Psoriasis is a debilitating inflammatory condition that affects physiological and psychological states of millions around the world. Conventional biologic and nonbiologic therapies are fraught with profound adverse side effect profiles, frequent injection requirements, suboptimal outcomes, and other detriments. An enhanced understanding of the role of cytokines in psoriasis, particularly interleukins 12, 17, and 23, has afforded improved therapeutic strategies. Herein, we described the role of cytokines in psoriasis as well as current and prospective therapeutic approaches to treat this debilitating disease. (JAAD Int 2022;9:82-91.)

Key words: biologic agents; cytokine modulators; interleukin inhibitors; plaque psoriasis.

INTRODUCTION

Greater than 7 million Americans have one of the 5 types of psoriasis: plaque, guttate, pustular, inverse, and erythrodermic. Of affected individuals, approximately 80% present with plaque psoriasis, making it the most common type. Plaque psoriasis is a chronic inflammatory skin disease characterized by well-demarcated, red plaques covered by silver scale, which may be painful and/or itchy. Patients may also experience depression, social seclusion, and increased mortality and morbidity. This constellation of, both psychologic and physiologic, comorbidities highlights the importance of effective therapies.

Historically, topical and oral agents were the primary means of plaque psoriasis treatment; however, suboptimal efficacy, repeat monitoring, and frequent dosing intervals rendered these therapeutic strategies subpar for treating moderate-to-severe disease. Elucidating the role of inflammatory mediators in psoriasis yielded new therapeutic targets, which prompted the development of biologic agents that target cytokines. Cytokines are intracellular signaling proteins. This term broadly includes interleukins (ILs), interferons, and growth factors, such as tumor necrosis factor alpha (TNF-α). Approved in 2004, the TNF-α inhibitor, etanercept, was one of the first biologics used for psoriasis treatment. Additional TNF-α inhibitors approved for psoriasis include infliximab, adalimumab, and certolizumab. Although these inhibitors yield superior clinical efficacy compared with nonbiologic therapies, TNF-α inhibitors elicit numerous side effects and require frequent dosing and monitoring. More selective therapies were therefore sought. To that end, biologic agents targeting IL-12, IL-17, and IL-23 emerged over the past 6 years as the most effective treatments of moderate-to-severe plaque psoriasis. Herein, we described the roles of select ILs in psoriasis as they relate to current and prospective IL-modulating therapies.

ROLE OF CYTOKINES IN PSORIASIS

Psoriasis is hypothesized to arise and abate via a 3-part cycle (Fig 1) comprising 1) initiation, 2) perpetuation, and 3) resolution. In part 1, exogenous and/or endogenous triggers compromise the integumentary barrier, damage keratinocytes, and initiate the

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inflammatory response. For example, “outside-in” triggers, or those that are external to the patient but induce the psoriatic cascade, may include trauma, stress, infections with Streptococcus, or exposure to some medications. Briefly, these outside-in triggers induce release of inflammatory mediators that initiate the psoriasis proinflammatory cascade. Furthermore, there is at least one report of onset of generalized erythrodermic psoriasis and one report of onset of plaque psoriasis after COVID-19 vaccination. In addition, there are numerous “inside-out” triggers, or those that are internal to the patient that elicit the psoriatic proinflammatory cascade. One of the primary inside-out culprits identified to-date is the keratinocyte, although numerous additional immune cells have also been implicated in the psoriasis etiology. Inside-out triggers include dysregulated immune cells that result in external manifestations or hallmarks of psoriasis, such as skin perturbations, as well as genetic predisposition. Furthermore, some of these endogenous factors function as autoantigens, and their role in psoriasis initiation and propagation is still under investigation. The 4 autoantigens that have been identified to-date are cathelicidin LL-37, melanocytic ADAMTSL5, lipid antigen PLA2G4D, and keratin 17.

Damaged keratinocytes, regardless of outside-in or inside-out trigger, release numerous inflammatory mediators. Inflammatory mediators stimulate plasmacytid dendritic cells, natural killer cells, and macrophages to release additional inflammatory mediators that activate myeloid dendritic cells (mDCs). Activated mDCs release IL-12 and IL-23, which play novel roles in Parts 2 and 3 of psoriasis.

