 125 mg/1 mL ClickJect autoinjector: 125 mg/mL	**RA:** IV: <60kg, 500 mg IV; 60 to 100 kg, 750 mg IV; >100 kg, 1,000 mg IV initially, then 2 and 4 weeks after the first infusion and every 4 weeks thereafter SQ: 125 mg SQ once weekly initiated with or without an IV loading dose. With IV loading dose, use single IV infusion as per body weight listed above, followed by the first 125 mg SQ injection within a day of the IV infusion and then once weekly. **PJIA:** IV: 6 to 17 years and <75 kg: 10 mg/kg IV initially, then 2 and 4 weeks after the first		IV infusion should be over 30 minutes. Use 100 mL bag for IV infusion. Do not administer with other drugs. Patients may be taught to self-inject the SQ dose. For SQ, injection sites should be rotated.

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
		infusion and every 4 weeks thereafter. >75 kg, follow adult RA IV schedule; maximum dose = 1,000 kg. SQ: 2 to 17 years, 10 to <25 kg, 50 mg once weekly; 25 to < 50 kg, 87.5 mg once weekly, ≥ 50 kg, 125 mg once weekly. **PsA:** IV: follow adult RA IV schedule. SQ: 125 mg once weekly without IV dose.		
Otezla (apremilast)	Tablet: 10 mg, 20 mg, and 30 mg	**PsA, PsO, Behçet's:** Day 1: 10 mg in the morning Day 2: 10 mg in the morning and in the evening Day 3: 10 mg in the morning and 20 mg in evening Day 4: 20 mg in the morning and evening Day 5: 20 mg in the morning and 30 mg in the evening Day 6 and thereafter: 30 mg twice daily.	Titrate according to the labeling when initiating therapy to reduce gastrointestinal symptoms. Dosage should be reduced to 30 mg once daily in patients with severe renal impairment (CrCl <30 mL/min as estimated by the Cockcroft-Gault equation). For initial dosing in these patients, use only the morning titration schedule listed above (evening doses should be excluded).	May be taken with or without food. Do not crush, split, or chew the tablets.
Remicade (infliximab)	Vial: 100 mg	**CD (≥6 years old), PsA, PsO and UC (≥6 years old)**: 5 mg/kg IV at 0, 2 and 6 weeks followed by a maintenance regimen of 5 mg/kg every 8 weeks. In adults with CD who lose response, can increase dose to 10	**RA:** give with MTX. **CD:** If no response by week 14, consider discontinuation.	Premedication to help stop infusion reactions can include antihistamines (anti-H1 ± anti-H2), acetaminophen and/or corticosteroids. Use 250 mL 0.9% sodium chloride for infusion.

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
		mg/kg. **RA:** 3 mg/kg IV at 0, 2 and 6 weeks followed by a maintenance regimen of 3 mg/kg every 8 weeks. Can increase to 10 mg/kg or give every 4 weeks. **AS:** 5 mg/kg IV at 0, 2 and 6 weeks followed by a maintenance regimen of 5 mg/kg every 6 weeks.		Infuse over 2 hours. Do not administer with other drugs.
Renflexis (infliximab-abda)	Vial: 100 mg	**CD (≥6 years old), PsA, PsO and UC (≥6 years old)**: 5 mg/kg IV at 0, 2 and 6 weeks followed by a maintenance regimen of 5 mg/kg every 8 weeks. In adults with CD who lose response, can increase dose to 10 mg/kg. **RA:** 3 mg/kg IV at 0, 2 and 6 weeks followed by a maintenance regimen of 3 mg/kg every 8 weeks. Can increase to 10 mg/kg or give every 4 weeks. **AS:** 5 mg/kg IV at 0, 2 and 6 weeks followed by a maintenance regimen of 5 mg/kg every 6 weeks.	**RA:** give with MTX. **CD:** If no response by week 14, consider discontinuation.	Premedication to help stop infusion reactions can include antihistamines (anti-H1 ± anti-H2), acetaminophen and/or corticosteroids. Use 250 mL 0.9% sodium chloride for infusion. Infuse over 2 hours. Do not administer with other drugs.
Rinvoq (upadacitinib)	Extended release tablet: 15 mg	**RA:** 15 mg once daily.		May be administered with or without food.
Rituxan (rituximab)	Vial: 100 mg/10 mL 500 mg/50 mL	**RA:** Two 1,000 mg IV infusions separated by 2 weeks (one course). Additional doses should be given every 24 weeks or based on clinical evaluation but no sooner than every 16 weeks.	Give with MTX.	Give methyl-prednisolone 100 mg IV 30 minutes prior to each infusion to reduce the incidence and severity of infusion reactions.

