# 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 five originator TNF inhibitors: CIMZIA® (certolizumab), ENBREL® (etanercept), HUMIRA® (adalimumab), REMICADE® (infliximab), and SIMPONI®/SIMPONI® ARIA™ (golimumab), as well as three biosimilar TNF inhibitors: AMJEVITA (adalimumab-atto), ERELZI (etanercept-szzs), and INFLECTRA (infliximab-dyyb). Other agents targeting different cells and cytokines are also FDA approved for RA treatment. 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), which has activity directed against the IL-6 receptor; and KINERET® (anakinra), which targets the IL-1 receptor. An oral agent on the market, XELJANZ® and XELJANZ® XR (tofacitinib), targets 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. COSENTYX™ (secukinumab) and TALTZ® (ixekizumab) bind and neutralize IL-17A and are indicated for the treatment of PsO; COSENTYX is additionally indicated to treat PsA and AS. A related agent, SILIQ™ (brodalumab), is an IL-17 receptor antagonist 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; these 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)
- RITUXAN is also approved for non–Hodgkin's lymphoma (NHL), chronic lymphocytic leukemia (CLL), and granulomatosis with polyangiitis (GPA) (Wegener's granulomatosis) and microscopic polyangiitis (MPA). 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, 2016). 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 AMJEVITA (adalimumab-atto) and ERELZI (etanercept-szzs) are pending and may be delayed; thus, information on AMJEVITA and ERELZI is not currently included in this review.
- 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 | Manufacturer | FDA Approval Date | Biosimilar or Generic Availability | Type of Agent |
|---|---|---|---|---|
| ACTEMRA (tocilizumab) | Genentech | 01/08/2010 | - | Human monoclonal antibody targeting the IL-6 receptor |
| CIMZIA (certolizumab) | UCB | 04/22/2008 | - | TNFα inhibitor |
| COSENTYX (secukinumab) | Novartis | 01/21/2015 | - | Human monoclonal antibody to IL-17A |
| ENBREL (etanercept) | Amgen | 11/02/1998 | -* | sTNFR fusion protein, TNFα inhibitor |
| ENTYVIO (vedolizumab) | Takeda Pharmaceuticals America, Inc. | 05/20/2014 | - | Human monoclonal antibody binds to the α4β7 integrin |
| HUMIRA (adalimumab) | Abbott | 12/31/2002 | -* | TNFα inhibitor |
| ILARIS (canakinumab) | Novartis | 06/17/2009 | - | Human monoclonal antibody that binds to IL-1ß |
| INFLECTRA (infliximab-dyyb) | Celltrion/ Hospira/Pfizer | 04/05/2016 | N/A† | TNFα inhibitor |
| KINERET (anakinra) | Swedish Orphan Biovitrum | 11/14/2001 | - | IL-1 receptor antagonist |
| ORENCIA (abatacept) | Bristol Myers Squibb | 12/23/2005 | - | sCTLA-4-Ig recombinant fusion protein |
| OTEZLA (apremilast) | Celgene Corporation | 03/21/2014 | - | Small-molecule phosphodiesterase 4 inhibitor |
| REMICADE (infliximab) | Janssen Biotech | 8/24/1998 | -† | TNFα inhibitor |
| RITUXAN (rituximab) | Genentech | 11/26/1997 | - | Anti-CD20 monoclonal antibody |
| SILIQ (brodalumab)‡ | Valeant | 02/15/2017 | - | Human monoclonal antibody directed against the IL-17 receptor A (IL-17RA) |
| SIMPONI/ SIMPONI ARIA (golimumab) | Janssen Biotech | 04/24/2009 and 07/18/2013 | - | TNFα inhibitor |
| STELARA (ustekinumab) | Janssen Biotech | 09/25/2009 | - | Human monoclonal antibody targeting the IL-12 and IL-23 cytokines |
| TALTZ (ixekizumab) | Eli Lilly | 03/22/2016 | - | Human monoclonal antibody to IL-17A |
| XELJANZ / XELJANZ XR (tofacitinib) | Pfizer | 11/06/2012 and 02/23/2016 | - | Small molecule Janus kinase (JAK) inhibitor |

*ERELZI (etanercept-szzs) and AMJEVITA (adalimumab-atto) have been FDA approved as biosimilars to ENBREL (etanercept) and HUMIRA (adalimumab), respectively. The specific launch dates for these products are pending and may be delayed. Further information on ERELZI and AMJEVITA will be included in this review closer to the time of launch.
†INFLECTRA (infliximab-dyyb) has been FDA approved as a biosimilar to REMICADE (infliximab). It is not an interchangeable biologic.
‡SILIQ is anticipated to be launched in the second half of 2017.

