26 Antibody-Based Biotherapeutics in Inflammatory Diseases

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INTRODUCTION

Inflammatory diseases encompass a broad and diverse spectrum of serious chronic disorders, many of which have significant need for safe and effective pharmacotherapies. The conventional drugs used to treat immune-mediated inflammatory diseases include nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, sulfasalazine, 5-aminosalicylates, methotrexate, azathioprine, and 6-mercaptopurine which have exhibited limited efficacy with significant side effects. The initial rationale and promise of antibody-based biotherapeutics, such as monoclonal antibodies (mAbs), was focused on oncology and organ transplantation (Ehrlich 1891; Gura 2002). Over the last two decades, there has been significant success in developing a number of antibody-based biotherapeutics as a very effective and relatively safe treatment for several inflammatory diseases, and this area of research and development is rapidly expanding. Five of the top-selling mAbs are for the treatment of chronic inflammatory conditions.

Antibody-based biotherapeutics are a subclass of protein therapeutics. These are large molecular weight glycoproteins designed and produced through recombinant DNA technology and require production in eukaryotic cells using bioreactor technology. These modalities have provided many efficacious therapeutic options for patients and are providing significant insights into the underlying complex pathological pathways of these disorders, which, in turn, are identifying new targets for treatment of these diseases. A significant translational insight derived from the clinical development programs of antibody-based pharmacotherapy is the dysregulation of common proinflammatory mediators, such as tumor necrosis factor alpha (TNFα), across diverse rheumatologic, dermatologic, and gastroenterological pathologies. In addition, the observation of patient subsets that are refractory to a particular therapy indicates that dysregulation of different mediators (targets) may be the primary driver of the underlying disease and require a different treatment. Antibody-based biotherapeutics embody structural, biochemical, and pharmacologic properties distinct from other biologic or chemically synthesized molecular drugs. In general, they exhibit relatively long half-lives (~2–3 weeks) at therapeutic doses, and have high affinity and target specificity with minimum off-target effects, which usually translate into potent and sustained pharmacodynamic (PD) effects.

Currently approved antibody-based therapies for autoimmune/inflammatory disorders include chimeric, humanized, human mAbs and fusion proteins. The mechanism of action of these agents includes either neutralizing a soluble ligand(s) such as cytokines or binding to receptors to block signaling through ligands, or acting as direct agonist or antagonist. The examples of neutralizing soluble ligands include TNFα (infliximab, golimumab, adalimumab, etanercept, certolizumab), interleukin (IL)-12/IL-23 (ustekinumab), IL-23 (guselkumab), IL-17A (secukinumab and ixekizumab), IL-5 (mepolizumab and reslizumab), IL-1β (canakinumab, rilonacept) and soluble immunoglobulin E (IgE, omalizumab). The examples of binding to receptors include IL-4 receptor (dupilumab), IL-5 receptor (benralizumab), IL-6 receptor (tocilizumab, sarilumab) and IL-17 receptor A (brodalumab). The examples of direct agonist or anti-agonist include anti-CD80/CD86 agents to inhibit lymphocyte activation (abatacept, belimumab), CD20 directed cytolytic agents (rituximab and ocrelizumab) and anti-integrin agents to inhibit lymphocyte migration (natalizumab and vedolizumab). Table 26.1 summarizes the 25 antibody-based biotherapeutics that are currently approved and

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Part A: Indication, mechanism of action, recommended dose regimen and pharmaceuticals considerations					
Product	**Target**	**Indication[a]**	**Mechanism of action**	**Recommended dose regimen[a]**	**Pharmaceutical considerations[a]**
Anti-TNFα					
Adalimumab (Humira®)	TNFα	RA, PsA, AS, pJIA, PsO, CD, pediatric CD, UC, HS and UV	Adalimumab binds specifically to TNFα and blocks its interaction with the p55 and p75 cell surface TNF receptors. Adalimumab also lyses surface TNF expressing cells *in vitro* in the presence of complement. Adalimumab does not bind or inactivate lymphotoxin (TNF-β)	Adalimumab should be administered as SC injection *RA*, *PsA*, *and AS*: The recommended dose of adalimumab is 40 mg SC q2w *pJIA (2 years and older):* The recommended dose of adalimumab is SC q2w at a dose level of 10, 20 and 40 mg for pediatric patients weighting 10 to <15 kg, 15 to <30 kg and ≥30 kg, respectively *PsO and UV*: The recommended dose of adalimumab is 80 mg initial SC dose followed by 40 mg SC q2w *CD and UC*: The recommended dose of adalimumab is 160 mg initial dose, 80 mg dose 2 weeks later, followed by 40 mg SC q2w *Pediatric CD (6 years and older)*: The recommended dose for pediatric patients weighing 17 to <40 kg is 80 mg initial dose, 40 mg dose 2 weeks later, followed by 20 mg SC q2w. Pediatric patients weighing ≥40 kg should be administered following the adult dose regimen *HS*: The recommended dose is 160 mg initial dose, 80 mg dose 2 weeks later, followed by 40 mg SC qw	Adalimumab is a human IgG1 mAb with an apparent MW of ~ 148 kDa Adalimumab is supplied as a preservative-free, sterile solution and is provided as single-use pens (80 mg/0.8 mL, 40 mg/0.8 mL, 40 mg/0.4 mL), prefilled syringes (80 mg/0.8 mL, 40 mg/0.8 mL, 40 mg/0.4 mL, 20 mg/0.4 mL, 20 mg/0.2 mL, 10 mg/0.2 mL, 10 mg/0.1 mL) and a single-use institutional use vial (40 mg/0.8 mL) Keep refrigerated at 2 °C–8 °C. Store in original carton until time of use. Do not freeze. If needed, may be stored at room temperature up to a maximum of 25 °C for a period of up to 14 days, with protection from light
Certolizumab pegol (Cimzia®)	TNFα	RA, PsA, AS and CD	Certolizumab pegol binds to human TNFα and selectively neutralizes TNFα (but not TNFβ) TNFα is a key pro-inflammatory cytokine with a central role in inflammatory processes	Certolizumab pegol should be administered as SC injection *RA and PsA*: The recommended dose of certolizumab pegol is 400 mg SC initially and at weeks 2 and 4, followed by 200 mg SC q2w. For maintenance dosing, 400 mg SC q4w can also be considered *AS*: The recommended dose of certolizumab pegol is 400 mg SC initially and at weeks 2 and 4, followed 200 mg SC q2w or 400 mg SC q4w *CD*: The recommended dose of certolizumab pegol is 400 mg SC initially and at weeks 2 and 4. For patients achieving clinical response, the recommended maintenance dose regimen is 400 mg SC q4w	Certolizumab pegol is a humanized antibody Fab' fragment, conjugated to an approximately 40-kDa PEG. The MW of certolizumab pegol is ~ 91 kDa Certolizumab pegol is a clear to opalescent solution that is colorless to pale yellow and essentially free from particulates. Certolizumab pegol is supplied as either 200 mg sterile, white, lyophilized powder for reconstitution in a single use vial or as a 200 mg/mL sterile solution in a single-use prefilled syringe Keep refrigerated at 2 °C–8 °C. Store in original carton until time of use. Protect from light. Do not freeze

Table 26.1 ■ Antibody-based biotherapeutics in immune-mediated inflammatory diseases

Etanercept (Enbrel®)	TNFα	RA, PsA, AS, pJIA and PsO	Etanercept is a dimeric soluble form of the p75 TNF receptor that can bind TNF molecules. Etanercept inhibits binding of TNF-α and TNF-β to cell surface TNF receptors, rendering TNF biologically inactive	Etanercept should be administered as SC injection *RA, PsA, and AS*: The recommended dose of etanercept is 50 mg SC qw with or without methotrexate *Adult PsO*: The recommended dose of etanercept is 50 mg twice weekly for 3 months, followed by 50 mg SC qw *pJIA (2 years and older) and pediatric PsO (4 years and older):* The recommended dose of etanercept is 0.8 mg/kg SC qw, with a maximum of 50 mg per week	Etanercept is a dimeric fusion protein with an apparent MW of ~ 150 kDa Etanercept is supplied as clear and colorless, sterile, preservative-free solution in single-dose prefilled syringes (50 mg/mL and 25 mg/mL) and a single-dose prefilled SureClick autoinjector (50 mg/mL). Etanercept is also supplied in a multiple-dose vial (25 mg/vial) as a sterile, white, preservative-free, lyophilized powder for reconstitution prior to injection Keep refrigerated at 2 °C–8 °C. Store in original carton until time of use. Protect from light. Do not freeze or shake. For convenience, storage of individual syringes or autoinjectors at room temperature (20 °C–25 °C) for a maximum single period of 14 days is permissible, with protection from light and sources of heat
Golimumab (Simponi®, Simponi Aria®)	TNFα	RA, PsA, AS, and UC nr-AxSpA and pJIA (EU only, SmPC)	Golimumab binds to both the soluble and transmembrane bioactive forms of human TNFα. This interaction prevents the binding of TNFα to its receptors, thereby inhibiting the biological activity of TNFα	Golimumab may be administered as IV infusion and SC injection *IV infusion for RA, PsA, and AS*: The recommended dose of golimumab is 2 mg/kg IV infusion over 30 mins at weeks 0 and 4, then 2 mg/kg IV q8w thereafter *SC injection for RA, PsA, AS and nr-AxSpA*: The recommended dose of golimumab is 50 mg SC monthly. Consider 100 mg SC monthly if no adequate clinical response after 3 or 4 doses *SC injection for UC*: The recommended dose of golimumab is 200 mg SC at week 0, followed by 100 mg SC at week 2 and then 100 mg SC q4w SC injection for pJIA (≥40 kg): The recommended dose of golimumab is 50 mg SC q4w	Golimumab is a human IgG1κ mAb with an apparent MW of ~ 150–151 kDa For IV use, golimumab used is supplied as a preservative-free, colorless to light yellow solution in a single-dose vial (50 mg/vial) For SC use, golimumab is supplied as a preservative-free, clear to slightly opalescent, colorless to light yellow solution in single-dose prefilled syringes (50 mg/0.5 mL and 100 mg/1 mL) and single-dose prefilled SmartJet® autoinjectors (50 mg/0.5 mL and 100 mg/1 mL) Keep refrigerated at 2 °C–8 °C. Store in original carton until time of use. Protect from light. Do not freeze or shake

Table 26.1 ■ (continued)

Part A: Indication, mechanism of action, recommended dose regimen and pharmaceuticals considerations					
Product	**Target**	**Indication[a]**	**Mechanism of action**	**Recommended dose regimen[a]**	**Pharmaceutical considerations[a]**
Infliximab (Remicade®)	TNFα	RA, PsA, AS, PsO, CD, UC, pediatric CD, pediatric UC	Infliximab neutralizes the biological activity of TNFα by binding to the soluble and transmembrane forms of TNFα and inhibits binding of TNFα with its receptors. Infliximab does not neutralize TNFβ	Infliximab should be administered as IV infusion *RA*: The recommended dose of infliximab is 3 mg/kg at 0, 2, and 6 weeks, followed by 3 mg/kg q8w thereafter. Some patients may benefit from increasing the dose up to 10 mg/kg or treating as often as q4w *PsA and PsO*: The recommended dose of infliximab is 5 mg/kg at 0, 2, and 6 weeks, followed by 5 mg/kg q8w thereafter *AS*: The recommended dose of infliximab is 5 mg/kg at 0, 2, and 6 weeks, followed by 5 mg/kg q6w thereafter *CD and UC*: The recommended dose of infliximab is 5 mg/kg at 0, 2, and 6 weeks, followed by 5 mg/kg q8w thereafter. Some CD patients who initially respond to treatment may benefit from increasing the dose to 10 mg/kg if they later lose their response *Pediatric CD and UC (6 years of age and older)*: The recommended dose of infliximab is 5 mg/kg at 0, 2, and 6 weeks, followed by 5 mg/kg q8w thereafter	Infliximab is a chimeric IgG1κ mAb with an apparent MW of ~ 149.1 kDa Infliximab is supplied as sterile, preservative free, white, lyophilized powder in a single-dose vial for reconstitution prior to IV infusion. Each vial contains 100 mg of infliximab for final reconstitution volume of 10 mL Keep refrigerated at 2 °C–8 °C. Store in original carton until time of use. Protect from light. Unopened infliximab vials may also be stored at temperatures up to a maximum of 30 °C for a single period of up to 6 months but not exceeding the original expiration date. Any unused portion of the infusion solution should not be stored for reuse
Anti-IL-1β					
Canakinumab (Ilaris®)	IL-1β	CAPS and sJIA	Canakinumab binds to human IL-1β and neutralizes its activity by blocking its interaction with IL-1 receptors, but it does not bind IL-1α or IL-1 receptor antagonist	Canakinumab may be administered as IV infusion and SC injection depending on the age and body weight categories *CAPS (4 years and older)*: The recommended dose of canakinumab is 150 mg SC q8w for patients weighing >40 kg and 2 mg/kg SC q8w for patients weighing ≥15 kg and ≤ 40 kg. For children 15–40 kg with an inadequate response, the dose can be increased to 3 mg/kg SC q8w *sJIA (2 years and older):* The recommended dose of canakinumab is 4 mg/kg (with maximum of 300 mg) SC q4w for pediatric patients weighing ≥7.5 kg	Canakinumab is a human IgG1κ mAb with an apparent MW of ~ 145 kDa For IV use, canakinumab is supplied as white, preservative-free, lyophilized powder in a single-dose vial (150 mg/vial) for reconstitution and dilution prior to IV infusion For SC use, canakinumab is supplied as a sterile, preservative-free, clear to opalescent, colorless to slightly pale-yellow solution in a single-dose glass vial (150 mg/mL) Keep refrigerated at 2 °C–8 °C. Store in original carton until time of use. Protect from light. Do not freeze

Rilonacept (Arcalyst®)	IL-1β	CAPS	Rilonacept blocks IL-1β signaling by acting as a soluble decoy receptor that binds IL-1β and prevents its interaction with cell surface receptors. Rilonacept also binds IL-1α and IL-1 receptor antagonist with reduced affinity	Rilonacept should be administered as SC injection *Adult CAPS*: The recommended dose of rilonacept is 320 mg SC as a loading dose, followed by a maintenance dose regime of 160 mg SC qw *Pediatric CAPS (12 years of age and older)*: The recommended dose of rilonacept is 4.4 mg/kg (up to 320 mg) SC as a loading dose, followed by a maintenance dose regime of 2.2 mg/kg (up to 160 mg) SC qw	Rilonacept is a dimeric fusion protein with an apparent MW of ~ 147 kDa Rilonacept is supplied as sterile, preservative-free, white to off-white, lyophilized powder in a single-use vial. After reconstitution, each vial contains 80 mg/mL rilonacept and a volume of up to 2 mL can be withdrawn. The resulting solution is viscous, clear, colorless to pale yellow, and essentially free from particulates Keep refrigerated at 2 °C–8 °C. Protect the vials from light by storing in the original package until time of use. After reconstitution, rilonacept may be kept at room temperature, should be kept from light, and should be used within 3 h of reconstitution
Anti-IL-5					
Mepolizumab (Nucala®)	IL-5	Asthma, EGPA	Mepolizumab binds to IL-5, inhibiting the bioactivity of IL-5 by blocking its binding to the alpha chain of the IL-5 receptor complex expressed on the eosinophil cell surface IL-5 is the major cytokine responsible for the growth and differentiation, recruitment, activation, and survival of eosinophils, which plays a role in the pathogenesis of asthma and EGPA	Mepolizumab should be administered as SC injection *PsO*: The recommended dose of mepolizumab is 300 mg administrated as three separate 100-mg SC injections q4w *EGPA*: The recommended dose of mepolizumab is 300 mg administrated as three separate 100-mg SC injections q4w	Mepolizumab is a humanized IgG1 mAb with an apparent MW of ~ 149 kDa Mepolizumab is supplied as sterile, clear, white to off-white, preservative-free, lyophilized powder in cartons of a single-dose glass vial and a flip-off seal for reconstitution and SC injection (100 mg/vial) Keep refrigerated below 25 °C. Store in the original package to protect from light
Reslizumab (Cinqair®)	IL-5	Asthma	Reslizumab binds to IL-5, inhibiting the bioactivity of IL-5 by blocking its binding to the α chain of the IL-5 receptor complex expressed on the eosinophil cell surface IL-5 is the major cytokine responsible for the growth and differentiation, recruitment, activation, and survival of eosinophils, which plays a role in the pathogenesis of asthma	Reslizumab should be administered as IV infusion *Asthma*: The recommended dose of reslizumab is 3 mg/kg q4w by IV infusion over 20–50 mins	Reslizumab is a human IgG4κ mAb with an apparent MW of ~ 147 kDa Reslizumab is a sterile, preservative-free, clear to slightly hazy/opalescent, colorless to slightly yellow solution and supplied in a single-use vial (100 mg/10 mL) Keep refrigerated at 2 °C–8 °C. Do not freeze or shake. Protect the vials from light by storing in the original package until time of use
Anti-IL-17A					
Ixekizumab (Taltz®)	IL-17A	PsA, PsO	Ixekizumab selectively binds with IL-17A and inhibits its interaction with the IL-17 receptor IL-17A is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. Ixekizumab inhibits the release of proinflammatory cytokines and chemokines	Ixekizumab should be administered as SC injection *PsO*: The recommended dose of ixekizumab is 160 mg SC at week 0, followed by 80 mg SC at weeks 2, 4, 6, 8, 10, and 12, then 80 mg SC q4w thereafter *PsA*: The recommended dose of ixekizumab is 160 mg SC at week 0, followed by 80 mg SC q4w thereafter. For PsA patients with coexistent moderate-to-severe PsO, the dose regimen for PsO can be used	Ixekizumab is a human IgG4 mAb with an apparent MW of ~ 146.2 kDa Ixekizumab is supplied as a sterile, preservative free, clear, colorless to light yellow solution in a single-dose prefilled syringe or single-dose prefilled autoinjector (80 mg/mL) Keep refrigerated at 2 °C–8 °C. Store in original carton until time of use. Protect from light. Do not freeze or shake. Discard any unused portion

Table 26.1 ■ (continued)

Part A: Indication, mechanism of action, recommended dose regimen and pharmaceuticals considerations					
Product	**Target**	**Indication**[a]	**Mechanism of action**	**Recommended dose regimen**[a]	**Pharmaceutical considerations**[a]
Secukinumab (Cosentyx®)	IL-17A	PsA, AS and PsO	Secukinumab binds to IL-17A and inhibits its interaction with the IL-17 receptor IL-17A is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. Secukinumab inhibits the release of proinflammatory cytokines and chemokines	Secukinumab should be administered as SC injection *PsO*: The recommended dose of secukinumab is 300 mg SC at weeks 0, 1, 2, 3, and 4 followed by 300 mg SC q4w. For some patients, a dose of 150 mg may be acceptable *PsA*: For PsA patients with coexistent moderate to severe PsO, use the secukinumab dose for PsO. For other PsA patients, the recommended dose of secukinumab is 150 mg SC q4w with or without of a loading dosage (i.e., 150 mg SC at weeks 0, 1, 2, 3, and 4). If a patient continues to have active PsA, consider a dosage of 300 mg *AS:* The recommended dose of secukinumab is 150 mg SC q4w with or without of a loading dosage (i.e., 150 mg SC at weeks 0, 1, 2, 3, and 4)	Secukinumab is a human IgG1κ mAb with an apparent MW of ~ 151 kDa Secukinumab is supplied in a single-dose Sensoready pen or prefilled syringe as a sterile, preservative-free, clear to slightly opalescent, colorless to slightly yellow solution (150 mg/1.14 mL). Secukinumab is also supplied as sterile, preservative free, white to slightly yellow, lyophilized powder in a single-use vial (150 mg /vial) for reconstitution and injection Keep refrigerated at 2 °C–8 °C. Protect from light by storing in the original package until time of use. Do not freeze or shake
Anti-IL12/IL-23					
Ustekinumab (Stelara®)	IL12/IL23	PsO, PsA, CD and adolescent PsO	Ustekinumab binds to the p40 protein subunit used by both the IL-12 and IL-23 cytokines IL-12 and IL-23 are naturally occurring cytokines that are involved in inflammatory and immune responses, such as natural killer cell activation and CD4+ T-cell differentiation and activation. IL-12 and IL-23 have been implicated as important contributors to chronic inflammations	Ustekinumab may be used as IV infusion and as SC injection *PsO*: The recommended dose of ustekinumab is 45 mg SC initially and 4 weeks later, followed by 45 mg SC q12w for patients weighing ≤100 kg; the recommended dose for patients weighing >100 kg is 90 mg SC initially and 4 weeks later, followed by 90 mg SC q12w *PsO adolescent (12 years of age and older):* The recommended dose of ustekinumab is SC weight-based-dosing (0.75 mg/kg, 45 mg and 90 mg for weight range of <60 kg, 60–100 kg and ≥100 kg, respectively) at the initial dose, 4 weeks later, then q12w thereafter *PsA*: The recommended dose of ustekinumab is 45 mg SC initially and 4 weeks later, followed by 45 mg SC q12w. For patients with co-existent moderate-to-severe PsO weighing >100 kg, consider a dosage of 90 mg *CD*: The recommended induction dose of ustekinumab is a singe IV infusion using weight-based-dosing (~ 6.g/kg, i.e., 260 mg, 390 mg, and 520 mg for weight range of ≤55 kg, 55–85 kg and >85 kg, respectively). The recommended maintenance dose of ustekinumab is 90 mg SC 8 weeks after the initial IV dose, then q8w thereafter	Ustekinumab is a human IgG1κ mAb with an apparent MW of ~ 148.1–149.7 kDa Ustekinumab is a sterile, preservative-free, colorless to light yellow solution and may contain a few small translucent or white particles For IV use, ustekinumab is supplied as a single-dose glass vial with a coated stopper (130 mg/26 mL) For SC use, ustekinumab is supplied in single-dose prefilled syringes (45 mg/0.5 mL and 90 mg/ 1 mL) or a single-dose vial with a coated stopper (45 mg/0.5 mL) Keep refrigerated at 2 °C–8 °C. Store vials upright. Do not freeze or shake. Keep the product in the original carton to protect from light until the time of use

Anti-IL-23					
Guselkumab (Tremfya®)	IL-23	PsO	Guselkumab selectively binds to the p19 subunit of IL-23 and inhibits its interaction with the IL-23 receptor IL-23 is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. Guselkumab inhibits the release of proinflammatory cytokines and chemokines	Guselkumab should be administered as SC injection *PsO*: The recommended dose of guselkumab is 100 mg SC at weeks 0 and 4, followed by 100 mg SC q8w thereafter	Guselkumab is a human IgG1λ mAb with an apparent MW of ~ 143.6 kDa Guselkumab is supplied as a sterile, preservative free, clear, colorless to light yellow solution that may contain small translucent particles in a single-dose prefilled syringe (100 mg/mL) Keep refrigerated at 2 °C–8 °C. Store in original carton until time of use. Protect from light. Do not freeze or shake
Anti-IL-4 receptor					
Dupilumab (Dupixent®)	IL-4 receptor subunit α	AD	Dupilumab inhibits IL-4 and IL-13 signaling by binding to the IL-4 receptor subunit α shared by the IL-4 and IL-13 receptor complexes Blocking IL-4 receptor subunit α with dupilumab inhibits IL-4 and IL-13 cytokine-induced responses, including the release of proinflammatory cytokines, chemokines and IgE	Dupilumab should be administered as SC injection *AD*: The recommended dose of dupilumab is 600 mg (two 300 mg injections) SC initially, followed by 300 mg SC q2w	Dupilumab is a human IgG4 mAb with an apparent MW of ~ 147 kDa Dupilumab is supplied as a sterile, preservative-free, clear to slightly opalescent, colorless to pale yellow solution in a single-use prefilled syringe with or without needle shield (300 mg/2 mL) Keep refrigerated at 2 °C–8 °C. Store in original carton until time of use. Protect from light. Do not freeze or shake. Do not expose to heat. If necessary, pre-filled syringes may be kept at room temperature up to 25 °C for a maximum of 14 days
Anti-IL-5 receptor					
Benralizumab (Fasenra®)	IL-5 receptor	Asthma	Benralizumab binds to the α subunit of the human IL-5 receptor, which expressed on the surface of eosinophils and basophils The absence of fucose in the Fc domain of benralizumab facilitates binding to FcγRIII receptors on immune effectors cells, such as natural killer cells, leading to apoptosis of eosinophils and basophils through antibody-dependent cell-mediated cytotoxicity (ADCC)	Benralizumab should be administered as SC injection *Asthma*: The recommended dose of benralizumab is 30 mg SC at weeks 0, 4 and 8, followed by 30 mg q8w	Benralizumab is a humanized afucosylate IgG1κ mAb with an apparent MW of 150 kDa Benralizumab is supplied in a single-dose prefilled syringe (30 mg/1 mL) with needle safety guard as few translucent or white to off-white particles may be present in the solution and may contain a few translucent or white to off-white particles Keep refrigerated at 2 °C–8 °C. Store in original carton to protect from light. Do not freeze or shake. Prior to administration, warm benralizumab by leaving carton at room temperature for about 30 mins. Administer benralizumab within 24 h

Table 26.1 ■ (continued)

Part A: Indication, mechanism of action, recommended dose regimen and pharmaceuticals considerations					
Product	**Target**	**Indication**[a]	**Mechanism of action**	**Recommended dose regimen**[a]	**Pharmaceutical considerations**[a]
Anti-IL-6 receptor					
Sarilumab (Kevzara®)	IL-6 receptor	RA	Sarilumab binds to both soluble and membrane-bound IL-6 receptors, and has been shown to inhibit IL-6-mediated signaling through these receptors IL-6 is a pleiotropic pro-inflammatory cytokine produced by a variety of cell types including T-and B-cells, lymphocytes, monocytes, and fibroblasts. IL-6 is also produced by synovial and endothelial cells leading to local production of IL-6 in joints affected by inflammatory processes	Sarilumab should be administered as SC injection *RA*: The recommended dose of sarilumab is 200 mg SC q2w	Sarilumab is a human IgG1 mAb with an apparent MW of ~ 150 kDa Sarilumab is supplied as a sterile, colorless to pale yellow, preservative-free solution in single-dose pre-filled syringes (150 mg/1.14 mL or 200 mg/1.14 mL) Keep refrigerated at 2 °C–8 °C. Protect from light by storing in the original package until time of use. Do not freeze or shake. If needed, sarilumab may be stored at room temperature up to 25 °C up to 14 days in the outer carton. Do not store above 25 °C. After removal from the refrigerator, use sarilumab within 14 days or discard