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
Siliq (brodalumab)	Prefilled syringe: 210 mg/1.5 mL	**PsO:** 210 mg SQ at weeks 0, 1, and 2 followed by every 2 weeks.	**PsO**: If an adequate response has not been achieved after 12 to 16 weeks, consider discontinuation.	Patients may self-inject when appropriate and after proper training. The syringe should be allowed to reach room temperature before injecting.
Simponi/Simponi Aria (golimumab)	SmartJect® autoinjector: 50 mg/0.5 mL and 100 mg/mL Prefilled syringe: 50 mg/0.5 mL and 100 mg/mL Aria, Vial: 50 mg/4 mL	**RA, PsA, and AS**: 50 mg SQ once monthly **UC:** 200 mg SQ at week 0; then 100 mg at week 2; then 100 mg every 4 weeks. **Aria (RA, PsA, and AS)**: 2 mg/kg IV at weeks 0 and 4, then every 8 weeks.	**RA:** give with MTX. **PsA and AS**: may give with or without MTX or other DMARDs. Needle cover of the syringe contains dry rubber (latex). **Aria (RA)**: give with MTX (**PsA, AS)**: give with or without MTX or other non-biologic DMARDs. Corticosteroids, NSAIDs, and/or analgesics may be continued. Efficacy and safety of switching between IV and SQ formulations have not been established.	Patients may be taught to self-inject the SQ dose. For SQ, injection sites should be rotated. For SQ, bring to room temperature for 30 minutes prior to injecting. **Aria**: IV infusion should be over 30 minutes. Dilute with 0.9% sodium chloride or 0.45% sodium chloride for a final volume of 100 mL. Do not administer with other drugs.
Skyrizi (risankizumab-rzaa)	Prefilled syringe: 75 mg/0.83 mL	**PsO:** 150 mg (two 75 mg injections) SQ at week 0, week 4, and every 12 weeks thereafter.	Product is not made with natural rubber latex.	Each dose must be administered in different anatomic locations. Patients may be taught to self-inject using the prefilled syringes.
Stelara (ustekinumab)	Prefilled syringe: 45mg/0.5 mL and 90 mg/mL Vial: 45 mg/0.5 mL and 130 mg/26 mL	**PsO**: ≤100 kg, 45 mg SQ initially and 4 weeks later, followed by 45 mg every 12 weeks. >100 kg, 90 mg SQ initially and 4 weeks later, followed by 90 mg	**Co-existent moderate-to-severe PsO with PsA weighing >100 kg**: 90 mg SQ initially and 4 weeks later,	Patients may be taught to self-inject using the prefilled syringes. Stelara for IV infusion must be diluted, prepared and infused by a healthcare

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
		every 12 weeks. **PsO (adolescents):** <60 kg, 0.75 mg/kg (injection volume based on weight) 60 to 100 kg, 45 mg >100 kg, 90 mg. **PsA:** 45 mg SQ initially and 4 weeks later, followed by 45 mg every 12 weeks. **CD and UC**: Initial single IV dose: ≤55 kg, 260 mg; >55 kg to ≤85 kg, 390 mg; >85 kg, 520 mg; followed by 90 mg SQ every 8 weeks (irrespective of body weight).	followed by 90 mg every 12 weeks. Needle cover of the syringe contains dry rubber (latex).	professional; it is diluted in 0.9% sodium chloride or 0.45% sodium chloride for a final volume of 250 mL and infuse over at least 1 hour. Rotate injection sites.
Taltz (ixekizumab)	Prefilled syringe: 80 mg/mL Autoinjector: 80 mg/mL	**PsO:** 160 mg by SQ injection at week 0, followed by 80 mg at weeks 2, 4, 6, 8, 10, and 12, then 80 mg every 4 weeks. **PsA, AS:** 160 mg by SQ injection at week 0, followed by 80 mg every 4 weeks. NOTE: For patients with PsA with coexistent moderate-to-severe PsO, use dosing regimen for PsO.		Patients may be taught to self-inject with either the prefilled syringe or the autoinjector. Bring to room temperature prior to injecting. Rotate injection sites.
Tremfya (guselkumab)	Prefilled syringe or single-dose patient-controlled autoinjector: 100 mg/mL	**PsO:** 100 mg by SQ injection at week 0, week 4, and then every 8 weeks		Patients may be taught to self-inject. Bring to room temperature (30 minutes) prior to injecting.
Xeljanz/Xeljanz XR (tofacitinib)	Tablet: 5 mg, 10 mg Extended-release Tablet: 11 mg, 22 mg	**RA:** 5 mg PO twice daily or 11 mg PO once daily **PsA:** 5 mg PO twice daily or 11 mg once daily used in	Patients may switch from Xeljanz 5 mg twice daily to Xeljanz XR 11 mg once daily the day following the last	May take with or without food. Swallow Xeljanz XR tablets whole; do not crush, split, or chew.

