Therapeutic Development in Psoriasis

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Abstract

Advances in molecular biology have provided the basis for development of new therapeutic approaches to psoriasis. New, more effective therapies target specific molecules in the inflammatory cascade involved in the pathogenesis of psoriasis.The biologic era of psoriasis therapy began with inhibitors of T-cell activation, tumor necrosis factor-α, and interleukin (IL)-12/23. Continued investigation has led to therapies and therapeutic candidates that target IL-17, IL-23, phosphodiesterase-4, and isomers of Janus kinase.

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Keywords

Apremilast; brodalumab; inflammation; interleukin-12/23; ixekizumab; JAK interlukin-17 inhibitors; Janus kinase inhibitors; monoclonal antibody; phosphodiesterase-4; psoriasis; secukinumab; tofacitinib; tumor necrosis factors

Pathophysiology of Psoriasis

Only relatively recently did clinicians and researchers come to recognize psoriasis as an immune-mediated inflammatory skin disease. The recognition was preceded by years of pursuing strategies to alter or correct defects in keratinocytes, the presumptive cause of uncontrolled cellular proliferation culminating in plaque psoriasis.

The concept of psoriasis as an immunologic disorder has its genesis in the observation that treatment with cyclosporine dramatically improved the condition. Even then, the proof was not definitive, because cyclosporine has a known effect on replicating keratinocytes.

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The pivotal point in understanding occurred with completion of the DAB-IL-2 trial using denileukin diftitox, which specifically targets T cells. Knowledge gained from that trial confirmed the T cell as central to the pathogenesis of psoriasis and provided the impetus for evaluation of immunologic strategies to treat the disease.[1]

The immunologic framework of psoriasis has evolved continually with advances in understanding the molecular basis of the disease. As recently as a decade ago, psoriasis pathophysiology was thought to begin with a yet-to-be identified antigen, which was transported by an antigen-presenting cell to a skin-draining lymph node, wherein T-cell activation began. The T cells were believed to be transported back to the skin through the vasculature, and, upon re-entry, to trigger the release of inflammatory mediators, including tumor necrosis factor (TNF)-α. This conceptual framework of psoriasis led to development of first-generation biologic agents, alefacept and efalizumab, which targeted T-cell activation.[2]

As understanding of psoriasis pathogenesis has continued to evolve, so have strategies to treat the disease (**Table**). As currently understood, psoriasis pathogenesis begins with activation of myeloid dendritic cells, leading to the release of interleukin (IL)-12 and IL-23. IL-12 plays a key role in the differentiation of T cells in the T-helper (T_H) 1 pathway, which has been the focus of therapeutic development for the past several years.

New Pathway for Drug Development

Investigation of IL-23 has shown that the proinflammatory cytokine facilitates activation and survival of T_H17 cells, which, in turn, stimulate release of inflammatory mediators such as IL-17 and IL-22. The inflammatory mediators interact with TNF and interferon-γ, leading to activation of keratinocytes.

In the context of psoriasis, IL-17 has several key activities.[3] IL-17 recruits T_H17 cells and myeloid dendritic cells into plaques, facilitates neutrophil migration and survival, and increases antimicrobial peptides to enhance innate immunity. Additionally, IL-17 stimulates angiogenesis and vascular inflammation associated with atherosclerosis, a possible clue to the increased cardiovascular risk that has been observed in patients with psoriasis.

Six isoforms of IL-17 have been identified (IL-17A, B, C, D, F, and γ).[4] With respect to psoriasis, IL-17A is highly expressed in skin lesions and has become a target of therapeutic development.

Secukinumab

Secukinumab is a fully human anti-IL-17A monoclonal antibody. The drug has been evaluated in four phase III trials, including two pivotal trials, known as ERASURE (Efficacy of Response and Safety of 2 Fixed Secukinumab Regimens in Psoriasis) and FIXTURE (Safety and Efficacy of Secukinumab Compared to Etanercept in Subjects With Moderate to Severe, Chronic Plaque-Type Psoriasis).