Tocilizumab (Actemra®)	IL-6 receptor	RA, pJIA, sJIA, GCA, and CRS	Tocilizumab binds to both soluble and membrane-bound IL-6 receptors, and has been shown to inhibit IL-6-mediated signaling through these receptors IL-6 is a pleiotropic pro-inflammatory cytokine produced by a variety of cell types including T-and B-cells, lymphocytes, monocytes, and fibroblasts. IL-6 is also produced by synovial and endothelial cells leading to local production of IL-6 in joints affected by inflammatory processes	Tocilizumab may be used as IV infusion and SC injection *RA*: for IV use, the recommended starting dose of tocilizumab is 4 mg/kg IV q4w, followed by an increase to 8 mg/kg IV q4w based on clinical response For SC use, the recommended dose of tocilizumab is 162 mg SC q2w, followed by an increase to qw based on clinical response for patients <100 kg; the recommended dose for patients ≥100 kg is 162 mg SC qw *pJIA (2 years of age and older)*: The recommended dose of tocilizumab is 10 mg/kg or 8 mg/kg IV q4w for patients weighing <30 kg or ≥30 kg, respectively, alone or in combination with methotrexate *sJIA (2 years of age and older)*: The recommended dose is 12 mg/kg or 8 mg/kg IV q2w for patients weighing <30 kg or ≥30 kg, respectively, alone or in combination with methotrexate *GCA*: The recommended dose is 162 mg SC qw, in combination with a tapering course of glucocorticoids. Dose regimen of 162 mg SC q2w in combination with a tapering course of glucocorticoids may be prescribed based on clinical considerations. Tocilizumab can be used alone following discontinuation of glucocorticoids *CRS (2 years of age and older)*: The recommended dose of tocilizumab is 12 mg/kg or 8 mg/kg IV for patients weighing <30 kg or ≥ 30 kg, respectively, alone or in combination with corticosteroids. If no clinical improvement after the first dose, up to three additional doses of tocilizumab may be administered. The interval between consecutive doses should be at least 8 h. Doses exceeding 800 mg per infusion are not recommended	Tocilizumab is a human IgG1κ mAb with an apparent MW of ~ 151 kDa For IV use, tocilizumab is supplied as a sterile, preservative-free, clear, colorless to pale yellow liquid in single-use vials at a concentration of 20 mg/mL (80 mg/4 mL, 200 mg/10 mL, and 400 mg/20 mL) for further dilution prior to IV infusion For SC use, tocilizumab is supplied as a sterile, preservative-free, clear, colorless to slightly yellowish solution and is provided in a single-dose prefilled syringe (162 mg/0.9 mL) Keep refrigerated at 2 °C–8 °C. Do not freeze. Protect from light by storing in the original package until time of use, and keep syringes dry

Table 26.1 ■ (continued)

Part A: Indication, mechanism of action, recommended dose regimen and pharmaceuticals considerations					
Product	**Target**	**Indication**[a]	**Mechanism of action**	**Recommended dose regimen**[a]	**Pharmaceutical considerations**[a]
Anti-IL-17 receptor A					
Brodalumab (Siliq®)	IL-17 receptor A	PsO	Brodalumab selectively binds to human IL-17 receptor A and inhibits its interactions with cytokines IL-17A, IL-17F, IL-17C, IL-17A/F heterodimer and IL-25 IL-17 receptor A is a protein expressed on the cell surface and is a required component of receptor complexes utilized by multiple IL-17 family cytokines. Blocking IL17 receptor A inhibits IL-17 cytokine-induced responses including the release of pro-inflammatory cytokines and chemokines	Brodalumab should be administered as SC injection *PsO*: The recommended dose of brodalumab is 210 mg SC at weeks 0, 1 and 2 followed by 210 mg q2w	Brodalumab is a human IgG2κ mAb with an apparent MW of ~ 144 kDa Brodalumab is supplied in a single-dose prefilled syringe (210 mg/1.5 mL) as a clear to slightly opalescent, colorless to slightly yellow solution and may contain a few translucent to white, amorphous particles Keep refrigerated at 2 °C–8 °C. Store in original carton until time of use. Do not freeze or shake. Protect from light. If needed, may be stored at room temperature up to a maximum of 25 °C for a single period of up to 14 days, with protection from light and source of heat
Anti-IgE					
Omalizumab (Xolair®)	IgE	Asthma and CIU	Omalizumab binds to IgE and lowers free IgE levels. Subsequently, IgE receptors (FcεRI) on cells down-regulate, such as mast cells and basophils Reduction in surface-bound IgE on FcεRI-bearing cells limits the degree of release of mediators of the allergic response	Omalizumab should be administered as SC injection *Asthma (6 years of age and older)*: The recommended dose of omalizumab is 75–375 mg SC q2w or q4w, with dose and dosing frequency determined by pretreatment serum IgE levels and body weight *CIU (12 years of age and older)*: The recommended dose of omalizumab is 150 or 300 mg SC q4w	Omalizumab is a humanized IgG1κ mAb with an apparent MW of ~ 149 kDa Omalizumab is supplied as sterile, preservative free, clear, white to off-white, lyophilized powder in a single-dose vial (150 mg/vial) for reconstitution and SC injection Keep refrigerated below 25 °C. Protect from light. Use the solution within 8 h following reconstitution when stored in the vial at 2–8 °C, or within 4 h of reconstitution when stored at room temperature
Anti-integrin					
Natalizumab (Tysabri®)	Integrin	CD and MS	Natalizumab binds to the α4-subunit of α4β1 and α4β7 integrins expressed on the surface of all leukocytes except neutrophils, and inhibits the α4-mediated adhesion of leukocytes to their counter-receptor(s)	Natalizumab should be administered as IV infusion *CD and MS*: The recommended dose of natalizumab is 300 mg q4w by IV infusion over 1 h	Natalizumab is a human IgG4κ mAb with an apparent MW of ~ 149 kDa Natalizumab is supplied as a colorless and clear to slightly opalescent solution for dilution prior to IV infusion and is provided in a sterile, single-use vial free of preservatives (300 mg/15 mL) Keep refrigerated at 2 °C–8 °C. Protect from light. Do not freeze or shake. If not used immediately, store the diluted Natalizumab solution for infusion at 2 °C–8 °C. Natalizumab solution for infusion must be administered within 8 h of preparation

Vedolizumab (Entyvio®)	Integrin	CD and UC	Vedolizumab binds to the α4β7 integrin and blocks the interaction of α4β7 integrin with MAdCAM-1 and inhibits the migration of memory T-lymphocytes across the endothelium into inflamed gastrointestinal parenchymal tissue. Vedolizumab does not bind to or inhibit function of the α4β1 and αEβ7 integrins and does not antagonize the interaction of α4 integrins with VCAM-1	Vedolizumab should be administered as IV infusion *CD and UC*: The recommended dose of vedolizumab is 300 mg at 0, 2, and 6 weeks by IV infusion over approximately 30 mins, then q8w thereafter	Vedolizumab is a humanized IgG1 mAb with an apparent MW of ~ 147 kDa Vedolizumab is supplied as sterile, preservative free, white to off-white, lyophilized cake in a single-use vial (300 mg/vial) for reconstitution and dilution prior to IV infusion Keep refrigerated at 2 °C–8 °C. Retain in original package to protect from light. Administer infusion solution within 4 h of reconstitution and dilution
Anti-CD80/CD86 Lymphocyte Activation Inhibitor					
Abatacept (Orencia®)	CTLA-4	RA, PsA, and pJIA	Abatacept is a selective costimulation modulator that inhibits T lymphocyte activation by binding to CD80 and CD86, thereby blocking interaction with CD28. This interaction provides a costimulatory signal necessary for full activation of T lymphocytes	Abatacept may be administered as IV infusion and SC injection *IV infusion for RA and PsA*: The recommended dose of abatacept is weight based dosing (~ 10 mg/kg, i.e., 500, 750, and 1000 mg for patients weighing <60 kg, 60–100 kg, and >100 kg, respectively) administered as IV infusion at weeks 0, 2, and 4 and q4w thereafter *SC injection for RA*: The recommended dose of abatacept is 125 mg SC qw with or without an initial IV loading dose (according to body weight categories described above) *SC injection for PsA*: The recommended dose of abatacept is 125 mg SC qw (without the need of an IV loading dose) *IV infusion for pJIA (6 years and older)*: The recommended dose for pediatrics weighing <75 kg is 10 mg/kg at weeks 0, 2, and 4 and q4w by IV infusion. Pediatric patients weighing ≥75 kg should be administered following the IV dose regimen for adult RA (not to exceed 1000 mg/injection) *SC injection for pJIA (2 years and older)*: The recommended dose is SC qw at a body-weight-tired dosing of 50, 87.5 and 125 mg for pJIA patients weighing 10 to <25 kg, 25 to <50 kg and ≥50 kg, respectively	Abatacept is a soluble fusion protein with an apparent MW of ~ 92 kDa For IV use, abatacept is supplied as sterile, white, preservative-free, lyophilized powder in a single-use vial (250 mg/vial) for reconstitution and dilution prior to IV infusion For SC use, abatacept is supplied as a sterile, preservative-free, clear to slightly opalescent, colorless to pale-yellow solution and is provided in single-dose prefilled syringes (50 mg/0.4 mL, 87.5 mg/0.7 mL, and 125 mg/mL), or in a single-dose prefilled ClickJect autoinjector (125 mg/mL) Keep refrigerated at 2 °C–8 °C. Do not freeze. Store in original carton until time of use. Protect from light

Table 26.1 ■ (continued)

Part A: Indication, mechanism of action, recommended dose regimen and pharmaceuticals considerations					
Product	**Target**	**Indication**[a]	**Mechanism of action**	**Recommended dose regimen**[a]	**Pharmaceutical considerations**[a]
Belimumab (Benlysta®)	BLyS	SLE	Belimumab is a BLyS-specific inhibitor that blocks the binding of soluble BLyS, a B-cell survival factor, to its receptors on B cells. Belimumab does not bind B cells directly, but by binding BLyS Belimumab inhibits the survival of B cells, including autoreactive B cells, and reduces the differentiation of B cells into immunoglobulin-producing plasma cells	Belimumab may be administered as IV infusion and SC injection *IV infusion for SLE*: The recommended dose of belimumab is 10 mg/kg q2w for the first three doses, followed by 10 mg/kg q4w thereafter *SC injection for SLE*: The recommended dose of belimumab is 200 mg qw	Belimumab is a human IgG1λ mAb with an apparent MW of ~ 147 kDa For IV use, belimumab is supplied as a sterile, white to off-white, preservative-free, lyophilized powder in single-dose vials (120 mg/vial or 400 mg/vial) for reconstitution and dilution prior to IV infusion For SC use, belimumab is supplied in a single-dose prefilled syringe or autoinjector as a sterile, preservative-free, clear to opalescent, colorless to pale-yellow solution (200 mg/mL) Keep refrigerated at 2 °C–8 °C. Store in original carton until time of use. Protect from light. Do not freeze or shake. May be stored outside of the refrigerator up to 30 °C for up to 12 h in the original container
Anti-CD-20 cytolytic agent					
Ocrelizumab (Ocrevus®)	CD20	MS	Ocrelizumab directed against CD20-expressing B-cells CD20 is a cell surface antigen present on pre-B and mature B lymphocytes. Following cell surface binding to B lymphocytes, ocrelizumab results in antibody-dependent cell-mediated cytotoxicity (ADCC) and complement-mediated lysis	Ocrelizumab should be administered as IV infusion *MS*: The recommended dose of ocrelizumab is 300 mg IV infusion initially, followed 2 weeks by a second 300 mg IV infusion, and then 600 mg IV infusion every 6 months Pre-medicate with methylprednisolone (or an equivalent corticosteroid) and an antihistamine (e.g., diphenhydramine) prior to each infusion. Monitor patients closely during and for at least 1 h after infusion	Ocrelizumab is a glycosylated human IgG1 mAb with an apparent MW of ~ 149 kDa Ocrelizumab is supplied as preservative-free, sterile, clear or slightly opalescent, and colorless to pale brown solution supplied as a carton containing one 300 mg/10 mL (30 mg/mL) single-dose vial Keep refrigerated at 2 °C–8 °C in the outer carton to protect from light. Do not freeze or shake
Rituximab (Rituxan®)	CD20	RA	Rituximab targets the CD20 antigen expressed on the surface of pre-B and mature B-lymphocytes. Upon binding to CD20, rituximab mediates B-cell lysis	Rituximab should be administered as IV infusion *RA*: The recommended dose of rituximab in combination with methotrexate is two 1000 mg IV infusions separated by 2 weeks (one course) every 24 weeks or based on clinical evaluation, but no more frequent than every 16 weeks. Methylprednisolone 100 mg IV or equivalent glucocorticoid is recommended 30 mins prior to each infusion	Rituximab is a chimeric IgG1κ mAb with an apparent MW of ~ 145 kDa Rituximab is supplied a sterile, clear, colorless, preservative-free liquid concentrate for IV infusion at a concentration of 10 mg/mL in either 100 mg/10 mL or 500 mg/50 mL single-use vials Keep refrigerated at 2 °C–8 °C. Protect from direct sunlight. Do not freeze or shake

Part B: Pharmacokinetics and pharmacokinetics/pharmacodynamics					
Product	**Target**	**Indication**	**Pharmacokinetics**	**Pharmacokinetics/Pharmacodynamics**	**Reference[a]**
Anti-TNFα					
Adalimumab (Humira®)	TNFα	RA, PsA, AS, pJIA, PsO, CD, pediatric CD, UC, HS and UV	Adalimumab exhibits linear pharmacokinetics with mean terminal half-life being about 2 weeks. The systemic clearance of adalimumab was approximately 12 mL/h. The mean bioavailability of SC adalimumab was 64% In patients with RA, the mean steady-state trough concentrations were about 5 and 8–9 μg/mL without and with concomitant methotrexate, respectively, following 40 mg q2w SC dosing. Methotrexate reduced adalimumab apparent clearance after single and multiple dosing by 29% and 44%, respectively, in patients with RA. Adalimumab concentrations in the synovial fluid from five rheumatoid arthritis patients ranged from 31–96% of those in serum In patients with PsA treated with 40 mg adalimumab SC q2w, the mean steady-state trough concentrations were slightly higher (6–10 μg/mL and 8.5–12 μg/mL, without and with methotrexate, respectively) compared to the concentrations in RA patients treated with the same dose	In patients with RA, relationships between adalimumab concentration and the time course in the reduction of DAS28-ESR score and the serum CRP level were characterized using a direct P/PD model and an indirect response PK/PD model respectively, following E_{max} relationship. The estimated EC_{50} was 11 and 3.6 μg/mL, respectively In patients with RA and PsA, analysis of the adalimumab trough concentration- effect relationship for reduction in DAS28 score suggested that steady-state trough concentration in a range of 5–8 μg/mL was sufficient to reach adequate clinical response In patients with PsO, analysis of the adalimumab trough concentration- effect relationship for improvement in PASI score adalimumab suggested that steady-state trough concentration in a range of 3.5–7 μg/mL was sufficient to reach adequate clinical response	Ternant et al. (2015) (RA) Vogelzang et al. (2014) (PsA), (2015) (RA) Menting et al. (2015) (PsO) Hoseyni et al. (2018) (CD/UC) EMA/CHMP/364731/2015 (2015b) (HS) EMA/501143/2016 (2016a) (UV) EMA/CHMP/829007/2017 (2017d) (pJIA) EMA/56352/2013 (2013a) (Pediatric CD) EMA/CHMP/177541/2015 (2015a) (Pediatric PsO)

Table 26.1 ■ (continued)

Part B: Pharmacokinetics and pharmacokinetics/pharmacodynamics					
Product	**Target**	**Indication**	**Pharmacokinetics**	**Pharmacokinetics/Pharmacodynamics**	**Reference[a]**
			In patients with AS, the pharmacokinetics of adalimumab were similar to those in patients with RA In patients with CD/UC, the adalimumab loading dose of 160 mg SC at week 0 followed by 80 mg SC at week 2 achieved mean serum trough concentrations of approximately 12 μg/mL at week 2 and week 4. Mean steady-state trough concentrations of 7–8 μg/mL were observed after receiving an adalimumab maintenance dose of 40 mg SC q2w In patients with PsO, the mean steady-state trough concentration was approximately 5–6 μg/mL during adalimumab 40 mg SC q2w monotherapy treatment In patients with HS, the adalimumab loading dose of 160 mg SC at week 0 followed by 80 mg SC at week 2 achieved mean serum adalimumab trough concentrations of 7–8 μg/mL at week 2 and week 4. The mean steady-state trough concentrations were 7–11 μg/mL during adalimumab 40 mg SC qw treatment In patients with UV, the mean steady-state trough concentration was 8–10 μg/mL during adalimumab 40 mg SC q2w treatment In pJIA patients 4–17 years of age, the mean steady-state trough serum adalimumab concentrations for patients weighing <30 kg who received 20 mg adalimumab SC q2w as monotherapy or with concomitant methotrexate were 6.8 μg/mL and 10.9 μg/mL, respectively. The mean steady-state trough concentrations for patients weighing ≥30 kg who received 40 mg SC q2w as monotherapy or with concomitant methotrexate were 6.6 μg/mL and 8.1 μg/mL, respectively. In pJIA patients weighing <15 kg, the mean steady-state trough concentrations following SC adalimumab of 24 mg/m^2 (maximum 20 mg) q2w as monotherapy or with concomitant methotrexate were 6.0 μg/mL and 7.9 μg/mL, respectively	In patients with CD and UC, several reports suggested that higher adalimumab trough concentrations were associated with higher proportions of patients achieving the desired clinical efficacy endpoints, including clinical remission, mucosal healing and CRP remission In patients with HS, Hidradenitis Suppurativa Clinical Response (HiSCR) responders had higher adalimumab trough concentrations compared to non-responders. In HiSCR responders, higher adalimumab concentrations were associated with less probability of loss of response In patients with UV, patients with treatment failure had lower adalimumab exposure compared to those without treatment failure. The estimated EC_{50} for inhibition of treatment failure event was 6.4–9.7 μg/mL In pediatric patients with CD, relationship between adalimumab concentration and the clinical remission rate over time was characterized by two types of PK/PD models, namely the indirect response model and the Markov chain model. Clear E-R relationship was established and the Markov chain model estimated EC_{50} was 3.4 μg/mL In pediatric patients with pJIA and PsO, relationships between adalimumab exposure and the probability of achieving pediatric ACR response (PedACR30/PedACR50) and the PASI75 response, respectively, were characterized by non-linear logistic regression models. Clear E-R relationships were shown in these two pediatric populations, with higher adalimumab concentration associated with higher probability of achieving the clinical endpoints In patients with RA, significant E-R relationship for effectiveness (ACR20/50/70 responses over time) was shown using a continuous-time Markov model. Increased certolizumab pegol exposure resulted in an increased probability of attaining higher level of ACR20/50/70 responses, with majority of the clinical effect being attained at the exposure associated with the recommended 200 mg q2w label maintenance dose. Additionally, change from baseline in DAS28(CRP) (ΔDAS) increased with certolizumab concentration, where certolizumab concentration threshold ≥24 μg/mL was associated with ΔDAS ≥2 at weeks 12 and 24	

Certolizumab pegol (Cimzia®)	TNFα	RA, PsA, AS and CD	In pediatric patients with CD weighing ≥40 kg, the mean serum concentrations were 15.7 μg/mL at week 4 following SC doses of 160 mg at week 0 and 80 mg at week 2, and the mean steady-state trough concentrations during maintenance therapy were 10.5 μg/mL following 40 mg SC q2w. In pediatric patients with CD weighing <40 kg, the mean serum concentrations were 10.6 μg/mL at week 4 following SC doses of 80 mg at week 0 and 40 mg at week 2, and the mean steady-state trough concentrations during maintenance therapy were 6.9 μg/mL following 20 mg SC q2w Certolizumab pegol exhibits linear pharmacokinetics with mean terminal half-life being about 14 days. The systemic clearance ranged from 9.21 to 14.38 mL/h in healthy subjects. The mean bioavailability of SC certolizumab pegol was 80%. Apparent clearance following SC injections were estimated to be 17 mL/h and 21 mL/h in CD and RA populations, respectively	In patients with CD, certolizumab pegol concentrations at weeks 2, 4, and 6 were higher in patients with clinical response, remission, CRP ≤ 5 mg/L and fecal calprotectin ≤250 μg/g at week 6 than without. Certolizumab concentrations of at least 36.1 μg/mL at week 6 and at least 14.8 μg/mL at week 12 were associated with the desired outcomes at weeks 6 and 26 respectively	Lacroix et al. (2014) (RA) Wolbink et al. (2016) (RA) Vande Casteele et al. (2018) (CD)
Etanercept (Enbrel®)	TNFα	RA, PsA, AS, pJIA and PsO	Etanercept exhibits linear pharmacokinetics with mean terminal half-life being 102 h. The mean clearance was 160 mL/h In patients with RA and PsO, the mean steady-state trough concentrations were 1.2 and 1.5 μg/mL, respectively, following 50 mg SC qw dosing In patients with pJIA, the mean serum concentrations were 2.1 μg/mL following 0.4 mg/kg SC twice weekly (maximum of 50 mg per week) dosing In pediatric PsO patients, the mean steady-state trough concentrations were 1.6–2.1 μg/mL following 0.8 mg/kg (maximum of 50 mg) SC qw dosing	In patients with RA, relationships between predicted etanercept cumulative AUC and the ACR20/50/70 responses rates and the reduction in DAS28 score over time were characterized by a logistic regression model and a direct inhibitory E_{max} model, respectively, with respect to time. Clear E-R relationships were established In patients with PsO, significant E-R relationship for effectiveness (probability of achieving PASI75 over time) was shown using time series logistic regression models with cumulative etanercept dose, predicted cumulative etanercept AUC and predicted etanercept trough before each PASI75 assessment as the exposure variables. Cumulative AUC was determined to be the most adequate exposure predictor	Lee et al. (2003) (RA) Hsu and Huang (2014) (RA) Hutmacher et al. (2007) (PsO)

Table 26.1 ■ (continued)

Part B: Pharmacokinetics and pharmacokinetics/pharmacodynamics					
Product	**Target**	**Indication**	**Pharmacokinetics**	**Pharmacokinetics/Pharmacodynamics**	**Reference[a]**
Golimumab (Simponi®, Simponi Aria®)	TNFα	RA, PsA, AS, and UC nr-AxSpA and pJIA (EU only, SmPC)	Golimumab exhibits linear pharmacokinetics with mean terminal half-life being about 2 weeks. The mean systemic clearance was estimated to be 7.6 mL/day/kg in patients with RA. The mean bioavailability of SC golimumab was 53% Following IV administration of 2 mg/kg golimumab at weeks 0, 4 and q8w thereafter, the mean steady-state serum trough concentrations in patients with active RA, PsA and AS were 0.4, 0.7 and 0.8 μg/mL respectively Following SC administration of 50 mg golimumab q4w with concomitant methotrexate, the mean steady-state trough concentrations in patients with active RA, PsA and AS were 0.4–0.6, 0.5 and 0.8 μg/mL respectively. Concomitant use of methotrexate reduced the apparent clearance of golimumab by approximately 52, 36 and 21% in patients with RA, PsA and AS respectively Treatment of patients with UC with 100 mg golimumab SC q4w during maintenance resulted in a mean steady-state trough concentration of approximately 1.8 μg/mL	In patients with RA, the relationship between golimumab concentration and the time course of ACRN (a continuous measure of clinical improvement derived from ACR20 response criteria) score following golimumab 50 or 100 mg q4w was characterized using an indirect response PK/PD model. E_{max} relationship was attempted but EC_{50} cannot be reliably estimated; golimumab 50 and 100 mg doses likely results in a range of exposures located in the upper domain of a saturating E-R response curve In patients with pJIA, the relationship between golimumab concentration and the time course of log-transformed Juvenile Arthritis Disease Activity Score (JADAS) score was characterized using an indirect response PK/PD model following E_{max} relationship. Clear E-R relationship was established and the estimated EC_{50} was 0.412 μg/ml In patients with UC, higher serum golimumab concentrations were associated with higher efficacy response rates (including clinical response, clinical remission and mucosal healing) during induction and maintenance. Golimumab concentrations of 2.5 μg/ml (induction at week 6) and 1.4 μg/ml (maintenance steady-state trough) are estimated to be the concentration targets for attainment of optimal clinical outcomes	Hu et al. (2011) (RA) EMA/CHMP/404217/2016 (2016b) (pJIA) Adedokun et al. (2017) (UC)

Infliximab (Remicade®)	TNFα	RA, PsA, AS, PsO, CD, UC, pediatric CD, pediatric UC	Infliximab exhibits linear pharmacokinetics with median terminal half-life being 7.7–9.5 days Following IV infusions of a maintenance dose of 3–10 mg/kg q8w, median steady-state serum infliximab concentrations ranged approximately 0.5–6 μg/mL. Development of antibodies to infliximab increased infliximab clearance and lead to lower infliximab concentration Infliximab pharmacokinetic characteristics were similar in pediatric (aged 6–17 years) and adult patients with CD or UC following infliximab 5 mg/kg IV dosing	In patients with RA, higher infliximab serum pre-infusion concentrations at week 54 were associated with increased magnitude of ACR response (assessed by ACRN, a continuous measure of clinical improvement derived from ACR20 response criteria), greater reduction from baseline in CRP, and less progression of radiographic joint damage at week 54, as shown by the graphical exploratory analysis and/or the regression modeling analysis In patients with PsO, the maintenance of clinical response was related to the achievement of stable infliximab serum concentrations. Patients who maintained their PASI improvement had median pre-infusion serum infliximab concentrations above 1 μg/mL during maintenance therapy, while patients who lost response had median pre-infusion serum infliximab concentrations less than 1 μg/mL In patients with luminal CD, higher infliximab serum pre-infusion concentrations at week 14 were associated with greater reduction from baseline in CDAI (CD activity index) and higher clinical remission rate at week 14. In patients with fistulizing CD, higher infliximab serum pre-infusion concentrations at week 30 were associated with a higher probability of complete fistula response at week 30 In patients with UC, higher serum infliximab concentrations were associated with higher efficacy response rates (including clinical response, clinical remission and mucosal healing) during induction and maintenance. Infliximab concentrations of 41 μg/ml (induction at week 8) and 3.7 μg/ml (maintenance steady-state trough) are estimated to be the concentration targets for attainment of optimal clinical outcomes In pediatric patients with UC (6–17 years of age), a positive E-R relationship was identified between infliximab serum concentration and clinical effect following induction therapy by a logistic regression analysis (similar to adults). In addition, maintaining trough serum infliximab concentrations above detectable levels may be associated with maintenance of clinical response	St. Clair et al. (2002) (RA) Reich et al. (2005) (PsO) Fasanmade et al. (2002) (CD) Fasanmade et al. (2003) (CD) Adedokun et al. (2014) (UC) Adedokun et al. (2013) (Pediatric UC)

Table 26.1 ■ (continued)