(Drugs@FDA, 2016; Prescribing information: ACTEMRA, 2016; CIMZIA, 2017; COSENTYX, 2016; ENBREL, 2016; ENTYVIO, 2014; HUMIRA, 2016; ILARIS, 2016; INFLECTRA, 2016; KINERET, 2016; ORENCIA, 2016; OTEZLA, 2015; REMICADE, 2015; RITUXAN, 2014; SILIQ, 2017; SIMPONI, 2017; SIMPONI ARIA, 2017; STELARA, 2016; TALTZ, 2016; XELJANZ/XELJANZ XR, 2016)

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: CAPS, FMF, HIDS/MKD, 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) | ✔ ‡‡ | ✔ ⌐ | | ✔ ∫ | ✔ ‡ | ✔ ∫∫ | ✔ | ✔ | ✔ | ✔ ▼ |

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|---|---|---|---|---|---|---|---|---|---|---|
| ILARIS" (canakinumab) | | | ✔ ** | | | | | | | |
| INFLECTRA (infliximab-dyyb) | ✔ ⊥ | ✔ ⌐⌐ | | | ✔ ‡‡‡ | ✔ | ✔ | ✔ ⊥⊥ | | |
| KINERET▼▼ (anakinra) | ✔ ∞ | | | | | | | | | |
| ORENCIA (abatacept) | ✔ ∞∞ | | | ✔ ⌂ | | | | | | |
| OTEZLA (apremilast) | | | | | ✔ ‡ | ✔ | | | | |
| REMICADE (infliximab) | ✔ ⊥ | ✔ ⌐⌐ | | | ✔ ‡‡‡ | ✔ | ✔ | ✔ ⊥⊥ | | |
| RITUXAN‴ (rituximab) | ✔ ⧺ | | | | | | | | | |

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|---|---|---|---|---|---|---|---|---|---|---|
| SILIQ (brodalumab) | | | | | ✓‡‡ | | | | | |
| SIMPONI (golimumab) | ✓† | | | | | ✓†† | ✓ | ✓~ | | |
| SIMPONI ARIA (golimumab) | ✓† | | | | | | | | | |
| STELARA (ustekinumab) | | ✓⌐⌐⌐ | | | ✓‡ | ✓ | | | | |
| TALTZ (ixekizumab) | | | | | ✓‡ | | | | | |
| XELJANZ / XELJANZ XR (tofacitinib) | ✓‡‡ | | | | | | | | | |

*Patients with moderately to severely active RA who have had an inadequate response to one or more Disease-Modifying Anti-Rheumatic Drugs (DMARDs).
**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.
‡‡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 patients.
▼▼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 6 years and old 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 one or more 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 only). The biosimilar INFLECTRA did not receive FDA approval for pediatric UC due to existing marketing exclusivity for Remicade for this indication (not for clinical reasons).
‘‘RITUXAN also indicated for Non–Hodgkin’s lymphoma (NHL), chronic lymphocytic leukemia (CLL), and granulomatosis with polyangiitis (GPA) (Wegener’s Granulomatosis) and microscopic polyangiitis (MPA).
╪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 one or more TNF 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.

## 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 had an inadequate response to MTX, and background MTX was continued during the trial. Although efficacy was comparable between abatacept and infliximab after six months of treatment, some differences in favor of abatacept were evident after one year of treatment. After one 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), both added to MTX, in a multicenter, investigator-blind, randomized controlled trial (N=646) of RA patients with inadequate response to MTX. After two 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 two groups after two 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 zero, two, and four then 200 or 400 mg every two weeks attained greater ACR 20, ACR 50 and ACR 70 responses over patients on placebo and MTX, respectively, after 24 weeks (P≤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 one 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).
- ievedCIMZIA (certolizumab)-treated patients achieved clinical disease activity index (CDAI) remission than placebo-treated patients (18.8% vs 6.1%, P≤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 six 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.
- The FDA approval of SIMPONI (golimumab) for RA was based on three multicenter, double-blind, randomized, controlled trials in 1,542 patients greater than or equal to18 years of age with moderate to severe active disease. A greater percentage of patients from all three 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 five years (Keystone et al, 2013a; Smolen et al, 2015b).

- SIMPONI ARIA (golimumab) was studied in patients with RA. In one 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 zero, four and then every eight 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 six 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 ages 18 years and older with active RA. Patients were diagnosed according to ACR criteria, with at least eight tender and six swollen joints at baseline. Tocilizumab was given every four 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 tumor necrosis factor (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 one of three treatment arms, tocilizumab 8 mg/kg every four weeks, MTX 7.5 mg/week and titrated to 20 mg/week within eight weeks, or placebo for eight 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 three 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 six months as compared to MTX (33% vs 4%), and these rates continued to increase over time to one year (47% vs 8%) (Kremer et al, 2011). These benefits were maintained or improved at two 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 four 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 less than 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 1,220 patients with active RA. Patients remained on stable doses of DMARDs and received tocilizumab 8 mg/kg or placebo every four 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 one or more TNF antagonists was randomly assigned to 8 or 4 mg/kg tocilizumab or placebo every four 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 one 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 subcutaneous formulation of ACTEMRA (tocilizumab) was based on one multicenter, double-blind, randomized, controlled trial in patients (N=1,262) with RA. Weekly tocilizumab SQ 162 mg was found to be non-inferior to tocilizumab IV 8 mg/kg every four 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).
- 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 six 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). 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 one or more 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.