TABLE Biologic Agents and Small Molecules in Psoriasis

Class/Target Pathway	Generic Drug Name/Description	Current Status*
Biologic agents		
TNF-α inhibition	Adalimumab: Recombinant human IgG1 monoclonal antibody specific for human TNF	Approved for psoriasis, 2008
	Etanercept: Dimeric fusion protein consisting of the extracellular ligand-binding portion of the p75 TNF receptor, linked to the Fc portion of human IgG1	Approved for psoriasis, 2004
	Infliximab: Chimeric IgG1κ monoclonal antibody, composed of human constant and murine variable regions, specific for human TNF	Approved for psoriasis, 2006
IL-12 and IL-23 inhibition	Ustekinumab: Human IgG1κ monoclonal antibody against the p40 subunit of the IL-12 and IL-23 cytokines	Approved for psoriasis, 2008
Direct inhibition of IL-17	Brodalumab: Fully human anti-IL-17 receptor monoclonal antibody	Phase III trials under way
	Ixekizumab: Humanized anti-IL-17A monoclonal antibody	Phase III trials under way
	Secukinumab: Fully human anti-IL-17A monoclonal antibody	Phase III trials complete
IL-23 blocker	Tildrakizumab: Humanized anti-IL-23p19 monoclonal antibody	Phase III trials under way
	Guselkumab: Fully human anti-IL-23p19 monoclonal antibody	Phase II trials complete
Small molecules		
PDE-4 inhibitor	Apremilast: Inhibitor of phosphodiesterase 4	Approved for psoriatic arthritis, 2014
JAK inhibitor	Tofacitinib: Inhibitor of Janus kinase	Phase III trials complete

IL=interleukin; JAK=Janus kinase; PDE-4=phosphodiesterase-4; TNF=tumor necrosis factor.
*The status listed for each agent is current as of June 23, 2014.

ERASURE was a randomized, placebo-controlled trial involving 738 patients with moderate or severe plaque psoriasis.[5] Patients received secukinumab 300 mg or 150 mg or placebo, administered once a week for 4 weeks and then every 4 weeks thereafter.

The primary end point was 75% improvement on the Psoriasis Area Severity Index (PASI75). Placebo-treated patients who did not have PASI75 responses after 12 weeks were randomized a second time to 300 or 150 mg of secukinumab. Maintenance therapy continued in all groups for an additional 40 weeks.[5]

The study population had a mean disease duration of about 17 years. Body surface area involvement averaged about 30%, and the patients had a baseline mean PASI score of 22. About 20% of the patients had psoriatic arthritis.[5]

The results showed a rapid onset of action in patients treated with secukinumab. After 12 weeks, 81.6% of patients in the 300-mg secukinumab group had met criteria for a PASI75 response, as had 71.6% of patients in the 150-mg group. By comparison, 4.5% of placebo-treated patients had a PASI75 response ($P<0.0001$). The PASI75 response rate reached a peak of 87.8% in the secukinumab 300-mg group at 16 weeks.[5]

Increasingly, the benchmark for efficacy is focusing on PASI90 (minimal residual disease) and PASI100 (clear) responses. In the secukinumab 300-mg group, 70% of patients had PASI90 responses at 16 weeks, and 40% had PASI100 responses.[5]

With continued monthly maintenance doses, the responses proved to be durable out to 52 weeks, as response rates were about 80% for PASI75, 70% for PASI90, and 40% for PASI100.[5]

The 52-week safety data provided reassurance. The incidence of serious adverse events was low and comparable in the secukinumab groups, and less than 5% of patients discontinued because of adverse events. The most common adverse events were nasopharyngitis (20%-25%), upper respiratory tract infections (11%-12%), and headache (9%).[5]

FIXTURE was a four-arm randomized trial involving 1,300 patients with moderate or severe psoriasis.[6] Patients received one of two doses of secukinumab, placebo, or etanercept 50 mg twice weekly for 12 weeks, then weekly thereafter. Similar to the patients in the ERASURE trial, the FIXTURE study population had a mean disease duration of 16 years, baseline mean PASI score of 24, and body surface area involvement of about 34%. About 15% of the patients had psoriatic arthritis.

PASI75 response rates at week 12 were 77% and 67% in the 300-mg and 150-mg secukinumab groups, respectively, compared to 44% in the etanercept arm. The PASI90 rate reached a maximum of 72.4% at 16 weeks with the 300-mg dose of secukinumab versus 41.5% with etanercept at 32 weeks. PASI100 scores peaked at 36.8% after 16 weeks with secukinumab 300 mg and 13.0% at 32 weeks with etanercept.[6]

Underscoring the rapid onset of action with secukinumab, 50% of patients treated with the 300-mg dose had a 50% reduction in baseline PASI score within 3 weeks. Patients treated with etanercept did not pass the 50% improvement mark until week 8.[6]

The safety profile of secukinumab was similar to what was observed in the ERASURE trial. Serious adverse events occurred in a similar proportion of patients treated with secukinumab or etanercept. The most frequently reported adverse events in all groups were nasopharyngitis and headache.[6]

Ixekizumab

Ixekizumab is a humanized anti-IL-17A monoclonal antibody. Results were reported recently from a phase II trial in which 132 patients with moderate to severe psoriasis were randomized to one of four subcutaneous doses of ixekizumab (10-150 mg) or placebo.[7] Patients received induction doses at baseline, 2 weeks, and 4 weeks, followed by monthly treatment at weeks 8, 12, and 16. The primary end point was PASI75 at 12 weeks.