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
		combination with nonbiologic DMARDs **UC (induction):** 10 mg PO twice daily or 22 mg PO once daily for 8 weeks, then, if needed, continue 10 mg twice daily or 22 mg once daily for a maximum of 16 weeks. Discontinue therapy after 16 weeks if an adequate therapeutic response is not achieved. **UC (maintenance):** 5 mg PO twice daily or 11 mg PO once daily; for patients with loss of response during maintenance, 10 mg twice daily or 22 mg once daily may be considered and limited to the shortest duration.	dose of Xeljanz 5 mg. Patients may switch from Xeljanz 10 mg twice daily to Xeljanz XR 22 mg once daily the day following the last dose of Xeljanz 10 mg. Use as monotherapy or in combination with MTX or other nonbiologic DMARDs in RA. Dose adjustment needed in patients taking CYP450 inhibitors and in lymphopenia, neutropenia, and anemia.	

ANC=absolute neutrophil count; AS=ankylosing spondylitis; CRS=cytokine release syndrome; DMARD=disease-modifying anti-rheumatic drug; GCA=giant cell arteritis; HS=hidradenitis suppurative; IV=intravenous infusion; JAK=Janus kinase; JIA=juvenile idiopathic arthritis; MTX=methotrexate; NOMID=neonatal-onset multisystem inflammatory disease; NRAS=nonradiographic axia spondyloarthritis; NSAID=non-steroidal anti-inflammatory drug; PJIA=polyarticular juvenile idiopathic arthritis; PO=orally; PsA=psoriatic arthritis; PsO=plaque psoriasis; RA=rheumatoid arthritis; SJIA=systemic juvenile idiopathic arthritis; SQ=subcutaneously; UC=ulcerative colitis.

SPECIAL POPULATIONS

Table 4. Special Populations

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy and Nursing
Actemra (tocilizumab)	Frequency of serious infection greater in ≥65 years. Use caution.	Not studied in children <2 years. Safety and efficacy only established in SJIA, PJIA, and CRS.	No dose adjustment in mild or moderate impairment. Not studied in severe impair-ment.	Not studied in patients with impairment.	Unclassified† Limited data in pregnant women not sufficient to determine risks. Unknown whether excreted in breast milk; risks and benefits should be considered.
Cimzia (certolizumab)	The number of subjects ≥65 years in clinical trials	Safety and effectiveness have not been	No data	No data	Unclassified† Limited data from

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy and Nursing
	was not sufficient to determine whether they responded differently from younger subjects. Use caution.	established.			ongoing pregnancy registry not sufficient to inform risks. Minimal exrection in breast milk; risks and benefits should be considered.
Cosentyx (secukinumab)	The number of subjects ≥65 years in clinical trials was not sufficient to determine whether they responded differently from younger subjects.	Safety and efficacy have not been established.	No data	No data	Unclassified† Data on use in pregnant women insufficient to inform risks. Unknown whether excreted in breast milk; use with caution.
Entyvio (vedolizumab)	The number of patients ≥65 years in clinical trials was not sufficient to determine whether they responded differently from younger subjects.	Safety and efficacy have not been established.	No data	No data	Unclassified† Available and ongoing data have not identified a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Available data suggest presence in milk; use with caution.
Enbrel (etanercept)	Use caution.	Not studied in children <2 years with PJIA or <4 years with PsO.	No data	No data	Unclassified† Available studies do not reliably support association with major birth defects. Present in low levels in breast milk; consider risks and benefits.
Humira (adalimumab)	Frequency of serious infection and malignancies is greater in ≥65 years. Use caution.	Only studied in PJIA, pediatric uveitis (ages 2 years and older), CD (6 years and	No data	No data	Unclassified† Available studies do not reliably support association with major birth defects.

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy and Nursing
		older), and HS (12 years and older).			Present in low levels in breast milk; consider risks and benefits.
Ilaris (canakinumab)	The number of patients ≥65 years in clinical trials was not sufficient to determine whether they responded differently from younger subjects.	Not studied in children <2 years (SJIA, TRAPS, HIDS/ MKD, and FMF) or <4 years (CAPS).	No data	No data	Unclassified† Limited data from postmarketing reports not sufficient to inform risks. Unknown whether excreted in breast milk; consider risks and benefits.
Ilumya (tildrakizumab-asmn)	The number of patients ≥65 years in clinical trials was not sufficient to determine whether they responded differently from younger subjects.	Safety and efficacy have not been established.	No data	No data	Unclassified† Data on use in pregnant women insufficient to inform risks. Unknown whether excreted in breast milk; consider risks and benefits.
Inflectra (infliximab-dyyb)	Frequency of serious infection is greater in ≥65 years. Use caution.	Not recom-mended in <6 years in children with CD or UC.	No data	No data	Unclassified† Available data have not reported a clear association with adverse pregnancy outcomes. Unknown whether excreted in breast milk; consider risks and benefits.
Kevzara (sarilumab)	Frequency of serious infection is greater in ≥ 65 years. Use caution.	Safety and efficacy have not been established.	Dosage adjustment not required in mild to moderate renal impairment. Kevzara has not been studied in severe renal impairment.	No data	Unclassified† Data on use in pregnant women insufficient to inform risks. Unknown whether excreted in breast milk; consider risks and benefits.