In Part 2, communication between IL-23 and IL-17 is significant. IL-23-mediated induction of IL-17 synthesis triggers 2 features of psoriasis: 1) keratinocyte proliferation and 2) release of proinflammatory mediators. Specifically, with regard to keratinocyte proliferation, IL-17 induces aberrant hyperproliferation, with corresponding disordered keratinization. With regard to release of proinflammatory mediators, IL-17 induces keratinocytes to release antimicrobial peptides, TNF-α, IL-1β, IL-6, IL-36, and others. Release of inflammatory mediators perpetuates the proinflammatory cycle, leading to further immune cell activation and a state of chronic inflammation complete with immune cell infiltration and neovascularization. Taken together, IL-17-mediated keratinocyte proliferation and sustained inflammation lead to thick, scaling, erythematous psoriatic lesions.

IL-17 and IL-23 are not the only proinflammatory cytokines implicated in psoriasis. Further, IL-12 induces naïve T cells to become Th1 cells. In addition, IL-12 stimulates Th1 and Th22 cells to release TNF-α, IFNγ, and IL-22, which yield keratinocyte hyperproliferation, disordered keratinization, and inflammation. Stressed keratinocytes release inflammatory mediators that stimulate the proinflammatory cycle anew; however, the role of IL-12 in this process is controversial, as discussed in a subsequent section.

In addition to IL-12, IL-17, and IL-23, IL-36 family members have recently been implicated in psoriasis. The stimulation of immune cells mediated by IL-36 releases TNF-α and IL-17. There are 3 IL-36 agonists: IL-36α, IL-36β, and IL-36γ. In healthy skin, inflammatory agonists IL-36α and IL-36β as well as anti-inflammatory antagonist IL-38 are detected. However, in psoriasis, a shift in IL-36 cytokines is observed, favoring the proinflammatory agonists more than the anti-inflammatory antagonists; in fact, IL-36γ expression is only significantly observed in psoriatic skin. Thus, in psoriasis, the proinflammatory and anti-inflammatory balance is disrupted, allowing IL-36α and γ in particular to perpetuate a robust proinflammatory cycle.

Regarding Part 3, resolution, initial research concluded that IL-12 exerted proinflammatory actions in psoriasis. However, more recent evidence
in psoriasis studies involving mouse and human keratinocytes indicated that IL-12 exerted anti-inflammatory actions. Briefly, IL-12 restored keratinocyte cytoskeletal homeostasis and basement membrane integrity in psoriatic lesions. In an IFNγ-independent manner, IL-12 subdued TNF-α’s proinflammatory transcriptome. Finally, IL-12 decreased the accumulation of proinflammatory cells, such as neutrophils and certain Th17 cells. Other cells and cytokines, including regulatory T cells and IL-10, play key roles in restoration of skin homeostasis; however, discussion of these is beyond the scope of this manuscript.

Based on the role of exacerbated IL signaling in psoriasis, numerous IL inhibitors have shown promise in psoriasis treatment, as depicted in Table I.

### SPECIFIC INTERLEUKIN-MODULATING THERAPIES

#### Interleukin-12/23 inhibitor

IL-23 is upregulated in psoriasis and perpetuates a proinflammatory cycle. Consequently, IL-23 is an effective therapeutic target. Discussion of IL-23-modulating therapies warrants a brief description of the composition of IL-23 and IL-12. Specifically, IL-23 has 2 subunits: p40 and p19. The p40 subunit is shared with IL-12. The p19 subunit is novel to IL-23. Approved in 2009, ustekinumab was the first biologic inhibitor targeting IL-12 and IL-23, rather than TNF-α. Ustekinumab binds the p40 subunit, which is common to both IL-12 and IL-23. Thus, ustekinumab inhibits actions of both IL-12 and IL-23. Blocking IL-23 inhibits the proinflammatory actions of IL-23. However, blocking IL-12 inhibits the proinflammatory actions of IL-12, blocking IL-12 may also blunt the protective actions of IL-12. This hypothesis is corroborated by the observation that ustekinumab elicits an inferior Psoriasis Area and Severity Index (PASI) response compared to at least 2 inhibitors that target the novel p19 subunit and do not affect IL-12, based on a head-to-head trial and a network meta-analysis.