The results showed that patients treated with the three highest doses of ixekizumab (25, 75, and 150 mg) had PASI75 rates of 77% to 83% at 12 weeks as compared with 29% in the ixekizumab 10-mg arm and 8% in the placebo group. The week 12 PASI90 rates ranged between 50% and 70% for the three highest doses of ixekizumab versus 20% for the lowest dose and 0% for the placebo group. PASI100 rates reached a maximum of about 40% at week 12 with the two highest doses of ixekizumab.[7]

No serious adverse events occurred in any group during the study. The most frequent adverse events across all treatment groups were infection and nasopharyngitis, rates of which were low and similar to placebo. Nonserious injection-site reactions were observed with the three highest doses of ixekizumab but occurred in 10% or less of patients in the groups.[7]

Closer inspection of the onset of action showed that achieving a PASI50 by 4 weeks was highly predictive of PASI75 success by week 12.[8] Patients who responded early (PASI50 at week 4) were significantly more likely to attain PASI75 and PASI100 responses at 8, 12, and 16 weeks than were patients who did not attain PASI50 at 4 weeks ($P<0.05$ to $P<0.001$).

Participants in the phase II trial of ixekizumab had an opportunity to enter a 52-week open-label extension study in which all patients received 120 mg of ixekizumab every 4 weeks.[7]

The results showed rapid, high, and sustained rates of PASI75, PASI90, and PASI100 responses through 52 weeks in patients who initially received ixekizumab or placebo. The favorable safety profile observed during the randomized study continued through the open-label extension portion of the study.[9]

Brodalumab

In contrast to secukinumab and ixekizumab, brodalumab is a fully human monoclonal antibody against the IL-17 receptor. The agent was evaluated in a phase II study in which patients with moderate to severe psoriasis were randomized to one of four doses of brodalumab or placebo for 12 weeks.[10]

Across the four dose groups, the highest response rates were 83% for PASI75, 75% for PASI90, and 63% for PASI100. The best results occurred with the two intermediate doses of brodalumab administered every 2 weeks (140 and 210 mg).[10]

Assessment of quality of life showed that a majority of patients had Dermatology Life Quality Index (DLQI) scores of 0 or 1, meaning that neither the disease nor the treatment had a negative effect on daily life. The findings were highest and similar in the two intermediate-dose groups.[10]

The drug had a favorable safety profile that included small increases in arthralgia, pharyngitis, pain in extremity, and injection-site reactions versus placebo when all brodalumab groups were combined.[10]

Brodalumab also was evaluated in a 96-week open-label extension study.[11] Patients received weight-adjusted doses at baseline and weeks 1 and 2, followed by treatment every 2 weeks. The primary outcomes were PASI response rates, adverse events, and serious adverse events.

Of 173 patients who began the study, 153 completed the 96 weeks of treatment and follow-up. By week 8, more than 90% of the patients had attained PASI75 responses, a rate that was maintained through the end of follow-up (as-observed analysis). The PASI90 rate surpassed 80% by week 12 and stabilized at that level to week 96. More than 60% of the patients had PASI100 responses by week 8, a rate that remained stable through the end of the extension study.[11]

Targeting IL-23

Agents have been developed to target the p40 subunit common to IL-12 and IL-23, most notably, ustekinumab. However, theoretical considerations suggest that targeting IL-23 in isolation might have advantages.[12] In particular, IL-12 affords protection against infection and malignancy. Furthermore, recent investigations reveal elevated levels of p19 (subunit of IL-23) in the psoriatic plaque, but not p35 (subunit of IL-12).[13]

Tildrakizumab is a humanized monoclonal antibody against IL-23p19. Investigators in a phase IIb clinical trial randomized 340 patients to one of four doses of tildrakizumab or placebo.[13] The primary end point was PASI response rates at week 16. The results showed PASI75 rates of 65.5% to 76.2% for the three highest doses of the antibody. The highest dose led to a PASI90 rate of 51.2% at 16 weeks.