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy and Nursing
Kineret (anakinra)	Use caution as there is a higher incidence of infections in the elderly in general.	For NOMID, has been used in all ages. Not possible to give a dose <20 mg.	CrCl<30 mL/min: give dose every other day.	No data	Unclassified† Data on use in pregnant women insufficient to inform risks. Unknown whether excreted in breast milk; use caution.
Olumiant (baricitinib)	No overall differences were observed in the safety and efficacy profiles of elderly patients.	Safety and efficacy have not been established.	Use not recommended in patients with estimated glomerular filtration rate < 30 mL/min/1.73 m^2; for estimated glomerular filtration rate between 30 and 60 mL/min/1.73m^2: administer 1 mg once daily.	No dose adjustment for mild or moderate impairment; not recommended in patients with severe hepatic impairment.	Unclassified† Data on use in pregnant women insufficient to inform risks. Unknown whether excreted in breast milk; avoid use.
Orencia (abatacept)	Frequency of serious infection and malignancies is greater in ≥65 years. Use caution.	Not recom-mended in <2 years old. IV dosing has not been studied in patients < 6 years old. ClickJect autoinjector subcutaneous injection has not been studied in patients < 18 years.	No data	No data	Unclassified† Data on use in pregnant women insufficient to inform risks. Unknown whether excreted in breast milk.
Otezla (apremilast)	No overall differences were observed in the safety profile of elderly patients.	Safety and efficacy have not been established.	The dose of Otezla should be reduced to 30 mg once daily in patients with severe renal impairment (CrCl<30	No dosage adjustment necessary.	Unclassified† Available data have not established a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes.

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy and Nursing
			mL/min).		Unknown whether excreted in breast milk; consider risks and benefits.
Remicade (infliximab)	Frequency of serious infection is greater in ≥65 years. Use caution.	Not recommended in <6 years in children with CD or UC.	No data	No data	Pregnancy category B* Unknown whether excreted in breast milk; discontinue nursing or discontinue the drug.
Renflexis (infliximab-abda)	Frequency of serious infection is greater in ≥ 65 years. Use caution.	Not recommended in < 6 years in children with CD or UC.	No data	No data	Unclassified† Available data do not report clear association with adverse outcomes. Unknown whether excreted in breast milk; consider risks and benefits.
Rinvoq (upadacitinib)	No differences in safety or efficacy were observed between older and younger patients; however, there was a higher rate of overall adverse events in elderly patients.	Safety and efficacy have not been established.	No dose adjustment required.	No dose adjustment required in mild or moderate hepatic impairment; not recommended in severe hepatic impairment.	Unclassified† Animal data suggest potential for fetal harm; females of reproductive potential should use effective contraception during treatment and for 4 weeks following completion of therapy. Unknown whether excreted in human breast milk, but excreted in animal milk; breastfeeding not recommended during treatment and for 6 days after last dose.

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy and Nursing
Rituxan (rituximab)	Rates of serious infections, malignancies, and cardiovascular events were higher in older patients.	Indicated for the treatment of GPA and MPA in children ≥2 years of age; safety and efficacy not established in children with NHL, CLL, PV, or RA.	No data	No data	Unclassified† May potentially cause B-cell lymphocytopenia due to in-utero exposure; advise women to use effective contraception during treatment and for at least 12 months after the last dose. Unknown whether excreted in breast milk; advise women not to breastfeed during treatment and for at least 6 months after the last dose.
Siliq (brodalumab)	No differences in safety or efficacy were observed between older and younger patients, but the number of patients ≥65 years in clinical trials was insufficient to determine any differences in response.	Safety and effectiveness in <18 years have not been established.	No data	No data	Unclassified† There are no human data in pregnant women to inform risks. Unknown whether excreted in breast milk; risks and benefits should be weighed before use.
Simponi/ Simponi Aria (golimumab)	SQ: No differences in AEs observed between older and younger patients. Use caution. IV Aria: Use caution.	Effectiveness in <18 years has not been established (Simponi). Safety and effectiveness in < 18 years have not been established (Aria).	No data	No data	Unclassified† No adequate and well-controlled trials in pregnant women. Unknown whether excreted in breast milk. Consider risks and benefits.
Skyrizi (risankizumab-rzaa)	No differences observed between older and younger patients. Use caution.	Safety and efficacy have not been established.	No data	No data	Unclassified† Limited data in pregnant women are insufficient to inform risks.

