FEATURE ARTICLE

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Mechanistic Insights Into Today's (and Tomorrow's) Treatments for Moderate-to-Severe Psoriasis

Melodie S. Young, Kristine J. Kucera

ABSTRACT: Psoriasis is a chronic immune-mediated disease, and several cytokine pathways in the psoriatic cascade have been identified and investigated as clinical targets for systemic therapy. This review provides an overview of psoriasis, including discussion of clinical variants, environmental and genetic risk factors, known comorbidities, treatment strategies, and limitations in evaluating disease severity. The manuscript then focuses on addressing how existing biologics target the various pathways described in the pathogenesis of psoriasis, how modulating these mechanisms can improve outcomes over time, and how new insights have led to the development of agents that can target different pathways associated with the disease. Overall, biologics that target tumor necrosis factor-α or interleukin-12/23 have established themselves as effective, well-tolerated treatment options for chronic plaque psoriasis that can quickly produce dramatic clinical improvement. Unlike topical, phototherapy, and conventional systemic therapies that do not specifically target the underlying pathogenesis of psoriasis, biologics have been, and continue to be, developed based on identifying therapeutic targets within the immune and inflammatory pathways associated with disease development and progression. Recently, interleukin-17A has been identified as a central cytokine driver in the pathogenesis of psoriasis, and biologic therapy targeting this cytokine has recently been approved.

Key words: Biologics, Pathogenesis, Psoriasis, Severity, Treatment

Melodie S. Young, MSN, A/GNP-C, DCNP, *Modern Dermatology–A Baylor Health Texas Affiliate, Graduate School of Nursing, The University of Texas at Arlington, Arlington, and Modern Research Associates, Dallas, TX.*

Kristine J. Kucera, PA-C, MPAS, DHS, *Dermatology Center of Frisco, Frisco; UT Southwestern Medical Center, Dallas; and UNT Health Science Center, Ft. Worth, TX.*

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Melodie S. Young is a speaker or consultant for AbbVie, Celgene, Janssen, and Lilly and a clinical investigator for Amgen, Janssen, Novartis, Merck, Celgene, Pfizer, Galderma, and Eli Lilly. Kristine J. Kucera is a speaker or advisor for AbbVie, Actavis, Amgen, Aqua, Bayer, Innocutis, Janssen, Novartis, Promius, and Valeant and a consultant for Eli Lilly.

Correspondence concerning this article should be addressed to Melodie S. Young, MSN, A/GNP-C, DCNP, Modern Research Associates, 9101 N Central Expressway, Suite 170, Dallas, TX 75205. E-mail: melodiey@baylorhealth.edu

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Psoriasis is a systemic inflammatory disease that affects innate and adaptive immune pathways (Chiricozzi & Krueger, 2013; Girolomoni, Mrowietz, & Paul, 2012). Although the etiology of psoriasis is complex and remains largely unknown, it has become clear over the past several years that psoriasis goes beyond the skin. To effectively target the underlying disease pathogenesis, drugs are needed that act systemically on specific molecular components of the immune system (Baker et al., 2013; Girolomoni et al., 2012; Sivamani et al., 2013). As understanding of the psoriatic disease process has improved, several biologic agents have become available that inhibit select cytokines associated with psoriatic plaque formation (e.g., antitumor necrosis factor-α [TNFα]—etanercept, adalimumab, infliximab; interleukin [IL]-12 and IL-23 inhibitor—ustekinumab; and IL-17A inhibitor—secukinumab; Sivamani et al., 2013). Apremilast, a small-molecule inhibitor of phosphodiesterase-4,

is also available (Schafer, 2012). In addition, several other small molecules are being investigated that inhibit a variety of kinases (in particular, Janus kinase and protein kinase C; Ortiz-Ibáñez, Alsina, & Muñoz-Santos, 2013; Schafer, 2012). Improvements in our understanding of psoriasis have subsequently led to the development of newer agents that may target the mechanism of disease more explicitly. Specifically, IL-17A has been identified as a central cytokine driver in the pathogenesis of psoriasis, and biologic agents targeting this cytokine are currently in late-stage clinical development (ixekizumab) or have been recently approved (secukinumab; Cai et al., 2011; Chiricozzi et al., 2011; Krueger et al., 2012; Langley et al., 2014; Leonardi et al., 2012).

This article reviews how existing biologics target known mechanisms of disease in psoriasis and how modulating these mechanisms can improve outcomes over time. It also presents new insights into the pathophysiology of psoriasis that have led to the development of additional agents that target specific pathways associated with the disease.

PSORIASIS: AN OVERVIEW

Psoriasis is a common immune-mediated disorder affecting an estimated 2%–3% of the population worldwide (National Psoriasis Foundation [NPF], n.d.-b). Psoriasis is a heterogeneous disease, both in terms of clinical presentation and risk factors. Table 1 provides a description of the variants of psoriasis, including the frequency and most common characteristics of each phenotype (Ladizinski et al., 2013; Villaseñor-Park et al., 2012). By far, the most common variant of psoriasis is plaque psoriasis, which is characterized by red, scaly plaques that typically appear on the scalp, elbows, knees, and trunk (Ladizinski et al., 2013). In addition to the skin lesions associated with psoriasis, an estimated 50% of psoriatic patients have fingernail involvement, and 35% have toenail involvement (Menter et al., 2008); nail changes may include pitting, oil spots, leukonychia, subungual hyperkeratosis, dystrophy, and onycholysis (Ladizinski et al., 2013; Villaseñor-Park et al., 2012). Psoriasis is also linked with a number of comorbidities, including psoriatic arthritis, metabolic syndrome (clustering of obesity, hypertension, dyslipidemia, and insulin resistance), Type 2 diabetes, and depression. Psoriatic arthritis is an inflammatory spondyloarthropathy that is estimated to affect anywhere from 6% to 42% of patients with psoriasis (Gottlieb et al., 2008); its presentation is somewhat heterogeneous, but characteristic features often include asymmetric distal oligoarthritis, sausage-like digits (dactylitis), and enthesitis (Gottlieb et al., 2008). In addition to the aforementioned comorbidities, patients with psoriasis are at increased risk for cardiovascular disease