#### Interleukin-17 inhibitors

Given the role of IL-17 in inducing keratinocyte hyperproliferation and exacerbated inflammation, IL-17 is another effective target for psoriasis therapy. The modulation of IL-17 occurs via sequestration of the IL-17 cytokine, itself, or binding to IL-17 receptor. Interleukin-17-specific cytokine and receptor inhibitors indicated for psoriasis include secukinumab, ixekizumab, and brodalumab. As shown in Table II, these inhibitors exert similar exceptionally high rates of clinical and immunologic improvement in psoriasis compared to 1) placebo, 2) ustekinumab (dual IL-12/23 inhibitor), and 3) etanercept (TNF-α inhibitor).

Although all the US Food and Drug Administration (FDA) approved IL-17 cytokine and IL-17 receptor inhibitors mitigated psoriasis symptoms, they also worsened Crohn’s disease. In addition, compromised IL-17 function alters the skin microbiome, as evidenced by development of chronic mucocutaneous candidiasis. Though this infection has not been clinically severe and has rarely resulted in discontinuation of IL-17 inhibitor therapy, the incidence of refractory fungal infections is on the rise, globally, so this manifestation should not be ignored. This increased risk of candidiasis is due to the protective role IL-17 plays in natural host defense against candidiasis, as it becomes activated in the presence of Candida to promote further cytokine, chemokine, and antimicrobial protein recruitment. Comparatively, other biologics for psoriasis are not known to worsen Crohn’s disease. In fact, several other biologics such as TNF-α inhibitors, the IL-12/23 inhibitor ustekinumab and an IL-23 inhibitor have demonstrated efficacy in the treatment of Crohn’s disease. One explanation for the lack of negative gastrointestinal effects with biologics outside of the IL-17 inhibitor class may be that IL-17 exerts a protective effect on the gut, to some degree. Thus, indirect, incomplete IL-17 inhibition, for example with pure IL-23 inhibitors, may improve psoriasis outcomes without exacerbating Crohn’s disease.

Although IL-17 inhibitors elicit fewer negative effects compared to TNF-α inhibitors, they carry increased risk of infection (ie, tuberculosis, lymphoma, and neurologic abnormalities including progressive multifocal leukoencephalopathy). Despite these detriments, psoriasis mitigation (PASI 75 improvement in at least 75% of treated patients) resulted in enthusiastic acceptance of this therapeutic modality. IL-17 inhibitors dramatically improved the health and emotional life of those affected by psoriasis; however, a residual percentage of patients do not achieve adequate skin clearance, spurring pursuit of alternative targets, such as pure IL-23 inhibitors.

