



In the Pipeline for Psoriasis: Upcoming Psoriasis Treatments

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Psoriasis is a chronic debilitating disease in which dermatologists take a frontline role in improving the quality of life of affected patients. Although recent years have seen the advent of numerous new medications for the treatment of psoriasis, there still is considerable room for improvement in our treatment of this condition. Novel insights into the underlying mechanisms of psoriasis have yielded exciting new potential medications, many with promising preliminary efficacy data. The upcoming systemic agents for the treatment of psoriasis are presented in this article, encompassing novel biologics and small-molecule medicines (eg, IL-17 receptor blockers, Janus kinase [Jak] inhibitors). The underlying mechanisms and currently available data for each drug will be discussed to impart a working knowledge of these new treatment options to dermatology residents, as these drugs may soon be added to our armamentarium for treating psoriasis.

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Psoriasis is an extremely important disease entity for dermatologists, affecting patients' quality of life to a similar degree as other chronic medical conditions such as diabetes mellitus and congestive heart failure.¹ The incidence of psoriasis in the United States is rising, doubling within the last

several decades according to one population-based study.² Currently, psoriasis affects 1% to 8% of the worldwide population depending on the country³ and certainly represents one of the bread-and-butter skin conditions that fall under the care of dermatologists.

Improvements in psoriasis therapies over the last decade have revolutionized the treatment of this debilitating condition, including increased use of biologics as well as refinements in both administration (dose timing) and mechanism of action. Meanwhile, many novel and exciting therapies currently are in the pipeline, ranging from developmental stages to clinical trials, that target various cytokines and regulatory molecules involved in the pathogenesis of psoriasis. This article will provide an overview of new and upcoming systemic agents for the treatment of psoriasis as well as the currently available data for each drug. It is important for dermatology residents to become familiar with these therapies, as they may soon become widely available.

Novel Biologics

Biologic agents, which are protein-based drugs made from living cells, constitute several currently available therapies for psoriasis. The earliest and most widely available drugs in this family include etanercept, adalimumab, and infliximab. Central to this class of drugs is the concept that psoriasis is a helper T cell (T_H1) disease that involves the interaction between T cells and antigen-presenting cells in psoriatic plaques. These agents target proinflammatory cytokines, such as tumor necrosis factor α (TNF- α). Although several TNF- α agents are already in use, new products are coming to market and gaining approval for psoriasis and/or psoriatic arthritis. For instance, certolizumab has shown not only a significantly increased achievement of psoriasis area

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and severity index (PASI) 75 response (ie, PASI $\geq 75\%$ decrease from baseline) but also a significantly improved PASI 90 response as compared to control ($P < .001$);⁴ to put this finding in context, the rates of PASI 90 for the higher dose (400 mg) of certolizumab approached 50%, while the PASI 90 for etanercept was approximately 23% in numerous studies.^{5,6} Golimumab, another TNF- α agent, also has been approved for the treatment of psoriatic arthritis.

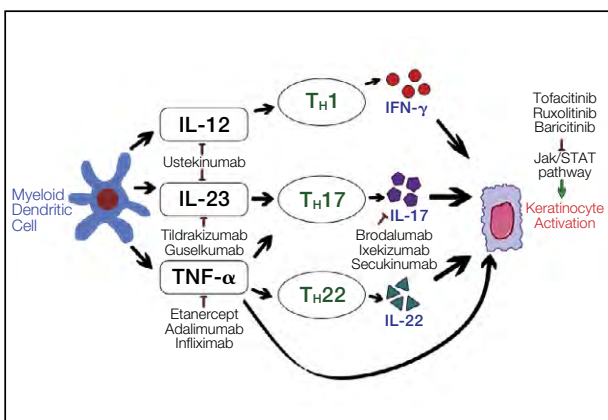
The arrival of ustekinumab, which targets the p40 protein subunit of IL-12 and IL-23, was accompanied by some degree of fanfare, as it went head-to-head against etanercept in a well-publicized trial that showed increased efficacy in treating psoriasis as measured by PASI scores.⁶ Development of novel therapeutics in this class has been centered on identifying new molecules in the proinflammatory cascade or more specific targets (Figure). For some time, it was thought that IL-12 played a more important role than IL-23 (both targeted by ustekinumab) due to the effects of IL-12 on IFN- γ ; however, further studies ultimately revealed that IL-23 is the more critical cytokine, as it is intimately involved in regulating T_H17 cells and is a potent activator of keratinocyte proliferation.^{7,8} Thus, although IL-12 does play a role in driving keratinocyte activation through IFN- γ production, IL-23 has proven to be the more important molecule. Several new drugs that specifically target IL-23 such as guselkumab and tildrakizumab also are under development. Meanwhile, further research has clarified that downstream of IL-23, T_H17 cells further secrete IL-17 and IL-22, which act as critical regulators of keratinocyte development, angiogenesis, and further cytokine release in psoriatic plaques.⁹ Although fezakinumab was being studied to target IL-22, development was discontinued as of August 2011.¹⁰ Following the general idea that more specific