Part B: Pharmacokinetics and pharmacokinetics/pharmacodynamics					
Product	**Target**	**Indication**	**Pharmacokinetics**	**Pharmacokinetics/Pharmacodynamics**	**Reference[a]**
Anti-IL-1β					
Canakinumab (Ilaris®)	IL-1β	CAPS and sJIA	Canakinumab exhibits linear pharmacokinetics with mean terminal half-life being 26 days. The mean bioavailability of SC canakinumab was 66%. Clearance of canakinumab varied according to body weight and was estimated to be 0.174 L/day in a CAPS patient weighing 70 kg and 0.11 L/day in a sJIA patient weighing 33 kg Pharmacokinetic properties of canakinumab are similar in CAPS and sJIA pediatric populations. In patients less than 2 years of age, the exposure of canakinumab were comparable to older age groups with a same weight-based-dose	In patients with CAPS, a mechanistic PK-biomarker-symptom model was developed to characterize the relationship between canakinumab concentration and the time course in the suppression of peripheral IL-1β, and IL-1β was linked further to the probability of flare and the changes in serum CRP, serum amyloid A and absolute neutrophil count over time. It indicated that CAPS is entirely mediated by IL-1β and that canakinumab treatment can restore physiological IL-1β production In patients with sJIA, the relationships between canakinumab concentration and the time course of peripheral IL-1β was characterized by a dynamic drug-ligand binding and turnover PK/PD model. The relationship between canakinumab exposure and sJIA flare reduction was characterized using a discrete hazard model. These modeling analyses supported the dose selection of canakinumab in patients with sJIA	Lachmann et al. (2009) (CAPS) Sun et al. (2016) (sJIA) Xiong et al. (2013) (sJIA)
Rilonacept (Arcalyst®)	IL-1β	CAPS	Following weekly SC doses of 160 mg in patients with CAPS, serum rilonacept concentration appeared to reach steady state by week 6 with average trough levels being approximately 24 μg/mL	In patients with CAPS, there was no apparent relationship between dose (or rilonacept concentrations at the respective time points) and either IL-1ß complex levels or total IL-1 receptor antagonist levels in blood in the Phase III study. The rilonacept concentrations were high compared to the affinity to the cytokines; therefore, cytokines were likely almost completely bound at any time and dose	EMEA/541561/2009 (2009) (CAPS)

Anti-IL-5					
Mepolizumab (Nucala®)	IL-5	Asthma, EGPA	Mepolizumab exhibited linear pharmacokinetics in patients with asthma, with mean terminal half-life being 16–22 days. Apparent clearance was estimated to be 0.28 L/day for a 70-kg individual. The bioavailability of SC mepolizumab was approximately 80% The pharmacokinetic properties of mepolizumab observed in patients with EGPA were similar to the pharmacokinetic properties displayed in patients with severe asthma	In patients with asthma, the relationship between mepolizumab concentration and the percentage change from baseline in blood eosinophils over time was described by an indirect response PK/PD model following E_{max} relationship. The estimated maximal decrease in eosinophil count was 85% from baseline and the estimated EC_{50} was 0.45 μg/mL	Smith et al. (2011)
Reslizumab (Cinqair®)	IL-5	Asthma	Reslizumab exhibits linear pharmacokinetics with a terminal half-life being about 24 days. The systemic clearance was approximately 7 mL/h. Peak serum concentrations were typically observed at the end of the infusion and serum concentrations generally declined from peak in a biphasic manner	In patients with asthma, clear E-R relationship between reslizumab exposure and the inhibition of peripheral blood eosinophil response over time was shown using an indirect response PK/PD model. Significant E-R relationships for improvement of lung function (forced expiratory volume in 1 s [FEV1]) and Asthma Control Questionnaire (ACR) score were also shown using the direct sigmoid E_{max} models. These analyses supported the proposed dose regimen for registration	US FDA Advisory Committee Briefing Document (BLA#761033) (2015a) (Asthma)
Anti-IL-17A					
Ixekizumab (Taltz®)	IL-17A	PsA, PsO	Ixekizumab exhibits linear pharmacokinetics in patients with PsO, with mean terminal half-life being 13 days. Apparent clearance was 0.39 L/day. The bioavailability of SC ixekizumab ranged from 60 to 81%. Administration of ixekizumab via SC injection in the thigh achieved a higher bioavailability relative to that achieved using other injection sites including the arm and abdomen Following SC administration of 160 mg ixekizumab at week 0 and 80 mg q2w thereafter, steady-state concentrations were achieved at week 8 in patients with PsO, with a mean trough level of 9.3 μg/mL. After switching from 80 mg q2w to 80 mg q4w dose regimen, steady-state concentrations were achieved 10 weeks later, with a mean trough level of 3.5 μg/mL The pharmacokinetic properties of ixekizumab observed in PsA patients were similar to the pharmacokinetic properties displayed in PsO patients	In patients with PsO, the relationship between ixekizumab concentration and Static Physicians Global Assessment (SPGA) response over time was characterized using an indirect response PK/PD model following E_{max} relationship. Clear E-R relationship was established and the modeling results supported the proposed dose regimen for registration	Choi et al. (2016)

Table 26.1 ■ (continued)

Part B: Pharmacokinetics and pharmacokinetics/pharmacodynamics

Product	Target	Indication	Pharmacokinetics	Pharmacokinetics/Pharmacodynamics	Reference[a]
Secukinumab (Cosentyx®)	IL-17A	PsA, AS and PsO	Secukinumab exhibited linear pharmacokinetics in patients with PsO, with mean terminal half-life being 22–31 days. Apparent clearance ranged from 0.14 to 0.22 L/day in patients with PsO. The bioavailability of SC secukinumab ranged from 55 to 77% The mean steady-state trough concentrations in PsO patients following 150 mg and 300 mg SC q4w dosing were 16.7 and 34.4 μg/mL, respectively Secukinumab concentrations in interstitial fluid in lesional and non-lesional skin of PsO patients ranged from 27% to 40% of those in serum at 1 and 2 weeks after a single SC dose of secukinumab 300 mg The pharmacokinetic properties of secukinumab observed in patients with PsA and AS were similar to the pharmacokinetic properties observed in patients with PsO	In patients with PsO, significant E-R relationship was shown between the observed secukinumab serum concentrations at week 12 and the PASI75 and IGA 0/1 at week 12, using logistic regression and/or graphical quartile analyses In patients with PsA, clear E-R relationships were observed at week 12 efficacy parameters of ACR, PASI, DAS28-CRP and HAQ-DI (Health Assessment Questionnaire Disability Index) by graphical exploratory analysis, with a trend of increased response with higher secukinumab trough concentration. E-R curves of endpoints reflecting the arthritic components of the disease (ACR20/50/70, DAS) appeared to plateau at trough levels higher than 20 μg/ml (20 μg/ml corresponds to the typical steady-state trough concentrations achieved following 150 mg SC q4w dosing) In patients with AS, clear E-R relationships were observed at week 16 efficacy parameters of ASAS (Assessment of SpondyloArthritis international Society response criterion), BASDAI (Bath Ankylosing Spondylitis Disease Activity Index), and SF36- PCS (short form 36—Physical Component Summary) by graphical exploratory analysis, with a trend of increased response with higher secukinumab trough concentration. The E-R curves appeared to plateau at trough levels higher than 25 μg/ml, which was approximate the mean trough concentrations following 150 mg SC q4w dosing	FDA Clinical Pharmacology Review (BLA#125504) (2015b) (RA) EMA/CHMP/665427/2015 (2015d) (PsA) EMA/CHMP/665405/2015 (2015c) (AS)

Anti-IL12/IL-23					
Ustekinumab (Stelara®)	IL12/IL23	PsO, PsA, CD and adolescent PsO	Ustekinumab exhibits linear pharmacokinetics In patients with PsO, the mean systemic clearance ranged from 1.90 to 2.22 mL/day/kg, with mean terminal half-life being 14.9–45.6 days. Following SC administration of 45 or 90 mg q12w, the mean steady-state trough concentrations were 0.31 and 0.64 μg/mL, respectively In patients with PsA, PK profiles were in general consistent with what were observed in patients with PsO In patients with CD, clearance was estimated to be 0.19 L/day with a median terminal half-life being approximately 19 days. Following the recommended IV induction dose (260 mg, 390 mg, and 520 mg for weight range of ≤55 kg, 55–85 kg and > 85 kg, respectively), mean peak serum ustekinumab concentration was 125.2 μg/mL. Mean steady-state trough concentration was 2.51 μg/mL following a maintenance dose of 90 mg SC q8w	In patients with PsO, relationship between ustekinumab exposure and the reduction of PASI score over time was characterized by an indirect response PK/PD model following an E_{max} relationship. The estimated median EC_{50} in partial responders (achieved 50% or more but less than 75% improvement in PASI score) was approximately 30-fold higher than that in responders (achieving 75% improvement in PASI score) In patients with PsA, the proportion of patients who achieved ACR20, ACR50, and PASI75 responses at week 24 was higher in patients with quantifiable serum ustekinumab concentrations at week 16 when compared with patients with serum ustekinumab concentrations below limit of quantitation (BLQ) at week 16 In patients with CD, relationship between ustekinumab concentration and the reduction of CDAI score over time were characterized by an indirect response PK/PD model following an E_{max} relationship with an autocorrelation residual error. Clear E-R relationship were established and the estimated EC_{50} was 6.37 μg/mL	Zhou et al. (2010) (PsO) EMA/CHMP/431551/2013 (2013b) (PsA) Hu et al. (2017a) (CD)
Anti-IL-23					
Guselkumab (Tremfya®)	IL-23	PsO	Guselkumab exhibited linear pharmacokinetics in patients with PsO, with mean terminal half-life being 15–18 days. Apparent clearance was approximately 0.516 L/day. The bioavailability of SC guselkumab was 49% in healthy subjects Following SC administration of 100 mg guselkumab at weeks 0 and 4, and q8w thereafter in PsO patients, mean steady-state serum guselkumab trough concentration was approximately 1.2 μg/mL	In patients with PsO, the relationship between guselkumab concentration and the time course of PASI75/90/100 responses rates and the Physician's Global Assessment (PGA) score was characterized using a joint indirect response PK/PD model following E_{max} relationship. Clear E-R relationship was established and the estimated EC_{50} was 0.0663 μg/ml	Hu et al. (2017b) (PsO)

Table 26.1 ■ (continued)

Part B: Pharmacokinetics and pharmacokinetics/pharmacodynamics					
Product	**Target**	**Indication**	**Pharmacokinetics**	**Pharmacokinetics/Pharmacodynamics**	**Reference[a]**
Tocilizumab (Actemra®)	IL-6 receptor	RA, pJIA, sJIA, GCA, and CRS	Tocilizumab exhibits target-mediated nonlinear pharmacokinetics. Clearance of tocilizumab decreased with increased doses. The terminal half-life of tocilizumab is concentration-dependent, up to 13 and 5 days at steady state for 162 mg SC qw and 162 mg SC q2w, respectively, in patients with RA. The bioavailability of SC tocilizumab was 80% In adult patients with RA, following 4 mg/kg IV q4w, the model-predicted mean steady state peak and trough concentrations were 88.3 and 1.49 μg/mL, respectively. Following 162 mg SC q2w, the estimated mean steady-state peak and trough concentrations were 12.3 and 5.6 μg/mL, respectively In patients with GCA, following 162 mg SC qw, the estimated mean steady-state peak and trough concentrations were 73 and 68.1 μg/mL, respectively In patients with pJIA, the estimated mean steady-state peak and trough concentrations were 182 and 7.49 μg/mL, respectively, and 175 and 2.35 μg/mL, respectively, following 8 mg/kg IV q4w (patients weighing ≥30 kg) and 10 mg/kg IV q4w (patients weighing <30 kg), respectively In patients with sJIA, the estimated mean steady-state peak and trough concentrations were 245 and 57.5 μg/mL, respectively, at the recommended dose regimen (8 and 12 mg/kg SC q2w for patients ≥30 kg and <30 kg respectively)	In patients with RA, relationship between tocilizumab exposure and the improvement in DAS28-ESR (erythrocyte sedimentation rate) score over time following tocilizumab IV administration were characterized using an indirect response PK/PD model following E_{max} relationship, with the estimated EC_{50} being 3.7 μg/mL. Following tocilizumab SC administration, clinical response (probability of achieving ACR20/50/70 responses) increased with increasing tocilizumab trough concentration as indicated by quartile analysis and/or logistic regression analysis In patients with sJIA, dosing regimens of 8 mg/kg in patients weighing ≥30 kg and 12 mg/kg in sJIA patients weighing <30 kg achieved uniform exposure across the entire bodyweight range, which were associated comparable changes in markers related to inflammation (CRP and ESR); markers related to tocilizumab mechanism of action (IL-6 and soluble IL-6 receptor); and efficacy results (JIAACR30 at week 12 with absence of fever). There was no apparent correlation between the tocilizumab exposure and the PD/efficacy end points, suggesting that adalimumab exposures associated with the doses studied in Phase III studies were at the plateau of the E-R curve In patients with pJIA following the recommended dose regimen, analysis by tocilizumab exposure (AUC) quartiles showed that the proportion of patients who achieved JIAACR50 and JIAACR70 responses at week 16 was slightly lower with lower exposure (quartile 1) than the upper three quartiles. There was no apparent correlation between the tocilizumab exposure and the other PD/efficacy end points, such as change from baseline in the 27-joint Juvenile Arthritis Disease Activity Score [JADAS-27], IL-6 and soluble IL-6 receptor. These data suggest the adalimumab exposures associated with the doses studied in Phase III were at the plateau of the E-R curve	Levi et al. (2013) (RA) Abdallah et al. (2017) (RA) Zhang et al. (2013) (sJIA) Zhang et al. (2017) (pJIA) Gibiansky et al. (2017) (GCA)

Anti-IL-4 receptor					
Dupilumab (Dupixent®)	IL-4 receptor subunit α	AD	Dupilumab exhibits nonlinear target-mediated pharmacokinetics with exposures increasing in a greater than dose-proportional manner. The systemic exposure increased by 30-fold when the dose increased eightfold following a single dose of dupilumab from 75 mg to 600 mg. The bioavailability of SC dupilumab was 64% Steady state was achieved by week 16 following 600 mg SC initially and 300 mg SC q2w thereafter, and the mean steady-state trough concentrations ranged from 73.3 to 79.9 μg/mL	In patients with AD, quartile analysis by dupilumab trough concentration at week 16 and predicted cumulative AUC from week 0 to week 16 showed clear E-R relationships for the efficacy endpoints including percent change from baseline eczema area and severity index (EASI) score, proportion of patients achieving IGA 0/1 and percent change from baseline for peak NRS (pruritus Numerical Rating Scale) Based on an E_{max} model linking dupilumab trough concentration and EASI score at week 16, EC_{50} was estimated to be 30 μg/mL	EMA/512262/2017 (2017b) (AD)
Anti-IL-5 receptor					
Benralizumab (Fasenra®)	IL-5 receptor	Asthma	Benralizumab exhibits linear pharmacokinetics n patients with asthma over a SC dose range of 20–200 mg, with mean terminal half-life being 15 days. The mean bioavailability of SC benralizumab was 58%. Typical systemic clearance of benralizumab was estimated to be 0.29 L/day for a subject weighing 70 kg	In patients with asthma (and heathy subjects), blood eosinophil count data following benralizumab treatment was characterized by a semi-mechanistic PK/PD model. Depletion of blood eosinophil counts was depicted by a hematopoietic transit model in which benralizumab induced depletion of eosinophils in each age compartment. Modeling results supported selection of dose regimen for future studies in patients with asthma	Wang et al. (2017) (Asthma)
Anti-IL-6 receptor					
Sarilumab (Kevzara®)	IL-6 receptor	RA	Sarilumab exhibits target-mediated nonlinear pharmacokinetics. The half-life of sarilumab is concentration-dependent, up to 8 and 10 days at steady state following 150 and 200 mg SC q2w dose regimens, respectively, in patients with RA. Steady state exposure over the dosing interval measured by area under curve (AUC) increased twofold with an increase in dose from 150 to 200 mg q2w Following 200 mg SC q2w, the estimated mean steady-state AUC, C_{min} and C_{max} of sarilumab were 395 mg·day/L, 16.5 mg/L, and 35.6 mg/L, respectively	In patients with RA, relationships between sarilumab exposure and DAS28-CRP score and the absolute neutrophil count over time were characterized using two separate indirect response PK/PD models following E_{max} relationships. Model estimated potency (EC_{50}) were 2.32 and 10.3 μg/mL, respectively	Ma et al. (2016a, b) (RA)

Table 26.1 ■ (continued)

Part B: Pharmacokinetics and pharmacokinetics/pharmacodynamics					
Product	**Target**	**Indication**	**Pharmacokinetics**	**Pharmacokinetics/Pharmacodynamics**	**Reference[a]**
Anti-IL-17 receptor A					
Brodalumab (Siliq®)	IL-17 receptor A	PsO	Brodalumab exhibits non-linear pharmacokinetics with exposures increased greater than dose-proportionally over the dose range of 140 mg SC to 350 mg SC in PsO patients. The clearance of brodalumab increased with decreasing doses due to nonlinear elimination. The mean apparent total clearance was 3.0 L/day following a single brodalumab SC dose of 210 mg. Bioavailability of SC brodalumab was 55% Steady-state was achieved by week 4 following 210 mg SC q2w, and the mean peak concentration and AUC over the two-week dosing interval were 20.6 μg/mL and 227 μg·day/mL, respectively	In patients with GCA, a Cox proportional hazards modeling analysis was conducted for time-to-first-flare (TFF). Risk for flare decreased with increasing tocilizumab exposure following an E_{max} relationship. Patients receiving tocilizumab 162 mg SC q2w compared to qw were at higher risk for shorter TFF In patients with PsO, relationship between brodalumab concentration and the time course of PASI score was characterized by an indirect response PK/PD model following E_{max} relationship. Clear E-R relationship was established and the estimated EC_{50} was 0.637 μg/mL	Salinger et al. (2014) (PsO)
Anti-IgE					
Omalizumab (Xolair®)	IgE	Asthma and CIU	Omalizumab exhibits target-mediated nonlinear pharmacokinetics (linear at doses greater than 0.5 mg/kg). The mean bioavailability of SC omalizumab was 62% In patients with asthma, the mean apparent clearance of omalizumab was estimated to be 2.4 mL/kg/day with a mean terminal half-life being 26 days In patients with CIU, the mean apparent clearance of omalizumab was estimated to be 240 mL/day with a mean terminal half-life being 24 days	In patients with asthma, relationship between omalizumab concentration and blood IgE level (total and free) over time was characterized by a dynamic drug-ligand binding and turnover model. Model predicted free IgE concentrations correlated well with clinical signs and symptoms, allowing a target concentration of 14 ng/mL, at the midpoint of 4-week clinical observation periods, to be set for the determination of dose regimen in asthma patients In patients with CIU, relationship between omalizumab concentration and blood IgE level over time was characterized by a target-mediated population PK/PD model incorporating omalizumab-IgE binding and turnover. Modeling results supported the flat dosing regimen for omalizumab in CIU patients	Hochhaus et al. (2003); Lowe et al. (2009) (Asthma) Zheng et al. (2014) (CIU)

Anti-integrin					
Natalizumab (Tysabri®)	Integrin	CD and MS	In patients with CD, the mean systemic clearance of natalizumab was 22 mL/h with mean half-life being 10 days. The mean steady-state trough concentration was 10 μg/mL following 300 mg IV infusion q4w dosing In patients with MS, the mean systemic clearance of natalizumab was 16 mL/h with mean half-life being 11 days. The mean steady-state trough concentrations ranged from 23 to 29 μg/mL following 300 mg IV infusion q4w dosing	In patients with CD, the probability of clinical response at week 6 was found to correlate with natalizumab cumulative AUC from week 0 to week 6 in a dose ranging study. However, an inverse U-shaped dose- and exposure-response relationship was found with the highest dose group of 6 mg/kg q4w having lower response rate compared to the lower dose of 3 mg/kg q4w; the reason was not identified In patients with MS, the relationship between predicted natalizumab concentration and α4 integrin saturation over time was described by a direct PK/PD model following sigmodal E_{max} relationship. The estimated EC_{50} was 2.51 μg/mL with a hill factor of 1.35. Using log-linear models with natalizumab average concentration during dosing interval as the exposure variable, significant E-R relationship for effectiveness was shown for gadolinium-enhancing lesion count data and annualized relapse rate (ARR) over time	US FDA Clinical Pharmacology Review (BLA# 125104/33) (2008) (CD) Muralidharan et al. (2017a, b) (MS)
Vedolizumab (Entyvio®)	Integrin	CD and UC	Vedolizumab exhibits nonlinear pharmacokinetics. Clearance depends on both linear and nonlinear pathways; the nonlinear clearance decreases with increasing concentrations. Linear clearance was estimated to be 0.157 L/day and the terminal half-life was approximately 25 days at 300 mg IV dosage In adult patients with CD and UC, the vedolizumab induction dose of 300 mg IV at weeks 0 and 2 achieved mean serum trough concentration of approximately 26–27 μg/mL at week 6. Mean steady-state trough concentration of 11–13 μg/mL were observed after receiving an a vedolizumab maintenance dose of 300 mg IV q8w	In patients with CD and UC, relationship between vedolizumab concentration and the time course in the percentage of peripheral MAdCAM-1 (mucosal addressin cell adhesion molecule-1) binding by lymphocytes expressing high levels of α4β7 integrin was characterized by a direct effect PK/PD model with sigmoid E_{max} relationship. Model estimated EC_{50} was 0.093 μg/mL with a hill factor of 0.801. Significant E-R relationships were also shown for remission at week 6 after induction therapy using logistic regression with predicted cumulative average concentration through week 6 as the exposure variable, and the E-R relationship was steeper for UC than CD	Rosario et al. (2015, 2017)

Table 26.1 ■ (continued)

Part B: Pharmacokinetics and pharmacokinetics/pharmacodynamics					
Product	**Target**	**Indication**	**Pharmacokinetics**	**Pharmacokinetics/Pharmacodynamics**	**Reference[a]**
Anti-CD80/CD86 lymphocyte activation inhibitor					
Abatacept (Orencia®)	CTLA-4	RA, PsA, and pJIA	Abatacept exhibits linear pharmacokinetics in adult RA patients with mean terminal half-life being 13.1–14.3 days. The mean systemic clearance was 0.22 mL/h/kg. The bioavailability of SC abatacept was 78.6%. Following IV infusions of 10 mg/kg q4w, the mean steady-state peak and trough concentrations were 295 and 24 μg/mL, respectively. Following SC injections of 125 mg weekly, the mean steady-state peak and trough concentrations were 48.1 and 32.5 μg/mL, respectively In patients with PsA, the geometric mean steady-state trough concentration was 24.3 μg/mL at 10 mg/kg IV dosing. Following 125 mg SC weekly dosing, the geometric mean of steady-state trough concentration was 25.6 μg/mL. Relative to the RA patients with the same body weight, abatacept clearance in PsA patients was approximately 8% lower In pJIA patients 6–17 years of age, the mean systemic clearance was estimated to be 0.4 mL/h/kg. Following IV infusions of 10 mg/kg q4w, the mean steady-state peak and trough concentrations were 217 and 11.9 μg/mL, respectively In pJIA patients 2–17 years of age, following SC weekly injections at the recommended body-weight–tiered dosing, the mean steady-state trough concentrations were 44.4, 46.6 and 38.5 μg/mL in patients weighing 10 to <25 kg, 25 to <50 kg, and ≥50 kg, respectively	In patients with RA, relationship between abatacept exposure and the time course in the suppression of serum IL-6 was characterized by an indirect-response PK/PD model following E_{max} relationship. Clear E-R relationship was established and the estimated EC_{50} was 11.3 μg/mL. Significant relationship between abatacept trough concentration and the probability of achieving ACR20 over time was also shown using time-series generalized estimating equations. Steady-state trough concentration over 10 μg/mL was suggested to be the target exposure for near-maximal efficacy In patients with PsA, relationships between abatacept exposure and the clinical endpoints (ACR20, ACR50, ACR70, PASI50, PASI75) on Day 169 were described by logistic regression models using steady-state trough, average and maximum concentration as the exposure variables. Steady state trough concentration was identified as the best exposure predictor for efficacy where patients with higher trough concentrations were associated with higher probability of achieving the binary efficacy endpoints. Significant E-R relationships between abatacept exposure and the DAS28-CRP score over time was also shown using an inhibitory E_{max} model with respect to time In pediatric patients with pJIA, a proportional odds model with a log linear function of steady-state abatacept trough concentration adequately described the E–R relationship for JIAACR responses (JIAACR30/50/70/100) at month 4. Steady state trough concentration threshold of 10 μg/mL provided a near-maximal efficacy response	Roy et al. (2017) (RA) Hasegawa et al. (2011) (RA) Li et al. (2017) (pJIA) EMA/455579/2017 (2017a) (PsA)

Belimumab (Benlysta®)	BLyS	SLE	The model predicted systemic clearance of belimumab was 215 mL/day with a terminal half-life being19.4 days. The peak concentration of belimumab was estimated to be 313 μg/mL following 10 mg/kg belimumab by IV infusion at 2-week intervals for the first 3 doses and at 4-week intervals thereafter Model predicted SC bioavailability of belimumab was 74%. Following SC belimumab dosing of 200 mg qw, the peak and trough concentration were estimated to be 108 and 97 μg/mL, respectively	In patients with SLE, belimumab 200 mg SC qw plus standard of care significantly improved the SLE responder index (SRI). However, at this dose, no apparent relationship was identified between belimumab average steady-state concentration and the SRI response at week 52 by the logistic regression analysis. Belimumab 200-mg dose likely results in a range of exposures located in the upper domain of a saturating E-R response curve	Struemper et al. (2017) (SLE)
Anti-CD-20 cytolytic agent					
Ocrelizumab (Ocrevus®)	CD20	MS	Ocrelizumab exhibits nonlinear pharmacokinetics with time-dependent clearance (linear at doses between 400 mg and 2000 mg). Constant clearance was estimated at 0.17 L/day, and initial time-dependent clearance at 0.05 L/day, which declined with a half-life of 33 weeks. The terminal elimination half-life was 26 days In patients with relapsing forms of MS, the maximum concentration was 212 μg/mL at a maintenance dose of 600 mg IV infusion every 6 months In patients with primary progressive MS, the mean maximum concentration was 141 μg/mL at a maintenance dose of two 300 mg infusions separated by 14 days every 6 months	In patients with primary progressive (PPMS) and relapsing forms (RMS) of MS, relationships between ocrelizumab exposure and the clinical efficacy endpoints were evaluated using ocrelizumab cumulative average concentration over treatment period as the main exposure metric. Although all ocrelizumab groups showed a benefit compared with control (hazard ratio < 1), there was no apparent E-R relationship for the primary endpoint of 12-week annualized relapse rate (ARR) in RMS patients. However, both RMS and PPMS patients showed a trend for greater risk reduction for 12-week clinical disability progression (CDP) with higher exposure of ocrelizumab	EMA/790835/2017 (2017c) (MS)
Rituximab (Rituxan®)	CD20	RA	The estimated clearance of rituximab was 0.335 L/day in patients with RA with mean terminal half-life being 18.0 days Following administration of two 1000 mg rituximab IV infusions separated by 2 weeks in patients with RA, the mean concentrations after the first infusion and second infusion were 318 and 381 μg/mL, respectively	There are no published reports describing E-R relationships of rituximab in patients with RA. However, significant relationships between rituximab exposure (AUC and trough concentration) and therapeutic effect had been shown in patients with B non-Hodgkin lymphoma (B-NHL) and chronic lymphocytic leukemia (CLL)	Golay et al. (2013) (review)

ACR20/50/70 20%,50% and 70% improvement in American College of Rheumatology (ACR) Criteria, *AS* ankylosing spondylitis, *AD* atopic dermatitis, *BLyS* B-lymphocyte stimulator, *CAPS* cryopyrin-associated periodic syndromes, *CD* Crohn's disease, *CD2* T-lymphocyte antigen CD2, *CD20/80/86* B-lymphocyte antigen CD20, CD80, CD86, *CIU* chronic idiopathic urticaria, *CRP* C-reactive protein, *CRS* cytokine release syndrome, *CTLA-4* cytotoxic T-lymphocyte-associated antigen 4, *DAS28-CRP* 28-joints disease activity score (DAS) using C-reactive protein, EC_{50} concentration to achieve half the maximal drug effect, E_{max} maximal drug effect, *E-R* exposure-response, *GCA* giant cell arteritis, *HS* hidradenitis suppurativa, *IGA0/1* investigator's global assessment (IGA) score of 1 or 1 and an improvement of 2 points or more compared to baseline, *IgE* immunoglobulin E, *IL* interleukin, *IV* intravenous, *JIAACR30/50/70/100* 30%, 50%, 70%, 100% improvement in the juvenile idiopathic arthritis ACR response criterion, *KD* kilodalton, *mAb* monoclonal antibody, *MAdCAM-1* mucosal addressin cell adhesion molecule-1, *MW* molecular weight, *MS* multiple sclerosis, *NLR-3* nucleotide-binding domain, leucine rich family (NLR), pyrin domain containing 3, nr-*Axial SpA* non-radiographic axial spondyloarthritis, *PASI50/75/90* 50%,75% and 90% improvement in Psoriasis Area and Severity Index (PASI) score from baseline, *pJIA* polyarticular juvenile idiopathic arthritis, *PK/PD* pharmacokinetics/pharmacodynamics, *PsA* psoriatic arthritis, *PsO* plaque psoriasis, *q12w* every 12 weeks, *q2w* every 2 weeks, *q4w* every 4 weeks, *q8w* every 8 weeks, *qw* every week, *RA* rheumatoid arthritis, *SC* subcutaneous, *SLE* systemic lupus erythematosus, *sJIA* systemic juvenile idiopathic arthritis, *TNFα* tumor necrosis factor alpha, *UC* ulcerative colitis, *UV* uveitis, *VCAM-1* vascular cell adhesion molecule-1

[a]From US prescription information (USPI), unless otherwise indicated

on market for the treatment of immune-mediated inflammatory diseases (as of February 2018).