- 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 two 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.
- Two studies, one double-blind and one 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 greater than 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.
- 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 three months but was significantly higher in the abatacept group at six 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 at six 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 one year, and then could receive 40 mg every other week for an additional nine 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 one of four 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 six 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% in the etanercept group compared to 4% (RR, 8.89; NNT, 3) and 1% (RR, 11.31; NNT, 7) in the control groups. 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, 2016b). 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). 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.
- 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 effects was small.
- 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 two biologic agents showed increased rate of serious AEs with limited or no increase in efficacy.
- s for the FDA approval of STELARA ,927) evaluated the efficacy of withdrawing biologics from patients with RA who 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 one 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 which 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 two 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 three 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 five years in an open-label extension trial (Deodhar et al, 2015). Safety profile through five 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 was 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 one 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 two weeks and certolizumab 400 mg every four 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 two 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 four 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).
- The safety and efficacy of ENTYVIO (vedolizumab) was demonstrated in two trials for CD in patients who responded inadequately to immunomodulator therapy, TNF blockers, and/or corticosteroids. In one 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 six (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).
- 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 one year. Serious cases of sepsis, cellulitis, and fungal pneumonia occurred in zero to 19% of patients in up to four 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 two 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 one or more 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 SC 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 two 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 zero, 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 (six 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 (four 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 six 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 seven patients (three placebo; four 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 four year extension trial met ACR Pedi 30; C-reactive protein (CRP) levels, articular severity scores, and patient pain assessment scores all decreased. There were five cases of serious AEs related to etanercept therapy after four 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 two 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 two 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).
- A meta-analysis of trials evaluating biologics for the treatment of SJIA included 5 trials; one 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 two 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 zero, four 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 zero 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 one 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 eight weeks. More partial responders at week 28 who received 90 mg every eight 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 1,212) 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 one (Thaçi et al, 2016), the impact of apremilast on health-related quality of life, 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 two 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=1,306), 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 four 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.

- A meta-analysis of seven 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 one-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=1,296) 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=1,224) 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=1,346) 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 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 zero, one, and two, followed by every two 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 two 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=1,831) and AMAGINE-3 (N=1,881) 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 zero, one, and two, followed by every two 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 two weeks or 140 mg every two, four, or eight weeks; patients receiving ustekinumab continued ustekinumab; and patients receiving placebo were switched to brodalumab 210 mg every two 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 two 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 two weeks was superior to the use of the less frequent maintenance regimens, and the 210 mg regimen was superior to the 140 mg regimen.

- 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 aged four years and older. 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 three infections) occurred in three 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.

**Psoriatic arthritis (PsA)**

- In two 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 one 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).

- 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 five 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 five were 62.8 to 69.9% for golimumab SQ 50 or 100 mg every four 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 one multicenter, double-blind, placebo controlled trial (N=409). Patients were randomized to receive placebo, CIMZIA 200 mg every two weeks, or CIMZIA 400 mg every four 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 two 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 health-related quality of life (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 two 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.

  - 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 three 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).
- 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 nine randomized controlled trials and six 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.
- 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, 2016b). 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.

**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 eight 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 eight, 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 zero, 80 mg at week two, 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 eight-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 two of the secondary end points at week eight, 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 eight. This may have been because of the high placebo response rates in ULTRA 1. A meta-analysis of three 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 zero and two were compared to patients receiving placebo. At week six, 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 six 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).

**Uveitis (UV)**

- The safety and efficacy of HUMIRA (adalimumab) were assessed in adult patients with non-infectious intermediate, posterior, and panuveitis in two 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 two 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 two 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.

**CAPS, FMF, HIDS/MKD, and TRAPs**

- 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 three to five years demonstrated sustained improvement in disease activity and inflammatory markers (Sibley et al, 2012).
- 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. 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) (ILARIS prescribing information, 2016).

**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. 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 (Singh et al, 2016c).
  - EULAR guidelines are similar to ACR guidelines. These guidelines state that if the treatment target is not reached with a conventional DMARD strategy in a patient with poor prognostic factors, addition of a biologic DMARD or a targeted synthetic DMARD (eg, tofacitinib) should be considered, with current practice being a biologic DMARD. Biologic and targeted synthetic DMARDs should be combined with a conventional DMARD, but in patients who cannot use a conventional DMARD concomitantly, a targeted synthetic DMARD or an IL-6 inhibitor (eg, tocilizumab) may have some advantages compared with other biologic DMARDs. The guideline notes that if a TNF inhibitor has failed, patients may receive another TNF inhibitor or an agent with another mode of action. An effective biologic should not be switched to another biologic for non-medical reasons (Smolen et al, 2017).
  - 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, 2016).
  - 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:
  - bwohl etican College of Rheumatology (ACR) published recommendations for the treatment of JIA in 2011, followed by an update in 2013 focusing on the management of SJIA (and tuberculosis screening) (Beukelman et al, 2011; Ringold et al, 2013).
    - According to the 2011 guideline, recommendations for JIA treatment vary based on factors such as disease characteristics and activity, current medication, and prognostic features. For patients with a history of arthritis in ≥5 joints (which includes extended oligoarthritis, polyarthritis, and some related subtypes), a TNF inhibitor is generally recommended in patients with continued disease activity after receiving an adequate trial of a conventional DMARD. In patients with a history of ≥5 affected joints failing a TNF inhibitor, treatment approaches may include switching to a different TNF inhibitor or abatacept (Beukelman et al, 2011).
    - According to the 2013 update, 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 one 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).
- UC:
  - For the treatment of UC, sulfasalazine is recommended by the American College of Gastroenterology (ACG) as first-line treatment of active disease. Balsalazide, mesalamine, olsalazine and sulfasalazine are recommended for maintenance of remission and reduction of relapses. If these therapies fail, infliximab should be considered (Kornbluth et al, 2010). Note that other immunomodulators were not indicated for UC when these guidelines were written; an update is currently in process.