TABLE 1. Variants of Psoriasis

Variation	Frequency	Common Signs and Sites of Involvement
Chronic plaque psoriasis	Most common (>80% of cases)	• Well-defined, erythematous plaques with adherent silvery scales • Preferred involvement sites are the scalp, extensor surfaces of the elbows and knees, and lower trunk • Chronic course, with periods of remission
Intertriginous psoriasis	Common	• Thin, well-defined, shiny erythematous plaques with minimal scaling • Preferred involvement sites are the various skin folds including the axillae, behind the ears, inframammary region, and lower trunk
Pustular psoriasis	Uncommon	• Eruption of sterile pustules; multiple patterns of pustule formation exist • Preferred involvement sites depend on pattern type
Erythrodermic psoriasis	Rare	• Generalized erythema and scaling; may affect more than 75% of body surface area • Hair loss and nail dystrophy may also be seen; patient may exhibit systemic symptoms such as fever, chills, and fatigue • May be acute or chronic • Potentially life threatening
Guttate psoriasis	Rare	• Pink, oval (drop-shaped) papules with silvery scaling • Preferred involvement sites of the trunk and extremities • May be acute or chronic • Occurs in younger patients; many progress to chronic plaque psoriasis • Often develops post-strep throat

Ladizinski et al., 2013; Villaseñor-Park, Wheeler, & Grandinetti, 2012.

including myocardial infarction, stroke, vascular inflammation, and atherosclerotic disease (Baker et al., 2013; Gelfand & Yeung, 2012; Kimball et al., 2008). Interestingly, it has been observed that patients' risk for developing many of these comorbidities is independent of traditional cardiovascular risk factors, especially for those with moderate-to-severe disease. This reinforces the notion that psoriasis is a systemic disorder affecting more than just the skin, requiring a systemic approach to care (Gelfand & Yeung, 2012; Kimball et al., 2008).

Several genetic factors are strongly linked to psoriasis. Ten chromosomal regions (designated PSORS1–PSORS10) have been identified as being significantly associated with psoriasis, and many of the genes linked to psoriasis are also known to regulate specific inflammatory pathways. Overall, it is estimated that individuals with a first-degree relative affected by psoriasis are four to six times more likely to develop psoriasis compared with the general population (Girolomoni et al., 2012). In individuals with a genetic predisposition for psoriasis, many different environmental triggers have been associated with precipitating the onset or worsening of psoriasis, including infection (e.g., streptococcal), skin trauma, use of certain prescription drugs (e.g., lithium, antimalarials, beta blockers, interferon), alcohol consumption, cigarette smoking, stress, excessive exposure to ultraviolet radiation (sunburn), and autoimmune disorders (e.g., vitiligo, celiac disease, thyroid disease; Mallbris et al., 2005; NPF, 2013; Villaseñor-Park et al., 2012; Wheeler, 2010).

Current consensus is that mild psoriasis can be successfully treated with topical agents, whereas phototherapy or systemic or biologic therapy is indicated for moderate-to-severe disease (Baker et al., 2013; Mrowietz et al., 2011). However, psoriasis at any level can have a significant negative impact on overall quality of life (e.g., even when only a small portion of body surface area [BSA] is affected), thereby challenging the label of "mild" disease. Results of a population-based survey on the burden of psoriasis estimate that, of the more than 4.5 million adults diagnosed with psoriasis in the United States, 2.6 million (~60%) have little or no skin involvement, yet more than 1 million patients are substantially dissatisfied with their treatment, and roughly half a million Americans report that psoriasis is a major problem in their everyday life (Stern, Nijsten, Feldman, Margolis, & Rolstad, 2004). An estimated 80% (~800,000) of those who report being very dissatisfied with treatment and more than 60% (~300,000) of those who report psoriasis is a major problem have psoriasis covering a BSA of less than 10% or 10 palms (Stern et al., 2004). Findings such as these highlight the limitations of current definitions used for diagnosis of mild versus moderate versus severe psoriasis.

European and Australian consensus guidelines for assessing the severity of psoriasis rely heavily on the use of Psoriasis Area and Severity Index (PASI) and Dermatology Life Quality Index (DLQI) scores, defining mild psoriasis as PASI $\leq$ 10 and DLQI $\leq$ 10 and moderate-to-severe psoriasis as PASI > 10 and DLQI > 10 (Baker et al., 2013; Mrowietz et al., 2011). In addition to the PASI and DLQI requirements, European consensus guidelines also include BSA $\leq$ 10% as a criterion for mild psoriasis and BSA > 10% as a criterion for moderate-to-severe psoriasis (Mrowietz et al., 2011). Although PASI and DLQI are generally considered to be rigorous, objective assessments of disease severity, clinical consensus from the NPF acknowledges that these classification instruments are often not practical for use in everyday clinical settings (Pariser et al., 2007). The NPF consensus states that disease severity is generally a subjective assessment based on the practitioner's estimation of BSA affected as well as disease location, lesion thickness, physical symptoms, and emotional and financial burdens of psoriasis on the patient's quality of life (Pariser et al., 2007). In studies conducted by the NPF, psoriasis is classified as moderate if there is as little as 3% BSA affected (Horn et al., 2007) and as moderate to severe if there is at least 5% BSA involvement (Pariser et al., 2007). However, in cases where psoriasis affects even small areas in visible or sensitive locations, such as the face, scalp, genitals, nails, and palms or soles, it is often appropriate to classify psoriasis covering a BSA < 5% as moderate to severe. Other sensitive areas that should be considered in psoriasis classification include the eyelids, lips, mouth, and skin folds (NPF, 2008). In addition, regardless of BSA affected, all cases of erythrodermic, pustular, and guttate psoriasis should be classified as moderate to severe and treated with systemic therapy and/or phototherapy (Pariser et al., 2007).

Other factors to consider when determining the severity of psoriasis include the burdens associated with symptoms of pain, itching, burning, stinging, and bleeding in affected areas (Baker et al., 2013; Bilac, Ermertcan, Bilac, Deveci, & Horasan, 2009). A recent study that examined the etiopathogenesis and burdens of these symptoms found that they are frequently associated with reduced quality of life, affecting mood, sleep, concentration, sexual desire, and appetite (Bilac et al., 2009). In a cross-sectional study, 42% of patients with psoriasis reported skin pain (primarily of moderate intensity), with sleep being the most severely affected function (Ljosaa et al., 2010). Severe itching can be particularly bothersome for patients, and scratching pruritic lesions can lead to excoriation, which can worsen or Koebnerize the lesions (Baker et al., 2013). In such cases, psoriasis defined as mild based on BSA should be reclassified as moderate to severe (Baker et al., 2013). Overall, it is important for dermatology practitioners to be aware of the frequency of these symptoms and the negative impact they can have on patients and their caregivers and personal relationships when determining psoriasis severity.