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy and Nursing
					Unknown whether excreted in breast milk; consider risks and benefits.
Stelara (ustekinumab)	No differences observed between older and younger patients. Use caution.	Safety and effectiveness have been established in children 12 to 17 years with moderate to severe PsO; safety and effectiveness not established in children with PsA, CD, or UC.	No data	No data	Unclassified† Limited data in pregnant women are insufficient to inform risks. Unknown whether excreted in breast milk; systemic exposure to breastfed infant expected to be low; consider risks and benefits.
Taltz (ixekizumab)	No differences observed between older and younger patients; however, the number of patients ≥65 years in clinical trials was not sufficient to determine differences.	Safety and effectiveness have not been established.	No data	No data	Unclassified† There are no available data in pregnant women to inform risks. Unknown whether excreted in breast milk; consider risks and benefits.
Tremfya (guselkumab)	No differences observed between older and younger patients; however, the number of patients ≥ 65 years in clinical trials was not sufficient to determine differences.	Safety and efficacy have not been established.	No data	No data	Unclassified† No available data in pregnant women to inform risks. Unknown whether excreted in breast milk; consider risks and benefits.

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy and Nursing
Xeljanz/Xeljanz XR (tofacitinib)	Frequency of serious infection is greater in ≥65 years. Use caution.	Safety and effectiveness have not been established.	Moderate to severe impairment: Patients with RA or PsA receiving Xeljanz XR should switch to Xeljanz and reduce dose to 5 mg once daily and those receiving Xeljanz 5 mg twice daily should reduce to 5 mg once daily. Patients with UC on Xeljanz should switch to 5 mg twice daily (if on 10 mg twice daily) or 5 mg once daily (if on 5 mg twice daily). Patients with UC on Xeljanz XR 22 mg once daily, should reduce to 11 mg once daily; if taking 11 mg once daily, reduce to Xeljanz 5 mg once daily.	Moderate impairment: Patients with RA or PsA receiving Xeljanz XR should switch to Xeljanz and reduce dose to 5 mg once daily and those receiving Xeljanz 5 mg twice daily should reduce to 5 mg once daily. Patients with UC on Xeljanz should switch to 5 mg twice daily (if on 10 mg twice daily) or 5 mg once daily (if on 5 mg twice daily). Patients with UC on Xeljanz XR 22 mg once daily, should reduce to 11 mg once daily; if taking 11 mg once daily, reduce to Xeljanz 5 mg once daily. Not recom-mended in severe hepatic impairment.	Unclassified† Available data are insufficient to inform a drug-associated risk; consider pregnancy planning and prevention for females of reproductive potential. Unknown whether excreted in breast milk; advise women to avoid breastfeeding during treatment and for at least 18 hours after the last dose of Xeljanz or 36 hours after the last dose of Xeljanz XR.

CLL=chronic lymphocytic leukemia; CrCl=creatinine clearance; CD=Crohn's disease; CAPS=cryopyrin-associated periodic syndromes; CRS=cytokine release syndrome; FMF=familial Mediterranean fever; GPA=granulomatosis with polyangiitis; HS=hidradenitis suppurative; HIDS/MKD=hyperimmunoglobulin D syndrome/mevalonate kinase deficiency; MPA=microscopic polyangiitis; NHL=non-Hodgkin's lymphoma; NOMID= Neonatal-Onset Multisystem Inflammatory Disease; PJIA=polyarticular juvenile idiopathic arthritis; PsA=psoriatic arthritis; PsO=plaque psoriasis; PV=pemphigus vulgaris; RA=rheumatoid arthritis; SJIA=systemic juvenile idiopathic arthritis; TRAPS=tumor necrosis factor receptor associated periodic syndrome; UC=ulcerative colitis; XR=extended-release.
*Pregnancy Category B = No evidence of risk in humans, but there remains a remote possibility. Animal reproduction studies have failed to demonstrate a risk to the fetus, and there are no adequate and well-controlled studies in pregnant women.

[†]In accordance with the FDA's Pregnancy and Lactation Labeling Rule (PLLR), this product is not currently assigned a Pregnancy Category. Consult product prescribing information for details.