One challenge in the long-term treatment with antibody-based biotherapeutics of immune-mediated disorders is to avoid the side effects due to the potent and sustained suppression of the immune system. The expectation for these newer therapies is that they can be used earlier in the course of disease to not only maintain control over episodic disease flares but also prevent the less reversible organ damage posed by long-term uncontrolled chronic inflammation or even reversal of disease such as joint damage caused by rheumatoid arthritis (Taylor et al. 2004).

The primary focus of this chapter is on describing the pharmacologic properties of approved biologic therapies for major classes of inflammatory diseases, such as arthritides, systemic lupus erythematosus (SLE), psoriasis, inflammatory bowel disease (IBD), asthma, and a few other less common inflammatory disorders (including atopic dermatitis [AD], chronic idiopathic urticaria [CIU], cryopyrin-associated periodic syndrome [CAPS], cytokine release syndrome [CRS], eosinophilic granulomatosis with polyangiitis [EGPA], giant-cell arteritis [GCA], hidradenitis suppurativa [HS], multiple sclerosis [MS], and uveitis [UV]). Within each of these disease category, biologic agents will be introduced according to their mechanisms of action, and listed alphabetically when having a same mechanism of action. Notably information described in this chapter is based on the original 'innovator' products.

ARTHRITIDES

Arthritides are a class of chronic autoimmune inflammatory conditions of unknown etiology, characterized by pain and stiffness of the affected joints and tissue (Davis and Mease 2008; McInnes and Schett 2011). Arthritides consist of a variety of clinical diseases, such as rheumatoid arthritis (RA), psoriatic arthritis (PsA), and ankylosing spondylitis (AS), involving skeletal joints. Juvenile idiopathic arthritis (JIA) is a chronic inflammatory arthropathy with an age of onset of <16 years, including polyarticular JIA (pJIA), and systemic JIA (sJIA). Although these arthritic diseases may have different clinical manifestations, they are considered to have a similar underlying etiology. RA is the most common of the autoimmune arthritides, affecting at least 1% of the general population in the United States. If not properly treated, the chronic inflammation can result in progressive and irreversible joint destruction. Although early intervention with corticosteroids and conventional non-biologic disease-modifying antirheumatic drugs (DMARDs) has been proven to attenuate inflammation, these therapies are not very effective in slowing down the progression of joint damage in large subsets of patients. In addition, these conventional therapies often have significant off-target side effects (O'Dell 2004).

Several biologic agents have been approved for patients with RA, PsA, AS, or JIA (Table 26.1). These therapeutic proteins provide valuable treatment options for patients, particularly for those who experience significant side effects and/or have inadequate clinical efficacy with conventional DMARDs. These biotherapeutics significantly improve the signs and symptoms of the disease, effectively inhibit (and sometimes even reverse) the progression of joint damage, and greatly improve physical functions and quality of life. Anti-TNFα agents (adalimumab, certolizumab, etanercept, golimumab and infliximab) are considered the gold standard biologic therapy for RA; however, the availability of biologic agents with different mechanisms of action such as anti-IL-6 receptor agents (sarilumab and tocilizumab) provides alternative options when patients do not achieve adequate response to anti-TNFα agents. Other non-TNFα targeting biologic agents demonstrating effectivness for the treatment of arthritides including agents neutralizing soluble cytokines such as IL-1β (canakinumab), IL-17A (ixekizumab and secukinumab) and IL-12/IL-23 (ustekinumab), and acting as direct agonist or anti-agonist to inhibit T-cell activation (abatacept) or depletion of B lymphocytes (rituximab). Compared to conventional DMARDs, the most attractive attribute of antibody-based therapeutic proteins is their binding to the target with high specificity, consequently producing greater efficacy and fewer off-target adverse effects. In addition, antibody-based therapeutic proteins usually have long half-lives (up to 2–3 weeks), which allow for infrequent dosing which is desirable for the patients with chronic diseases.

■ Anti-TNFα Agents

TNFα is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. Elevated levels of TNFα are found in the synovial fluid of patients with RA, JIA, PsA, and AS and play an important role in both the pathologic inflammation and the joint destruction that are hallmarks of these diseases.

The approved anti-TNFα agents such as etanercept, infliximab, adalimumab, golimumab, and certolizumab pegol, are presently one of the most successful classes of therapeutic proteins with many approved clinical indications. Etanercept, a dimeric fusion protein consisting of the p75 human TNFα receptor linked to the Fc portion of human IgG1, was the first anti-TNFα biologic agent approved for an arthritide indication. Infliximab is a chimeric IgG1 mAb containing

~ 25% mouse sequence and ~ 75% human sequence. Certolizumab pegol is a Fab antibody fragment linked to polyethylene glycol that enhances solubility and prolongs elimination half-life. Adalimumab and golimumab are two human IgG1 mAbs, which were created using phage display libraries and the expression of human immunoglobulin genes by transgenic mice, respectively. Human antibodies were developed to minimize immunogenicity; however, patients treated with either adalimumab or golimumab still develop antidrug antibodies. Future efforts are still required to generate therapeutic mAbs that not only have the human sequence as the primary structure, but also have secondary and tertiary structures like natural human immunoglobulins. Although no head-to-head comparative trials are currently available, these anti-TNFα agents appear to have similar efficacy for the treatment of adult RA patients alone or as an add-on to methotrexate (Salliot et al. 2011). These anti-TNFα agents have different elimination half-lives and offer a variety of dosing options. Infliximab is administered intravenously, while the other three anti-TNFα agents can be administered subcutaneously. Golimumab can also be administrated either intravenously or subcutaneously. Etanercept has the shortest half-life (~ 4 days) and needs to be dosed once or twice a week. Infliximab is administered intravenously every 4–8 weeks, while adalimumab, certolizumab, and golimumab are administered subcutaneously every 2 weeks, every 2–4 weeks, or monthly, respectively (Tracey et al. 2008).

Although these antibody-based drugs offer targeted therapy with high specificity, there are adverse effects associated with them that need to be closely monitored (Bongartz et al. 2006; Brown et al. 2002; Ellerin et al. 2003). Certain adverse events such as infections are the result of inhibition of the protective functions of the targeted cytokines and related immune cells. Serious infections due to bacterial, mycobacterial, invasive fungal, viral, protozoal, or other opportunistic pathogens have been reported in patients with RA, PsA, AS, or JIA who received TNFα blockers and other immunosuppressant therapeutic proteins. Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with these therapeutic proteins, including the development of tuberculosis in patients who tested negative for latent tuberculosis infection prior to the initiation of therapy. Malignancy, albeit rare, has been another important concern when using these immunosuppressant therapeutic proteins. In controlled clinical trials of TNFα blockers, more cases of lymphoma and leukemia have been observed among patients receiving anti-TNFα treatment compared to patients in the control groups; however, there are confounders when assessing the risk of malignancy associated with the use of these therapeutic proteins in patients with chronic inflammatory diseases. Patients with chronic inflammatory diseases, particularly patients with highly active disease and/or chronic exposure to immunosuppressant therapies, may be at higher risk (up to several folds) than the general population for the development of lymphoma and leukemia, even in the absence of TNF-blocking therapy (Smedby et al. 2008). Other notable adverse events associated with these complex proteins include demyelinating disorders, liver enzyme elevation, autoimmune diseases (such as lupus), immunogenicity (formation of antibodies to the therapeutic protein), infusion/injection site reactions, and other hypersensitivity reactions. Overall, a large number of clinical trials have demonstrated that the benefits outweigh the risks for anti-TNF biologic agents in patients with various arthritides.

Adalimumab

Adalimumab (Humira®) is a recombinant human IgG1 mAb, which was created using phage display technology resulting in a human antibody. Adalimumab binds specifically to TNF-α and blocks its interaction with the p55 and p75 cell surface TNF receptors. Adalimumab does not bind or inactivate lymphotoxin (Humira®, US prescribing information 2017).

The efficacy and safety of adalimumab have been assessed in various adult RA populations (DMARD [including methotrexate]-inadequate responders and methotrexate-naïve patients), polyarticular JIA, PsA, and AS. In a randomized, double-blind, controlled Phase III study in patients with active RA despite methotrexate therapy, 6-month treatment with subcutaneous adalimumab in combination with methotrexate at the recommended dose regimen (40 mg every 2 weeks) resulted in 63, 39, and 21% of RA patients achieving ACR20, ACR50, and ACR70 (20, 50 and 70% improvement in the American College of Rheumatology response criterion), respectively, while the control group (methotrexate plus placebo) had only 30, 10, and 3% of patients with ACR20, ACR50, and ACR70 responses, respectively.

Serious infection and malignancy Black-Box warnings were placed on the adalimumab label (Humira®, US prescribing information 2017), similar to the labels of other TNF antagonists. Patients treated with adalimumab are at increased risk for developing serious infections involving various organ systems and sites that may lead to hospitalization or death. Adalimumab should not be started during an active infection. If an infection develops, monitor carefully, and stop adalimumab if infection becomes serious. Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers including adalimumab.

Risks and benefits of TNF-blocker treatment including adalimumab should be considered prior to initiating therapy in patients with a known malignancy other than a successfully treated non-melanoma skin cancer (NMSC) or when continuing a TNF blocker in patients who develop a malignancy.

The concomitant use of a TNF blocker and abatacept (lymphocyte activation inhibitor) or anakinra (IL-1 receptor antagonist) was associated with a higher risk of serious infections in patients with RA. Therefore, the concomitant use of adalimumab and these biologic products is not recommended in the treatment of patients with RA (Humira®, US prescribing information 2017).

For the treatment of arthritides, adalimumab is indicated for the treatment of adult patients with moderately to severely active RA, active PsA, or active AS. Adalimumab is also indicated for reducing signs and symptoms in pediatric patients 2 years of age and older with moderately to severely active polyarticular JIA (Humira®, US prescribing information 2017).

Certolizumab Pegol

Certolizumab pegol (Cimzia®) is a recombinant, humanized antibody Fab fragment that is conjugated to an approximately 40 kDa polyethylene glycol. Certolizumab pegol binds to human TNFα with high affinity and selectively neutralizes TNFα activity, but does not neutralize lymphotoxin (Cimzia®, US prescribing information 2016).

The efficacy and safety of certolizumab pegol have been assessed in adult RA patients who had active disease despite methotrexate therapy or who had failed at least one conventional DMARD other than methotrexate. Assessments in adult patients with active PsA and active AS have also been conducted. In a randomized, double-blind, controlled Phase III study in patients with active RA despite methotrexate therapy, 6-month treatment with subcutaneous certolizumab pegol at the recommended dose regimen (400 mg initially and at weeks 2 and 4, following by 200 mg every 2 weeks) in combination with methotrexate resulted in 59, 37, and 21% of RA patients achieving ACR20, ACR50, and ACR70, respectively, while the control group (methotrexate plus placebo) had only 14, 8, and 3% of patients with ACR20, ACR50, and ACR70 response, respectively.

Serious infection and malignancy Black-Box warnings were placed on the certolizumab pegol label (Cimzia®, US prescribing information 2016), similar to the labels of other TNF antagonists.

Of the arthritides, certolizumab pegol is indicated for the treatment of adult patients with moderately to severely active RA, active PsA and active AS. Certolizumab pegol is not indicated for use in pediatric patients (Cimzia®, US prescribing information 2016).

Etanercept

Etanercept (Enbrel®) is the first anti-TNF biologic agent approved for arthritide indication. Etanercept is a dimeric fusion protein consisting of the extracellular ligand-binding portion of the human 75 kDa (p75) TNF receptor linked to the Fc portion of human IgG1. Etanercept inhibits binding of TNF-α and TNF-β (lymphotoxin alpha) to cell surface TNF receptors, rendering TNF biologically inactive (Enbrel®, US prescribing information 2016).

The efficacy and safety of etanercept have been assessed in various adult RA populations (DMARD [including methotrexate]-inadequate responders and methotrexate-naïve patients), active polyarticular JIA, active PsA, and active AS. In a randomized, double-blind, controlled Phase III study in patients with active RA despite methotrexate therapy, 6-month treatment with subcutaneous etanercept in combination with methotrexate at the recommended dose regimen (50 mg weekly) resulted in 71, 39, and 15% of RA patients achieving ACR20, ACR50, and ACR70, respectively, while the control group (methotrexate plus placebo) had only 27, 3, and 0% of patients exhibiting ACR20, ACR50, and ACR70 responses, respectively.

Serious infection and malignancy Black-Box warnings were placed on the etanercept label (Enbrel®, US prescribing information 2016), similar to the labels of other TNF antagonists.

Use of etanercept with anakinra (IL-1 receptor antagonist) or abatacept (T-lymphocyte activation inhibitor) is not recommended. Concurrent administration of etanercept with anakinra or abatacept resulted in increased incidences of serious adverse events, including infections, and did not demonstrate increased clinical benefit. In a 24-week study in patients with active RA on background methotrexate, the ACR50 response rate was 31% for patients treated with the combination of anakinra and etanercept and 41% for patients treated with etanercept alone, indicating no added clinical benefit of the combination over etanercept alone. A higher rate of serious infections was observed in RA patients with concurrent anakinra and etanercept therapy (7%) than in patients treated with etanercept alone (0%). Therefore, use of anakinra in combination with TNF blocking agents is not recommended (Enbrel®, US prescribing information 2016). In controlled clinical trials in patients with active RA, patients receiving concomitant intravenous abatacept and etanercept therapy experienced more infections (63%) and serious infections (4.4%) compared to patients treated with only etanercept (43% and 0.8%, respectively). In addition, these trials failed to

demonstrate an enhancement of efficacy with concomitant administration of abatacept with etanercept (Orencia®, US prescribing information 2017). As a result, abatacept should not be given concomitantly with TNF antagonists.

For the treatment of arthritides, etanercept is indicated for the treatment of adult patients with moderately to severely active RA, active PsA, or active AS. Etanercept is also indicated for reducing signs and symptoms of polyarticular JIA in pediatric patients 2 years of age and older (Enbrel®, US prescribing information 2016).

Golimumab

Golimumab (Simponi®[subcutaneous], Simponi Aria®[intravenous]) is a human IgG1κ mAb which was created using genetically engineered mice immunized with human TNF. Golimumab binds to both the soluble and transmembrane bioactive forms of human TNFα and therefore inhibits the biologic activity of TNFα. There is no evidence of golimumab binding to other TNF superfamily ligands; golimumab does not bind or neutralize human lymphotoxin. Golimumab does not lyse human monocytes expressing transmembrane TNF in the presence of complement or effector cells (Simponi®, US prescribing information 2017a; Simponi Aria®, US prescribing information 2017).

The efficacy and safety of golimumab have been assessed in various adult RA populations (methotrexate-inadequate responders, methotrexate-naïve patients, and patients with previous use of other anti-TNFα agents), active PsA, active AS and pediatric patients with active polyarticular JIA. In a randomized, double-blind, controlled Phase III study in patients with active RA despite methotrexate therapy, six-month treatment with subcutaneous golimumab in combination with methotrexate at the recommended dose regimen (50 mg every 4 weeks) resulted in 60, 37, and 20% of RA patients achieving ACR20, ACR50, and ACR70, respectively, while the control group (methotrexate plus placebo) had only 28, 14, and 5% of patients exhibiting ACR20, ACR50, and ACR70 responses, respectively. Recently, another Phase III study demonstrated similar efficacy and safety for treating adult RA patients with intravenous golimumab with a longer dosing interval (every 8 weeks) as an alternative to the previously established subcutaneous route of administration (every 4 weeks).

Serious infection and malignancy Black-Box warnings were placed on the golimumab label, similar to the labels of other TNF antagonists. The concomitant use of golimumab with biologics approved to treat RA, PsA, or AS is not recommended because of the possibility of an increased risk of infection (Simponi®, US prescribing information, 2017a; Simponi Aria®, US prescribing information 2017).

Within arthritides, golimumab is indicated for the treatment of adult patients with moderately to severely active RA, active PsA, or active AS (Simponi®, US prescribing information, 2017a; Simponi Aria®, US prescribing information 2017). Golimumab is also indicated for the treatment of adult patients with nonradiographic axial spondyloarthritis (nr-AxSpA), and children with polyarticular JIA with a body weight of at least 40 kg, who have responded inadequately to previous therapy with methotrexate (Simponi®, SmPC 2017b).

Infliximab

Infliximab (Remicade®) is a chimeric IgG1κ mAb that is composed of human constant and murine variable regions. Infliximab neutralizes the biologic activity of TNFα by binding with high affinity to the soluble and transmembrane forms of TNFα and inhibits binding of TNFα with its receptors. Infliximab does not neutralize TNFβ (lymphotoxin-α) (Remicade®, US prescribing information 2017).

The efficacy and safety of infliximab have been assessed in various adult RA populations (methotrexate-inadequate responders and methotrexate-naïve patients), active PsA, and active AS. In a randomized, double-blind, controlled Phase III study in patients with active RA despite methotrexate therapy, 30-week treatment with intravenous infliximab (3 mg/kg at 0, 2, and 6 weeks, following by 3 mg/kg every 8 weeks thereafter) in combination with methotrexate resulted in 50, 27, and 8% of RA patients achieving ACR20, ACR50, and ACR70, respectively, while the control group (methotrexate plus placebo) had only 20, 5, and 0% of patients exhibiting ACR20, ACR50, and ACR70 responses, respectively.

Serious infection and malignancy Black-Box warnings were placed on the infliximab label (Remicade®, US prescribing information 2017), similar to the labels of other TNF antagonists.

There is insufficient information regarding the concomitant use of infliximab with other biological therapeutics used to treat the same conditions as infliximab. The concomitant use of infliximab with these biologics is not recommended because of the possibility of an increased risk of infection. An increased risk of serious infections has been seen in clinical RA trials of other TNF blockers used in combination with anakinra or abatacept, with no added benefit (described earlier in this chapter); therefore, use of infliximab with abatacept or anakinra is not recommended. The use of tocilizumab (IL-6 receptor antagonist) in combination with TNF antagonists, including infliximab, should also be avoided because of the possibility of increased immunosuppression and increased risk of infection (Remicade®, US prescribing information 2017).

Within arthritides, infliximab is indicated for reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in patients with moderately to severe active RA. Infliximab is also indicated for reducing signs and symptoms in patients with active AS and in patients with active PsA, inhibiting the progression of structural damage, and improving physical function in patients with PsA (Remicade®, US prescribing information 2017).

■ Anti-IL-1β Biologic Agent

As of February 2018, canakinumab (Ilaris®) is the only anti-IL-β biologic agent approved for arthritides related disorders, i.e., systemic JIA (sJIA). Systemic JIA (sJIA) is a severe autoinflammatory disease, driven by innate immunity by means of proinflammatory cytokines such as IL-1β.

Canakinumab

Canakinumab (Ilaris®) is a recombinant human IgG1κ anti-IL-1β mAb. Canakinumab binds to human IL-1β and neutralizes its activity by blocking its interaction with IL-1 receptors, but it does not bind IL-1α or IL-1 receptor antagonist (IL-1Ra) (Ilaris®, US prescribing information 2016).

The efficacy and safety of canakinumab have been assessed in two Phase III studies (Study 1 and Study 2) in sJIA patients aged 2 to less than 20 years. Study 1 was a randomized, double-blind, placebo-controlled, single-dose 4-week study in sJIA patients who were randomized to receive a single subcutaneous dose of 4 mg/kg canakinumab or placebo. At Day 29, 81, 79 and 67% of sJIA patients who received a single subcutaneous dose of 4 mg/kg canakinumab achieved PEDACR30, PEDACR50, and PEDACR70 responses (30, 50 and 70% improvement in an adapted Pediatric American College of Rheumatology response criterion), respectively, while the control group had only 10, 5, and 2% of patients with PEDACR30, PEDACR50, and PEDACR70 responses, respectively. Study 2 was a two-part study to assess the flare prevention by canakinumab in patients with active sJIA, with an open-label, single-arm active treatment period (Part I) followed by a randomized, double-blind, placebo-controlled, event-driven withdrawal design (Part II). The probability of experiencing a flare (defined by worsening of greater than or equal to 30% in at least 3 of the 6 core Pediatric ACR response variables combined with improvement of greater than or equal to 30% in no more than 1 of the 6 variables, or reappearance of fever not due to infection for at least 2 consecutive days) over time in Part II was statistically lower for the canakinumab group than for the placebo group. This corresponded to a 64% relative reduction in the risk of flare for patients in the canakinumab group as compared to those in the placebo group.

An increased incidence of serious infections and an increased risk of neutropenia have been associated with administration of another IL-1 blocker in combination with TNF inhibitors (anakinra in combination with etanercept) in another patient population (adult RA). Use of canakinumab with TNF inhibitors may also result in similar toxicities and is not recommended because this may increase the risk of serious infections (Ilaris®, US prescribing information 2016).

Of the arthritides, canakinumab is indicated for the treatment of active systemic JIA in patients aged 2 years and older (Ilaris®, US prescribing information 2016).

■ Anti IL-17A Agent

Two anti-IL-17A biologic agents have been approved for arthritides related disorders, ixekizumab (Taltz®) and secukinumab (Cosentyx®). Ixekizumab is a humanized IgG4 mAb while secukinumab (Cosentyx®) is a human IgG1κ mAb. Each of these two agents selectively binds with the IL-17A cytokine and inhibits its interaction with the IL-17 receptor. IL-17A is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. Ixekizumab or secukinumab inhibits the release of proinflammatory cytokines and chemokines.

Ixekizumab

Ixekizumab (Taltz®) is a humanized anti-IL17A IgG4 mAb produced by recombinant DNA technology in a recombinant mammalian cell line (Taltz®, US prescribing information 2017).

The efficacy and safety of ixekizumab have been assessed in two randomized, double-blind, controlled Phase III studies in patients with active PsA despite NSAIDs, corticosteroid or non-biologic conventional DMARD therapy. In the randomized, double-blind, controlled Phase III study in biologic-naive PsA patients (43% patients with concomitant methotrexate use), 6-month treatment with subcutaneous ixekizumab at the recommended dose regimen (160 mg at week 0, followed by 80 mg every 4 weeks thereafter) resulted in 58, 40, and 23% of RA patients achieving ACR20, ACR50, and ACR70, respectively, while the control group had only 30, 15, and 6% of patients with ACR20, ACR50, and ACR70 responses, respectively. In the other Phase III study in anti-TNFα experienced PsA patients, greater responses compared to placebo were seen regardless of prior anti-TNF exposure.

Of the arthritides, ixekizumab is indicative for the treatment of adult patients with moderately to severely active PsA (Taltz®, US prescribing information 2017).

Secukinumab

Secukinumab (Cosentyx®) is a recombinant human anti-IL-17A IgG1/κ mAb expressed in a recombinant Chinese Hamster Ovary cell line (Cosentyx®, US prescribing information 2017).

The efficacy and safety of secukinumab have been assessed in adult patients with active PsA and active AS. In a randomized, double-blind, controlled Phase III study in patients with active PsA despite NSAIDs, corticosteroid or DMARD therapy, 6-month treatment with subcutaneous secukinumab at the recommended dose regimen (150 mg every 4 weeks) resulted in 51, 35, and 21% of RA patients (55% of these patients had concomitant methotrexate use) achieving ACR20, ACR50, and ACR70, respectively, while the control group had only 15, 7, and 1% of patients with ACR20, ACR50, and ACR70 responses, respectively.

Of the arthritides, secukinumab is indicated for the treatment of adult patients with active PsA and active AS (Cosentyx®, US prescribing information 2017).

■ Anti-IL-12/IL-23 Agent

As of February 2018, ustekinumab (Stelara®) is the only anti-IL-12/IL-23 biologic agent approved for arthritides related disorders, i.e., PsA. IL-12 and IL-23 are naturally occurring cytokines that are involved in inflammatory and immune responses, such as natural killer cell activation and CD4+ T-cell differentiation and activation.

Ustekinumab

Ustekinumab (Stelara®) is a human IgG1κ mAb that binds with high affinity and specificity to the p40 protein subunit used by both the IL-12 and IL-23 cytokines. In *in vitro* models, ustekinumab was shown to disrupt IL-12- and IL-23-mediated signaling and cytokine cascades by disrupting the interaction of these cytokines with a shared cell surface receptor chain, IL-12β1 (Stelara®, US prescribing information 2017).

The safety and efficacy of ustekinumab have been assessed in adult patients with active PsA (≥5 swollen joints and ≥ 5 tender joints) despite NSAIDs or DMARD therapy. In a randomized, double-blind, controlled Phase III studies in TNF blocker naïve PsA patients (approximately 50% of patients continued on stable doses of methotrexate), 6-month treatment in patients received subcutaneous ustekinumab treatment at the recommend dose regimen (45 mg at weeks 0 and 4 followed by every 12 weeks thereafter) resulted in 42, 25, 12 and 57% of PsA patients achieving ACR20, ACR50, ACR70, and PASI75 (at least a 75% reduction in PASI [Psoriasis Activity and Severity Index] score from baseline) respectively, while the control group (placebo) had only 23, 9, 2, and 11% of patients with ACR20, ACR20, ACR50, ACR70, and PASI75 respectively.