regulators of psoriasis may have increased efficacy and created a more favorable safety profile, several drugs targeting IL-17 are under development, with some extremely promising early-stage results.

Perhaps no class of drugs is as anxiously awaited as the IL-17 receptor blockers.¹¹ The IL-17 family of cytokines encompasses 6 different molecules: IL-17A to IL-17F.¹² Of these molecules, at least IL-17A and IL-17F have been implicated in a wide variety of inflammatory diseases, including psoriasis, multiple sclerosis, systemic lupus erythematosus, inflammatory bowel disease, and chronic mucocutaneous candidiasis.¹³⁻¹⁷ Overall, development of specific IL-17 treatment reflects the paradigm that targeting more specific key regulators in the pathway of keratinocyte activation may lead to improved clinical efficacy while mitigating side effects, such as having less suppressive effects on overall immune defense. Indeed, the preliminary data from trials of agents targeting IL-17 are very promising. Brodalumab is a human monoclonal antibody targeting the IL-17 receptor that inhibits binding of most of the IL-17 subtypes to the receptor. In phase 2 trials (N=198), the mean PASI scores were greater than 85% for the higher doses tested (40, 210, and 280 mg), which were significantly greater compared to placebo ($P < .001$), with a large proportion of patients achieving PASI 90 or PASI 100.¹⁸ These results were remarkable, as such high rates of clearance had not been previously observed with any other biologics. At the same time, results of a phase 2 trial of ixekizumab (N=142), a humanized IgG4 monoclonal antibody against IL-17A, were released.¹⁹ Psoriasis area and severity index scores were significantly improved versus placebo ($P < .001$). In the high-dose group (150 mg), more than 80% of patients achieved PASI 75, more than 70% of patients achieved PASI 90, and nearly 40% of patients achieved PASI 100 with complete clearance of psoriatic lesions.¹⁹ A third agent, secukinumab was developed as a human IgG1 monoclonal antibody to IL-17A. Phase 2 trials encompassing 404 patients also were conducted showing PASI 75 rates of more than 50% and more than 40% in the early and monthly dosing regimens, respectively, both significantly improved from placebo ($P < .001$).^{20,21}

Small Molecules

Although the field of biologic therapy is experiencing rapid growth with many new agents under development, the manufacture of biologic agents remains expensive and complex. An advantage of small molecules is that they are easier to manufacture and may be administered orally, a characteristic that would certainly be preferable over injections



Psoriasis pathway and targets of selected agents.

for many patients. Although older medications (eg, methotrexate) have long been a part of the dermatologist's armamentarium for treatment of psoriasis, there also are newer targeted therapies on the horizon.

Janus kinases (Jak) are intracellular tyrosine kinases that respond to cytokine signaling to mediate the STAT pathway. Overall, these kinases are involved in responding to signals from proinflammatory interleukins such as IL-2, and by phosphorylating STAT, they activate transcription of target genes in the nucleus.²² Although target genes in the proinflammatory cascade have been identified as part of the Jak/STAT pathway, ongoing research is being conducted to try to fully elucidate the intricacies of this signaling pathway, which has extensive cross talk toward other signaling pathways such as Ras/MAPK, PI3K, and transforming growth factor β .²³ Of these kinases, Jak1 and Jak2 signaling pathways are ubiquitously expressed along with Tyk2, a member of the Jak family; Jak3 is mainly expressed within the immune system in hematopoietic cells. For psoriasis, Jak inhibition was shown to attenuate psoriasiform inflammation in a mouse model of psoriasis and also downregulated systemic levels of IL-17, IL-22, IL-23, and TNF- α .²⁴ Tofacitinib is a small-molecule Jak3 inhibitor that has been studied in phase 2 trials (N=197). The highest dose (15 mg) achieved a PASI 75 of 66.7%, which was significantly improved from placebo ($P<.0001$).²⁵ Results from phase 3 trials are expected shortly. Baricitinib and ruxolitinib are 2 other Jak inhibitors under investigation for the treatment of psoriasis. In conjunction with these medications, a topical formulation of ruxolitinib has been developed (formerly known as INCB018424). In a preliminary study, this topical Jak inhibitor was shown to significantly decrease psoriatic lesion thickness, erythema, scaling, and area as compared to a vehicle control ($P<.05$).²⁶