Because psoriasis is such a visually apparent disease, it can cause patients to feel embarrassed, stigmatized, stressed, and depressed. It can also negatively affect body image, personal relationships, intimacy, and employment

(Kimball, Jacobson, Weiss, Vreeland, & Wu, 2005; Schmitt & Ford, 2006; Young, 2005). As discussed, the psychological impact of psoriasis does not always correlate with disease severity based on BSA involvement (Kimball et al., 2005; Schmitt & Ford, 2006). Even small amounts of psoriasis can greatly affect patients; therefore, it is critical for practitioners to evaluate each patient for unique emotional burdens when recommending treatment strategies, recognizing that aggressive therapies may be appropriate even with limited disease. Studies have shown that women and younger patients (<40 years old) may be especially vulnerable to the social stigma associated with psoriasis and prone to depression (NPF, 2013; Wheeler, 2010). In addition to feeling heightened social stigma, teenage patients may also be sensitive about their need for physical privacy and independence. They may be reluctant to show practitioners the full extent of their disease or to ask a parent for help with medication (e.g., applying a topical treatment to a hard-to-reach area; Wheeler, 2010).

CURRENT TREATMENTS AND FUTURE DIRECTIONS

Table 2 presents an overview of available treatments for psoriasis (Cosentyx [secukinumab] injection prescribing information, 2015; Dovonex [calcipotriene] cream prescribing information, 2009; Ladizinski et al., prescribing information, 2013; NPF prescribing information, n.d.-a; Otezla [apremilast] tablets prescribing information, 2014; Tazorac [tazarotene] cream prescribing information, 2011; Vectical [calcitriol] ointment prescribing information, 2012; Zithranol-RR [anthralin] cream prescribing information, 2009). Topical agents, including corticosteroids, Vitamin D analogs, retinoids, coal tar preparations, and keratolytics, are only recommended for the management of mild, localized psoriasis (Mrowietz et al., 2011; Pariser et al., 2007). Topical agents cannot effectively control moderate-to-severe psoriasis and do not target the underlying disease process (Ladizinski et al., 2013; Mrowietz et al., 2011; Poulin et al., 2012). Patient satisfaction with topical agents is generally low because of their limited efficacy and inconvenient administration (Poulin et al., 2012), and topical preparations can be greasy, messy, malodorous, and time-consuming to apply. Certain agents (e.g., coal tars) can also stain skin and clothing (Ladizinski et al., 2013).

To significantly clear skin symptoms and improve patients' quality of life, it is recommended that patients with moderate-to-severe psoriasis receive systemic therapy with Food and Drug Administration-approved conventional agents (e.g., methotrexate, cyclosporine) or biologic agents (e.g., secukinumab, infliximab, adalimumab, etanercept, ustekinumab; Mrowietz et al., 2011). In addition, the new small-molecule apremilast should also be considered as it is approved for adults with moderate-to-severe plaque-type psoriasis. The American Academy of Dermatology released a position statement in 2013 stating that "psoriasis patients with moderate-to-severe psoriasis and, thus, candidates for systemic therapy, should be placed on the appropriate therapy from the beginning, i.e., phototherapy, or systemic therapy including biologic therapy" (American Academy of Dermatology and AAD Association, 2013). However, despite consensus guidelines issued by the NPF (Pariser et al., 2007) and expert panels from 19 European countries (Mrowietz et al., 2011) and across Australia (Baker et al., 2013) recommending the use of systemic therapy (possibly in combination with phototherapy) for the treatment of moderate-to-severe psoriasis, many dermatology practitioners are still reluctant to use systemic agents as first-line therapy or to switch to systemic agents when topical agents are ineffective (Mrowietz et al., 2011). For example, a study by Horn and colleagues that surveyed 1657 patients with moderate (BSA of 3%–10%) or severe (BSA > 10%) psoriasis from 2003 to 2005 found that, among those who were receiving any treatment for their psoriasis, most patients with moderate psoriasis (73%) or severe psoriasis (57%) were receiving only topical therapy (Horn et al., 2007). More recently, Armstrong, Robertson, Wu, Schupp, and Lebwohl (2013) confirmed that undertreatment of moderate-to-severe psoriasis was still problematic in surveys conducted through 2011. In their survey of 5604 patients with psoriasis or psoriatic arthritis, these authors found that, in 2011, 23.6% of patients with moderate disease and 9.4% of patients with severe disease were receiving no treatment, and 29.5% and 21.5% (51% combined), respectively, were receiving only topical therapy (Armstrong et al., 2013). Furthermore, in this population with high rates of psoriasis undertreatment, most (52%) of survey respondents were dissatisfied with their treatment (Armstrong et al., 2013). More concerning is the limited success of topical treatments beyond mild disease, yet they continue to be the first-line therapy in practice and have no known therapeutic benefit for managing comorbidities such as psoriatic arthritis. In contrast, a 2012 study that evaluated patient satisfaction by class of therapy for moderate-to-severe psoriasis found that most (63%) of the patients treated with biologics were "very satisfied" with their treatment (Poulin et al., 2012). Taken together, the above survey findings highlight the need to increase education and advocacy about systemic agents and treatment goals to ensure that patients are appropriately treated and have realistic expectations regarding the benefits and risks of such therapy.

The decision to treat patients with conventional systemic agents or biologics should be based on individualized needs, convenience, and safety and efficacy considerations of a particular agent. For many patients, conventional systemic agents are contraindicated, or their use is limited by common or potentially serious side effects (Table 2). Methotrexate is associated with numerous drug interactions and contraindicated in patients with elevated liver enzymes or a history of alcohol abuse, liver disease, or bone marrow hyperplasia. It is also a concern for patients of reproductive age. Side effects of methotrexate include nausea, vomiting, anorexia, stomatitis, macrocytic anemia,