CONCLUSION

- Immunomodulators for a variety of conditions associated with inflammation are available. Mechanisms of action and indications vary among the products. Products in this class have clinical trial data supporting efficacy for their FDA-approved indications.
- Limited head-to-head clinical trials between the agents have been completed.
    - In patients with RA, abatacept and infliximab showed comparable efficacy at 6 months, but abatacept demonstrated greater efficacy after 1 year on some endpoints such as DAS28-ESR, EULAR response, LDAS, and ACR 20 responses (*Schiff et al 2008*).
    - In patients with RA, abatacept and adalimumab were comparable for ACR 20 and ACR 50 responses over 2 years in a single-blind study (*Schiff et al 2014*).
    - In patients with RA and an inadequate response or intolerance to MTX, sarilumab significantly improved change from baseline in DAS28-ESR over adalimumab (*Burmester et al 2017*). DAS28-ESR remission, ACR 20/50/70 response rates, and improvements in HAQ-DI scores were also more likely with sarilumab.
    - Patients with severe arthritis who could not take MTX were randomized to monotherapy with tocilizumab or adalimumab for 24 weeks in a randomized, double-blind study (*Gabay et al 2013*). The patients in the tocilizumab group had a significantly greater improvement in DAS28 at week 24 than patients in the adalimumab group.
    - In patients with RA and inadequate response or intolerance to MTX, upadacitinib was associated with significantly greater ACR 20 response compared with adalimumab at weeks 12 and 26 *(Fleischman et al 2018).*
    - In biologic-naïve patients with RA and an inadequate response to DMARDs, initial treatment with rituximab was demonstrated to have non-inferior efficacy to initial TNF inhibitor treatment (*Porter et al 2016*).
    - A randomized, open-label trial evaluated biologic treatments in patients with RA who had had an inadequate response to a TNF inhibitor. In this population, a non-TNF biologic (tocilizumab, rituximab, or abatacept) was more effective in achieving a good or moderate disease activity response at 24 weeks than use of a second TNF inhibitor. However, a second TNF inhibitor was also often effective in producing clinical improvement (*Gottenberg et al 2016*). Another recent randomized trial did not demonstrate clinical efficacy differences between abatacept, rituximab, and use of a second TNF inhibitor in this patient population *(Manders et al 2015*).
    - Secukinumab and ustekinumab were compared for safety and efficacy in the CLEAR and CLARITY studies, which were double-blind, randomized controlled trials in 676 and 1102 patients, respectively, with moderate to severe PsO (*Bagel et al 2018, Thaçi et al 2015*). In both studies, the proportion of patients achieving PASI 90 was significantly higher with secukinumab compared to ustekinumab (CLEAR: 79% vs 57.6%, $p < 0.0001$; CLARITY: 66.5% vs 47.9%, $p < 0.0001$) at week 16 in CLEAR and at week 12 in CLARITY.
    - In the IXORA-S study, the proportion of patients achieving PASI 90 at week 12 was significantly higher with ixekizumab compared to ustekinumab (72.8% vs 42.2%, respectively; $p < 0.001$) (*Reich et al 2017[b]).*
    - A greater proportion of PsO patients achieved the primary outcome, PASI 75 at week 12, with ustekinumab 45 mg (67.5%) and 90 mg (73.8%) compared to etanercept 50 mg (56.8%; $p = 0.01$ vs ustekinumab 45 mg; $p < 0.001$ vs ustekinumab 90 mg). In this trial, etanercept therapy was associated with a greater risk of injection site erythema than ustekinumab (14.7% vs 0.7%) (*Griffiths et al 2010*).
    - In the FIXTURE study in patient with moderate to severe PsO, 77.1%, 67%, 44%, and 4.9% of patients achieved PASI 75 with secukinumab 300 mg, secukinumab 150 mg, etanercept at FDA-recommended dosing, and placebo, respectively (*Langley et al 2014*).
    - In the UNCOVER-2 and UNCOVER-3 studies, the proportions of patients achieving PASI 75 and achieving PGA 0 or 1 were higher in patients treated with ixekizumab compared to those treated with etanercept.
    - In the AMAGINE-2 and AMAGINE-3 studies, the proportions of patients achieving PASI 100 were higher in patients treated with brodalumab compared to those treated with ustekinumab (*Lebwohl et al 2015*).
    - In the VOYAGE 1 and VOYAGE 2 studies, the proportions of patients with moderate to severe PsO achieving IGA 0 or 1 and PASI 90 were higher with guselkumab compared to those treated with adalimumab *(Blauvelt et al 2017, Reich et al 2017[a]*).
    - In two trials of patients with moderate to severe chronic PsO, risankizumab was associated with significant improvement in PASI 90 response at week 16 vs ustekinumab *(Gordon et al 2018)*.