Other small-molecule drugs acting on several steps in the proinflammatory signaling cascade in psoriasis that results in keratinocyte activation also are under development. Apremilast is a phosphodiesterase-4 inhibitor that works on the cAMP pathway. In immune regulation, cAMP acts on protein kinase A to prevent the activation of transcription factors, ultimately resulting in decreased proinflammatory cytokine production. Phosphodiesterase-4 blocks the degradation of cAMP, thereby enhancing its function in negatively regulating inflammation.²⁷ A phase 2 trial of apremilast (N=352) showed significantly improved PASI 75 compared to control ($P<.001$) for the 2 higher doses (20 or 30 mg twice daily) tested, with 41% of patients in the highest dose category achieving PASI 75.²⁸ A topical

formulation of phosphodiesterase-4 also is under development, with phase 2 trials of AN2728 revealing significantly improved overall target plaque severity score of areas treated with the higher concentration 2% ointment as compared to control ($P<.004$) (discrete untreated plaques on the same individual served as self-controls in this trial).²⁹ Another novel target is sphingosine-1-phosphate receptor 1, or S1P1, which is a G protein-coupled receptor on endothelial cells that has important effects on lymphocyte migration.³⁰ In short, modulation of S1P1 abrogates the ability of lymphocytes to sense sphingolipid gradients, which normally serves as a signal for egress from lymphoid tissue into peripheral circulation, thereby reducing lymphocyte recruitment to sites of inflammation. Ponesimod is an S1P1 agonist that has been studied in phase 2 trials, with nearly half of patients in 2 dose ranges achieving PASI 75 at week 16, significantly better than control ($P<.001$).³¹ Other drugs in development include SRT2104, which acts on sirtuin 1, an enzyme involved in cellular regulation; FP187, a controlled-release dimethyl fumarate that is thought to act on nuclear factor κ B-dependent transcription of TNF- α genes, leading to decreased peripheral T lymphocytes³²; and sotrastaurin, a protein kinase C inhibitor that blocks T-cell activation, reduces IL-2 production, and was shown in preliminary trials to significantly improve PASI scores for treatment cohorts compared to control,³³ albeit with a short 2-week treatment period ($P<.001$ for the highest-dose [300 mg] group). Additional small molecules are being studied and no doubt the pipeline for psoriasis will continue to grow as new discoveries in basic science are made.

Safety

Adverse events are a primary concern raised in all clinical trials. As we have learned through multiple lessons in the development of psoriasis treatments, efficacy is nothing without patient safety. The very promising drug efalizumab, a CD11a blocker, was voluntarily withdrawn from the market by the manufacturer due to development of progressive multifocal leukoencephalopathy in several patients.³⁴ Although ustekinumab has been approved for use, its cousin briakinumab in the same class did not have a similar fate, as concerns of major adverse cardiovascular events prompted its withdrawal from the market by the manufacturer, with 4 cardiovascular deaths reported in trials.³⁵ Several of the trials described here had adverse events, and many of the major adverse events were related to neutropenia or lymphopenia, as may be expected from the mechanisms of action for these immunoregulatory drugs.³⁶ These adverse events need to be balanced against the concerns of

considerable side effects from other psoriasis treatments, such as methotrexate or acitretin, which each carry their own notable adverse effects such as hepatotoxicity and teratogenicity. Although some of the study results reported portend a bright future for the treatment of psoriasis, these exciting results should be approached with cautious optimism. Only further experience with these drugs will reveal the full story on the side-effect profile and long-term efficacy.

Conclusion

The pipeline for psoriasis treatment contains many promising new drugs in injectable, oral, and topical formulations. In the next several years, we should see the release and public availability of a wealth of new agents for the treatment of psoriasis, many of these with previously unattainable levels of efficacy. For those unwilling or unable to pursue biologic therapy, oral agents with similar efficacy as some of the earlier biologics also should become available. Familiarity with these medications and their mechanisms of action will help dermatologists decide what the best treatment strategy is for each patient.

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