- 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 have not responded despite complete and adequate therapy with a corticosteroid or an immunosuppressive agent. These TNF inhibitors may also be used as alternatives to steroid therapy in selected patients in whom corticosteroids are contraindicated or not desired. Maintenance therapy with TNF inhibitors is effective. An update to these guidelines is currently in process (Lichtenstein et al, 2009).
  - The American Gastroenterological Association (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).
  - The European Crohn's and Colitis Organisation (ECCO) recommends TNF inhibitors for patients with CD who have relapsed or are refractory to corticosteroids, depending on disease location and severity, and states that early TNF inhibitor therapy should be initiated in patients with high disease activity and features indicating a poor prognosis. Furthermore, the ECCO guideline states that all currently available TNF inhibitors seem to have similar efficacy in luminal CD and similar AE profiles; therefore the choice depends on availability, route of administration, patient preference, and cost. Vedolizumab is noted to be an appropriate alternative to TNF inhibitors for some patients (Gomollón et al, 2017).
- 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, 2016b).
- 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 (Gottleib et al, 2008; Menter et al, 2008; Menter et al, 2009a; Menter et al, 2009b; Menter et al, 2010; Menter et al, 2011). Biologic agents are routinely used when one or more 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.
  - 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 one 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 quality of life 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 one synthetic DMARD, such as MTX. For patients with peripheral arthritis and an inadequate response to at least one 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 one 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).
- AS:
  - Joint recommendations for the management of axial spondyloarthritis are available from ASAS and EULAR. (Ankylosing spondylitis [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).
  - The 2015 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 particular TNF inhibitor is preferred over another, except in patients with concomitant inflammatory bowel disease or recurrent iritis, in whom infliximab or adalimumab would be preferred over etanercept (Ward et al, 2016).
- 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.
- 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).
  - No recent guidelines were identified for CAPS, HIDS/MKD, or TRAPS.

## SAFETY SUMMARY

- Contraindications:
  - ACTEMRA (tocilizumab), COSENTYX (secukinumab), ENTYVIO (vedolizumab), ILARIS (canakinumab), INFLECTRA (infliximab-dyyb), KINERET (anakinra), OTEZLA (apremilast), REMICADE (infliximab), STELARA (ustekinumab), and TALTZ (ixekixumab) use in patients with hypersensitivity to any component of the product.
  - SILIQ is contraindicated in patients with Crohn's disease 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) and INFLECTRA (infliximab-dyyb) 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), REMICADE (infliximab), 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), REMICADE (infliximab), SIMPONI / SIMPONI ARIA (golimumab), and XELJANZ (tofacitinib) all have warnings for increased risk of malignancies.
  - 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.
- 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
  - Increased lipid parameters and liver function tests with XELJANZ / XELJANZ XR (tofacitinib)
  - Increased incidence of CD and UC with COSENTYX (secukinumab) and TALTZ (ixekixumab); risk of new-onset CD or exacerbation of CD with SILIQ (brodalumab)
  - 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 five-year study in RA and a 10-year study in patients with early RA (Keystone et al, 2014a; Burmester et al, 2014b). In the five-year extension study, overall rates of serious AEs and serious infections were 13.8 events per 100 patient-years and 2.8 events per 100 patient-years, respectively. The rate of serious events was highest in the first six months and then declined. No new safety signals were reported in the 10-year study.
    - Certolizumab plus MTX had a consistent safety profile over five 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 patient-years), and upper respiratory infections (rate of 7.3 per 100 patient-years). Serious AE rates were 5.9 events per 100 patient-years for serious infections and 1.2 events per 100 patient-years for malignancies.
    - Abatacept has been evaluated in two long-term extension studies. Abatacept IV plus MTX demonstrated a similar safety profile between the seven 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 patient-years), malignancies (3.2 events per100 patient-years), and autoimmune events (1.2 events per 100 patient-years). In a five-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 one and year five, respectively.
    - Data from five 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 one dose of tocilizumab. Mean duration of tocilizumab treatment was 3.07 years (up to 4.6 years); total duration of observation was 12,293 patient-years (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 six months, 12 months, and two years. At three 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 six months, flu-like syndrome at six months and two years, infection at six months and two years, malignancy at 12 months and two years, pneumonia at 12 months, and serious infection at 12 months and two 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.