Of the arthritides, ustekinumab is indicated for the treatment of adult patients with active PsA, alone or in combination with methotrexate (Stelara®, US prescribing information 2017).

■ Anti-IL-6 Receptor Agent

Two anti-IL-6 receptor biologic agents have been approved for arthritides related disorders, sarilumab (Kevzara®) and tocilizumab (Actemra®). Sarilumab is a human IgG1 mAb while tocilizumab is a humanized IgG1κ mAb. Each of these two agents selectively binds to both soluble and membrane-bound IL-6 receptors (sIL-6R and mIL-6R), and has been shown to inhibit IL-6-mediated signaling through these receptors. IL-6 is a pleiotropic pro-inflammatory cytokine produced by a variety of cell types including T- and B-cells, lymphocytes, monocytes and fibroblasts. IL-6 has been shown to be involved in diverse physiological processes such as T-cell activation, induction of immunoglobulin secretion, initiation of hepatic acute phase protein synthesis, and stimulation of hematopoietic precursor cell proliferation and differentiation. IL-6 is also produced by synovial and endothelial cells leading to local production of IL-6 in joints affected by inflammatory processes such as RA (Actemra®, US prescribing information 2017).

Sarilumab

Sarilumab (Kevzara®) is a human recombinant anti-IL-6 receptor mAb of the IgG1 subclass, which is produced by recombinant DNA technology in Chinese Hamster Ovary cell suspension culture (Kevzara®, US prescribing information 2017).

The efficacy and safety of sarilumab have been assessed in patients with moderately to severely active RA who had inadequate clinical response to methotrexate and who had an inadequate clinical response or were intolerant to one or more TNFα antagonists. In a randomized, double-blind, controlled Phase III study in RA patients with inadequate clinical response to methotrexate, 6-month treatment with subcutaneous sarilumab at the recommended dose regimen (200 mg every 2 weeks) with concomitant methotrexate use resulted in 66, 46, and 25% of RA patients achieving ACR20, ACR50, and ACR70, respectively, while the control group had only 33, 17, and 7% of patients with ACR20, ACR50, and ACR70 responses, respectively.

Serious infection Black-Box warning was placed on the sarilumab label (Kevzara®, US prescribing information 2017). Serious infections leading to hospitalization or death including bacterial, viral, invasive fungal, and other opportunistic infections have occurred in patients receiving sarilumab. In the 52-week placebo-controlled population, the rate of serious infections in the 200 mg and 150 mg sarilumab

with concomitant DMARD group was 4.3 and 3.0 events per 100 patient-years, respectively, compared to 3.1 events per 100 patient-years in the placebo plus DMARD group. In the long-term safety population, the overall rate of serious infections was consistent with rates in the controlled periods of the studies. The most frequently observed serious infections included pneumonia and cellulitis. Cases of opportunistic infections have been reported. Therefore, signs and symptoms of infection should be closely monitored during treatment with sarilumab. Sarilumab use should be avoided during an active infection.

Sarilumab was approved for the treatment of adult patients with moderately to severely active RA who have had an inadequate response or intolerance to one or more DMARDs (Kevzara®, US prescribing information 2017).

Tocilizumab

Tocilizumab (Actemra®), a recombinant humanized anti-IL-6 receptor mAb of IgG 1κ, was the first drug approved in this class (Actemra®, US prescribing information 2017).

The efficacy and safety of tocilizumab have been assessed in various adult RA populations (DMARD [including methotrexate]-inadequate responders, and methotrexate-naïve patients, and patients with an inadequate clinical response or intolerant to one or more TNF antagonist therapies), and pediatrics with polyarticular JIA and systemic JIA. In a randomized, double-blind, controlled Phase III study in RA patients, treatment with intravenous tocilizumab (4 or 8 mg/kg) in combination with methotrexate resulted in 51–56%, 25–32%, and 11–13% of RA patients achieving ACR20, ACR50, and ACR70, respectively, at week 24, while the control group (methotrexate plus placebo) had only 27, 10, and 2% of patients exhibiting ACR20, ACR50, and ACR70 responses, respectively. Recently, another Phase III study demonstrated similar efficacy and safety for treating RA patients using a subcutaneous route of administration as an alternative to the previously established intravenous route of administration.

Serious infection Black-Box warning was placed on the tocilizumab label (Actemra®, US prescribing information 2017). Serious infections leading to hospitalization or death including tuberculosis (TB), bacterial, viral, invasive fungal, and other opportunistic infections have occurred in patients receiving tocilizumab. In the 24-week, controlled clinical studies, the rate of serious infections in the tocilizumab intravenously administrated 8 mg/kg monotherapy group was 3.6 per 100 patient-years compared to 1.5 per 100 patient-years in the methotrexate group. The rate of serious infections in the 8 mg/kg intravenously administrated tocilizumab plus DMARD group was 5.3 events per 100 patient-years, respectively, compared to 3.9 events per 100 patient-years in the placebo plus DMARD group. Therefore, tocilizumab should not be administered during an active infection, including localized infections. If a serious infection develops, interrupt tocilizumab until the infection is controlled.

Of the arthritides, tocilizumab is indicated as a second-line biologic therapy 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. It is also indicated for the treatment of pediatric patients 2 years of age and older with active polyarticular JIA and systemic JIA (Actemra®, US prescribing information 2017).

■ Anti-CD80/CD86 Agent to Inhibit Lymphocyte Activation

Abatacept

Abatacept (Orencia®) is a soluble fusion protein that consists of the extracellular domain of human cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) linked to the Fc portion of human IgG1. Abatacept inhibits T-lymphocyte activation by binding to CD80 and CD86 on antigen presenting cells (APC), thereby blocking interaction with CD28 on T-cells which is required for their activation (Orencia®, US prescribing information 2017). Activated T lymphocytes are implicated in the pathogenesis of RA.

The efficacy and safety of abatacept have been assessed in various adult RA populations (DMARD [including methotrexate]-inadequate responders, anti-TNFα-inadequate responders, and methotrexate-naïve patients), active polyarticular JIA and active PsA. In a randomized, double-blind, controlled Phase III study in patients with active RA despite methotrexate therapy, 6-month treatment with intravenous abatacept in combination with methotrexate at the recommended dose regimen (500, 750, and 1000 mg for patients weighing <60 kg, 60–100 kg, and > 100 kg, respectively) resulted in 68, 40, and 20% of RA patients achieving ACR20, ACR50, and ACR70, respectively, while the control group (methotrexate plus placebo) had only 40, 17, and 7% of patients achieving ACR20, ACR50, and ACR70 responses, respectively. Recently, another Phase III study demonstrated similar efficacy and safety for treating RA patients using a subcutaneous route of administration as an alternative to the previously established intravenous route of administration.

As described earlier in this chapter, abatacept should not be given concomitantly with TNF antagonists due to an increased risk of serious adverse events, including infections, whereas no clear signal in clinical benefit when compared to anti-TNF therapy alone.

Abatacept is indicated for the treatment of adult patients with moderately to severely active RA and

PsA. It is also indicated for reducing signs and symptoms in pediatric patients 2 years of age and older with moderately to severely active polyarticular JIA (Orencia®, US prescribing information 2017).

■ Anti-CD20 Cytolytic Agent

Rituximab

Rituximab (Rituxan®) is a genetically engineered chimeric murine/human IgG1κ mAb that binds specifically to the antigen CD20 on pre-B and mature B lymphocytes. In the pathogenesis of RA, B cells may be involved in the autoimmune/inflammatory process through production of rheumatoid factor (RF) and other autoantibodies, antigen presentation, T-cell activation, and/or proinflammatory cytokine production. Rituximab binds to the CD20 antigen on B lymphocytes, and the Fc domain recruits immune effector functions to mediate B-cell lysis, resulting in B-cell depletion of circulating and tissue-based B cells (Rituxan®, US prescribing information 2016).

The efficacy and safety of rituximab have been assessed in adult patients with moderately to severely active RA who had a prior inadequate response to at least one anti-TNFα agent. In a randomized, double-blind, controlled Phase III study in RA patients, treatment with one course of intravenous rituximab (2 doses of 1000 mg rituximab separated by 2 weeks) in combination with methotrexate resulted in 51, 27, and 12% of RA patients achieving ACR20, ACR50, and ACR70, respectively, at week 24, while the control group (methotrexate plus placebo) had only 18, 5, and 1% of patients exhibiting ACR20, ACR50, and ACR70 responses, respectively.

Black-Box warnings of fatal infusion reactions, severe mucocutaneous reactions, hepatitis B virus (HBV) reactivation and progressive multifocal leukoencephalopathy (PML) were placed on the rituximab label (Rituxan®, US prescribing information 2016). Rituximab can cause severe, including fatal, infusion reactions. Severe reactions typically occurred during the first infusion with time to onset of 30–120 min. Therefore, rituximab should only be administered by a healthcare professional with appropriate medical support to manage severe infusion reactions that can be fatal if they occur. The incidence of serious infections was 2% in the rituximab-treated patients with RA and 1% in the placebo group in the pre-marketing trials. Mucocutaneous reactions, some with fatal outcome, can occur in patients treated with rituximab. These reactions include paraneoplastic pemphigus, Stevens-Johnson syndrome, lichenoid dermatitis, vesiculobullous dermatitis, and toxic epidermal necrolysis. The onset of these reactions has been variable and includes reports with onset on the first day of rituximab exposure. HBV reactivation, in some cases resulting in fulminant hepatitis, hepatic failure and death, can occur in patients treated with drugs classified as CD20-directed cytolytic antibodies, including rituximab. John Cunningham virus infection resulting in PML and death can occur in rituximab treated patients with autoimmune diseases. Most cases of PML were diagnosed within 12 months of their last infusion of rituximab. Rituximab should be discontinued in patients who experienced/developed these reactions, and rituximab is not recommended for use in patients with severe, active infections.

Within arthritides, rituximab is indicated as a second-line biologic therapy 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. The estimated median terminal half-life of rituximab is 18 days in RA patients; however, the pharmacodynamic effect on B cells lasts much longer than the drug presence. B-cell recovery begins at approximately 6 months, and median B-cell levels return to normal by 12 months following completion of treatment with rituximab. Consequently, treatment courses of rituximab should be administered every 24 weeks or based on clinical evaluation, but no more frequent than every 16 weeks (Rituxan®, US prescribing information 2016).

SYSTEMIC LUPUS ERYTHEMATOSUS

Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by the involvement of multiple organ systems, a clinical pattern of unpredictable exacerbations and remissions, and the presence of autoantibodies. The immunopathogenic characteristic of this disease is polyclonal B-cell activation that leads to hyperglobulinemia, autoantibody production, and immune complex formation, which in turn leads to inflammation and damage that can affect multiple organ systems. Generalized SLE symptoms may include fever, fatigue, rash, oral ulceration, hair loss, and arthralgias. US prevalence estimates for various types of lupus, including SLE, vary greatly, with estimates as high as 100 per 100,000 persons affected. Approximately 80–90% of patients with SLE are women.

The primary causes of SLE remain unclear. Current therapies tend to be generally immunosuppressive, often providing suboptimal control over disease manifestation and long-term outcomes due to ineffectiveness or side effects. These SLE therapies have targeted nonspecific sites for inflammatory reduction (e.g., NSAIDs and antimalarials) and immune system suppression (e.g., corticosteroids, azathioprine, cyclophosphamide, methotrexate and mycophenolate). Belimumab (Benlysta®), a B-lymphocyte stimulator (BLyS) neutralizing agent, is currently the only approved biologic therapy for SLE.

■ Anti- BLyS Agent

Belimumab

Belimumab (Benlysta®) is a human IgG1λ mAb specific for B-lymphocyte stimulator (BLyS) produced by recombinant DNA technology in a murine cell (NS0) expression system. Belimumab blocks the binding of soluble BLyS, a B-cell survival factor, to its receptors on B cells. Belimumab does not bind B cells directly, but by binding BLyS, it inhibits the survival of B cells, including autoreactive B cells, and reduces the differentiation of B cells into immunoglobulin-producing plasma cells (Benlysta®, US prescribing information 2017).

The safety and effectiveness of belimumab were evaluated in four randomized, double-blind, placebo-controlled studies in patients with SLE according to criteria from the American College of Rheumatology, with intravenous belimumab administration in Trials 1–3 and subcutaneous belimumab administration in Trial 4. Patients were on a stable SLE standard of care treatment regimen comprising any of the following (alone or in combination): corticosteroids, antimalarials, NSAIDs, and immunosuppressives.

The first Phase III study (Trial 1) evaluated intravenous doses of 1, 4, and 10 mg/kg belimumab plus standard of care compared to placebo plus standard of care over 52 weeks in patients with SLE. The co-primary endpoints were percent changes in SELENA-SLEDAI score (a sum of all marked SLE-related descriptors) at week 24 and time to flare over 52 weeks. Exploratory analysis of this study identified a subgroup of patients (72%), who were autoantibody positive, in whom belimumab appeared to offer benefit. The results of this study informed the design of the next two Phase III studies (Trial 2 and Trial 3) and led to the selection of a target population and indication that was limited to autoantibody-positive SLE patients. Trial 2 and Trial 3 were both randomized, double-blind, placebo-controlled trials in patients with SLE. The studies were similar in design except Trial 2 had a 52-week duration and Trial 3 had a 76-week duration. Both studies compared intravenous belimumab 1 and 10 mg/kg plus standard of care to placebo plus standard of care. Eligible patients had active SLE disease, defined as a SELENA-SLEDAI score ≥ 6, and positive autoantibody test results at screening. The primary efficacy determination was based on a composite endpoint (SLE Responder Index or SRI) response at week 52 compared to baseline. The proportion of SLE patients achieving a SRI response in Trial 2 and Trial 3 was significantly higher in the belimumab 10 mg/kg group than in the placebo group (odds ratio of 1.5–1.8 after 52 weeks of treatment). Trial 4 is another randomized, double-blind, placebo-controlled Phase III study in autoantibody-positive SLE patients, who received subcutaneous administrated belimumab (200 mg weekly dosing plus standard of care) or placebo plus standard of care. Statistically significant efficacy was achieved in the subcutaneous belimumab group versus the placebo group, with odds ratio of 1.7 after 52 weeks of treatment.

In Phase III trials, reports suggest that overall rates for adverse events, infections, treatment discontinuations due to adverse events, and fatalities were not significantly different between the belimumab- and the placebo-treated patients; however, serious and severe infusion-related reactions were reported more often in belimumab-treated patients.

Belimumab is indicated for the treatment of adult patients with active autoantibody-positive SLE who are receiving standard therapy (Benlysta®, US prescribing information 2017).

PSORIASIS

Psoriasis is the most common chronic, immune-mediated skin disorder, affecting approximately 2% of the world's population (Nestle et al. 2009). Thickened epidermal layers resulting from excessive keratinocyte cell proliferation characterize psoriasis. The majority of sufferers are afflicted with psoriasis for most of their lives. Symptoms typically present between the ages of 15 and 35, with the majority of individuals diagnosed before the age of 40. Plaque psoriasis is the most common form, affecting approximately 85–90% of individuals with the condition. The disease manifests as raised, well-demarcated, erythematous, and frequently pruritic and painful plaques with silvery scales (Christophers 2001; Griffiths and Barker 2007). Approximately 25% of individuals with psoriasis develop moderate to severe disease with widely disseminated lesions. In clinical development and in managing patient care, the Psoriasis Activity and Severity Index (PASI) is commonly used as an instrument to measure and evaluate patient care and treatment effects of anti-psoriasis therapies (Feldman and Krueger 2005).

Prior to the availability of biologic agents in psoriasis, multiple therapeutic options existed for the treatment of the disease; however, a significant unmet need remained for a safe, highly effective, convenient systemic therapy for patients with moderate to severe forms of the disease (Papp et al. 2011). Psoralen plus ultraviolet A light therapy, while effective, is inconvenient and is associated with an increased risk of skin malignancies and photodamage. Significant safety concerns and organ toxicity are associated with chronic administration of conventional systemic agents such as methotrexate, cyclosporine, and acitretin, thus limiting their use in long-term psoriasis management.

Three anti-TNFα biologic agents are approved for use in psoriasis: etanercept, adalimumab, and infliximab. Two anti-IL-17A mAbs are approved for treatment of psoriasis, ixekizumab and secukinumab. Other approved biologic agents for the treatment of psoriasis include ustekinumab (anti-IL-12/IL-23), guselkumab (anti-IL23) and brodalumab (anti-IL-17 receptor A) (Table 26.1). Efalizumab (Raptiva®) is a humanized IgG1 mAb directed against CD11 and inhibits leukocyte function. Efalizumab was approved in 2003 for the treatment of moderate to severe psoriasis but was voluntarily withdrawn in 2009 due to reports of PML, an opportunistic viral infection of the brain that usually leads to death or severe disability. Alefacept (Amevive®), is a CD2-directed human leukocyte function antigen-3 (LFA-3)/Fc fusion protein. It interferes with lymphocyte activation via CD2 and causes a reduction in subsets of CD2+ T lymphocytes and circulating total CD4+ and CD8+ T-lymphocyte counts. Alefacept was approved in 2003 for the treatment of moderate to severe psoriasis; however, because of the availability of better tolerated and more effective biologics for psoriasis, alefacept was withdrawn from use by its sponsor in 2011.

■ Anti-TNFα Agents

TNFα antagonists (adalimumab, etanercept, and infliximab) block the binding of TNFα to its receptor, interrupting the subsequent signaling and inflammatory pathways driven by TNFα. This activity suppresses inflammation and the increased activation of T cells that are characteristics of psoriasis (Humira®, US prescribing information 2017; Enbrel®, US prescribing information 2016; Remicade®, US prescribing information 2017).

An evidence-based comparison from clinical trials of three TNFα antagonists (adalimumab, etanercept, and infliximab) has indicated better efficacy of infliximab and adalimumab than etanercept in treating psoriasis (Langley 2012).

A meta-analysis comparing three TNFα antagonists and traditional systemic therapy (e.g., cyclosporine) used in the treatment of moderate to severe psoriasis demonstrated high efficacy and tolerability of TNFα antagonists (Langley 2012). Due to the mode of action, there is a concern that patients receiving TNFα antagonists may become more susceptible to infection; however, a meta-analysis of trial data for these TNFα antagonists showed that serious infection rates were not much higher than those in placebo-treated patients.

Another meta-analysis was completed from 20 trials employing anti-psoriatic biologics. Based on an indirect comparison and a placebo PASI50 (50% improvement in PASI score from baseline) response of 13%, infliximab had the highest predicted mean probability of response of 93, 80, and 54% for PASI50, PASI75, and PASI90 (50%, 75% and 90% improvement in PASI score from baseline), respectively, followed by ustekinumab 90 mg at 90, 74, and 46%, respectively, and then ustekinumab 45 mg, adalimumab, etanercept, and efalizumab (Reich et al. 2012).

A more recent network meta-analysis (Gomez-Garcia et al. 2017) based on 27 randomized controlled trials was conducted to assess the short-term efficacy and safety of biologic therapies for psoriasis. From the available evidence (direct and indirect comparison) collected from six biologics (infliximab, adalimumab, etanercept, secukinumab and ustekinumab), infliximab and secukinumab were shown to be the most effective short-term treatments (as ranked by PASI75 and PASI90 responses), but were the biologics most likely to produce at least one adverse event or an infectious adverse event, respectively. Ustekinumab demonstrated the best efficacy–safety profile among the six biologics (it had the third most efficacious treatment effect, and was the only agent that did not show increased risk of adverse events compared with placebo). These results are consistent with results from another recent meta-analysis (Jabbar-Lopez et al. 2017) where ustekinumab was shown to fall into the category of high efficacy and tolerability for the treatment of (together with adalimumab and secukinumab).

Adalimumab, etanercept, and infliximab have been indicative for the treatment of plaque psoriasis in adult patients. In addition, etanercept is approved for pediatric plaque psoriasis (age 4 years and older) based on the beneficial clinical evidence from a randomized, double-blind, placebo-controlled study in children 4–17 years of age with moderate to severe plaque psoriasis.

■ Anti IL-17A Agents

Two anti-IL-17A biologic agents have been approved for psoriasis, ixekizumab (Taltz®) and secukinumab (Cosentyx®).

Ixekizumab

An overview of ixekizumab, a humanized anti-IL-17A mAb, has been provided earlier in this chapter (Taltz®, US prescribing information 2017). In addition to the use of this antibody for the treatment of PsA, ixekizumab has also been evaluated in patients with moderate to severe plaque psoriasis. Elevated levels of IL-17A are found in psoriatic plaques. Treatment with IL-17A antagonists may reduce epidermal neutrophils and IL-17A levels in psoriatic plaques.

The safety and effectiveness of ixekizumab have been evaluated in three randomized, double-blind, placebo-controlled Phase III trials (Trials 1, 2, and 3) in

patients with moderate to severe psoriasis. In the two active comparator trials (Trials 2 and 3), patients who randomized to the etanercept arm received subcutaneous etanercept 50 mg twice weekly. Three-month treatment with subcutaneous ixekizumab at the recommended dose regimen (160 mg at week 0, followed by 80 mg at weeks 2, 4, 6, 8 10, and 12, then 80 mg every 4 weeks thereafter) resulted in 87–90%, 68–71%, and 35–40% of psoriatic patients achieving PASI75, PASI90, and PASI100, respectively, while the etanercept group had 41%, 18% and 4% of patients achieving PASI75, PASI90 and PASI100, respectively; and the placebo control group had only 2–7%, 1–3% and 0–1% of patients exhibiting PASI75, PASI90 and PASI100 responses, respectively. Among clinical responders at week 12, the percentage of patients who maintained this response (i.e., static Physician Global Assessment [sPGA] score 0 or 1) at week 60 (48 weeks following re-randomization) in Trials 1 and 2 was higher for patients treated with ixekizumab (75%) compared to those treated with placebo (7%).

Ixekizumab is indicated for the treatment of adults with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy (Taltz®, US prescribing information 2017).

Secukinumab

An overview of secukinumab has been provided earlier in this chapter (Cosentyx®, US prescribing information 2017). In addition to the use of this human anti-IL17A mAb for the treatment of PsA and AS, secukinumab has also been evaluated in patients with plaque psoriasis.

Four randomized, double-blind, placebo-controlled Phase III trials (Trials 1, 2, 3, and 4) have been conducted for secukinumab in patients with moderate to severe psoriasis. In the active comparator trial (Trial 2), patients who randomized to the etanercept arm received subcutaneous etanercept 50 mg twice weekly. Three-month treatment with secukinumab of 300 mg subcutaneously administrated at weeks 0, 1, 2, 3 and 4, and every 4 weeks thereafter resulted in 75–87% of psoriasis patients achieving PASI75, while the etanercept group had 44% of patients achieving PASI75; and the placebo control group had only 0–5% of patients exhibiting PASI75 response (Langley et al. 2014). With continued treatment over 52 weeks, PASI75 responders maintained their responses in 81–84% patients treated with secukinumab (300 mg every 4 weeks).

A head-to-head randomized controlled trial was conducted comparing the efficacy and safety between secukinumab and ustekinumab in patients with moderate to severe psoriasis (Blauvelt et al. 2017). Secukinumab was administered 300 mg subcutaneously at baseline and at weeks 1, 2, and 3, and then every 4 weeks from week 4 onward. Ustekinumab was dosed subcutaneously at 45 mg in patients ≤100 kg and at 90 mg in those >100 kg, and given at baseline, at week 4, and then every 12 weeks. Secukinumab has demonstrated superior efficacy to ustekinumab at weeks 4 and 16 in patients with plaque psoriasis. This superior efficacy is sustained over 52 weeks in the proportion of patients achieving PASI90 (76% vs. 61%) and PASI100 (46% vs. 36%). In addition, patients received secukinumab had greater improvement in health-related quality of life and comparable safety.

Secukinumab is indicated for the treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy (Cosentyx®, US prescribing information 2017).

■ Anti-IL-12/IL-23 Agents

Ustekinumab

An overview of ustekinumab has been provided earlier in this chapter (Stelara®, US prescribing information 2017). In addition to its use for the treatment of PsA, the efficacy and safety of ustekinumab have been assessed in adult and adolescent patients (12 years or older) with moderate to severe psoriasis.

The safety and efficacy of ustekinumab in treatment of psoriasis were assessed in two Phase III trials (PHOENIX 1 and PHOENIX 2). The results from these two trials demonstrated that ustekinumab was effective in ameliorating psoriatic plaques, pruritus, and nail psoriasis (Leonardi et al. 2008; Papp et al. 2008). Within 12 weeks of initiating subcutaneous ustekinumab treatment (45 or 90 mg/kg at weeks 0 and 4), more than two-thirds of patients exhibited ≥75% reduction in PASI (PASI75 response). Maximum efficacy was achieved at approximately 24 weeks after initiation of therapy, with approximately 75% of ustekinumab-treated patients achieving a PASI75 response. Clinical response to ustekinumab was associated with serum ustekinumab concentrations that were somewhat correlated with patient body weight. While efficacy of the 45 and 90 mg doses of ustekinumab was similar in patients weighing ≤100 kg, the 90-mg dose was more effective than the 45-mg dose in patients weighing >100 kg, who represented approximately one-third of the combined PHOENIX 1 and PHOENIX 2 population. Thus, to optimize efficacy in all patients while minimizing unnecessary drug exposure, fixed dose administration of ustekinumab based on body weight is indicated, i.e., for patients weighing >100 kg, the recommended dose is 90 mg initially and 4 weeks later, followed by 90 mg every 12 weeks; for patients weighing ≤100 kg, the recommended dose is 45 mg initially and 4 weeks later, followed by 45 mg every 12 weeks.

Results of the Phase III psoriasis clinical trials indicated that ustekinumab was generally well tolerated. Rates and types of adverse events, serious adverse events, adverse events leading to treatment discontinuation, and laboratory abnormalities were generally comparable among patients receiving subcutaneously administration of placebo, ustekinumab 45 or 90 mg during the 12-week placebo-controlled phases of PHOENIX 1 and PHOENIX 2. Dose–response relationships for safety events were not apparent. Rates of serious infections and malignancies in PHOENIX 1 and PHOENIX 2 were low and comparable across treatment groups during the placebo-controlled phases, no apparent increase in the frequency of these adverse events was observed through 18 months of treatment, and no mycobacterial or salmonella infections were reported (Leonardi et al. 2008; Papp et al. 2008).

A head-to-head controlled trial was conducted comparing the efficacy and safety of a TNFα antagonist, etanercept, and ustekinumab in patients with moderate to severe psoriasis (Griffiths et al. 2010). Ustekinumab was administered subcutaneously at either 45 or 90 mg at weeks 0 and 4, and etanercept was administered subcutaneously 50 mg twice weekly for 12 weeks. There was at least 75% improvement in the PASI (PASI75) at week 12 in 67.5% of patients who received 45 mg of ustekinumab and 73.8% of patients who received 90 mg of ustekinumab, as compared to 56.8% of those who received etanercept ($p = 0.01$ and $p < 0.001$, respectively). The efficacy of ustekinumab at 45 or 90 mg was superior to that of etanercept over a 12-week period while the safety profiles were similar.