  - In ECLIPSE, patients with moderate-to-severe plaque PsO were randomly assigned to Tremfya (guselkumab) or Cosentyx (secukinumab) (*Reich et al 2019[a]*). Results revealed that the proportion of patients with a PASI 90 response at week 48 was greater in the guselkumab group as compared to the secukinumab group (84% vs 70%; p < 0.0001).
  - No meaningful differences were shown in the treatment of RA and PsA in comparisons of infliximab and infliximab-dyyb conducted to establish biosimilarity between these agents (*Park et al 2013, Park et al 2016, Park et al 2017, Yoo et al 2013, Yoo et al 2016, Yoo et al 2017*). Similarly, no meaningful differences between infliximab and infliximab-abda were found in treatment of RA in clinical studies to establish biosimilarity (*Choe et al 2017, Shin et al 2015*).
  - In patients with CD, UC, RA, PsA, spondyloarthritis, and PsO who were treated with the originator infliximab for ≥ 6 months, infliximab-dyyb was noninferior to infliximab originator group for disease worsening (*Jørgensen et al 2017*).
  - Entyvio (vedolizumab) was directly compared to Humira (adalimumab) in the VARSITY trial (*Sands et al 2019*). Results revealed that clinical remission at week 52 occurred in significantly more patients in the vedolizumab group (31.3% vs 22.5%; difference, 8.8%; 95% CI, 2.5 to 15; p = 0.0006). Endoscopic improvement was also significantly improved with vedolizumab (39.7% vs 27.7%; difference, 11.9%; 95% CI, 5.3 to 18.5; p < 0.001). However, corticosteroid-free clinical remission was better with adalimumab (12.6% vs 21.8%; difference, -9.3%; 95%, -18.9 to 0.4).
  - More comparative studies are needed.
- For RA, patients not responding to initial DMARD treatment may be treated with combination DMARDs, TNF inhibitors, non-TNF inhibitor biologics, and/or tofacitinib per ACR guidance (*Singh et al 2016c*). EULAR guidelines for RA management were recently updated (*Smolen et al 2020*). EULAR recommends that therapy with DMARDs should be initiated as soon as the RA diagnosis is made with treatment aimed at reaching a target of sustained remission or low disease activity in every patient. If the treatment target is not achieved with the first conventional synthetic DMARD strategy, in the absence of poor prognostic factors, others should be considered. If poor prognostic factors are present with treatment failure, a biological or targeted synthetic DMARD should be added. If a biological or targeted synthetic DMARD has failed, treatment with another should be considered. If one TNF inhibitor therapy has failed, patients may receive an agent with another mode of action or a second TNF inhibitor. EULAR has also released guidelines for use of antirheumatic drugs in pregnancy, which state that the TNF inhibitors etanercept and certolizumab are among possible treatment options for patients requiring therapy (*Götestam Skorpen et al 2016*).
- For the management of PsO, biologic agents are routinely used when ≥ 1 traditional systemic agents are not tolerated, fail to produce an adequate response, or are unable to be used due to patient comorbidities (*Gottleib et al 2008, Menter et al 2008, Menter et al 2009a, Menter et al 2009b, Menter et al 2011, Nast et al 2015b*). EULAR 2015 PsA guidelines recommend TNF inhibitors in patients with peripheral arthritis and an inadequate response to at least 1 synthetic DMARD, such as MTX (*Gossec et al 2016, Ramiro et al 2016*). For patients with peripheral arthritis and an inadequate response to at least 1 synthetic DMARD, in whom a TNF inhibitor is not appropriate, biologics targeting IL-12/23 or IL-17 pathways may be considered. Apremilast is considered a treatment option in patients with peripheral arthritis and an inadequate response to at least 1 synthetic DMARD, in whom biologics are not appropriate. Guidelines from GRAPPA recommend various biologics for the treatment of PsO and PsA based on patient-specific factors, including TNF inhibitors, IL-17 and IL-12/23 inhibitors, and PDE-4 inhibitors (*Coates et al 2016*). Joint guidelines from the American Academy of Dermatology/National Psoriasis Foundation on the treatment of psoriasis with biologics do not provide ranking for preferences of individual biologics, but do note that etanercept, infliximab, adalimumab, ustekinumab, secukinumab, ixekizumab, brodalumab, guselkumab, risankizumab, and tildrakizumab can be recommended as a monotherapy option for patients with moderate to severe PsO (*Menter et al 2019*).
- The American College of Rheumatology/National Psoriasis Foundation guideline on PsA recommends that a TNF inhibitor is preferred in treatment-naïve patients with active PsA, although an oral therapy can be a first-line option in patients without severe PsA and without severe psoriasis, or if a patient has another compelling reason to avoid a TNF inhibitor. In patients who fail oral therapy, a switch to a TNF inhibitor is preferred and placed ahead of IL-17 biologics, IL-12/23 biologics, abatacept, and tofacitinib (*Singh et al 2019*).
- The ACR guideline for SJIA notes that IL-1 and IL-6 play a central role in the inflammatory process for this condition, and recommend agents such as anakinra, canakinumab, tocilizumab, abatacept, and TNF inhibitors among either first- or second-line treatments (*Ringold et al 2013*). Patients with JIA and active sacroiliitis or enthesitis are recommended to receive TNF inhibitor therapy, and patients with non-systemic polyarthritis are recommended to

receive TNF inhibitor therapy, abatacept, or tocilizumab. Patients with continued disease activity and primary TNF inhibitor failure are recommended to receive abatacept or tocilizumab *(Ringold et al 2019)*.