o PsO
  - A total of 3,117 patients treated with at least one dose of STELARA (ustekinumab) for moderate to severe PsO were evaluated for long-term safety. At least four years of ustekinumab exposure was seen in 1,482 patients (including 838 patients with greater than or equal to five 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 five. 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 one to year five, 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 five-year extension study, a total of 2,510 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 five-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 six and remained stable through five 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 eight 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 five 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 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 five Phase 3 trials of SQ golimumab over at least three 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 one 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%.
- Several recent 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 one to 36 months) and seven open-label extension studies (follow-up six 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 two to 36 months) and six open-label extension trials (follow-up six 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 two immunomodulators together.
  - For XELJANZ / XELJANZ XR (tofacitinib), do not give with potent inhibitors of cytochrome P450 (CYP) 3A4; medications that result in both moderate inhibition of CYP3A4 and potent inhibition of CYP2C19; potent CYP3A4 inducers; and potent immunosuppressive drugs.
- Risk Evaluation and Mitigation Strategy (REMS)
  - STELARA (ustekinumab) has a REMS program in place, which consists of a communication plan regarding potential risk of serious infections, malignancy, and reversible posterior leukoencephalopathy syndrome (RPLS).
  - 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:<br>80 mg/4 mL;<br>200 mg/10 mL;<br>400 mg/20 mL<br><br>Prefilled syringe:<br>162 mg/0.9 mL | **RA:** 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 to every week based on clinical response. >100 kg, 162 mg administered SQ every week.<br>**PJIA:** <30 kg, 10 mg/kg IV every 4 weeks; ≥30 kg, 8 mg/kg IV every 4 weeks.<br>**SJIA:** <30 kg, 12 mg/kg IV every 2 weeks;<br>≥30 kg, 8 mg/kg IV every 2 weeks. | **RA:** Can give with MTX or other DMARDs.<br>**PJIA and SJIA:** Can give with MTX.<br>Adjust dose for liver enzyme abnormalities, low platelet count and low ANC. | Give as a single 60-minute intravenous infusion.<br><30 kg, use a 50 mL infusion bag.<br>≥30 kg, use a 100 mL infusion bag.<br>Before infusion, allow bag to come to room temperature.<br>Do not administer with other drugs.<br><br>Patients can self-inject with the prefilled syringe. |
| CIMZIA (certolizumab) | Powder for reconstitution: 200 mg<br>Prefilled syringe: 200 mg/mL | **CD:** 400 mg SQ initially and at weeks 2 and 4. Maintenance dose is 400 mg every 4 weeks.<br>**RA, PsO:** 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.<br>**AS:** 400 mg SQ initially and at weeks 2 and 4. Maintenance dose is 200 mg every 2 weeks or 400 mg every 4 weeks. | Patients can self-inject with the prefilled syringe. | When a 400 mg dose is required, give as two 200 mg SQ injections in separate sites in the thigh or abdomen. |
| COSENTYX (secukinumab) | Sensoready pen:<br>150 mg/1 mL<br>Prefilled syringe:<br>150 mg/1 mL<br>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<br>**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 | **PsO:** For some patients, a dose of 150 mg may be acceptable.<br><br>**PsA:**<br>For PsA patients with coexistent moderate to severe PsO, dosing for PsO | Each 300 mg dose is given as two subcutaneous injections of 150 mg.<br><br>Patients may self-administer with the pen or prefilled syringe.<br>The vial is for healthcare professional use only. |

| Drug | Dosage Form: Strength | Usual Recommended Dose | Other Dosing Considerations | Administration Considerations |
|---|---|---|---|---|
| | | every 4 weeks | should be followed.<br><br>If active PsA continues, consider 300 mg dose. | |
| ENBREL (etanercept) | Prefilled syringe: 25 mg and 50 mg<br>Prefilled SureClick autoinjector: 50 mg<br>Multiple-use vial: 25 mg | **RA, AS, PsA:** 50 mg SQ weekly<br>**PsO (adults):** 50 mg SQ twice weekly for three months, then 50 mg weekly<br>**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<br>**JIA:** NSAIDs glucocorticoids, or analgesics may be continued | Patients may be taught to self-inject.<br>May bring to room temperature prior to injecting. |
| ENTYVIO (vedolizumab) | Lyophilized cake for injection in single dose 20 mL vials: 300 mg | **CD and UC:** 300 mg administered by intravenous infusion at time zero, two and six weeks, and then every eight weeks thereafter.<br><br>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:<br>10 mg/0.2 mL<br>20 mg/0.4 mL<br>40 mg/0.4 mL<br>40 mg/0.8 mL<br><br>Single-use pen:<br>40 mg/0.8 mL<br><br>Single-use vial:<br>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.<br>**PJIA:** 10 kg to <15 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<br>**CD, HS and UC:** 160 mg SQ on Day 1 (given as four 40 mg injections in one day or as two 40 mg injections per day for two consecutive days), followed by 80 mg SQ two weeks later (Day 15). Two weeks later (Day 29) begin a maintenance dose of 40 mg SQ every other week.<br>**PsO and UV:** initial | **RA, AS, PsA:** MTX, other non-biologic DMARDS, glucocorticoids, NSAIDs, and/or analgesics may be continued.<br>**JIA:** NSAIDs, MTX, analgesics, and/or glucocorticoids, may be continued.<br>**CD and UC:** aminosalicylates and/or corticosteroids may be continued. Azathioprine, 6-MP or MTX may be continued if necessary.<br>Needle cover of the syringe contains dry rubber (latex). | Patients may be taught to self-inject.<br>Injections should occur at separate sites in the thigh or abdomen.<br>Rotate injection sites. |