### Pure interleukin-23 inhibitors

Developed after the dual IL-12/23 inhibitor (ustekinumab) and IL-17 inhibitors, pure IL-23 inhibitors target the IL subunit novel to IL-23: p19. Pure IL-23 inhibitors indicated for psoriasis include guselkumab, tildrakizumab, and risankizumab. Compared to the dual IL-12/IL-23 inhibitor, ustekinumab, the pure IL-23 inhibitors guselkumab and risankizumab inhibitors elicit an improved PASI...
Fig 1. Role of cytokines in psoriasis. Psoriasis is hypothesized to arise and abate via a 3-part cycle comprised of 1) initiation, 2) perpetuation, and 3) resolution. In Part 1, infectious entities, drugs, or trauma (select “outside-in” triggers) compromise the integumentary barrier, damage keratinocytes, and initiate the inflammatory response. Alternatively, autoantigens may initiate the inflammatory response. Numerous other “outside-in” and “inside-out” triggers may also initiate the inflammatory response; they are omitted here for clarity. Damaged keratinocytes release numerous inflammatory mediators, including TNF-α and ILs 1b, 6, 19, 20, and 36. Inflammatory mediators stimulate plasmacytoid dendritic cells, natural killer cells, and macrophages to produce numerous additional mediators, which promote myeloid dendritic cell (mDC) maturation. Activated mDCs release ILs 12 and 23, which play novel roles in Parts 2 and 3 of psoriasis. In Part 2, perpetuation, IL-23 induces naïve T helper cells to become Th17 cells, which include γδ T cells, αβ T cells, and innate lymphoid cells. These Th17 cells then produce IL-17 cytokine family members, of which A and F are the predominant members. Finally, IL-23 activates Th22 cells, which stimulates secretion of interleukin 22, a proinflammatory cytokine that induces inflammation in keratinocytes. Release of inflammatory mediators perpetuates the proinflammatory cycle, leading to further immune cell activation and a state of chronic inflammation complete with immune cell infiltration and neovascularization. Taken together, IL-17-mediated keratinocyte proliferation and sustained inflammation lead to thick, scaling, erythematous psoriatic lesions. IL-17 and IL-23 are not the only proinflammatory cytokines implicated in psoriasis. IL-12 induces naïve T cells to become Th1 cells. Stressed keratinocytes release inflammatory mediators that stimulate the proinflammatory cycle anew, however, the role of IL-12 in this process is controversial, as discussed in a subsequent section. In addition to ILs 12, 17, and 23, IL-36 family members have recently been implicated in psoriasis. IL-36-mediated stimulation of immune cells releases TNF-α and IL-17. In healthy skin, inflammatory agonists IL-36α and IL-36β and anti-inflammatory antagonist IL-38 are detected. In psoriasis, however, a shift in IL-36 cytokines is observed, favoring the proinflammatory agonists more than the anti-inflammatory
Thus, pure IL-23 inhibitors afford excellent improvement in cutaneous and rheumatologic manifestations of psoriasis in most patients. However, some patients, still have an inadequate response to therapy. These biologic treatment failures may be due to aberrant mediator signaling of yet another mediator, IL-36.

**Interleukin-36 Inhibitors**

Given IL-36’s role in psoriasis as described earlier, IL-36 is a promising target for the development of new psoriasis therapy. To that end, imsidolimab and spesolimab are investigational IL-36 receptor inhibitors currently in Phase II and III trials, discussed in a subsequent section.

**CONSIDERATIONS FOR THE TREATMENT OF PLAQUE PSORIASIS**

Many patient and drug-specific factors guide selection of therapeutic agent(s). One such factor is comparative efficacy as determined by PASI response, presented in Table II. Ustekinumab (IL-12/23), secukinumab (IL-17), ixekizumab (IL-17), and tildrakizumab (IL-23) exhibited superior PASI response compared with the TNF-α inhibitor etanercept. Interestingly, although the 2019 psoriasis guidelines state that IL-17 inhibitors are comparable to each other, some notable inter and intrabiologic class differences are being elucidated. For example, a 2019 network meta-analysis found that secukinumab (IL-17), ixekizumab (IL-17), brodalumab (IL-17), guselkumab (IL-23), and risankizumab (IL-23) were more effective at inducing a PASI response compared with all TNF-α inhibitors, tildrakizumab (IL-23), ustekinumab (IL-12/23), and placebo. These findings suggest that more selective inhibition of inflammatory mediators implicated in psoriasis may enhance efficacy.

In addition to the variable PASI outcomes, various biologics exert differences between time to skin clearance (how fast a PASI response is achieved) and sustained skin clearance (how long a PASI response is maintained). Ixekizumab (IL-17) elicited a superior PASI 100 response compared guselkumab (IL-23) at week 12 but was non-inferior or comparable at week 24. Compared to secukinumab (IL-17), both guselkumab (IL-23) and risankizumab (IL-23) demonstrated superior sustained PASI 90 responses at week 48 and week 52, respectively. Taken together, this may indicate that although IL-17 inhibitors like ixekizumab may clear psoriatic lesions faster, pure IL-23 inhibitors like guselkumab and risankizumab may provide a more durable sustained response.

**PROSPECTIVE TREATMENTS**

Evolving evidence of cytokines’ roles in psoriasis has spurred development of additional specific interleukin-modulating therapies.