In the pivotal PHOENIX 1 (Psoriasis Followed by Long-Term Extension) trial of ustekinumab, PASI75 rates were 76% and 85% with two different doses of the drug. However, full efficacy was not reached until week 24. At week 16, the PASI75 rates were similar to those observed with tildrakizumab, supporting the hypothesis that blocking IL-12 has minimal therapeutic relevance in psoriasis.[14]

The most common adverse event in the phase IIb trial of tildrakizumab was nasopharyngitis. Overall, the frequency or type of adverse events did not differ substantially between the tildrakizumab and placebo groups.[13]

Patients who achieved PASI75 responses in the trial were eligible to enter an extension phase that continued to week 52. Results of the extension study showed that response to tildrakizumab remained stable out to 52 weeks.[15]

Small-Molecule Inhibitors

Recent therapeutic development in psoriasis has focused primarily on injectable agents. However, several oral small-molecular inhibitors are in development and evaluation.

Apremilast

Apremilast is an inhibitor of phosphodiesterase-4. In contrast to specifically targeted biologic agents, the key mechanism of action is unclear, as apremilast has multifaceted anti-inflammatory properties. The agent reduces levels of TNF-α, IL-2, interferon-γ, several leukotrienes, and nitric oxide synthase.

The pivotal phase III ESTEEM 1 (Study to Evaluate Safety and Effectiveness of Oral Apremilast (CC-10004) in Patients With Moderate to Severe Plaque Psoriasis) trial compared apremilast and placebo in 844 patients with moderate or severe psoriasis, including patients who had not achieved adequate responses to anti-TNF therapy.[16] The primary end point was PASI75 rate at 16 weeks.

A third of patients attained PASI75 responses after 16 weeks, significantly better than placebo ($P=0.0273$ to $P<0.0001$). The highest response rates (38.7% and 35.8%) occurred in the subgroups of patients who had no prior exposure to systemic therapy or to biologic agents.[16]

Placebo-treated patients could switch to apremilast after 16 weeks if they had not attained or maintained a PASI75 response. Similar to patients who started treatment with apremilast, a third of those who crossed over to apremilast attained PASI75 responses by week 32.[16]

Analysis of secondary end points consistently demonstrated superiority of apremilast to placebo, including pruritus, DLQI, Physician Global Assessment, and improvement in nail scores.[16]

Apremilast also was evaluated in a phase III trial involving patients with psoriatic arthritis.[17] The patients were randomized to one of two doses of apremilast or placebo, and the trial's primary end point was 20% improvement in disease status by American College of Rheumatology (ACR20) criteria at week 12.

About 30% of patients attained ACR20 responses in both apremilast groups combined versus 17% in the placebo group. After 52 weeks of treatment and follow-up, ACR20 rates were 53.4% and 58.7% with the 20-mg twice-daily and 30-mg twice-daily treatment groups.[17]

The ACR20 response rates at 52 weeks are comparable to rates observed in randomized clinical trials of TNF inhibitors. However, the response rates with TNF inhibitors were attained in less than half the time (24 vs 52 weeks).[18,19]

Tofacitinib

A member of the Janus kinase (JAK) inhibitor class, tofacitinib has US Food and Drug Administration (FDA) approval for the treatment of rheumatoid arthritis (RA). The drug inhibits three isomers of JAK but is more specific for JAK1 and JAK3 than for JAK2. Tofacitinib has multiple downstream effects on inflammatory cytokines and chemokines and other proinflammatory cells, including T cells and natural killer cells. Trials in psoriasis have shown the agent is highly efficacious and relatively well tolerated.[20]

Tofacitinib was evaluated in a phase IIb randomized dose-finding study.[20] Patients were randomized to placebo or to one of three doses of the JAK inhibitor. The results showed a dose-dependent increase in the PASI75 response rate versus placebo, achieving separation from placebo as early as 4 weeks and continuing to 12 weeks. The 12-week PASI75 rate approached 70% in patients treated with the highest dose (15 mg twice daily).

Five serious adverse events occurred, three of which involved the same patient. Tofacitinib was associated with minor decreases in hemoglobin, transient decreases in polymorphonuclear neutrophils, and dose-related increases in both high-density and low-density lipoprotein cholesterol.[21]

FDA approval of the drug for RA included a required black-box warning related to a numerical increase in the rate of malignancy other than nonmelanoma skin cancer. Although not statistically significant, the observation is consistent with an association between increasing exposure to tofacitinib and increased risk of malignancy.