| Drug | Dosage Form: Strength | Usual Recommended Dose | Other Dosing Considerations | Administration Considerations |
|---|---|---|---|---|
| | | dose of 80 mg SQ, followed by 40 mg SQ every other week starting one week after the initial dose.<br>**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 two weeks later (on day 15); maintenance dose is 20 mg every other week starting at week 4.<br><br>≥40 kg: 160 mg on day (given as four 40 mg injections in one day or as two 40 mg injections per day for two consecutive days) and 80 mg two weeks later (on day 150); maintenance dose is 40 mg every other week starting at week 4. | | |
| 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).<br><br>**CAPS**: ≥15 to ≤40 kg, 2 mg/kg SQ; >40 kg, 150 mg SQ; frequency every 8 weeks<br><br>**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<br><br>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. |
| INFLECTRA (infliximab-dyyb) | Vial: 100 mg | **CD (≥6 years old), PsA, PsO and UC**: 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<br><br>**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.<br>**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.<br>**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.<br>Do not administer with other drugs. |
| KINERET (anakinra) | Prefilled syringe: 100 mg/0.67 mL | **RA:** 100 mg SQ once daily.<br>**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.<br>A new syringe must be used for each dose. |
| ORENCIA (abatacept) | Vial: 250 mg<br><br>Prefilled syringe: 125 mg/1 mL<br><br>ClickJect autoinjector: 125 mg/mL | **RA:** <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.<br>**PJIA:** 6 to 17 years and <75 kg: 10 mg/kg IV initially, then 2 and 4 weeks after the first infusion and every 4 weeks thereafter. >75 kg, follow adult RA IV schedule; maximum dose = 1,000 kg. | | IV infusion should be over 30 minutes.<br>Use 100 mL bag for IV infusion.<br>Do not administer with other drugs.<br>Patients may be taught to self-inject the SQ dose.<br>For SQ, injection sites should be rotated. |
| OTEZLA (apremilast) | Tablet: 10 mg, 20 mg, and 30 mg | **PsA, PsO:**<br>Day 1: 10 mg in the morning<br>Day 2: 10 mg in the morning and in the evening<br>Day 3: 10 mg in the | Titrate according to the labeling when initiating therapy to reduce gastrointestinal symptoms. | May be taken with or without food.<br><br>Do not crush, split, or chew the tablets. |

| Drug | Dosage Form: Strength | Usual Recommended Dose | Other Dosing Considerations | Administration Considerations |
|---|---|---|---|---|
| | | morning and 20 mg in evening<br>Day 4: 20 mg in the morning and evening<br>Day 5: 20 mg in the morning and 30 mg in the evening<br>Day 6 and thereafter: 30 mg twice daily | 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). | |
| 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 mg/kg.<br>**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.<br>**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<br><br>**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.<br>Use 250 mL 0.9% sodium chloride for infusion.<br>Infuse over 2 hours.<br>Do not administer with other drugs. |
| RITUXAN (rituximab) | Vial:<br>100 mg<br>500 mg | **RA:** 1,000 mg IV every 2 weeks times two doses. Additional doses should be given every 24 weeks or based on clinical evaluation but no sooner than 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.<br><br>The syringe should be allowed to reach room temperature before injecting. |
| SIMPONI/ SIMPONI ARIA (golimumab) | SmartJect® autoinjector: 50 mg and 100 mg<br>Prefilled syringe: 50 mg and 100 mg<br>ARIA, Vial: 50 mg/4 mL | **RA, PsA, and AS**: 50 mg SQ once monthly<br>**UC:** 200 mg SQ at week 0; then 100 mg at week 2; then 100 mg every 4 weeks.<br><br>**ARIA**: 2 mg/kg IV at weeks 0 and 4, then every 8 weeks. | **RA:** give with MTX<br>**PsA and AS**: may give with or without MTX or other DMARDs.<br><br>Needle cover of the syringe contains dry rubber (latex).<br><br>**ARIA**: give with MTX<br><br>Efficacy and safety of switching between IV and SQ formulations have not been established. | Patients may be taught to self-inject the SQ dose.<br>For SQ, injection sites should be rotated.<br>For SQ, bring to room temperature for 30 minutes prior to injecting.<br><br>**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.<br>Do not administer with other drugs. |
| STELARA (ustekinumab) | Prefilled syringe: 45 mg and 90 mg<br>Vial: 130 mg | **PsO, PsA**: ≤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 every 12 weeks.<br><br>**CD**: 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) | Needle cover of the syringe contains dry rubber (latex). | Patients may be taught to self-inject using the prefilled syringes.<br>STELARA for IV infusion must be diluted, prepared and infused by a healthcare professional; it is diluted in 0.9% sodium chloride and infused over at least one hour.<br>Rotate injection sites. |
| TALTZ (ixekizumab) | Prefilled syringe: 80 mg<br><br>Autoinjector: 80 mg | **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 | | Patients may be taught to self-inject with either the prefilled syringe or the autoinjector. Bring to room temperature prior to injecting.<br>Rotate injection sites. |