**Bimekizumab: IL-17A/IL-17F inhibitor**

Bimekizumab is a selective inhibitor of IL-17 family members A and F. IL-17A is generally considered the most biologically active IL-17 cytokine; however, IL-17F is clinically significant because it is elevated in psoriatic skin. In a Phase III trial of patients with moderate-to-severe psoriasis, 91% of patients in the bimekizumab arm achieved PASI 90 at week 16 compared to placebo, indicating relatively high and fast skin clearance. Bimekizumab also demonstrated greater efficacy versus ustekinumab (IL-12/23), secukinumab (IL-17), and adalimumab (TNF-α). Novel inhibition of the IL-17F subtype may account for bimekizumab’s higher PASI scores compared to other IL-17 inhibitors. In September 2020, the FDA accepted the Biologic License Application for bimekizumab. In August 2021, bimekizumab was approved in the European Union. It is being marketed there under the trade name Bimzelx. In May 2022, after delayed facility inspections due to COVID-19, the FDA issued a Complete Response Letter stating that preapproval inspection observations needed to be addressed and resolved before moving forward with bimekizumab consideration for a psoriasis indication in the United States.
Mirikizumab: IL-23 p19 subunit-specific inhibitor

Similar to currently available pure IL-23 inhibitors, mirikizumab binds the p19 subunit of IL-23. In a Phase III trial, mirikizumab was more effective at achieving PASI 90 response at week 52 versus IL-17 inhibitor secukinumab (59% vs 43%, respectively).69 Despite these encouraging results, the manufacturer plans to target inflammatory bowel disease indications in lieu of dermatologic indications at this time.70

Imsidolimab and spesolimab: IL-36R inhibitors

Early phase trials suggest that IL-36R may be a viable target in psoriasis, in particular for less common subtypes such as generalized pustular psoriasis (GPP) and palmoplantar psoriasis.52,53,71 Imsidolimab, an IL-36R inhibitor, is undergoing Phase III trials for GPP.52 A recent Phase II study assessed spesolimab for palmoplantar psoriasis.71 Unfortunately, the sample size was low and the primary endpoint was not met; however, some positive trends were observed. Another phase II trial recently evaluated spesolimab for GPP.72 The results were promising regarding skin clearance after 1 week of a spesolimab infusion but infections and antidrug antibody development were noted.72 The trial investigators concluded that large and long-term trials were needed to determine efficacy and adverse effect risk.72

CLINICAL CONSIDERATIONS

The next iteration of psoriasis guidelines will have a lot to consider. Based on the authors’ clinical experience and above literature review, IL-17 and pure IL-23 inhibitors should be considered first-line agents for moderate-to-severe psoriasis. Ustekinumab, which was novel when it first came out in 2009, should be relegated to a 2nd line agent owing to its inferiority to IL-17 and pure IL-23 inhibitors. Finally, TNF-α inhibitors, which have been a first-line therapeutic agent for years, should be considered 3rd line owing to their comparative efficacy and safety profile.
CONCLUSIONS AND FUTURE DIRECTIONS

Psoriasis is a debilitating chronic disease that results from sustained activation of IL-mediated cell signaling pathways that culminates in inflammation, keratinocyte proliferation, epidermal dysfunction, and disrupted keratinization. Conventional therapies are inadequate, exhibiting poor side effect profiles and suboptimal efficacy. Recent evidence describing cytokines’ roles in psoriasis etiology have spurred the development of specific interleukin modulators that restore homeostatic keratinocyte proliferation and function. Indeed, these novel interleukin inhibitors exhibit superior efficacy compared with TNF-α inhibitors and nonbiologic therapies. Additional topical, biologic, and intracellular therapeutic strategies are also being enthusiastically explored. For example, topical tapinarof, an aryl hydrocarbon receptor modulator, and topical roflumilast, a phosphodiesterase-4 inhibitor, were approved by the FDA for the treatment of mild, moderate, and severe psoriasis in May 2022 and July 2022, respectively.\textsuperscript{73-75} Janus kinus (JAK)-signal transducer and activator of transcription (STAT), IL-36, and IB\textsubscript{z} may also be fruitful therapeutic targets.\textsuperscript{20,76,77} Ultimately, continued efforts to elucidate the complex etiology of psoriasis will afford exquisitely targeted therapies with improved safety profiles and superior therapeutic efficacy for individuals suffering from this debilitating chronic inflammatory disease.