- According to the ACG, for induction of remission in moderately to severely active UC, TNF inhibitor therapy, vedolizumab, or tofacitinib are recommended, and should be continued to maintain remission. Vedolizumab and tofacitinib are recommended in patients with previous failure to TNF inhibitor therapy (*Rubin et al 2019*). For adult outpatients with moderate to severe UC, the AGA strongly recommends using infliximab, adalimumab, golimumab, vedolizumab, tofacitinib, or ustekinumab over no treatment (*Feuerstein et al 2020*). The AGA recommends that for patients at high risk for colectomy, anti-TNF drugs and vedolizumab can be considered for induction and maintenance therapy (*Dassopoulos et al 2014*). ECCO guidelines recommend thiopurine, anti-TNF drugs, vedolizumab, or methotrexate for patients with UC who have active steroid-dependent disease and anti-TNF agents or vedolizumab for patients who have steroid- or immunomodulator-refractory disease (*Harbord et al 2017*).
- The ACG states that the anti-TNF monoclonal antibodies adalimumab, certolizumab, and infliximab are effective in the treatment of moderate to severely active CD in patients who are resistant to corticosteroids or are refractory to thiopurines or methotrexate. These agents can be considered for treating perianal fistulas, and infliximab can also treat enterocutaneous and rectovaginal fistulas in CD. Adalimumab, certolizumab, and infliximab are effective for the maintenance of anti-TNF induced remission as monotherapy or in combination with azathioprine/6-mercaptopurine or methotrexate. The combination of infliximab with an immunomodulator (thiopurine) is more effective than monotherapy with individual agents in patients with moderate to severe CD and who are naïve to both agents. Infliximab can also treat fuliminant CD. Vedolizumab with or without an immunomodulator can be used for induction and maintenance of remission in patients with moderate to severe CD. Patients are candidates for ustekinumab therapy, including for the maintenance of remission, if they have moderate to severe CD and have failed corticosteroids, thiopurines, methotrexate, or anti-TNF inhibitors. The guideline acknowledges the effectiveness of biosimilar infliximab and biosimilar adalimumab for the management of moderate to severe CD (*Lichtenstein et al 2018*). The AGA recommends using anti-TNF drugs to induce remission in patients with moderately severe CD (*Terdiman et al 2013*). In 2020, ECCO released a guideline on medical treatment in CD (*Torres et al 2020*). Regarding immunomodulators, these guidelines recommend the use of TNF inhibitors (infliximab, adalimumab, and certolizumab pegol) to induce remission in patients with moderate-to-severe CD who have not responded to conventional therapy, among other recommendations.
- Consensus statements for the management of inflammatory bowel disease in pregnancy, from the Canadian Association of Gastroenterology and from the AGA, recommend that biologics can be continued during pregnancy and delivery as the benefits of maintaining disease remission outweigh any risks associated with biologic maintenance therapy (*Mahadevan et al 2019, Nguyen et al 2016[b]*).
- Based upon guidelines from the European Dermatology Forum, adalimumab is recommended among first-line therapies for HS, with infliximab a potential second-line option (*Gulliver et al 2016, Zouboulis et al 2015*).
- Joint guidelines from ASAS and EULAR state that biologic DMARDs should be considered in patients with AS and persistently high disease activity despite conventional treatments (*van der Heijde et al 2017[b]*). The 2019 ACR, Spondylitis Association of America, and Spondyloarthritis Research and Treatment Network guidelines strongly recommend TNF inhibitors for patients who have active disease despite NSAIDs; no TNF inhibitor is preferred over another for AS for most patients. Secukinumab or ixekizumab are recommended in patients with active disease who have primary nonresponse with a TNF inhibitor (*Ward et al 2019*).
- Infliximab and adalimumab are recommended over etanercept for various ocular inflammatory disorders (*Levy-Clarke et al 2016*).
- Caution is warranted with these biologic agents due to severe infections and malignancies that can occur with their use. Tocilizumab, TNF inhibitors, tofacitinib, sarilumab, baricitinib, and upadacitinib have boxed warnings regarding a risk of serious infections. TNF inhibitors, tofacitinib, baricitinib, and upadacitinib also have boxed warnings regarding an increased risk of malignancies. Brodalumab has a boxed warning regarding the risk of suicidal ideation and behavior. Tofacitinib (10 mg twice daily dose), upadacitinib, and baricitinib also have boxed warnings regarding thrombosis risk.
- Warnings, precautions, and AE profiles vary in this class.
- All of the biologic agents with the exception of apremilast, baricitinib, tofacitinib, and upadacitinib are given by subcutaneous injection and/or intravenous infusion. Administration schedule varies among the injectable agents in the class. Apremilast, baricitinib, tofacitinib, and upadacitinib are given orally.
- Selection of an agent for a patient is determined by approved indications, response, administration method, tolerability, AE profile, and cost of the agent.

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