TABLE 2. Current Treatments for Psoriasis

Drug	Brand Name	Mode of Action	Dosage/Administration	Contraindications	Side Effects	Comments
Topicals						
Anthralin	Zithranol-RR (Elorac)	Antiproliferative and anti-inflammatory effects on skin	1.2% cream applied once daily for 5–30 minutes and then removed by washing	Acute or actively inflamed psoriatic eruptions	Skin irritation, staining of hair, and unaffected skin	Messy, time consuming to apply and rinse
Calcipotriene	Dovonex (Leo)	Synthetic Vitamin D_3 analog; slows skin cell growth, flattens lesions, removes scale	0.005% cream or scalp solution applied to affected area twice daily	Hypercalcemia, Vitamin D toxicity	Skin irritation, dry skin, peeling, rash, dermatitis, worsening of psoriasis	Not for use on the face
Calcitriol	Vectical (Galderma)	Naturally occurring active form of Vitamin D_3; controls excessive skin cell production	Applied to affected area twice daily; maximum dose, 200 g/week	None	Hypercalciuria, pruritus, changes in calcium metabolism	Not for use on the face, lips, or eyes
Tazarotene	Tazorac (Allergan)	Vitamin A derivative (retinoid); thought to slow skin growth	Applied to affected area once daily, in the evening, to cover lesions with a thin film	Pregnancy (may cause fetal harm)	Skin irritation, dry skin, susceptibility to sunburn	Can be used on the face, hairline, scalp, and nails Women of childbearing age must use reliable birth control during treatment
Corticosteroids (e.g., clobetasol, fluocinonide, desoximetasone, hydrocortisone, fluticasone, others)	Many brands/ potencies	Anti-inflammatory properties reduce swelling and redness of lesions	Varying strengths and formulations available; generally applied once or twice daily	None	Skin thinning, pigmentation changes, easy bruising, stretch marks, redness, dilated surface blood vessels, acne	Not for use on face or other sensitive areas for long periods Can lose efficacy over time; abrupt discontinuation can cause flares Pulse dosing can minimize risk of side effects

(continues)

TABLE 2. Current Treatments for Psoriasis, Continued

Drug	Brand Name	Mode of Action	Dosage/Administration	Contraindications	Side Effects	Comments
Salicylic acid	Many generic OTC formulations	Keratolytic; acts as a scale lifter to soften and remove psoriasis scales	Applied as needed in concentrations up to 3% (creams, gels, ointments, shampoos, soap)	None	Skin irritation	By removing scales, salicylic acid may allow other topical agents to better penetrate the skin
Coal tar	Many generic OTC formulations	Can slow skin growth and restore normal appearance	Can be applied directly or added to bath water; generally left on skin for ≥2 hours	None	Skin irritation, redness, and dryness; increased sensitivity to sunburn Known carcinogen at high concentrations	Messy, strong odor, stains, very time-consuming
Conventional systemic therapies						
Cyclosporine	Neoral (Novartis) and others	Immunosuppressant; slows growth of skin cells	Usually taken orally twice daily at a starting dose of 2.5 mg/kg/day	Compromised immune system, active serious infections, abnormal kidney function, uncontrollable hypertension, cancer or history of cancer (other than certain skin cancers), severe gout, radiation therapy, pregnancy	Decreased renal function, hypertension, elevated cholesterol and/or triglycerides, excessive hair growth, tingling or burning in the arms or legs, skin sensitivity, swelling or growth of gum tissue, flu-like symptoms, upset stomach, fatigue, muscle or joint pain, neurologic symptoms (e.g., headache, tremor)	Increased risk of skin cancer in patients treated with PUVA, methotrexate, or other immunosuppressants Many drug–drug reactions (e.g., antibiotics, anti-inflammatory agents, antifungals, calcium channel blockers, anticonvulsants) Improvement can occur within 2 weeks; complete response may take 3–4 months

(continues)

TABLE 2. Current Treatments for Psoriasis, Continued

Drug	Brand Name	Mode of Action	Dosage/Administration	Contraindications	Side Effects	Comments
Methotrexate	Usually sold as a generic formulation	Antimetabolite; slows the rate of skin cell growth	Usually taken orally once a week; injectable formulations available	Alcoholism, alcoholic or other chronic liver disease, immunodeficiency syndromes, women or their partners planning pregnancy, active peptic ulcers, significant kidney or liver abnormalities, active infectious disease, hematologic disorders	Nausea, fatigue, difficulty sleeping, lightheadedness, mouth ulcers, vomiting, headache, easy bruising and bleeding, fever, diarrhea with bloody stools, chills, sensitivity to sunlight, burning sensation in lesions, hair loss, liver fibrosis	Regular blood tests needed to check for side effects on the liver, blood, or bone marrow Women should wait ≥4 months after stopping treatment before becoming pregnant; men should wait ≥3 months before a couple tries to conceive Folic acid can reduce risk of side effects Improvement can occur within 3–6 weeks; complete response may take 6 months
Acitretin	Soriatane (Stiefel)	Oral retinoid; exact mechanism unknown; retinoids regulate cell behavior, including rate of skin cell growth and shedding	Taken orally once daily with food (available in 10-, 17.5-, and 25-mg doses)	Pregnancy, breastfeeding, severe liver or kidney disease, uncontrolled hyperlipidemia	Hair loss, chapped lips, dry mouth, dry skin and eyes, bleeding gums, nosebleeds, sensitivity to sunlight, peeling fingertips, nail changes, changes in serum lipids, depression, aggressive thoughts or thoughts of self-harm, headache, joint pain, decreased night vision, elevated liver enzymes	Can cause severe birth defects; women must use ≥2 birth control methods, should not become pregnant for 3 years after discontinuation Should not donate blood for 3 years after discontinuation Women must avoid alcohol during treatment and for 2 months after discontinuation Improvement may be slow (8–16 weeks; peak effect after 6 months)

(continues)

TABLE 2. Current Treatments for Psoriasis, Continued

Drug	Brand Name	Mode of Action	Dosage/Administration	Contraindications	Side Effects	Comments
Small-molecule inhibitors						
Apremilast	Otezla (Celgene)	Oral small-molecule inhibitor of phosphodiesterase-4	Titrate to recommended dose of 30 mg twice daily	Known hypersensitivity to apremilast or any excipients in formulation	Diarrhea, nausea, headache, upper respiratory tract infection, vomiting, nasopharyngitis, upper abdominal pain	In clinical trials, ~30% of patients achieved PASI 75 after 16 weeks
Biologics						
Etanercept	Enbrel (Amgen)	Fusion protein of TNFα receptor extracellular domain and Fc portion of human IgG	SC injection 50 mg twice weekly for 3 months, then maintenance doses once weekly thereafter	Active serious infection; history of recurrent infections; history of heart failure, multiple sclerosis, or other demyelinating disease	Dizziness, sore throat, cough, stomach pain, injection-site reactions, upper respiratory infections, headache, rhinitis	Side effects are generally mild and may decrease over time In clinical trials, ~49% of patients achieved PASI 75 after 3 months
Adalimumab	Humira (AbbVie)	Human recombinant IgG monoclonal antibody specific for TNFα	SC injection of 80 mg on Day 1, then 40 mg every other week starting on Day 8	Active serious infection; history of recurrent infections; history of heart failure, multiple sclerosis, or other demyelinating disease	Upper respiratory tract infections, abdominal pain, headache, rash, injection-site reactions, urinary tract infections	Side effects are generally mild and may decrease over time In clinical trials, ~70% of patients achieved PASI 75 after 3 months
Infliximab	Remicade (Janssen)	Chimeric monoclonal IgG antibody targeting TNFα	IV infusion of 5 mg/kg; three infusions during the first 6 weeks, then once every 8 weeks	Active serious infection; history of recurrent infections; history of heart failure, multiple sclerosis, or other demyelinating disease	Infusion reactions, upper respiratory tract infections, headache, rash, cough, stomach pain	Side effects are generally mild and may decrease over time In clinical trials, ~80% of patients achieved PASI 75 after 10 weeks