| Drug | Dosage Form: Strength | Usual Recommended Dose | Other Dosing Considerations | Administration Considerations |
|---|---|---|---|---|
| XELJANZ / XELJANZ XR (tofacitinib) | Tablet: 5 mg<br>Extended release Tablet: 11 mg | **RA:** 5 mg PO twice daily or 11 mg PO once daily | Patients may switch from XELJANZ 5 mg twice daily to XELJANZ XR 11 mg once daily the day following the last dose of XELJANZ 5 mg.<br><br>Use as monotherapy or in combination with MTX or other nonbiologic DMARDs. Use of XELJANZ in combination DMARDs or with potent immunosuppres-sants such as azathioprine and cyclosporine is not recommended.<br><br>Dose interruption is recommended for management of lymphopenia (< 500 cells/$mm^3$), neutropenia (absolute neutrophil count [ANC] < 500 cells/$mm^3$) and anemia.<br><br>Dose adjustment needed for hepatic and renal impairment and patients taking CYP450 inhibitors. | May take with or without food.<br><br>Swallow XELJANZ XR tablets whole; do not crush, split, or chew. |

ANC=absolute neutrophil count; AS=ankylosing spondylitis; DMARD=disease-modifying anti-rheumatic drug; HS=hidradenitis suppurativa; IV=intravenous infusion; JIA=juvenile idiopathic arthritis; MTX=methotrexate; NOMID= neonatal-onset multisystem inflammatory disease; 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 and PJIA. | No dose adjustment in mild impairment. Not studied in moderate to severe impair-ment. | Not studied in patients with impairment. | Uncategorized†<br><br>Limited data in pregnant women not sufficient to determine risks.<br><br>Unknown whether excreted in breast milk; risks and benefits should be considered. |
| CIMZIA (certolizumab) | The number of subjects ≥65 years in clinical trials was not sufficient to determine whether they responded differently from younger subjects. Use caution. | Safety and effectiveness have not been established. | No data | No data | Uncategorized†<br><br>Limited data from ongoing pregnancy registry not sufficient to inform risks.<br><br>Unknown whether excreted in breast milk, but data suggest systemic exposure to a breastfed infant is expected to be low; 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 | Pregnancy category B*<br><br>Unknown whether excreted in breast milk; use with caution. |
| ENTYVIO (vedolizumab) | The number of patients ≥65 years in clinical trials was insufficient to determine differences. | Safety and efficacy have not been established. | Safety and efficacy have not been established. | Safety and efficacy have not been established. | Pregnancy category B*<br><br>Unknown whether excreted in breast 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 | Pregnancy category B*<br><br>Present in low levels in breast milk; use caution. |

| Drug | Population and Precaution | | | | |
|---|---|---|---|---|---|
| | Elderly | Pediatrics | Renal Dysfunction | Hepatic Dysfunction | Pregnancy and Nursing |
| HUMIRA (adalimumab) | Frequency of serious infection and malignancies is greater in ≥65 years. Use caution. | Only studied in PJIA (ages 2 years and older) and CD (6 years and older). | No data | No data | Uncategorized†<br><br>Present in low levels in breast milk; use caution. |
| ILARIS (canakinumab) | The number of patients ≥65 years in clinical trials was insufficient to determine differences. | Not studied in children <2 years (SJIA, TRAPS, HIDS/ MKD, and FMF) or <4 years (CAPS). | No data | No data | Uncategorized †<br><br>Limited data from postmarketing reports not sufficient to inform risks.<br><br>Unknown whether excreted in breast milk; use caution. |
| INFLECTRA (infliximab-dyyb) | Frequency of serious infection is greater in ≥65 years. Use caution. | Not recom-mended in <6 years in children with CD. | No data | No data | Pregnancy category B*<br><br>Unknown whether excreted in breast milk; discontinue nursing or discontinue the drug. |
| KINERET (anakinra) | Use caution. | 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 | Pregnancy category B*<br><br>Unknown whether excreted in breast milk; use caution. |
| ORENCIA (abatacept) | Frequency of serious infection and malignancies is greater in ≥65 years. Use caution. | Not recom-mended in <6 years.<br><br>SQ formulation has not been studied in patients <18 years. | No data | No data | Uncategorized †<br><br>Data on use in pregnant women insufficient to inform risks.<br><br>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 mL/min). | No dosage adjustment necessary. | Pregnancy category C*<br><br>Unknown whether excreted in breast milk; use caution. |