Ustekinumab is indicated for the treatment of adult patients with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy. Ustekinumab is also indicative for adolescent patients (12 years or older) with moderate to severe plaque psoriasis (Stelara®, US prescribing information 2017).

■ Anti-IL-23 Agents

As of February 2018, guselkumab (Tremfya®) is the only anti-IL-23 biologic agent approved for psoriasis. IL-23 pathway is suggested contributing to the chronic inflammation underlying the pathophysiology of psoriasis. Guselkumab, by neutralizing IL-23, inhibits the release of proinflammatory cytokines and chemokines.

Guselkumab

Guselkumab (Tremfya®) is a human IgG1λ mAb, which is produced in a mammalian cell line using recombinant DNA technology. It selectively binds to the p19 subunit of IL-23 and inhibits its interaction with the IL-23 receptor (Tremfya®, US prescribing information 2017).

The safety and efficacy of guselkumab have been evaluated in three multicenter, randomized, double-blind Phase III trials (VOYAGE 1, VOYAGE 2 and NAVIGATE) in patients with moderate to severe plaque psoriasis. In VOYAGE 1 and VOYAGE 2, patients were randomized to either guselkumab (100 mg SC at weeks 0 and 4 and every 8 weeks thereafter), placebo or U.S. licensed adalimumab (80 mg SC at week 0 and 40 mg at week 1, followed by 40 mg every other week thereafter). Sixteen-weeks treatment with subcutaneous guselkumab resulted in 70–73% of psoriasis patients achieving PASI90, while the placebo control group had only 2–3% patients exhibiting PASI90 response. An analysis based on clinical data from all the North America sites (i.e., U.S. and Canada) demonstrated superiority of guselkumab to U.S. licensed adalimumab. The PASI90 response rates at weeks 16, 24 and 48 were 64–73%, 71–80% and 73% respectively, for guselkumab; and 41–42%, 44–51% and 46% respectively, for adalimumab. NAVIGATE evaluated the efficacy of guselkumab in patients who had not achieved an adequate response at week 16 after initial treatment with ustekinumab (dosed 45 mg or 90 mg according to the subject's baseline weight [≤ and > 100 kg respectively] at week 0 and week 4). These patients were randomized to either continue with ustekinumab treatment every 12 weeks or switch to guselkumab. Twelve-weeks after randomization, a greater proportion of patients on guselkumab treatment compared to ustekinumab (31% vs. 14%) achieved an Investigator's Global Assessment (IGA) score of 0 or 1 with a ≥ 2 grade improvement.

Results of the Phase III moderate to severe plaque psoriasis clinical trials indicated that guselkumab was generally well tolerated at the recommended dose regimen. Rates and types of adverse events, serious adverse events, adverse events leading to treatment discontinuation, and laboratory abnormalities were generally comparable among patients receiving placebo and guselkumab during the 16-week placebo-controlled periods of the pooled clinical trials (VOYAGE 1 and VOYAGE 2). Infections occurred in 23% of the guselkumab group compared to 21% of the placebo group. The most common (≥ 1%) infections were upper respiratory infections, gastroenteritis, tinea infections, and herpes simplex infections; all cases were mild to moderate in severity and did not lead to discontinuation of guselkumab. Through week 48, no new adverse reactions were identified with guselkumab use and the frequency of the adverse reactions was similar to the safety profile observed during the first 16 weeks of treatment.

Guselkumab is indicated for the treatment of adult patients with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy (Tremfya®, US prescribing information 2017).

■ Anti-IL-17 Receptor A Agents

As of February 2018, brodalumab (Siliq®) is the only anti-IL-17 receptor A (IL-17RA) biologic agent approved for psoriasis. IL-17RA is a protein expressed on the cell surface and is a required component of receptor complexes utilized by multiple IL-17 family cytokines. Blocking IL-17RA inhibits IL-17 cytokine-induced responses including the release of pro-inflammatory cytokines and chemokines.

Brodalumab

Brodalumab (Siliq®) is a human IgG2κ mAb expressed in a Chinese Hamster Ovary cell line. It selectively binds to human IL-17 receptor A (IL-17RA) and inhibits its interactions with cytokines IL-17A, IL-17F, IL-17C, IL-17A/F heterodimer and IL-25. (Siliq®, US prescribing information 2017).

The safety and effectiveness of brodalumab have been evaluated in three multicenter, randomized, double-blind, controlled Phase III trials (Trials 1, 2, and 3) in patients with moderate to severe plaque psoriasis. In these trials, patients were randomized to placebo or subcutaneous brodalumab treatment of 210 mg at weeks 0, 1, and 2, followed by 210 mg every 2 weeks thereafter. In the two active comparator trials (Trials 2 and 3), patients randomized to the subcutaneous ustekinumab group received a 45-mg dose if their weight was ≤100 kg and a 90-mg dose if their weight was >100 kg at weeks 0, 4, and 16, followed by the same dose every 12 weeks. Treatment with brodalumab resulted in 83–86% and 37–42% of psoriatic patients achieving PASI75 and PASI100, respectively, at week 12, while the ustekinumab group had 69–70% and 19–22% of patients achieving PASI75 and PASI100, respectively; and the placebo control group had only 3–8% and 0–1% of patients exhibiting PASI75 and PASI100 responses, respectively. Maintenance of the treatment effect of brodalumab was demonstrated. Among PASI100 responders at week 12, 72% of the patients who continued on brodalumab 210 mg every 2 weeks maintained the response at week 52.

Suicidal ideation and behavior Black-Box warnings were placed on the brodalumab label (Siliq®, US prescribing information 2017). Suicidal ideation and behavior, including four completed suicides, occurred in patients treated with brodalumab in the psoriasis pre-marketing trials. There were no completed suicides in the 12-week placebo-controlled portion of the trials. A causal association between treatment with brodalumab and increased risk of suicidal ideation and behavior has not been established. Because of the observed suicidal ideation and behavior in subjects treated with brodalumab, in the United States, brodalumab is only available through a restricted program under REMS (Risk Evaluation and Mitigation Strategy). Prescribers should weigh the potential risks and benefits before using brodalumab in patients with a history of depression or suicidality. Patients with new or worsening suicidal thoughts and behavior should be referred to a mental health professional, as appropriate.

Brodalumab is indicated for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy and have failed to respond or have lost response to other systemic therapies (Siliq®, US prescribing information 2017).

INFLAMMATORY BOWEL DISEASE

Inflammatory bowel disease (IBD) refers to a group of chronic inflammatory diseases of the gastrointestinal tract that mainly comprise two well-defined clinical entities, Crohn's disease (CD) and ulcerative colitis (UC). A study in 2012 (Molodecky et al. 2012) found that prevalence of UC in North America between 1980 and 2008 was 198.1–298.5 cases per 100,000 persons and prevalence of CD was 135.7–318.5 cases/100,000 persons. CD and UC are two idiopathic IBD. They have some similarities and unique differences (Baumgart and Sandborn 2007).

CD is a relapsing, transmural inflammatory disease of the gastrointestinal mucosa that can affect the entire gastrointestinal tract from the mouth to the anus, while UC is a relapsing, nontransmural inflammatory disease that is restricted to the colon. CD may involve all layers of the intestine, and there can be normal healthy bowel between patches of diseased bowel, while UC does not affect all layers of the bowel but only affects the top layers of the colon in an even and continuous distribution. In CD, pain is commonly experienced in the lower right abdomen, while in UC, in the lower left part of the abdomen. In CD, colon wall may be thickened and may have a rocky appearance, while in UC the colon wall is thinner and shows continuous inflammation. In clinical practice, disease activity of CD is typically described as mild to moderate (ambulatory patients able to tolerate oral alimentation without manifestations of dehydration, toxicity, abdominal tenderness, painful mass, obstruction, or > 10% weight loss), moderate to severe disease (failure to respond to treatment for mild disease, more prominent symptoms of fever, weight loss, abdominal pain or tenderness, intermittent nausea and vomiting without obstruction, or significant anemia), and severe to fulminant disease (persisting symptoms on corticosteroids, high fevers, persistent vomiting, evidence of intestinal obstruction, rebound tenderness, cachexia, or evidence of an abscess). While disease activity of UC is typically described as mild (up to four bloody stools

daily and no systemic toxicity), moderate (four to six blood stools daily and minimal toxicity), or severe (more than six stools daily and signs of toxicity, such as fever, tachycardia, anemia, and raised erythrocyte sedimentation rate), patients with fulminant UC usually have more than ten bloody stools daily, continuous bleeding, anemia requiring blood transfusion, abdominal tenderness, and colonic dilation on plain abdominal radiographs (Baumgart and Sandborn 2007).

Conventional pharmacologic treatments for IBD include aminosalicylates, corticosteroids, immunomodulators (azathioprine, 6-mecaptopurine, methotrexate, cyclosporine), and antibiotics (metronidazole, ciprofloxacin, clarithromycin). The aim of traditional therapy is to induce and maintain remission in patients. Treatment guidelines generally recommend initiating treatment with first-line agents such as sulfasalazine and systemic corticosteroids, followed by immunomodulators. These conventional pharmacologic therapies are often effective in patients with IBD, particularly in those with mildly to moderately active disease; however, a significant proportion of patients have severely active disease that is often refractory to these conventional therapies. Furthermore, these small molecule drugs have limitations in the treatment of IBD. Corticosteroids have many side effects and are not suitable for long-term maintenance therapy. Corticosteroids are also ineffective for healing bowel ulcerations (Modigliani et al. 1990). Immunomodulators promote mucosal healing, but the onset of action is slow. The use of anti-TNFα agents can overcome the shortcomings of the conventional treatment options and provide greater improvement for severe or refractory IBD. Anti-TNFα therapy can rapidly improve signs and symptoms (i.e., induce and maintain clinical response and clinical remission), promote mucosal healing, eliminate corticosteroid use, and has the potential to alter the natural history of IBD. Historically, therapeutic proteins have been used as rescue therapy for patients with IBD refractory to conventional therapies. Recently, evidence has emerged that early use of anti-TNFα therapy in patients at high risk may induce a greater response and prevent irreversible damage to the intestine (D'Haens et al. 2008). There are also concerns with respect to increased risks of infections and malignancy associated with the use of anti-TNFα agents in patients with IBD (Hoentjen and van Bodegraven 2009). The timing of initiating therapy with therapeutic proteins and the identification of the subset of patients who can achieve maximal benefit from treatment using therapeutic proteins remain active areas of debate, and further clinical research is required to provide evidence-based guidelines. Anti-integrin and anti-IL-12/IL-23 agents are non-TNF biologic therapies developed recently for the treatment of IBD; they provide alternative in case of treatment failures to conventional drugs (such as glucocorticoids and immunomodulators) and/or anti-TNFα therapies.

There are seven biologic agents approved for the treatment of CD and/or UC; those are four anti-TNFα agents (infliximab, adalimumab, certolizumab pegol and golimumab), one anti-IL-12/IL-23 agent (ustekinumab), and two anti-integrin agents (natalizumab and vedolizumab) (Table 26.1).

■ Anti-TNFα Agents

Four anti-TNFα agents (infliximab, adalimumab, certolizumab pegol and golimumab) have been approved for the treatment of CD and/or UC. Not all anti-TNFα agents have been shown to be effective for IBD. For example, infliximab, the first-in-class anti-TNFα biologic agent approved for treating CD, has been shown to be highly effective in the treatment of CD, but etanercept was shown to be ineffective for this disease. A mechanism postulated to explain the differential effects of infliximab and etanercept for CD was that infliximab could bind membrane-associated TNFα and induce apoptosis of activated T cells and macrophages, but etanercept only binds to soluble TNFα (Van den Brande et al. 2003). However, this theory is questioned by later data showing induction of apoptosis by etanercept and clinical efficacy of certolizumab pegol, a non-apoptotic anti-TNFα agent (Chaudhary et al. 2006; Sandborn et al. 2006). As of February 2018, infliximab is the only antibody-based therapeutic protein approved for pediatric patients with CD or UC. For pediatric patients with CD, adalimumab is also approved as an anti-TNFα biologic therapy.

Adalimumab

An overview of adalimumab, a human anti-TNFα mAb, has been provided earlier in this chapter (Humira®, US prescribing information 2017). In addition to the use of this therapeutic protein for the treatment of arthritides and psoriasis, the efficacy and safety of adalimumab have been assessed in adult and pediatric patients with active CD, and adult patients with active UC.

The efficacy and safety of adalimumab in the treatment of adult CD have been evaluated in patients with moderately to severely active CD (Crohn's Disease Activity Index [CDAI] ≥ 220 and ≤ 450) in three randomized, double-blind, controlled Phase III studies (CD-1I, CD-II and CD-III). In a Phase III Study (CD-I) in CD patients who were naïve to TNF blocker, treatment with subcutaneous adalimumab at the recommended induction dose regimen (160 and 80 mg at weeks 0 and 2, respectively) resulted in 58 and 36% of patients achieving clinical response (defined as a

decrease in CDAI of at least 70 points) and clinical remission (defined as CDAI <150), respectively, at week 4, while the control group (placebo) had 34 and 12% of patients with clinical response and clinical remission, respectively. A greater percentage of the patients treated with adalimumab also achieved induction of clinical response and remission versus placebo at week 4 in CD patients who had lost response to or were intolerant to infliximab in another Phase III trial (CD-II). The adalimumab group had 52 and 21% of patients who were in clinical response and clinical remission, respectively, at week 4, while the placebo group had 34 and 7% of patients in clinical response and clinical remission, respectively. In the third Phase III trial (CD-III), maintenance of clinical remission was evaluated. Among clinical responders at week 4, further maintenance treatment with 40 mg adalimumab administrated subcutaneously every other week demonstrated greater efficacy than the placebo maintenance group. The adalimumab maintenance group had 43 and 36% of patients who were in clinical response and clinical remission, respectively, at week 56, while the placebo maintenance group had 18 and 12% of patients in clinical response and clinical remission, respectively.

Two randomized, double-blind, placebo-controlled Phase III studies (UC-I and UC-II) have been conducted for adalimumab in patients with moderately to severely active UC (Mayo score 6–12 on a 12-point scale, with an endoscopy subscore of 2–3 on a scale of 0–3) despite concurrent or prior treatment with immunosuppressants such as corticosteroids, azathioprine, or 6-mercaptopurine. All patients in Study UC-I were TNF blocker naïve and 40% patients enrolled in Study UC-II had previously used another TNF-blocker. In both UC-I and UC-II studies, a greater percentage of the patients treated with subcutaneous adalimumab at the recommended subcutaneous dose regimen (160 and 80 mg at weeks 0 and 2, respectively) compared to patients treated with placebo (16.5–18.5% vs. ~ 9%) achieved induction of clinical remission (defined as Mayo score ≤ 2 with no individual subscores >1). In Study UC-II, a greater percentage of the patients treated with maintenance adalimumab of 40 mg every other week compared to patients treated with placebo (8.5% vs. 4.1%) achieved sustained clinical remission (defined as clinical remission at both weeks 8 and 52). The subgroup of patients with prior TNF-blocker use in Study UC-II achieved induction of clinical remission at 9% in the adalimumab group versus 7% in the placebo group, and sustained clinical remission at 5% in the adalimumab group versus 1% in the placebo group.

In addition to adult CD and UC, safety and efficacy of adalimumab for pediatric patients 6 years of age or older with CD have also been established. Use of adalimumab in this age group is supported by evidence from adult CD trials with additional data in pediatric CD patients (6–17 years of age) from a randomized, double-blind Phase III study.

Among IBD indications, adalimumab is indicated for treatment of CD by reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with moderately to severely active CD who have had an inadequate response to conventional therapy, and by reducing signs and symptoms and inducing clinical remission in these patients if they have also lost response to or are intolerant to infliximab. Adalimumab is also indicated for treatment of UC by inducing and sustaining clinical remission in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to immunosuppressants such as corticosteroids, azathioprine or 6-mercaptopurine. Adalimumab is also indicated for treatment of pediatric CD in patients 6 years of age and older who have had an inadequate response to corticosteroids or immunomodulators (Humira®, US prescribing information 2017).

Certolizumab Pegol

An overview of certolizumab pegol, a TNF blocker, has been provided earlier in this chapter (Cimzia®, US prescribing information 2016). In addition to its use for the treatment of RA and PsA, the efficacy and safety of certolizumab pegol have also been assessed in adult patients with moderately to severely active CD.

In a randomized, double-blind, controlled Phase III study in patients with active CD (CDAI ≥220 and ≤ 450), treatment with subcutaneous certolizumab pegol at the recommended induction dose regimen (400 mg at weeks 0, 2, and 4) resulted in 35 and 22% of patients achieving clinical response (defined as a decrease in CDAI ≥100) and clinical remission (defined as CDAI ≤150), respectively, at week 6, while the control group (placebo) had 27 and 17% of patients with clinical response and clinical remission, respectively. Among clinical responders at week 6, further maintenance treatment with 400 mg certolizumab pegol administrated subcutaneously every 4 weeks demonstrated greater efficacy than the placebo maintenance group. The certolizumab pegol maintenance group had 63 and 48% of patients who were in clinical response and clinical remission, respectively, at week 26, while the placebo maintenance group had 36 and 29% of patients in clinical response and clinical remission, respectively.

Among IBD indications, Certolizumab pegol is indicated for reducing signs and symptoms of CD and maintaining clinical response in adult patients with moderately to severely active disease who have had an inadequate response to conventional therapy (Cimzia®, US prescribing information 2016).

Golimumab

An overview of golimumab, an anti-TNFα human mAb, has been provided earlier in this chapter (Simponi®, US prescribing information, 2017a; Simponi Aria®, US prescribing information 2017). In addition to its use for the treatment of RA, PsA and AS, the efficacy and safety of golimumab have been assessed in adult patients with moderately to severely active UC.

In a randomized, double-blind, controlled Phase III study in patients with active UC (Mayo score of 6–12), treatment with subcutaneous golimumab at the recommended induction dose regimen (200 mg at week 0, followed by 100 mg at week 2) resulted in 51 and 18% of patients achieving clinical response (defined as a decrease from baseline in the Mayo score of ≥30% and ≥ 3 points, accompanied by a decrease in the rectal bleeding subscore of ≥1 or a rectal bleeding subscore of 0 or 1) and clinical remission (defined as defined as a Mayo score ≤ 2 points, with no individual subscore >1; improvement of endoscopic appearance of the mucosa was defined as a Mayo endoscopy subscore of 0 [normal or inactive disease] or 1 [erythema, decreased vascular pattern, mild friability]), respectively, at week 6, while the control group (placebo) had 30 and 6% of patients with clinical response and clinical remission, respectively. Among clinical responders at week 6, further maintenance treatment with 100 mg subcutaneous golimumab every 4 weeks demonstrated greater efficacy than the placebo maintenance group. The golimumab maintenance group had 50 and 28% of patients who were in clinical response at week 54 and clinical remission at both week 30 and week 54, respectively, while the placebo maintenance group had 31 and 16% of patients in clinical response and clinical remission, respectively.

Among IBD indications, golimumab is indicated for adult patients with moderately to severely active UC with an inadequate response or intolerant to prior treatment or requiring continuous steroid therapy who have had an inadequate response to conventional therapy, 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 (Simponi®, US prescribing information 2017a).

Infliximab

An overview of infliximab, an anti-TNFα chimeric mAb, has been provided earlier in this chapter (Remicade®, US prescribing information 2017). In addition to its use for the treatment of arthritides and psoriasis, the efficacy and safety of infliximab have also been assessed in adult and pediatric patients with moderately to severely active CD or UC.

In a randomized, double-blind, controlled Phase III study in patients with moderately to severely active CD (CDAI ≥220 and ≤ 400), treatment with an initial intravenous dose of 5 mg/kg infliximab at week 0 resulted in 57% of patients achieving clinical response (defined as a decrease in CDAI ≥70) at week 2. All patients who received 5 mg/kg infliximab at week 0 were then randomized to placebo or infliximab maintenance groups (5 or 10 mg/kg at weeks 2 and 6, followed by every 8 weeks). Maintenance treatment with infliximab demonstrated greater efficacy than placebo maintenance treatment. The 5 and 10 mg/kg infliximab maintenance groups had 25 and 34% of patients who were in clinical remission and discontinued corticosteroid use, respectively, at week 54, while the placebo maintenance group had 11% of patients in clinical remission with corticosteroid discontinuation.

In another randomized, double-blind, controlled Phase III study in patients with moderately to severely active UC (Mayo score of 6–12, Endoscopy subscore ≥2), patients were randomized at week 0 to receive either placebo or infliximab at weeks 0, 2, and 6 and every 8 weeks thereafter. At week 8, a greater proportion of patients in the 5 mg/kg infliximab treatment group were in clinical response (defined as a decrease in Mayo score by ≥30% and ≥ 3 points;) and clinical remission (defined as a Mayo score ≤ 2 points with no individual subscore >1) compared to the placebo treatment group (69% vs. 37% for clinical response; 39% vs. 15% for clinical remission). The clinical efficacy was maintained over time. At week 54, the 5 mg/kg infliximab maintenance group had 45 and 35% of patients who were in clinical response and clinical remission, respectively, while the placebo maintenance group had 20 and 17% of patients in clinical response and clinical remission, respectively.

For both CD and UC, maintenance therapy with infliximab every 8 weeks significantly reduced disease-related hospitalizations and surgeries. A reduction in corticosteroid use and improvements in quality of life were observed. In addition, the safety and efficacy of infliximab for pediatric patients 6 years of age or older with CD or UC have also been established.

Among IBD indications, infliximab is indicated for treatment of CD by 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 by reducing the number of draining enterocutaneous and rectovaginal fistulas and maintaining fistula closure in adult patients with fistulizing disease. Infliximab is also indicated for treatment of UC by 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. Additionally, infliximab is indicated for treatment of pediatric patients 6 years of age or older with CD or UC who have had an inadequate response to conventional therapy (Remicade®, US prescribing information 2017).

■ Anti-IL-12/IL-23 Agents

Ustekinumab

An overview of ustekinumab, a human anti-IL-12/IL-23 mAb, has been provided earlier in this chapter (Stelara®, US prescribing information 2017). In addition to its use for the treatment of PsA and psoriasis, the safety and efficacy of ustekinumab, an IL-12/IL-23 inhibitor, in treatment of CD has been recently established (Stelara®, US prescribing information 2017). IL-12 and IL-23 have been implicated as important contributors to the chronic inflammation that is a hallmark of CD and UC.

The efficacy and safety of ustekinumab have been assessed in three randomized, double-blind, placebo-controlled Phase III studies in adult patients with moderately to severely active CD (CDAI ≥220 and ≤ 450). These were two 8-week intravenous induction studies (CD-1 and CD-2) followed by a 44-week subcutaneous randomized withdrawal maintenance study (CD-3) representing 52 weeks of therapy. In both induction studies (CD-1 and CD-2), patients were randomized to receive a single intravenous administration of ustekinumab at either approximately 6 mg/kg (recommended induction dose), placebo, or 130 mg (a lower dose than recommended). Patients who had failed or were intolerant to prior treatment with a TNF blocker were enrolled for Study CD-1, while patients who had never received a TNF blocker or previously received but had not failed a TNF blocker were enrolled for Study CD-2. Concomitant stable dosages of aminosalicylates, corticosteroids, and immunomodulators were allowed in both studies. In Study CD-1, the ustekinumab group had 34 and 21% of patients who were in clinical response (defined as reduction in CDAI score by at least 100 points) at week 6 and clinical remission (defined as CDAI score < 150) at week 8, respectively, while the placebo group had 21 and 7% of patients in clinical response at week 6 and clinical remission at week 8, respectively. In Study CD-2, the ustekinumab group had 56 and 40% of patients who were in clinical response at week 6 and clinical remission at week 8, respectively, while the placebo group had 29 and 20% of patients in clinical response at week 6 and clinical remission at week 8, respectively. The maintenance study (CD-3) evaluated patients who achieved clinical response at week 8 of induction in studies CD-1 or CD-2. At week 44 of the maintenance treatment (i.e., week 52 from the initiation of induction therapy), 47% of patients received 90 mg subcutaneous ustekinumab every 8 weeks maintenance treatment demonstrated corticosteroid-free and in clinical remission, compared to 30% of patients in the placebo group.

Among IBD indications, ustekinumab is indicated for treatment of adult patients with moderately to severely active CD who have failed or were intolerant to treatment with immunomodulators or corticosteroids, but never failed a TNF blocker or who failed or were intolerant to treatment with one or more TNF blockers (Stelara®, US prescribing information 2017).

■ Anti-integrin Agent

Natalizumab and vedolizumab are both anti-integrin agents approved for treatment of CD (vedolizumab is also indicated for the treatment of UC). Natalizumab has a more restricted use with a requirement for patient registration due to its potential risk of PML. It has been hypothesized that preventing α4β1/α4β7 integrin binding to vascular cell adhesion molecule-1 (VCAM-1) may result in decreased immune surveillance within the central nervous system (CNS), in turn increasing the risk of developing PML. Unlike natalizumab, vedolizumab specifically targets α4β7 and does not inhibit binding at VCAM-1 (Soler et al. 2009). Overall, vedolizumab seems to be safe with respect to the risk of PML but continuous and careful monitoring of patients is needed to explore its full safety profile.

Natalizumab

Natalizumab (Tysabri®) is a recombinant humanized IgG4κ mAb that is produced in murine myeloma cells. Natalizumab binds to the α4-subunit of α4β1 and α4β7 integrins expressed on the surface of all leukocytes, and inhibits the α4-mediated adhesion of leukocytes to their counter-receptor(s). Disruption of these molecular interactions prevents transmigration of leukocytes across the endothelium into inflamed parenchymal tissue (Tysabri®, US prescribing information 2017).

The efficacy and safety of natalizumab have been assessed in adult patients with moderately to severely active CD (CDAI ≥220 and ≤450). In a randomized, double-blind, controlled Phase III study in patients with active CD, treatment with intravenous natalizumab at the recommended induction dose regimen (300 mg every 4 weeks) resulted in 56% of patients achieving clinical response (defined as a decrease in CDAI ≥70 from baseline) at week 10, while the control group (placebo) had 49% of patients achieving clinical response ($p = 0.067$). Among clinical responders at both weeks 10 and 12, maintenance treatment with 300 mg natalizumab every 4 weeks demonstrated greater efficacy than that observed in the placebo maintenance

group. The natalizumab maintenance group had 54 and 40% of patients who were in clinical response and clinical remission (defined as CDAI score < 150) at month 15, respectively, while the placebo maintenance group had 20 and 15% of patients in clinical response and clinical remission, respectively.

Natalizumab was first approved in November 2004 and was suspended soon after (February 2005) because of the occurrence of three cases of PML, an opportunistic viral infection of the brain that usually leads to death or severe disability. Two of the three PML cases were reported in multiple sclerosis patients (another indication of natalizumab) and one in a patient with CD. In June 2006, the US FDA and European Medicine Agency (EMA) granted approval for the reintroduction of natalizumab under a specific risk management plan designed to redefine the safety profile of natalizumab (with Black-Box Warning in label) (Gold et al. 2007).