(continues)

TABLE 2. Current Treatments for Psoriasis, Continued

Drug	Brand Name	Mode of Action	Dosage/Administration	Contraindications	Side Effects	Comments
Secukinumab	Cosentyx (Novartis)	Human monoclonal antibody targeting IL-17A	SC injection of 300 mg at Weeks 0, 1, 2, 3, and 4, then once every 4 weeks	Caution should be used when considering use in patients with chronic infection or a history of recurrent infection and in patients with active Crohn's disease	Nasopharyngitis, diarrhea, and upper respiratory tract infection	In clinical trials, ~80% of patients achieved PASI 75 after 12 weeks, and ~67% of patients achieved IGA of clear or almost clear
Ustekinumab	Stelara (Janssen)	Human monoclonal antibody targeting the p40 subunit of IL-12 and IL-23	SC injections at Weeks 0 and 4, then every 12 weeks of 45 mg if weight ≤ 220 lbs or 90 mg if weight > 220 lbs	Active infections, history of recurrent infections	Upper respiratory infections, headache, fatigue, redness at injection site, back pain	In clinical trials, ~67% of patients achieved PASI 75 after 12 weeks

None of the agents are approved for use in children with psoriasis (Cosentyx [secukinumab] injection prescribing information, 2015; Dovonex [calcipotriene] cream prescribing information, 2009; Ladizinski et al., prescribing information, 2013; NPF, prescribing information, n.d.-a; Otezla [apremilast] tablets prescribing information, 2014; Tazorac [tazarotene] cream prescribing information, 2011; Vectical [calcitriol] ointment prescribing information, 2012; Zithranol-RR [anthralin] cream prescribing information, 2009). IGA = investigator's global assessment; IL = interleukin; IV = intravenous; OTC = over-the-counter; PASI = Psoriasis Area and Severity Index; PUVA = psoralen plus ultraviolet light; RR = rapid release; SC = subcutaneous; TNF = tumor necrosis factor.

phototoxicity, seizures, hepatotoxicity, renal failure, bone marrow suppression, and pulmonary fibrosis (Aaronson & Lebwohl, 2004; Christophers, Griffiths, Gaitanis, & van de Kerkhof, 2006). In addition, methotrexate has more black box warnings than any other therapy for psoriasis. Cyclosporine is contraindicated in patients with elevated creatinine levels or a history of hypertension, renal disease, gout, or hyperuricemia. Side effects of cyclosporine include nephrotoxicity, hypertension, hyperlipidemia, hypomagnesemia, hyperkalemia, and increased susceptibility to infection and malignancy (Aaronson & Lebwohl, 2004; Christophers et al., 2006). Retinoids are highly teratogenic and can cause hair loss, dry skin or lips, cheilitis, dermatitis, increased serum lipids and liver enzymes, and osteoporosis (Aaronson & Lebwohl, 2004). Given the long lists of safety concerns associated with conventional systemic agents, it is not surprising that a survey of 301 patients with psoriasis treated at European outpatient clinics found that more than 90% of patients had comorbidities that could preclude the use of conventional systemics (most commonly, hypertension, abnormal liver enzymes, and hyperlipidemia; Christophers et al., 2006).

The biologic agents approved for the treatment of moderate-to-severe psoriasis are all comparably safe and well tolerated; however, cases of serious infection have been observed with these agents, and they may increase risk of malignancy (Cosentyx [secukinumab] injection prescribing information, 2015; Enbrel [etanercept] solution prescribing information, 2015; Humira [adalimumab] injection prescribing information, 2014; Remicade [infliximab] lyophilized concentrate for injection prescribing information, 2015; Stelara [ustekinumab] injection prescribing information, 2014). Recent studies suggest that the increased risks for infection and malignancy are small and may not be statistically significant (Dommasch et al., 2011), but many practitioners choose to avoid using biologics in patients with a history of malignancy or with active or frequent infections. All patients who are candidates for biologic therapy should be screened for tuberculosis, Hepatitis B and C and other serious infections, nonmelanoma skin cancer, and other malignancies (Ortleb & Levitt, 2012; Sivamani et al., 2013).

Although data are limited on the comparative efficacy of conventional systemics versus biologics (Lee et al., 2012), two randomized controlled trials published to date showed that adalimumab (Saurat et al., 2008) and infliximab (Barker et al., 2011) were associated with significantly higher PASI 75% improvement (PASI 75) responses compared with methotrexate. Furthermore, a network meta-analysis of data from 20 randomized controlled trials of approved biologic agents for the treatment of moderate-to-severe psoriasis showed that 52% of patients treated with etanercept, 59% treated with adalimumab, 69%–75% treated with ustekinumab, and 80% treated with infliximab achieved PASI 75 responses with a standard course of therapy (Reich, Burden, Eaton, & Hawkins, 2012).

Overall, many experts believe that, over the last 10 years, biologic agents have revolutionized the treatment of moderate-to-severe psoriasis because available biologics target cytokines that regulate the immune system and control the underlying pathogenesis of psoriasis (Sivamani et al., 2013). As further improvements have been made in the understanding of psoriasis, new cytokines have been identified as potential targets for drug development (Chiricozzi & Krueger, 2013). Drugs designed to address these and future targets may provide new solutions for disease management and have the potential to positively impact the patient experience. The next section will review the immunology of psoriasis, highlighting how existing biologics function and how new biologics in development target key inflammatory pathways associated with psoriatic activity.