| Drug | Population and Precaution | | | | |
|---|---|---|---|---|---|
| | Elderly | Pediatrics | Renal Dysfunction | Hepatic Dysfunction | Pregnancy and Nursing |
| 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*<br><br>Unknown whether excreted in breast milk; discontinue nursing or discontinue the drug. |
| RITUXAN (rituximab) | Rates of serious infections, malignancies, and cardiovascular events were higher in older patients. | Safety and effectiveness have not been established. | No data | No data | Pregnancy category C*<br><br>Unknown whether excreted in breast milk; risks and benefits should be weighed before use. |
| SILIQ (brodalumab) | No differences in safety or efficacy were observed between older and younger patients, but the number of patients ≥65 years was insufficient to determine any differences in response. | Safety and effectiveness in <18 years have not been established. | No data | No data | Uncategorized †<br><br>There are no human data in pregnant women to inform risks.<br><br>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.<br><br>IV ARIA: Use caution. | Safety and effectiveness in <18 years have not been established. | No data | No data | Pregnancy category B*<br><br>Unknown whether excreted in breast milk; discontinue nursing or discontinue the drug. |
| STELARA (ustekinumab) | No differences observed between older and younger patients. Use caution. | Safety and effectiveness have not been established. | No data | No data | Uncategorized †<br><br>Limited data in pregnant women are insufficient to inform risks.<br><br>Unknown whether excreted in breast milk; systemic exposure to breasted infant expected to be low; consider risks and benefits. |

| Drug | Population and Precaution | | | | |
|---|---|---|---|---|---|
| | Elderly | Pediatrics | Renal Dysfunction | Hepatic Dysfunction | Pregnancy and Nursing |
| TALTZ (ixekizumab) | No differences observed between older and younger patients; however, the number of patients ≥65 years was not sufficient to determine differences. | Safety and effectiveness have not been established. | No data | No data | Uncategorized †<br><br>There are no available data in pregnant women to inform risks.<br><br>Unknown whether excreted in breast milk; consider risks and benefits. |
| XELJANZ / XELJANZ XR (tofacitinib) | Frequency of serious infection is greater in ≥65 years. Use caution. | Safety and effectiveness have not been established. | Reduce dose to 5 mg daily in moderate to severe impairment. | Reduce dose to 5 mg daily in moderate hepatic impairment. Not recom-mended in severe hepatic impairment. | Pregnancy category C*<br><br>Unknown whether excreted in breast milk; discontinue nursing or discontinue the drug. |

CrCl=creatinine clearance; NOMID= Neonatal-Onset Multisystem Inflammatory Disease; PJIA=polyarticular juvenile idiopathic arthritis; SJIA=systemic juvenile idiopathic arthritis
*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.
Pregnancy Category C = Risk cannot be ruled out. Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.
†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 six months, but abatacept demonstrated greater efficacy after one 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 two years in a single-blind study (Schiff et al, 2014).
    - 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 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 study, a double-blind, randomized controlled trial in 676 patients with moderate to severe PsO (Thaçi et al, 2015). The proportion of

patients achieving PASI 90 at week 16 was significantly higher with secukinumab compared to ustekinumab (79% vs 57.6%; P<0.0001).
    - 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).
    - 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).
    - 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 (Singh et al, 2016c; Smolen et al, 2017). EULAR has 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 one or more traditional systemic agents are not tolerated, fail to product an adequate response, or are unable to be used due to patient comorbidities (Gottlieb et al, 2008; Menter et al, 2008; Menter et al, 2009a; Menter et al, 2009b; Menter et al, 2010; 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 one 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 one 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 one 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).
- In patients with JIA and involvement of ≥5 joints, the ACR recommends the use of a TNF inhibitor after an adequate trial of a conventional DMARD (Beukelman et al, 2011). The ACR updated 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).
- According to the ACG, for the treatment of UC, infliximab should be considered after failure of first-line non-biologic agents (Kornbluth et al, 2010). Other immunomodulators were not indicated for UC when these guidelines were written.
- Based on ACG guidelines, the anti-TNF monoclonal antibodies adalimumab, certolizumab, and infliximab are effective in the treatment of moderate to severely active CD in patients who have not responded despite complete and adequate therapy with a corticosteroid or an immunosuppressive agent. These TNF inhibitors may also be used as alternatives to steroid therapy in selected patients in whom corticosteroids are contraindicated or not desired (Lichtenstein et al, 2009). The AGA recommends using anti-TNF drugs to induce remission in patients with moderately severe CD (Terdiman et al, 2013). ECCO recommends TNF inhibitors for patients with CD who have relapsed or are refractory to corticosteroids, depending on disease location and severity, and states that early TNF inhibitor therapy should be initiated in patients with high disease activity and features indicating a poor prognosis; vedolizumab is an alternative for some patients (Gomollón et al, 2017).
- 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 (Nguyen et al, 2016b).
- 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). The 2015 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 (Ward et al, 2016).

- 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, and tofacitinib have boxed warnings regarding a risk of serious infections. TNF inhibitors and tofacitinib also have boxed warnings regarding an increased risk of malignancies. Brodalumab has a boxed warning regarding the risk of suicidal ideation and behavior.
- Warnings, precautions, and AE profiles vary in this class.
- All of the biologic agents with the exception of apremilast and tofacitinib are given by subcutaneous injection and/or intravenous infusion. Administration schedule varies among the injectable agents in the class. Apremilast and tofacitinib 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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