Among IBD indications, natalizumab is indicated for the induction and maintenance of clinical response and remission in adult patients with moderately to severely active CD with evidence of inflammation who have had an inadequate response to, or are unable to tolerate, conventional CD therapies and TNF-α inhibitors. Natalizumab should not be used in combination with immunosuppressants or inhibitors of TNFα in CD (Tysabri®, US prescribing information 2017).

■ Vedolizumab

Vedolizumab (Entyvio®) is a humanized IgG1 mAb produced in Chinese hamster ovary cells. Vedolizumab specifically binds to the α4β7 integrin and blocks the interaction of α4β7 integrin with mucosal addressin cell adhesion molecule-1 (MAdCAM-1) and inhibits the migration of memory T-lymphocytes across the endothelium into inflamed gastrointestinal parenchymal tissue. Vedolizumab does not bind to or inhibit function of the α4β1 and αEβ7 integrins and does not antagonize the interaction of α4 integrins with VCAM-1. The interaction of the α4β7 integrin with MAdCAM-1 has been implicated as an important contributor to the chronic inflammation that is a hallmark of CD and UC. (Entyvio®, US prescribing information 2014).

The efficacy and safety of vedolizumab have been assessed in three randomized, double-blind, placebo-controlled Phase III studies (Trials CD-1, CD-II and CD-III) in adult patients with moderately to severely active CD (CDAI ≥220 and ≤450). Trials CD-I and CD-II both assessed induction regimens. A higher number of patients who had an inadequate response, loss of response, or intolerance to one or more TNF blockers were enrolled in CD-II when compared to CD-II (76% vs. 46%). Concomitant stable dosages of aminosalicylates, corticosteroids, and immunomodulators were allowed in both CD-1 and CD-II. In Study CD-I, a statistically significantly higher proportion of patients treated with vedolizumab at the recommended dose regimen (300 mg intravenous infusion at weeks 0 and 2) achieved clinical remission (defined as CDAI ≤150) as compared to placebo at week 6 (15% vs. 7%, $p = 0.041$). In Study CD-II, among patients who had an inadequate response, loss of response, or intolerance to one or more TNF blockers, no statistical significant difference was shown in the proportion of patients achieving clinical remission between the 300 mg vedolizumab group and the placebo group at week 6 (15% vs. 12%). Study CD-III evaluated the maintenance regimen. Among clinical responders ((≥70 decrease in CDAI score from baseline) at week 6, 39% of patients who received maintenance treatment with 300 mg vedolizumab intravenous infusion every 8 weeks demonstrated clinical remission (defined as the proportion of patients in this subgroup that discontinued corticosteroids by week 52 and were in clinical remission at week 52), compared to 22% of patients in the placebo group.

The efficacy and safety of vedolizumab have also been assessed in two randomized, double-blind, placebo-controlled Phase III studies (Trials UC-1 and UC-II) in adult patients with moderately to severely active UC (Mayo score of 6–12 with endoscopy subscore of 2 or 3). UC-I assessed the induction therapy and UC-II assessed the maintenance therapy. Concomitant stable dosages of aminosalicylates, corticosteroids, and immunomodulators were allowed in both studies. Six-weeks treatment with vedolizumab (300 mg intravenous infusion at week 0 and week 2) compared to placebo resulted in a greater proportion of patients achieved clinical response at week 6 (47% vs. 26%, defined as reduction in complete Mayo score of ≥3 points and ≥30% from baseline with an accompanying decrease in rectal bleeding subscore of ≥1 point or absolute rectal bleeding subscore of ≤1 point), clinical remission at week 6 (17% vs. 5%, defined as complete Mayo score of ≤2 points and no individual subscore >1 point), and improvement of endoscopic appearance of the mucosa at week 6 (41% vs. 25%, defined as Mayo endoscopy subscore of 0 [normal or inactive disease] or 1 [erythema, decreased vascular pattern, mild friability]). Among clinical responders at week 6, 42% of patients who received maintenance treatment with 300 mg vedolizumab intravenous infusion every 8 weeks demonstrated clinical remission at week 52, compared to 16% of patients in the placebo group.

Among IBD indications, vedolizumab is indicated for treatment of adult patients with moderately to severely active CD and UC who have had an inadequate response with, lost response to, or were intolerant to a TNF blocker or immunomodulator; or had an

inadequate response with, were intolerant to, or demonstrated dependence on corticosteroids (Entyvio®, US prescribing information 2014).

ASTHMA

Asthma is a complex chronic inflammatory syndrome of the airways and is characterized by variable symptoms of cough, breathlessness, and wheezing. These episodes may be punctuated by periods of more severe and sustained deterioration in control of symptoms, termed exacerbations, which can result in potentially life-threatening bronchospasm. Asthma affects almost 20 million individuals in the USA, six million of which are children. Pharmacotherapeutic management of the disease has progressed but is suboptimal for a subset of moderately to severely affected patients. Treatment with inhaled corticosteroids and short- and long-acting β-adrenoceptor agonists is considered the standard of care and is generally effective at attenuating symptoms, particularly in mild to moderate asthma; however, these therapeutic modalities do not necessarily address the underlying pathology of the disease. A subset of patients with moderate to severe asthma remain symptomatic despite treatment with corticosteroids, suggesting persistent inflammation of the airways.

The limitations of existing asthma therapies justify continued research into novel interventions, particularly those that modify disease processes. To that aim, a number of therapeutic proteins targeting cytokines linked to the underlying pathology of the disease have been developed, and four biologic agents have been approved for use in asthma, including omalizumab (Xolair®), a humanized mAb against IgE; mepolizumab (Nucala®) and reslizumab (Cinqair®), two humanized mAbs against IL-5; and benralizumab (Fasenra®), a humanized mAb against IL-5 receptor.

■ Anti-IgE Agent

Omalizumab

Omalizumab (Xolair®) is a recombinant human IgG1κ mAb that selectively binds IgE and inhibits the binding of IgE to the high-affinity IgE receptor (FcεRI) on the surface of mast cells and basophils. IgE plays a central role in increasing allergen uptake by dendritic cells, activated mast cells, and basophils. Reduction in surface-bound IgE on FcεRI-bearing cells limits the degree of the allergic response. Omalizumab also reduces the number of FcεRI receptors on basophils in atopic patients. Omalizumab is a first-in-class selective IgE inhibitor approved for use by patients with allergic asthma inadequately controlled by inhaled corticosteroids (Xolair®, US prescribing information 2016).

The safety and efficacy of omalizumab in treatment of asthma have been evaluated in in three randomized, double-blind, placebo-controlled, multicenter trials in patients 12–76 years old, with moderate to severe persistent asthma for at least 1 year, and a positive skin test reaction to a perennial. Omalizumab dosing was based on body weight and baseline serum total IgE concentration. All patients were required to have a baseline IgE between 30 and 700 IU/mL and body weight not more than 150 kg. Patients were treated according to a dosing table to administer at least 0.016 mg/kg/IU (IgE/mL) of omalizumab or a matching volume of placebo over each 4-week period. The maximum omalizumab dose per 4 weeks was 750 mg. Two of the Phase III trials (Trials 1 and 2) were conducted in patients with concomitant controller medications of inhaled corticosteroids (ICS) and short acting β2-agonists. Both trials included a run-in period followed by randomization to omalizumab or placebo. Patients received omalizumab for 16 weeks with an unchanged corticosteroid dose unless an acute exacerbation necessitated an increase. Patients then entered a 12-weeks ICS reduction phase during which ICS dose reduction was attempted in a step-wise manner. Omalizumab efficacy was based primarily on the reduction of asthma exacerbations, which were defined as a worsening of asthma that required treatment with systemic corticosteroids or a doubling of baseline-inhaled corticosteroid dose. In Trial 1 and Trial 2, the number of exacerbations per patient was reduced in patients treated with omalizumab compared with placebo in both the 12-weeks steroid free period (asthma exacerbation frequencies of 0, 1 and ≥2 per patient in 86–87%, 11–12% and 1–2% of patients receiving omalizumab, and in 70–77%, 17–25% and 5–7% of patients receiving placebo) and the 16-week steroid reduction period (asthma exacerbation frequencies of 0, 1 and ≥2 per patient in 79–84%, 14–19% and 1–2% of patients receiving omalizumab, and in 68–70%, 26–28%, 3–4% of patients receiving placebo). Trial 3 had a similar design to that of Trials 1 and 2, but long-acting β2-agonists were allowed. In Trial 3, the number of exacerbations in patients treated with omalizumab was similar to that in placebo-treated patients. The absence of an observed treatment effect in Trial 3 may be related to differences in the patient population compared with Asthma Trials 1 and 2, study sample size (lower in Trial 3), or other factors.

The safety and efficacy of omalizumab in treatment of asthma have also been evaluated in children 6 to <12 years of age with moderate to severe asthma who had a positive skin test or *in vitro* reactivity to a perennial aeroallergen. Omalizumab-treated children had a statistically significant reduction in the rate of asthma exacerbations versus the placebo group.

An anaphylaxis Black-Box warning was placed on the omalizumab (Xolair®) label based on clinical evi-

dence. Anaphylaxis has been reported to occur after administration of omalizumab in pre-marketing clinical trials and in post-marketing spontaneous reports. In pre-marketing clinical trials in patients with asthma, anaphylaxis was reported in 3 of 3507 (0.1%) patients. In post-marketing spontaneous reports, the frequency of anaphylaxis attributed to omalizumab use was at least 0.2% of patients based on an estimated exposure of about 57,300 patients from June 2003 through December 2006. Anaphylaxis has occurred after the first dose of omalizumab but also has occurred beyond 1 year after beginning treatment. Therefore, omalizumab should be available only in a healthcare setting by healthcare providers prepared to manage anaphylaxis that can be life-threatening (Xolair®, US prescribing information 2016).

Omalizumab is indicated for moderate to severe persistent asthma in patients 6 years of age and older with a positive skin test or *in vitro* reactivity to a perennial aeroallergen and symptoms that are inadequately controlled with inhaled corticosteroids. (Xolair®, US prescribing information 2016).

■ Anti-IL-5 Agents

Two anti-IL-5 biologic agents have been approved for asthma, mepolizumab (Nucala®) and reslizumab (Cinqair®). Mepolizumab is a humanized Ig1κ mAb while reslizumab is a humanized IgG4κ mAb. IL-5 is the major cytokine responsible for the growth and differentiation, recruitment, activation, and survival of eosinophils. Mepolizumab or reslizumab binds to IL-5, inhibiting the bioactivity of IL-5 by blocking its binding to the α chain of the IL-5 receptor complex expressed on the eosinophil cell surface. Mepolizumab or reslizumab, by inhibiting IL-5 signaling, reduces the production and survival of eosinophils; however, their mechanism of action in asthma has not been definitively established (Nucala®, US prescribing information 2017; Cinqair®, US prescribing information 2016).

Mepolizumab

Mepolizumab (Nucala®) is a humanized IgG1κ mAb against IL-5, which is produced by recombinant DNA technology in Chinese hamster ovary cells (Nucala®, US prescribing information 2017).

The safety and efficacy of mepolizumab as add-on treatment of severe asthma have been evaluated in patients aged 12 years and older who had asthma despite regular use of high-dose inhaled corticosteroid (ICS) plus additional controller(s), or use of daily oral corticosteroids (OCS) in addition to regular use of high-dose ICS plus additional controller(s). These patients had markers of eosinophilic airway inflammation and continued their background asthma therapy throughout the duration of the trials. In a 32-week double-blind, randomized, placebo- controlled Phase III trial, patients receiving add-on mepolizumab treatment at the recommended dose regimen (100 mg administrated subcutaneously every 4 weeks) in combination with background therapy, compared with placebo (plus background therapy), experienced significantly fewer (52% reduction) exacerbations (defined as worsening of asthma requiring use of oral/systemic corticosteroids and/or hospitalization and/or emergency department visits). Additionally, compared with placebo (plus background therapy), there were fewer exacerbations requiring hospitalization and/or emergency department visits and exacerbations requiring only in-patient hospitalization with mepolizumab add-on treatment. In a 24-week OCS-reduction trial, effect of mepolizumab on reducing the use of maintenance OCS was evaluated. Compared with placebo (plus background therapy), add-on mepolizumab at the recommended dose regimen for 24 weeks resulted in greater reductions in daily maintenance OCS dose, while maintaining asthma control. Twenty-three per cent (23%) patients in the add-on mepolizumab treatment group versus 11% in the placebo group (plus background therapy) had a 90–100% reduction in their OCS dose. Thirty-six per cent (36%) patients in the add-on mepolizumab group versus 56% in the placebo group (plus background therapy) were classified as having no improvement for OCS dose (i.e., no change or any increase or lack of asthma control or withdrawal of treatment). Additionally, 54% of patients receiving add-on mepolizumab treatment achieved at least half reduction in the daily prednisone dose compared with 33% of subjects who received placebo (plus background therapy).

In the Phase III trials for asthma, total 28 adolescents aged 12–17 years with severe asthma were enrolled. These adolescent patients showed a reduction in the rate of exacerbations that trended in favor of mepolizumab. The adverse event profiles in adolescents was generally comparable to the overall population in the Phase III studies.

Mepolizumab is indicated for add-on maintenance treatment of patients with severe asthma aged 12 years and older, and with an eosinophilic phenotype.

Reslizumab

Reslizumab (Cinqair®) is a humanized IL-5 antagonist IgG4κ mAb produced by recombinant DNA technology in murine myeloma non-secreting 0 (NS0) cells (Cinqair®, US prescribing information 2016).

The safety and efficacy of reslizumab as add-on treatment of asthma have been evaluated in adult and adolescent patients aged 12 years and older who had at

least one asthma exacerbation requiring systemic corticosteroid use over the past 12 months. Most patients had markers of eosinophilic airway inflammation and all patients continued their background asthma therapy throughout the duration of the trials. While patients aged 12–17 years were included in these trials, reslizumab is not approved for use in this age group. The safety and effectiveness of reslizumab in pediatric patients (aged 17 years and younger) have not been established.

In two 52-week double-blind, randomized, placebo-controlled Phase III trials, patients receiving add-on reslizumab treatment at the recommended dose regimen (3 mg/kg administrated intravenously every 4 weeks), compared with placebo (with background therapy), had significantly reduction (50–59% reduction) in the rate of all asthma exacerbations (defined as worsening of asthma requiring use of systemic corticosteroids or twofold increase in the use of ICS for 3 or more days, and/or asthma-related emergency treatment including visit to their healthcare professional for nebulizer treatment or other urgent treatment to prevent worsening of asthma symptoms, or a visit to the emergency room or hospitalization). Exacerbations requiring the use of a systemic corticosteroid such as OCS as well as exacerbations resulting in hospitalization or an emergency room visit were also reduced with add-on reslizumab treatment. In two other 16-week double-blind, randomized, placebo-controlled Phase III trials, add-on reslizumab treatment at the recommended dose regimen resulted in improvements in lung function (as assessed by FEV1 [forced expiratory volume in 1 s]) 4 weeks following the first dose of reslizumab and maintained through week 52.

An anaphylaxis Black-Box warning was placed on the reslizumab (Cinqair®, US prescribing information 2016) label. Anaphylaxis occurred with reslizumab infusion in 0.3% of patients in placebo-controlled Phase III studies. Patients should be observed for an appropriate period of time after reslizumab infusion; healthcare professionals should be prepared to manage anaphylaxis that can be life-threatening.

Reslizumab is indicated for add-on maintenance treatment of patients with severe asthma aged 18 years and older, and with an eosinophilic phenotype. (Cinqair®, US prescribing information 2016).

■ Anti-IL-5 Receptor Agent

In addition to directly neutralizing the IL-5 cytokine, blockage of IL-5 receptor has also been explored as an alternative mechanism of action to target the IL-5 pathway for the treatment of asthma, such as benralizumab.

Benralizumab

Benralizumab (Fasenra®) is a humanized afucosylated IL-5 receptor antagonist IgG1κ mAb produced by recombinant DNA technology in Chinese hamster ovary cells. The IL-5 receptor is expressed on the surface of eosinophils and basophils, Inflammation is an important component in the pathogenesis of asthma. Multiple cell types (e.g., mast cells, eosinophils, neutrophils, macrophages, lymphocytes) and mediators (e.g., histamine, eicosanoids, leukotrienes, cytokines) are involved in inflammation. Benralizumab, by binding to the α chain of IL-5 receptor, reduces eosinophils through antibody-dependent cell-mediated cytotoxicity (ADCC); however, its mechanism of action in asthma has not been definitively established (Fasenra®, US prescribing information 2017).

The safety and efficacy of benralizumab have been evaluated in patients aged 12 years and older who had at least two asthma exacerbation requiring systemic corticosteroid use over the past 12 months. Most patients had markers of eosinophilic airway inflammation and all patients continued their background asthma therapy throughout the duration of the trials. In a 48-week double-blind, randomized, placebo-controlled Phase III trial, patients receiving add-on benralizumab treatment at the recommended dose regimen (30 mg administrated subcutaneously at weeks 0, 4 and 8, followed by every 8 weeks), compared with placebo (plus background therapy of high dose ICS), had significant reduction (35% vs. 51%) in the rate of all asthma exacerbations (defined as a worsening of asthma requiring use of oral/systemic corticosteroids for at least 3 days, and/or emergency department visits requiring use of oral/systemic corticosteroids and/or hospitalization). Exacerbations requiring hospitalization or an emergency room visit and exacerbations requiring hospitalization were also reduced with add-on benralizumab treatment. Compared to placebo (plus background therapy), add-on benralizumab treatment at the recommended dose regimen also provided consistent improvements over time in the mean change from baseline in lung function, s assessed by FEV1.

Benralizumab is indicated for add-on maintenance treatment of patients with severe asthma aged 12 years and older, and with an eosinophilic phenotype. (Fasenra®, US prescribing information 2017).

ATOPIC DERMATITIS

Atopic dermatitis (AD) is a common chronic pruritic inflammatory skin disease with the prevalence rates worldwide up to 2–5% for adults and up to 10–20% for children. It is the most common form of eczema and is characterized by rashes on the skin that can include

symptoms such as intense, persistent itching and skin dryness, cracking, redness, crusting, and oozing. The pathogenesis of AD is multifactorial and is not completely understood. The abnormalities in the skin of AD patients include an activation of the immune system (especially the type 2 T helper [Th2]-pathway) without an adequate stimulus, epithelial barrier dysfunction (often associated with a mutation of filaggrin gene), and an imbalance in the skin microbiota composition. Treatment of patients suffering from mild or moderate AD includes the use of emollients and topical glucocorticoids or topical calcineurin inhibitors. Patients with chronic and severe AD where topical therapy is usually insufficient require the use of systemic immunosuppressive drugs, which is often limited due to toxicity and severe adverse effects. There is an immense unmet need for new therapy concepts for moderate to severe AD, which impacts the quality of life of patients and has become a global health problem.

With a better understanding of the pathophysiology of the disease, multiple new therapeutic proteins have been developed for the treatment of AD (Boguniewicz 2017). These biologic agents exhibit several novel mechanisms of action including anti-IL-31 (nemolizumab) (Ruzicka et al. 2017), anti-IL-12/IL-23 (ustekinumab) (Saeki et al. 2017; Khattri et al. 2017), anti-IL-4 receptor α (dupilumab) (Kraft and Worm 2017), and anti-IL-13 (tralokinumab [NCT02347176, NCT03160885, ClinicalTrials.gov, accessed 22Jan2018] and lebrikizumab [NCT02340234, NCT02465606, ClinicalTrials.gov, accessed 22Jan2018]). One of these agents, dupilumab (Dupixent®) was recently approved by the FDA and EMA for the treatment of adults with inadequately controlled moderate to severe AD. Dupilumab is the first biologic medicine approved for AD.

■ Dupilumab

Dupilumab (Dupixent®) is a human mAb of the IgG4 subclass, which is produced by recombinant DNA technology in Chinese Hamster Ovary cell suspension culture. Dupilumab inhibits IL-4 and IL-13 signaling by specifically binding to the IL-4 receptor α (IL-4Rα) subunit shared by the IL-4 and IL-13 receptor complexes. Blocking IL-4Rα with dupilumab inhibits IL-4 and IL-13 cytokine-induced responses, including the release of proinflammatory cytokines, chemokines and IgE (Dupixent®, US prescribing information 2017).

The efficacy and safety of dupilumab have been evaluated in three randomized, double-blind, controlled Phase III trials in adult patients with moderate to severe AD who were not adequately controlled by topical medication(s). Disease severity was defined by an Investigator's Global Assessment (IGA) score ≥ 3 in the overall assessment of AD lesions on a severity scale of 0–4, and an Eczema Area and Severity Index (EASI) score ≥ 16 on a scale of 0–72. In the two dupilumab monotherapy Phase III trials, 12-week treatment with subcutaneous dupilumab at the recommended dose regimen (600 mg initially followed by 300 mg every 2 weeks) resulted in 36–38% and 44–51% of AD patients achieving IGA 0/1 (IGA 'clear' or 'almost clear' with a reduction of ≥2 points on a 0–4 IGA scale) and EASI 75 (improvement of at least 75% in EASI score from baseline) responses, respectively, while the control group had only 9–10% and 12–15% of patients with IGA 0/1 and EASI 75 responses, respectively. Clinical efficacy was also shown in the concomitant Phase III trial, where 12-week treatment with dupilumab at the recommended subcutaneous dose regimen (600 mg initially followed by 300 mg every 2 weeks) in combination with topical corticosteroids resulted in 39 and 69% of AD patients achieving IGA 0/1 and EASI 75 responses, respectively, while the control group (placebo plus topical corticosteroids) had only 12 and 23% of patients with IGA 0/1 and EASI 75 responses, respectively.

Dupilumab is indicated for the treatment of adult patients with moderate-to-severe atopic dermatitis (AD) whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. Dupilumab can be used with or without topical corticosteroids (Dupixent®, US prescribing information 2017).

CHRONIC IDIOPATHIC URTICARIA

Chronic idiopathic urticaria (CIU) is a common autoimmune skin condition characterized by spontaneously recurring hives, occurring either intermittently or continuously for 6 weeks or longer (Vestergaard and Deleuran 2015). A significant association of CIU is a deeper localized swelling called angioedema, which is observed in about one-third of patients. This leads to remarkable psychosocial morbidity with a negative impact on overall quality of life. CIU occurs largely in young women between 20 and 40 years of age. The exact prevalence of CIU is difficult to determine. A recently published article indicated a point prevalence of at least 0.5% in the general population for CIU (Maurer et al. 2011). Conventional treatment for CIU prescribes a stepwise approach with non-sedating non-impairing antihistamines as first-line agents followed by increasing to four times the licensed doses as second-line treatment. However, close to half of CIU patients do not achieve adequate symptom relief with antihistamines alone. Third-line treatments include cyclosporine, which is associated with toxicity and requires frequent monitoring.

An autoimmune mechanism is thought to mediate the disease process in up to 50% of patients with CIU. Autoantibody to the α chain of the high affinity IgE receptor and/or intrinsic IgE immune modulation may play an important role. Toward this, omalizumab, a humanized anti-IgE antibody, is developed as an alternative treatment option for patients with CIU. Omalizumab (Xolair®) is the first and only biologic agent currently approved for the treatment of CIU. Rituximab, a humanized anti-CD-20 mAb, has been reported in a few cases to be effective in the treatment of CIU; whereas other case did not show any effect (Mallipeddi and Grattan 2007). Antibodies against TNFα have also been used in the treatment of CIU but with variable success and only in small numbers of patients (Cooke et al. 2015).

■ Omalizumab

An overview of omalizumab, a humanized anti-IgE mAb, has been provided earlier in this chapter (Xolair®, US prescribing information 2016). In addition to asthma, the efficacy and safety of omalizumab have been evaluated in patients with CIU. The mechanism of action has been described earlier as an antibody targeting IgE; however, the specific mechanism by which omalizumab results in an improvement of CIU symptoms has not been fully defined.

Two randomized, placebo-controlled, multiple-dose clinical trials have been conducted for omalizumab in adult and adolescent patients 12 years of age and older with CIU. Disease severity was measured by a weekly urticaria activity score (UAS7, range 0–42), which is a composite of the weekly itch severity score (range 0–21) and the weekly hive count score (range 0–21). In both trials, patients who received subcutaneous omalizumab 150 mg or 300 mg every 4 weeks in addition to their baseline antihistamine therapy had greater decreases from baseline in itch severity scores and hive count scores than patients receiving placebo (plus background therapy) at week 12. In one trial, the change from baseline to week 12 were −3.63, −6.66, −9.40 for placebo, omalizumab 150 mg and 300 mg, respectively, in itch severity score, and were −4.37, −7.78, −11.35 for placebo, omalizumab 150 mg and 300 mg, respectively, in hive count score. Similar results were shown in the other trial.

In addition to asthma, omalizumab is also indicated for chronic idiopathic urticaria in adults and adolescents 12 years of age and older who remain symptomatic despite antihistamine treatment. (Xolair®, US prescribing information 2016).

CRYOPYRIN-ASSOCIATED PERIODIC SYNDROMES

Cryopyrin-associated periodic syndrome (CAPS) comprises three genetic autoinflammatory disorders including familial cold autoinflammatory syndrome (FCAS), Muckle-Wells syndrome (MWS), and neonatal-onset, multisystem, inflammatory disorder (NOMID) (Kubota and Koike 2010). These three phenotypically distinct disorders are recognized as a clinical continuum of the same disease in an increasing order of severity since all three disorders are associated with mutations in the NACHT, LRR and PYD domains-containing protein 3 (NLRP3) gene that encodes the cryopyrin protein. NLRP3 mutations result in overactivation of caspase-1, the enzyme that cleaves precursors of IL-1β, IL-18, and IL-33 into active cytokine forms. CAPS is rare with a prevalence of one in about one million people, however many cases of this disease are believed to be undiagnosed.

Therapeutic treatments of CAPS include nonsteroidal anti-inflammatory drugs, colchicine, immunosuppressants, corticosteroids, and the recent addition of anti-IL-1β biologic therapy (Kubota and Koike 2010). Anti-IL-1β therapy is very effective for the treatment of CAPS since it exerts pharmacologic action directly against the underlying cause of the disease. Clinical evidence suggests that use of anti-IL-1β agents can achieve rapid and complete control of both clinical manifestations and laboratory parameters.

■ Anti-IL-1β Agents

Currently, there are two long-acting anti-IL-1β therapeutic proteins (canakinumab [Ilaris®] and rilonacept [Arcalyst®]) that have been approved for the treatment of CAPS, although a short-acting IL-1 receptor antagonist, anakinra, is also effective for this disease (Hawkins and Lachmann 2003). Excessive production of IL-1β is the central pathophysiology of CAPS. Both canakinumab and rilonacept were generally well tolerated in the Phase III trials with infections being a commonly reported adverse event due to the immunosuppressant effect of anti-IL-1β therapy.

Canakinumab

An overview of canakinumab, a human anti-IL-1β mAb, has been provided earlier in this chapter (Ilaris®, US prescribing information 2016). In addition to the use of this therapeutic protein for the treatment of sJIA, canakinumab has also been evaluated in patients with CAPS. Canakinumab binds to human IL-1β and neutralizes its activity.