PSORIASIS IMMUNOLOGY AND THE RATIONALE FOR TODAY'S (AND TOMORROW'S) BIOLOGICS

Immune responses in the skin provide critical defense against microbial pathogens and chemical and physical insults; however, when skin immune responses are excessive, chronic inflammation can result, such as that observed in psoriasis (Nestle, Di Meglio, Qin, & Nickoloff, 2009). Figure 1 presents a model of psoriasis immunopathogenesis illustrating that, in genetically predisposed individuals, environmental factors and other triggers can initiate psoriasis by instigating the production of multiple cytokines associated with plaque formation (Lynde, Poulin, Vender, Bourcier, & Khalil, 2014; Nestle et al., 2009). Specifically, stressed keratinocytes trigger production of IL-1β, IL-6, and TNFα, and keratinocyte self-DNA forms complexes with

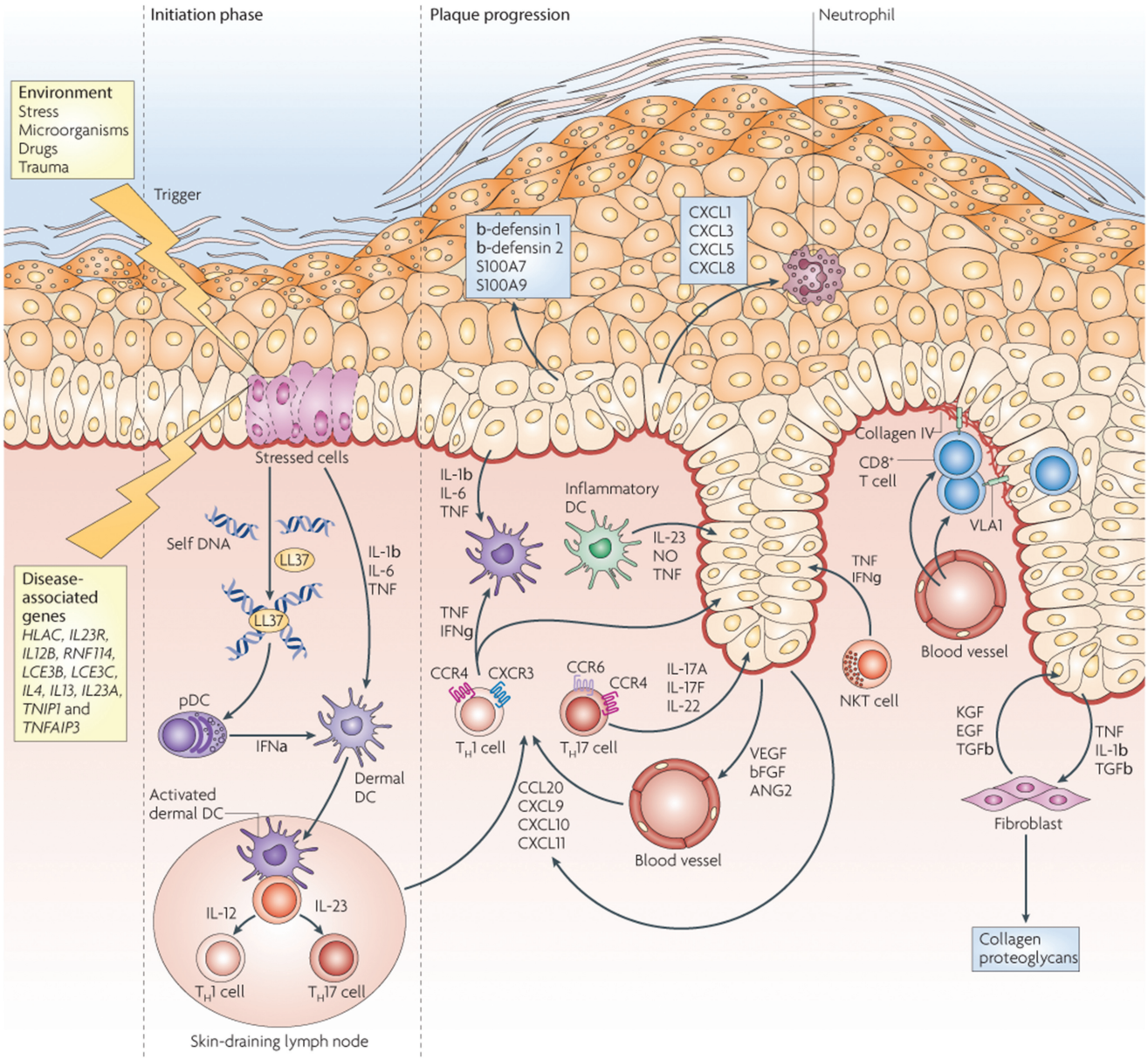

FIGURE 1. Psoriasis immunopathogenesis. Reprinted with permission from Macmillan Publishers Ltd. (Nestle et al., 2009).

antimicrobial peptides to activate plasmacytoid dendritic cells to produce interferon-α. In turn, these cytokines that are produced in response to stimulus activate dermal dendritic cells (Lynde et al., 2014; Nestle et al., 2009). In addition, other unknown factors may activate dendritic cells, which may explain observed psoriatic plaque formation in the absence of a defined stimulus (Nickoloff & Nestle, 2004).

Activated dendritic cells in the dermis secrete IL-12 and IL-23, which promote differentiation and proliferation of naive T cells into helper T1 (T_H1) and T_H17 cells, respectively (Lynde et al., 2014; Nestle et al., 2009). When matured, T_H17 cells secrete IL-17A, IL-17F, and IL-22, which stimulate keratinocyte proliferation and release of antimicrobial peptides, neutrophil-recruiting chemokines, and growth factors, thus promoting progression of psoriatic plaque formation and activation of additional dendritic cells and T cells. These events result in a self-reinforcing cascade or "vicious cycle" of cytokine production and cell activation.

Cytokines targeted by available biologics—TNFα, IL-12, IL-23, and IL-17A—are involved in many of the aforementioned processes (Lynde et al., 2014; Nestle et al., 2009; Nickoloff & Nestle, 2004). TNFα, as a broadly acting cytokine mediator of inflammatory and immune responses, is secreted by a number of other cell types (e.g., macrophages, mast cells, natural killer [NK] cells, and granulocytes) and thus may be associated with the initial response to the events precipitating keratinocyte hyperproliferation and formation of psoriatic plaque as well as the inflammation associated with both psoriasis and psoriatic arthritis (Croft, Benedict, & Ware, 2013; Ware, 2013). TNFα is involved in many pathways in the self-reinforcing cascade, and biologics targeting these cytokines are designed to disturb these processes and help restore skin to a more normal, nonpsoriatic state (Marble, Gordon, & Nickoloff, 2007; Yost & Gudjonsson, 2009).