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Conflicts of interest
None disclosed.

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Table II. Comparative Efficacy of IL Inhibitors in Plaque Psoriasis

| Class               | Medication             | Efficacy                                                                 |
|---------------------|------------------------|--------------------------------------------------------------------------|
| IL-17 inhibitors    | Secukinumab (Cosentyx) | 77% achieved PASI 75 at week 12 vs 44% etanercept\textsuperscript{34a}   |
|                     |                        | 84% maintained PASI 75 at week 52 vs 73% etanercept\textsuperscript{34a} |
|                     |                        | 79% achieved PASI 90 at week 16 vs 58% ustekinumab\textsuperscript{39a}  |
|                     |                        | 75% achieved PASI 90 at week 52 vs 61% ustekinumab\textsuperscript{39a}  |
|                     | Ixekizumab (Taltz)     | 87% achieved PASI 75 at week 12 vs 41% etanercept\textsuperscript{31a}  |
|                     |                        | 77% achieved PASI 90 at week 52 vs 59% ustekinumab\textsuperscript{39a}  |
|                     |                        | 41% achieved PASI 100 at week 12 vs 25% guselkumab\textsuperscript{36a}  |
|                     |                        | 50% achieved PASI 100 at week 24 vs 52% guselkumab\textsuperscript{37}   |
|                     | Brodalumab (Siliq)     | 85% achieved PASI 75 at week 12 vs 69% ustekinumab and 6% placebo\textsuperscript{35a} |
|                     |                        | 37% achieved PASI 100 at week 12 vs 19% ustekinumab\textsuperscript{35a} |
|                     | Bimekizumab            | 91% achieved PASI 90 at week 16 vs 1% placebo\textsuperscript{63a}         |
|                     |                        | 85% achieved PASI 90 at week 16 vs 50% ustekinumab and 5% placebo\textsuperscript{64a} |
|                     |                        | 61.7% achieved PASI 100 at week 16 vs 48.9% secukinumab\textsuperscript{65a} |
|                     |                        | 86.2% achieved PASI 90 at week 16 vs 47.2% adalimumab\textsuperscript{66a} |
| IL-12/-23 inhibitor | Ustekinumab (Stelara)  | 67% (45 mg) and 76% (90 mg) achieved PASI 75 at week 12 vs 4% placebo\textsuperscript{30} |
|                     |                        | 68% (45 mg) and 74% (90 mg) achieved PASI 75 at week 12 vs 57% etanercept\textsuperscript{34a} |
| IL-23 inhibitors    | Guselkumab (Tremfya)   | 73% achieved PASI 90 at week 16 vs 50% adalimumab and 3% placebo\textsuperscript{37a} |
|                     |                        | 84% achieved PASI 90 at week 48 vs 70% secukinumab\textsuperscript{58a} |
|                     | Tildrakizumab-asmn (Ilumya) | 61% achieved PASI 75 at week 12 vs 48% etanercept and 6% placebo\textsuperscript{52a} |
|                     | Risankizumab-rzaa (Skyrizi) | 72% achieved PASI 90 at week 16 vs 47% adalimumab\textsuperscript{38a} |
|                     |                        | 75% achieved PASI 90 at week 16 vs 48% ustekinumab and 2% placebo\textsuperscript{29a} |
|                     |                        | 87% achieved PASI 90 at week 52 vs 57% secukinumab\textsuperscript{39a} |

Table II compares efficacy of current FDA-approved interleukin inhibitors and bimekizumab (not FDA-approved) to other biologics and/or placebo. Efficacy is determined by PASI 75, 90, and/or 100 response and is presented based on relevant clinical trial primary endpoints and superiority data.

*Superiority achieved
Update on US-FDA Review of Biologics-License Application-BLA for Bimekizumab

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