The efficacy and safety of canakinumab for the treatment of CAPS has been assessed in a double-blind, placebo-controlled, randomized withdrawal trial in in

patients 9–74 years of age with the MWS phenotype of CAPS. This study consisted of three parts. Part 1 was an 8-week open-label, single-dose period where all patients received canakinumab. Patients who achieved a complete clinical response and did not relapse by week 8 were randomized to receive either placebo or canakinumab every 8 weeks for 24 weeks in Part 2 of the study. Patients who completed Part 2 or experienced a disease flare entered Part 3, a 16-week open-label active treatment phase. Throughout the trial, patients weighing more than 40 kg received subcutaneous canakinumab 150 mg and patients weighing 15–40 kg received canakinumab 2 mg/kg. In Part 1, a complete clinical response was observed in 71% of patients 1 week following initiation of treatment and in 97% of patients by week 8. In the randomized withdrawal period, a total of 81% of the patients randomized to placebo flared compared to none (0%) of the patients randomized to canakinumab treatment. In a second trial, patients 4–74 years of age with both MWS and FCAS phenotypes of CAPS were treated in an open-label manner. Treatment with canakinumab resulted in clinically significant improvement of signs and symptoms in majority of patients within 1 week.

Among inflammatory diseases, in addition to sJIA, canakinumab is also indicated for the treatment of CAPS, including FCAS and MWS, in adults and children 4 years of age and older (Ilaris®, US prescribing information 2016).

Rilonacept

Rilonacept (Arcalyst®) is a dimeric fusion protein consisting of the ligand-binding domains of the extracellular portions of the human IL-1 receptor component (IL-1RI) and IL-1 receptor accessory protein (IL-1RAcP) linked in-line to the Fc portion of human IgG1. Rilonacept blocks IL-1β signaling by acting as a soluble decoy receptor that binds IL-1β and prevents its interaction with cell surface receptors. Rilonacept also binds IL-1α and IL-1 receptor antagonist (IL-1RA) with reduced affinity (Arcalyst®, US prescribing information 2016).

The safety and efficacy of rilonacept for the treatment of CAPS have been assessed in a randomized, double-blind, placebo-controlled Phase III trial in patients with FCAS and MWS phenotypes of CAPS. After 6 weeks of treatment, a higher proportion of adult patients in the rilonacept group at the recommended subcutaneous dose regimen (320 mg initially followed by 160 mg every week onward) experienced improvement from baseline in a composite CAPS disease score by at least 30% (96% vs. 29% of patients), by at least 50% (87% vs. 8%), and by at least 75% (70% vs. 0%) compared to the placebo group. Six pediatric patients (12–17 years of age) were enrolled directly into the open-label extension phase of this study and improvements in symptoms were shown in these patients following rilonacept treatment.

Taking rilonacept with TNF inhibitors is not recommended because this may increase the risk of serious infections. An increased incidence of serious infections has been associated with administration of an IL-1 blocker in combination with TNF inhibitors. IL-1 blockade may interfere with the immune response to infections. Serious, life-threatening infections have been reported in patients taking rilonacept. In an open-label extension study, one patient developed bacterial meningitis and died (Arcalyst®, US prescribing information 2016).

Rilonacept is indicated for the treatment of CAPS, including FCAS and MWS, in adults and children 12 years of age and older (Arcalyst®, US prescribing information 2016).

CAR-T CELL-INDUCED CYTOKINE RELEASE SYNDROME

T lymphocytes can be genetically modified to target tumors through the expression of a chimeric antigen receptor (CAR). Most notably, CAR T cells have demonstrated clinical efficacy in hematologic malignancies with more modest responses when targeting solid tumors. However, CAR T cells also have the capacity to elicit expected and unexpected toxicities, including neurologic toxicity, "on target/off tumor" recognition, anaphylaxis, and the life-threating cytokine release syndrome (CRS) (Bonifant et al. 2016).

■ Tocilizumab

An overview of tocilizumab, a human anti-IL-6 receptor mAb, has been provided earlier in this chapter (Actemra®, US prescribing information 2017). In addition to use of this therapeutic protein for the treatment of RA, pJIA and sJIA (and giant-cell arteritis as described later in this chapter), tocilizumab is also indicated for treatment of CAR T cell-induced severe or life-threatening CRS in adults and pediatric patients 2 years of age and older (Actemra®, US prescribing information 2017).

The efficacy of tocilizumab for the treatment of CRS have been assessed in a retrospective analysis of pooled outcome data from clinical trials of CAR T-cell therapies for hematological malignancies. Evaluable patients had been treated with intravenous tocilizumab 8 mg/kg (12 mg/kg for patients <30 kg) with or without additional high-dose corticosteroids for severe or life-threatening CRS; only the first episode of CRS was included in the analysis. The study population included 24 male and 21 female subjects of median age 12 years

(range, 3–23 years). The median time from start of CRS to first dose of tocilizumab was 4 days (range, 0–18 days). Resolution of CRS was defined as lack of fever and off vasopressors for at least 24 h. Patients were considered responders if CRS resolved within 14 days of the first dose of tocilizumab, no more than two doses of tocilizumab were needed, and no drugs other than tocilizumab and corticosteroids were used for treatment. Thirty-one patients (69%) achieved a response. Achievement of resolution of CRS within 14 days was confirmed in a second study using an independent cohort that included 15 subjects (range: 9–75 years old) with CAR T cell-induced CRS.

EOSINOPHILIC GRANULOMATOSIS POLYANGIITIS

Eosinophilic granulomatosis with polyangiitis (EGPA) is a rare disease characterized by disseminated necrotizing vasculitis with extravascular granulomas occurring exclusively among patients with asthma and tissue eosinophilia (Greco et al. 2015). EGPA usually manifests between 7 and 74 years of age, with a mean age at onset of 38–54 years. The estimated incidence is approximately 0.11–2.66 new cases per one million people per year, with an overall prevalence of 10.7–14 per one million adults. Although still considered an idiopathic condition, EGPA is generally considered a Th2-mediated disease. Recent evidence also points to B cells and the humoral response as further contributors to EGPA's pathogenesis. EGPA patients without poor-prognosis factors are usually treated with glucocorticoids alone, whereas those with a worse prognosis are recommended glucocorticoids and immunosuppressants. Recently, biologic agents such as mepolizumab (anti-IL-5 antibody) are considered promising therapeutic alternatives for EGPA.

■ Mepolizumab

An overview of mepolizumab, a humanized anti-IL-5 mAb, has been provided earlier in this chapter (Nucala®, US prescribing information 2017). In addition to the use of this therapeutic protein for the treatment of asthma, mepolizumab has also been evaluated in patients with EGPA. Eosinophils and their mediators are considered to be critical effectors to EGPA. Mepolizumab, by inhibiting IL-5 signaling, reduces the production and survival of eosinophils; however, its mechanism of action in EGPA has not been definitively established (Nucala®, US prescribing information 2017).

In a randomized, placebo-controlled, multicenter study, patients with EGPA received 300 mg mepolizumab or placebo administered subcutaneously once every 4 weeks while continuing their stable OCS therapy. A greater percentage of the patients receiving 300 mg mepolizumab treatment achieved remission versus placebo within the first 24 weeks and remained in remission for the remainder of the 52-week treatment period (19% vs. 1%).

In addition to severe asthma, mepolizumab is indicated for the treatment of adult patients with EGPA (Nucala®, US prescribing information 2017).

GIANT CELL ARTERITIS

Giant-cell arteritis (GCA) is an inflammatory vasculopathy that typically occurs in medium and large arteries with well-developed wall layers and adventitial vasa vasorum (Pradeep and Smith 2018). It is the most common systemic vasculitis in the elderly with an estimated incidence of 27 cases in 100,000 people in those over 50 years old with peak incidence at 70–80 years of age. GCA is a medical emergency which, if left untreated, can result in vision loss. Current standard of care is prompt initiation of glucocorticoid treatment when there is a suspicion of GCA. In most patients with GCA, administration of glucocorticoids can improve signs and symptoms; however, glucocorticoid-related morbidity is a common treatment challenge. When glucocorticoids are tapered, disease flares may occur frequently (an average of one to two episodes per person-year). Recent findings suggested a fundamental failure of T regulatory cell function as a main contributor to GCA's pathogenesis. This represents an opportunity for novel therapeutic medicines as possible glucocorticoid-sparing agents, such as abatacept (a lymphocyte activation inhibitor by targeting CTLA-4) (Langford et al. 2017) and tocilizumab (an IL-6 receptor antagonist). In 2017, tocilizumab (Actemra®) was approved for GCA by US FDA (and EMA). This is the first FDA-approved therapy specific to the disorder.

■ Tocilizumab

An overview of tocilizumab, a human anti-IL-6 receptor mAb, has been provided earlier in this chapter (Actemra®, US prescribing information 2017). In addition to use of this therapeutic protein for the treatment of RA, pJIA, sJIA, and CRS, tocilizumab is also indicative for the treatment of GCA in adult patients (Actemra®, US prescribing information 2017).

In a randomized, double-blind, placebo-controlled Phase III study in patients with active GCA, treatment with subcutaneous tocilizumab 162 mg weekly and 162 mg every other week (in combination with 26 weeks prednisone taper) resulted in 56 and 53% of GCA patients, respectively, achieving sustained remission (defined as absence of GCA signs and symptoms from week 12 through week 52, along with normalization of erythrocyte sedimentation rate [ESR], normalization of C-reactive protein [CRP], and adher-

ence to the prednisone taper regime), while the control groups (placebo with 26- or 52-week prednisone taper) had only 14–18% of patients with sustained remission.

HIDRADENITIS SUPPURATIVA

Hidradenitis suppurativa (HS) is a chronic, inflammatory, recurrent, debilitating skin disease of the hair follicle that usually presents with painful, deep-seated, inflamed lesions in the apocrine gland-bearing areas of the body, most commonly the axillae, inguinal and anogenital regions. The prevalence of HS is approximately 1–4% in general population, with an onset after puberty and before age of 40, peaking in the second and third decades of life. HS has the highest impact on patients' quality of life among the overall dermatological diseases, and is associated with multiple comorbidities, including obesity, metabolic syndrome, inflammatory bowel disease, and spondyloarthropathy. The general approach to HS includes non-medical interventions, topical and systemic medications, and surgery. Until now, surgery remains the first-line therapy for HS patients with extensive disease. However, even with extensive surgical intervention HS often recurs. This led to the recent interest in the use of adjunctive biologic therapy in the management of HS (Shanmugam et al. 2017).

The role of immune system in the pathophysiology of HS is being increasingly recognized and several therapeutic proteins are under investigation. The TNF antagonists of infliximab and adalimumab are considered to be efficacious in the treatment of moderate to severe HS, as demonstrated in case series, retrospective studies and randomized controlled trials (Shanmugam et al. 2017). Some benefits of ustekinumab, an anti-IL12/IL-23 mAb, in HS have been indicated in case reports and a prospective open-label study (Blok et al. 2016). Use of IL-1 receptor antagonist (such as anakinra) in HS had mixed results with some studies showing lack of efficacy, but a recent randomized controlled trial (Tzanetakou et al. 2016) have shown efficacy. IL-17 antagonist therapy is also being investigated in the clinic such as bimekizumab (NCT03248531, ClinicalTrials.gov, accessed 22Jan2018) and secukinumab (NCT02421172, ClinicalTrials.gov, accessed 22Jan2018). Recently, adalimumab (Humira®) was approved by US FDA (and EMA) for the treatment of moderate to severe HS. This is the first biologic medicine approved for HS.

■ Adalimumab

An overview of adalimumab, a human anti-TNFα mAb, has been provided earlier in this chapter (Humira®, US prescribing information 2017). In addition to arthritides, psoriasis, CD and UC (and uveitis as described later in this chapter), adalimumab is also indicated for the treatment of moderate to severe HS in adult patients (Humira®, US prescribing information 2017). Elevated levels of TNFα, an inflammatory cytokine, are seen in blood and skin lesions of patients with HS.

The safety and efficacy of adalimumab for the treatment of HS have been assessed in two randomized, double-blind, placebo-controlled Phase III studies in adult patients with moderate to severe HS with Hurley Stage II or III disease and with at least three abscesses or inflammatory nodules. Hurley staging system is a three-stage classification system developed for assessing extent and severity of HS, with Stage 0 being no active HS and Stages I-III associated with increased severity. All patients used topical antiseptic wash daily in these two studies. Concomitant oral antibiotic use was allowed in Study HS-II but not Study HS-I. Hidradenitis Suppurativa Clinical Response (HiSCR) was used to assess the treatment effect, which was defined as at least a 50% reduction in total abscess and inflammatory nodule count with no increase in abscess count and no increase in draining fistula count relative to baseline. Twelve-week treatment with subcutaneous adalimumab at the recommended dose regimen (160 mg initial dose, 80 mg 2 weeks later, followed by 40 mg weekly dosing thereafter) resulted in 42 and 59% of HS patients achieving HiSCR in Study HS-I and Study HS-II, respectively, while the control group had only 26 and 28% of patients with HiSCR response in Study HS-I and Study HS-II, respectively.

MULTIPLE SCLEROSIS

Multiple sclerosis (MS) is a chronic demyelinating disease of the CNS. The main pathological findings in MS are inflammation, demyelination, and axonal degeneration. Inflammation and demyelination are responsible for the acute symptoms of the disease, and axonal degeneration is the underlining cause of the progressive disability associated with MS. Although the etiology of MS remains undetermined, it is considered to be an autoimmune disorder. Blood autoreactive T and B lymphocytes, once activated against myelin constituents, migrate across the blood–brain barrier and initiate inflammatory and demyelinating processes within the CNS leading to MS lesions. Currently, two therapeutic proteins have been approved for the treatment of MS, including an α4β1/α4β7 integrin antagonist, natalizumab (Tysabri®), and a CD20-directed cytolytic agent, ocrelizumab (Ocrevus®).

■ Anti-integrin Agents

Natalizumab

An overview of natalizumab, a α4β1/α4β7 integrin antagonist, has been provided earlier in this chapter (Tysabri®, US prescribing information 2017). In addition to the use of this therapeutic protein for the treatment of

CD, natalizumab (Tysabri®) was the first mAb developed for the treatment of MS. The mechanism of action has been described earlier as an antibody targeting integrins; however, the specific mechanism(s) by which natalizumab exerts its effects in MS has not been fully defined (Tysabri®, US prescribing information 2017).

The safety and efficacy of natalizumab in treatment of MS have been evaluated in two randomized, double-blind, placebo-controlled, multicenter Phase III studies in patients with relapsing forms of MS who had not received any interferon (IFN)-β or glatiramer acetate (Study MS1) (Polman et al. 2006) or patients who had experienced relapses despite INF-β-1a treatment (Study MS2) (Rudick et al. 2006). In Study MS1, 2-years treatment with intravenous natalizumab monotherapy at the recommended intravenous dose regimen (300 mg every 4 weeks), when compared to the placebo treatment, lowered the proportion of patients with increased disability (17% vs. 29%) and the annualized relapse rate (68% reduction). Natalizumab also suppressed the formation of new gadolinium enhancing lesions and reduced the mean number of active lesions based on MRI assessment. In Study MS2, natalizumab or placebo was evaluated in combination with IFN-β-1a. The clinical and MRI-associated efficacies associated with natalizumab treatment were similar to those observed in Study MS1. However, Study MS2 ended 1 month earlier than planned because of the occurrence of PML in two patients receiving natalizumab plus IFN-β-1a.

PML is a demyelinating infectious disease of the CNS caused by reactivation of the John Cunningham virus (JCV). PML may be fatal or result in severe disability. Risk factors for the development of PML include duration of therapy, prior use of immunosuppressants, and presence of anti-JCV antibodies. These factors should be considered in the context of expected benefit when initiating and continuing treatment with natalizumab (Tysabri®, US prescribing information 2017). As of July 2001, 145 cases of PML have been reported among 88,100 patients treated with natalizumab worldwide in the post-marketing setting (Laffaldano et al. 2011).

In addition to CD, natalizumab is also indicated as monotherapy for the treatment of patients with relapsing forms of multiple sclerosis (MS). It is generally recommended for patients who have had an inadequate response to, or are unable to tolerate, an alternate MS therapy. Because of the risk of PML, in the United States, natalizumab is available only through a restricted program under REMS called the TOUCH® Prescribing Program. Natalizumab must be given as monotherapy, and any prior immunomodulator or immunosuppressive therapy must be discontinued prior to use (Tysabri®, US prescribing information 2017).

■ Anti-CD20 Cytolytic Agent

Ocrelizumab

Ocrelizumab (Ocrevus®) is a humanized CD20-directed cytolytic IgG1 antibody. The precise mechanism by which ocrelizumab exerts its therapeutic effects in MS is unknown, but is presumed to involve binding to CD20, a cell surface antigen present on pre-B and mature B lymphocytes. Following cell surface binding to B lymphocytes, ocrelizumab results in antibody-dependent cellular cytolysis (ADCC) and complement-mediated lysis (Ocrevus®, US prescribing information 2017).

The safety and efficacy of ocrelizumab have been evaluated in patients with relapsing or primary progressive forms of MS. In two double-blind, randomized, active comparator-controlled Phase III trials, treatment of ocrelizumab at the recommended dose regimen (initial treatment of two 300 mg IV infusions administered 2 weeks apart, and subsequent doses administered as a single 600 mg IV infusion every 24 weeks) in patients with relapsing forms of MS resulted in significantly lower annualized relapse rate compared with placebo (46–47% reduction, $p < 0.0001$), as well as the proportion of patients with confirmed disability progression (40% reduction, $p = 0.0006$). In a double-blind, randomized, placebo-controlled Phase III trial, treatment of ocrelizumab at the recommended dose regimen in patients with primary progressive form of MS resulted in significantly lower proportion of patients with confirmed disability progression (24% reduction, $p = 0.0321$).

Ocrelizumab is indicated for the treatment of patients with relapsing or primary progressive forms of MS (Ocrevus®, US prescribing information 2017).

UVEITIS

Uveitis (UV) is a term that describes a heterogeneous collection of diseases including infections, systemic immune-mediated diseases like sarcoidosis, and immune-mediated syndromes confined to the eye like sympathetic ophthalmia. Uveitis is rare with a prevalence of 115.3 cases per 100,000 people; however, it can damage vital eye tissue, leading to permanent vision loss. Most uveitis is anterior in location, which generally permits successful therapy with topical medication alone. Challenge in the treatment of uveitis relates to patients who have inflammation involving the posterior segment, either primarily in the vitreous (intermediate uveitis), the choroid or retina (posterior uveitis), or involving the entire eye (panuveitis). These patients can have refractory uveitis where systemic corticosteroids or other immunosuppressive therapy are required. Weighting of the risk of blindness and the

complications related to these drugs need to be carefully planned (Lin et al. 2014).

Uveitis is considered an immune-mediated disease. A recent literature review suggests that anti-TNFα agents, such as infliximab, adalimumab and golimumab, are reasonably effective for controlling ocular inflammation and sparing patients corticosteroid treatment in non-infectious refractory uveitis (Borrás-Blasco et al. 2015). Adalimumab (Humira®) is currently the first and only FDA-approved non-corticosteroid therapy for uveitis, though other anti-TNFα agents are also being used 'off-label'.

■ Adalimumab

An overview of adalimumab, a human anti-TNFα mAb, has been provided earlier in this chapter (Humira®, US prescribing information 2017). In addition to arthritides, psoriasis, CD, UC and HS, adalimumab is also indicated for the treatment of moderate to severe uveitis (UV) in adult patients (Humira®, US prescribing information 2017).

The safety and efficacy of adalimumab in treatment of uveitis have been assessed in two randomized, double-masked, placebo-controlled Phase III studies (UV I and UV II) in adult patients with non-infectious intermediate, posterior and panuveitis despite corticosteroids therapy. The primary efficacy endpoint was 'time to treatment failure'. Treatment failure was a multi-component outcome defined as the development of new inflammatory chorioretinal and/or inflammatory retinal vascular lesions, an increase in anterior chamber cell grade or vitreous haze grade or a decrease in best corrected visual acuity. Statistically significant reductions in the time to treatment failure were demonstrated in patients treated with subcutaneous adalimumab at the recommended dose regimen (80 mg initial dose followed by 40 mg every 2 weeks) versus patients receiving placebo, with hazard ratio of 0.50 (95% CI: 0.36–0.70) and 0.57 (95% CI: 0.39–0.84) in Study UV I and Study UV II, respectively.

CONCLUSION

The Introduction of more than 20 antibody-based biotherapeutics in the last decades has fundamentally changed the treatment paradigm in immune-mediated inflammatory diseases such as RA, IBD, and psoriasis. Though these "targeted biotherapies" are expensive compared to traditional "small molecular" therapies such as methotrexate, they have provided effective treatment alternatives with highly specific targeted novel mechanisms of action. Some of these biotherapeutics can not only provide relief of symptoms but also offer an opportunity to modify or even reverse the course of these diseases, as has been demonstrated in RA. Notably, despite the remarkable clinical improvement in the treatment of inflammatory diseases using antibody-based biotherapeutics, there is still unmet medical need in achieving 'permanent cure' for these complex multifactorial disorders. Inflammatory diseases such as RA and IBD are not the products of dysfunction in isolated individual entities or linear pathways; they arise from perturbations in complex dynamic networks that shift from patterns representing normal function to others that give rise to disease. Therefore, treatment of the disease is unlikely to be resolved using a one-size-fits-all approach by targeting a single target. It is important to understand how individual biological components interact for a given patient, which could then be used to guide personalization of therapies and the segmentation or stratification of treatment populations. With the further advance in protein engineering technology and better understanding of the etiology and disease progression of immune-mediated inflammatory diseases, equipped with more predictive and diagnostic biomarkers, it is reasonable to anticipate that more effective and safe "targeted biotherapeutics" tailored to the individual patients' needs will be added to the therapeutic armory to successfully treat inflammatory diseases.

SELF-ASSESSMENT QUESTIONS

■ Questions

1. Are targeted biologic therapies for autoimmune diseases only to be used once drugs like corticosteroids and methotrexate have had an adequate trial of use and have failed to control the patient's symptoms?
2. What is the primary clinical concern with the immunogenicity of biologic therapies?
3. What is the most likely explanation for why a patient who receives a dose of omalizumab might have an increase in their total serum IgE level for many weeks after the first dose?
4. Why do some cell subsets in the peripheral blood increase after dosing with natalizumab?
5. If a trial reports an ACR70 of 20% on active drug, what does that mean?
6. What does PASI 75 mean?
7. Given that there are currently five anti-TNFα biotherapeutic agents on the market, how would you compare and contrast them?
8. What are the key differences in the indication for use of rituximab vs. abatacept in RA?
9. What is the mechanism of action for guselkumab in treating plaque psoriasis?

Answers

1. Though the standard of care in diseases like RA is still to start with older DMARDs like methotrexate, the decision of when to start or switch therapies is complex and impacted by individual issues linked to clinical response like tolerance/adherence to a particular therapeutic regimen, severity and course of disease and its progression, and concomitant medications and medical issues. It is likely that the standard of care will continue to change and incorporate earlier use of biologic therapies that can modify the disease course with fewer generalized side effects.
2. If a biologic therapy is highly immunogenic, there is a concern that an increasing number of patients exposed to the drug, particularly upon repeated exposure after a hiatus, because their antidrug antibodies could sometimes neutralize the majority of the drug and they would not likely get the full dose or effect. Though less likely there are also rare examples of antidrug antibodies resulting in an autoimmune or allergic-type reaction.
3. Therapeutic monoclonal antibodies that target soluble molecules like IgE form complexes. Though immune complexes are typically cleared from the blood more quickly than monomeric IgG, soluble target molecules typically have a shorter serum half-life than IgG. So an assay detecting the soluble target (in this case IgE) that can detect target even when it is bound to the drug (which is typically an longer-lived IgG) will show more target present in the serum post-dosing as compared to baseline. This is called a carrier effect. Assuming the drug neutralized the bound target, the test detecting the target can be misleading, because the target, though present, is effectively inactive.
4. Natalizumab is a monoclonal antibody that blocks lymphocyte movement between the blood and tissues ("trafficking"); when this movement is effectively blocked in one direction (from the blood into the tissues), an apparent increase in the peripheral lymphocyte population will be evident on assessment by flow cytometry (or perhaps even on a CBC with differential) post-dosing.
5. An ACR70 of 20% means the 20% of the patients had a 70% improvement in their RA disease.
6. The PASI score stands for Psoriasis Area and Severity Index. This tool allows researchers and dermatologists to put an objective number on what would otherwise be a very subjective idea: how bad is a person's psoriasis. The PASI evaluates the degree of erythema, thickness, and scaling of psoriatic plaques and estimates the extent of involvement of each of these components in four separate body areas (head, trunk, upper, and lower extremities).
   - If in a clinical study a certain proportion of patients experienced a 75% reduction in their PASI scores, it is reported as a percentage of people achieving "PASI 75."
7. Although the five anti-TNFα biologics have broadly similar efficacy and safety profiles in RA, there are significant differences in the five anti-TNFα agents particularly with respect to dosing characteristics and also in the details of the approved indications for use.
   - Infliximab is the first approved anti-TNFα agent given intravenously, has the longest dosing interval, and is the first FDA-approved anti-TNFα agent for IBD indication. All the other anti-TNFα agents are administered by subcutaneous administration. It is a chimeric monoclonal antibody that neutralizes TNF-α and has approvals in the most indications (including rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, adult and pediatric ulcerative colitis, adult and pediatric Crohn's disease, and psoriasis).
   - Etanercept is a dimeric soluble fusion protein and has approvals for use in several indications (rheumatoid arthritis, polyarticular juvenile rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, and psoriasis). It is used as weekly injection.
   - Adalimumab is a human monoclonal antibody that neutralizes TNF-α and has FDA approvals for use in patients with rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, psoriasis, Crohn's disease, Pediatric Crohn's disease, ulcerative colitis, hidradenitis suppurative, and uveitis. It is used at a frequency of every week or every other week.
   - Golimumab is a human monoclonal antibody that neutralizes TNF-α and has FDA approvals for use in patients with rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis, and ulcerative colitis via subcutaneous route of administration. It is used at a frequency of every month. It can also be given via intravenous route of administration with a frequency of every 8 weeks for the treatment of rheumatoid arthritis.
   - Certolizumab pegol is a recombinant, humanized antibody Fab fragment, with specificity for human tumor necrosis factor alpha (TNFα), conjugated to an approximately 40-kDa polyethylene glycol (PEG2MAL40K). It has been approved by FDA for the treatment of rheumatoid arthritis and Crohn's disease.
8. Rituximab in combination with methotrexate is indicated for the treatment of adult patients with moderate to severe rheumatoid arthritis who have had an inadequate response to one or more TNF antagonist therapies. Abatacept is indicated for use as monotherapy or in combination with DMARDS

in patients with moderate to severe active rheumatoid arthritis who have had an inadequate response to DMARDs or TNF antagonists.

9. IL-23 is a naturally occurring cytokine that is involved in inflammatory and immune responses, such as natural killer cell (NK) activation and CD4+ T-cell differentiation and activation. Guselkumab, a human IgG1λ monoclonal antibody that binds with high affinity and specificity to the p19 protein subunit used by IL-23, can prevent human IL-23 from binding to the IL-23 (IL-12Rβ1/23R) receptor complexes on the surface of NK and T cells.

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