IL-12 and IL-23 are also key cytokine mediators of cellular immunity. Dendritic cells, macrophages, and keratinocytes produce IL-12 in response to microbial stimulation, which triggers induction of lymphokine-activated killer cells, activation of NK cells and T lymphocytes, and differentiation of naive T cells to T_H1 cells (Benson et al., 2011; Torti & Feldman, 2007). Activated NK cells and T_H1 cells then induce T-cell migration to the epidermis and stimulate keratinocyte proliferation (Torti & Feldman, 2007). IL-23, together with other cytokines including IL-1β, IL-6, and transforming growth factor-β, promotes differentiation of naive T cells to T_H17 cells (Benson et al., 2011; Damsker, Hansen, & Caspi, 2010). Continued IL-23 signaling is also critical for survival and proliferation of mature T_H17 cells (Damsker et al., 2010). These T_H17 cells are central drivers of inflammation and immune responses, and the IL-23/T_H17 pathway is recognized as a major immune pathway in the pathogenesis of psoriasis (Chiricozzi & Krueger, 2013; Damsker et al., 2010). The biologic agent ustekinumab binds to the common p40 subunit of IL-12 and IL23, thereby blocking the downstream signaling of both cytokines in the psoriasis cascade and providing significant improvements in the clinical symptoms of psoriasis (Benson et al., 2011; Leonardi et al., 2008; Papp et al., 2008).

New psoriasis treatment strategies are focused on disrupting mechanistic pathways associated with the development or severity of immunologic responses occurring early in the sequence of events leading to plaque formation. For example, the recently Food and Drug Administration-approved phosphodiesterase-4 inhibitor (apremilast), on the basis of its ability to potentially block the production of proinflammatory cytokines (Schafer, 2012), and kinase inhibitors (e.g., tofacitinib) are being investigated based on the rationale that these small molecules will dampen the cellular responses to various cytokines produced in this cascade (Ortiz-Ibáñez et al., 2013). Apremilast acts upstream in the psoriasis inflammatory cascade to decrease expression of inducible nitric oxide synthase, TNFα, and IL-23, and it acts to increase expression of IL-10 (Schafer, 2012). Tofacitinib also targets initial immune responses by suppressing IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21 and inhibiting the differentiation of T_H cells (T_{H1}, T_{H2}, and T_{H17}; Ghoreschi et al., 2011; Ortiz-Ibáñez et al., 2013).

Recent studies have highlighted IL-17A as a central driver of altered skin function in the pathogenic pathways of psoriasis and have made this cytokine an important downstream target for agents in development (Chiricozzi et al., 2011; Chiricozzi & Krueger, 2013; Gaffen, 2011; Krueger et al., 2012). In addition to being a key product of T_H17 cells, IL-17A is produced by neutrophils, mast cells, and cytotoxic T cells (T_C17 cells), all of which are found in excess in psoriatic lesions (Girolomoni et al., 2012; Res et al., 2010). Dermal γδ T cells are also found in higher levels in psoriatic lesions compared with healthy skin; these proinflammatory cells produce IL-17A in response to IL-23 and/or IL-1β stimulation (Cai et al., 2011; Cai, Fleming, & Yan, 2013; Laggner et al., 2011).

Numerous roles of IL-17A have been identified in the pathogenesis of psoriasis: recruitment of myeloid dendritic cells and activated T_H17 cells to psoriatic lesions, upregulation of neutrophil-chemoattracting chemokines on keratinocytes, stimulation of antimicrobial peptide expression on keratinocytes, stimulation of IL-36 expression by keratinocytes, disruption of skin barriers, upregulation of IL-6 production by fibroblasts and myeloid dendritic cells, upregulation of IL-1 and IL-23, and chemokine (C-C motif) ligand 20 production by keratinocytes (Girolomoni et al., 2012; Marwaha, Leung, McMurchy, & Levings, 2012). In addition, synergistic action of IL-17A with TNFα has been observed to promote T_H17 cell-driven inflammation (Girolomoni et al., 2012; Marwaha et al., 2012).

There are several possible advantages of targeting IL-17A instead of more broadly acting upstream cytokines. For example, targeting IL-17A has the potential to reduce psoriatic skin inflammation while leaving other immune functions undisturbed (Girolomoni et al., 2012; Patel, Lee,

Kolbinger, & Antoni, 2013). In addition, because it is more intrinsically involved in formation of the psoriatic plaque, targeting IL-17A may result in fewer broad immune system side effects (e.g., serious infection, malignancies) compared with blocking TNFα or IL-12 and IL-23 (Girolomoni et al., 2012). Further research will provide the necessary data to help clinicians determine if agents targeting IL-17A have a different safety profile from other biologics.

One biologic that targets IL-17 has been approved (secukinumab), and another is currently in clinical development (ixekizumab). Secukinumab is a human immunoglobulin (Ig)G1κ monoclonal antibody that selectively binds and neutralizes IL-17A (Hueber et al., 2010; Langley et al., 2014). Ixekizumab is a humanized IgG4 monoclonal antibody that binds and neutralizes IL-17A (Krueger et al., 2012; Leonardi et al., 2012). Brodalumab is a fully human monoclonal antibody that binds to the receptor subunit IL-17RA, blocking all IL-17 family members that bind to this receptor, including IL-17A, IL-17C, IL-17F, IL-17A/F, and IL-17E (IL-25). In clinical studies, patients treated with IL-17A inhibitors have experienced rapid and marked improvements in psoriasis severity (Hueber et al., 2010; Krueger et al., 2012; Langley et al., 2014; Leonardi et al., 2012; Papp et al., 2013); for example, Figure 2 shows one patient's clinical response four weeks after receiving a single infusion of secukinumab in a proof-of-concept study (Hueber et al., 2010). In a Phase 3 study of secukinumab in patients with moderate-to-severe psoriasis, significant improvements in PASI scores were observed at Week 12 compared with placebo and etanercept, and these improvements were maintained to 52 weeks (Langley et al., 2014). Interestingly, the clinical improvements observed in patients treated with IL-17A inhibitors correlate with histological improvements and reduced gene expression (Chiricozzi & Krueger, 2013). In a Phase 2a study in patients with moderate-to-severe plaque psoriasis, significant PASI improvements observed four weeks after treatment with secukinumab were associated with reduced T-cell infiltration in skin lesions and reduced production of inflammatory cytokines (Hueber et al., 2010). A Phase 1 study of ixekizumab in patients with moderate-to-severe plaque psoriasis also showed that keratinocyte proliferation, hyperplasia, epidermal thickness, and keratinocyte expression of innate defense peptides were reduced two weeks after dosing, and normal histological skin appearance was achieved by Week 6 (Krueger et al., 2012). Overall, the investigational agents targeting IL-17A have been generally well tolerated in early-stage clinical studies without unexpected safety signals (Leonardi et al., 2012; Papp et al., 2013; Rich et al., 2013). However, larger-scale studies are underway to better establish the long-term safety profiles of these agents.

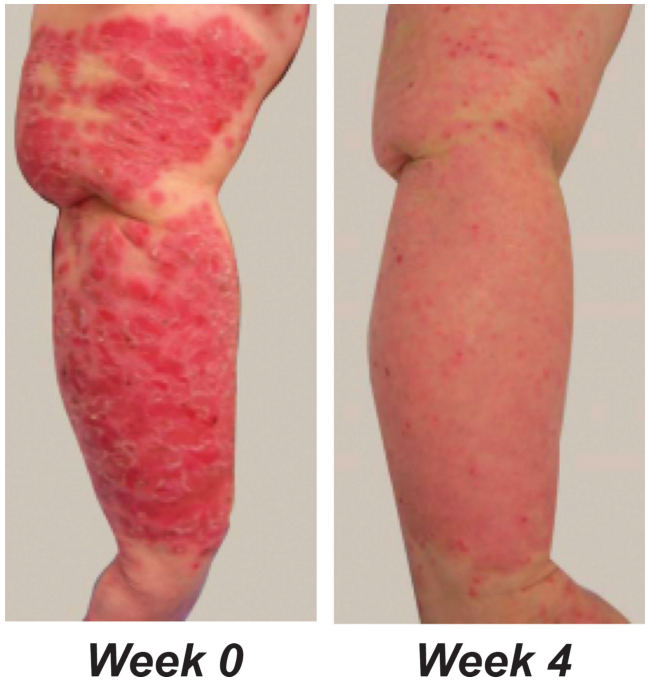

FIGURE 2. Clinical response in a patient with chronic plaque psoriasis after a single intravenous infusion of secukinumab 3 mg/kg (Hueber et al., 2010). Reprinted with permission.

DISCUSSION

Biologics are effective, well-tolerated treatment options for chronic plaque psoriasis that can produce dramatic clinical improvements in a relatively short period (Sivamani et al., 2013; Wheeler, 2010). Unlike topical and conventional systemic therapies that were discovered serendipitously and do not specifically address the underlying pathogenesis of psoriasis, biologics have been, and continue to be, developed based on scientific evidence identifying therapeutic targets within the critical immune and inflammatory pathways associated with the development and progression of disease (Nickoloff & Nestle, 2004). Furthermore, because biologics target underlying inflammation, earlier use of biologics may slow disease progression and prevent inflammatory comorbidities, such as atherosclerosis and metabolic syndrome (Golden, McCormick, & Ward, 2013).

When selecting appropriate psoriasis therapies, it is important for practitioners to consider a variety of factors such as efficacy, onset of action, sustainability of efficacy, route of administration, convenience, safety, and tolerability. From a patient perspective, many have referred to biologics as "wonder drugs" based on the high degree of skin clearance, relatively few side effects, and convenient administration (Wheeler, 2010). In addition, results of recent surveys evaluating patient experiences with psoriasis treatments have shown that satisfaction with biologics is notably higher than with topicals or conventional systemic therapies (Callis Duffin et al., 2014; Poulin et al., 2012). Meta-analyses of data from randomized controlled trials of available biologics have found that infliximab is the most effective TNFα inhibitor (in terms of mean PASI improvement), and etanercept is the least effective, although the clinical implications of these differences are unclear

(Reich et al., 2012; Schmitt, Zhang, Wozel, Meurer, & Kirch, 2008). Comparative trials may also prove helpful in choosing among the biologics; however, such studies are limited to date. Of the few head-to-head trials, secukinumab and ustekinumab were found to be significantly more effective than etanercept over 12 weeks of treatment (Griffiths et al., 2010; Langley et al., 2014). These efficacy differences may be explained, in part, by differences in pharmacokinetic properties. Etanercept is cleared from serum roughly six times faster than adalimumab or infliximab and has a shorter half-life (4 days for etanercept compared with 8–10 days for infliximab, 10–20 days for adalimumab, ~21 days for ustekinumab, and ~28 days for secukinumab; Baeten et al., 2010; Benson et al., 2011; Ware, 2013). Additionally, secukinumab was found to be significantly more effective than ustekinumab after 16 weeks of treatment (Thaçi et al., 2015).

In terms of safety, all available biologics are generally well tolerated, and although biologics may increase patients' risk of serious infection and malignancy, these events are rare (Dommasch et al., 2011). Infliximab is associated with the highest risk of neutralizing antibodies because it is a human-murine chimeric monoclonal anti-TNF antibody, producing the risk for an infusion reaction or loss of benefit requiring a dose adjustment or other change. In contrast, etanercept is a chimeric fusion of the human TNF receptor with an antibody Fc fragment, and adalimumab, secukinumab, and ustekinumab are human IgG1 antibodies (Benson et al., 2011; Langley et al., 2014; Ware, 2013; Yost & Gudjonsson, 2009).

All available biologics, with the exception of infliximab, are administered subcutaneously, with initial dosing schedules ranging from twice weekly (etanercept) to once every four weeks (secukinumab and ustekinumab) with less frequent dosing over time for most agents (Langley et al., 2014; Sivamani et al., 2013). Infliximab is administered by intravenous injection, as two initial injections two weeks apart followed by dosing every 12 weeks (Sivamani et al., 2013). Survey results indicate that patients rate the convenience of self-administered subcutaneous biologics higher than intravenous infliximab (Callis Duffin et al., 2014).

Overall, it is important to have multiple treatment options with different mechanisms of action, as not all agents work for all patients, and switching from one biologic to another is a valid strategy when patients fail to respond or lose the response to any given agent (Gottlieb et al., 2012; Strober et al., 2011). Furthermore, psoriasis is a lifelong, chronic disease, and over time, many patients will likely need to access numerous therapies for a host of reasons, such as loss of efficacy, comorbidities, life changes, development of side effects, cost/insurance issues, and convenience. Development of drugs that target new pathways in psoriasis will increase the number of options practitioners have to more effectively treat this complex disease in more patients.

Improved understanding of psoriasis as a chronic systemic disease and of the pathways responsible for the manifestation of psoriatic plaques and inflammation has provided scientists with the opportunity to develop agents with more specific targets. Clinicians, patients, and investigators are hopeful that the results from early-stage clinical trials of newer agents will be confirmed in late-stage development. If this is the case, new treatments will join the most recently approved biologic, secukinumab, as additions to an ever-expanding psoriasis armamentarium—progress that should continue to open new, life-changing doors for patients with all types and degrees of psoriatic disease. ■

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