A recent analysis of tofacitinib-associated malignancy in patients with RA did not clearly demonstrate a numerical increase in risk over time.[22] However, the data also did not provide clear evidence of a decreased risk, which would be expected in the late phases of long-term treatment where there is an enrichment of study subjects who tolerate the drug and are responding well.

The FDA also has taken note of opportunistic infections, including tuberculosis, in tofacitinib-treated patients with RA. In the RA development program, almost three dozen opportunistic infections were documented, all occurring in tofacitinib-treated patients. Additionally, 14 of 15 patients who died of infection were treated with tofacitinib. The observed pattern of infectious events is consistent with significant immunosuppression, according to the FDA.[23]

Summary

After years with few effective options for treatment of psoriasis, a steady pattern of market expansion has given clinicians and patients reason for optimism that the difficult, frequently treatment-resistant disease can be controlled. Therapeutic development continues at a rapid pace as compared with historical experience. New biologic agents have driven response rates to new heights. Advances in understanding the molecular biology of psoriasis has led to new therapeutic strategies that have shown promise for continued improvement of outcomes.

References

1. Martin A, Gutierrez E, Muglia J, et al. A multicenter dose-escalation trial with denileukin diftitox (ONTAK, DAB(389)IL-2) in patients with severe psoriasis. *J Am Acad Dermatol*. 2001;45:871-881.
2. Nestle FO, Kaplan DH, Barker J. Psoriasis. *N Engl J Med*. 2009;361:496-509.
3. Girolomoni G, Mrowietz U, Paul C. Psoriasis: Rationale for targeting interleukin-17. *Br J Dermatol*. 2012;167:717-724.
4. Johansen C, Usher PA, Kjellerup RB, Lundsgaard D, Iversen L, Kragballe K. Characterization of the interleukin-17 isoforms and receptors in lesional psoriatic skin. *Br J Dermatol*. 2009;160:319-324.
5. Elewski B et al. ERASURE study of secukinumab phase 3 study. Presented at: 22nd Annual Congress of the European Academy of Dermatology and Venereology; October 2-6, 2013; Istanbul, Turkey.
6. Langley R et al. Secukinumab compared with placebo and etanercept: The first 52-week head-to-head comparison of two biologics in a randomized, double-blind, phase 3 study in subjects with moderate-to-severe psoriasis. Presented at: 22nd Annual Congress of the European Academy of Dermatology and Venereology; October 2-6, 2013; Istanbul, Turkey.
7. Leonardi C, Matheson R, Zachariae C, et al. Anti-interleukin-17 monoclonal antibody ixekizumab in chronic plaque psoriasis. *N Engl J Med*. 2012;366:1190-1199.
8. Zhu B, Edson-Heredia E, Cameron GS, et al. Early clinical response as a predictor of subsequent response to ixekizumab treatment: Results from a phase II study of patients with moderate-to-severe plaque psoriasis. *Br J Dermatol*. 2013;169:1337-1341.
9. Gordon K, Leonardi C, Braun D, et al. Results after at least 52 weeks of open label treatment with ixekizumab, an anti-IL-17A monoclonal antibody, in a phase 2 study in chronic plaque psoriasis. *J Am Acad Dermatol*. 2014;70(5 suppl 1):AB183.
10. Papp KA, Leonardi C, Menter A, et al. Brodalumab, an anti-interleukin-17-receptor antibody for psoriasis. *N Engl J Med*. 2012;366:1181-1189.
11. Papp K, Leonardi C, Menter A, et al. Improvement of psoriasis in patients with and without prior brodalumab (AMG 827) treatment in an open-label extension study. Presented at: Canadian Dermatology Association's 88th Annual Conference; June 27-30, 2013; Quebec City, QC, Canada.
12. Yuzhalin AE, Kutikhin AG. Interleukin-12: Clinical usage and molecular markers of cancer susceptibility. *Growth Factors*. 2012;30:176-191.
13. Thaci D et al. Poster presented at: 22nd Annual Congress of the European Academy of Dermatology and Venereology; October 2-6, 2013; Istanbul, Turkey. P1537.
14. Leonardi CL, Kimball AB, Papp KA, et al. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 76-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 1). *Lancet*. 2008;371:1665-1674.
15. Reich K et al. Poster presented at: 22nd Annual Congress of the European Academy of Dermatology and Venereology; October 2-6, 2013; Istanbul, Turkey. Poster 1540.
16. Reich K et al. Apremilast, an oral phosphodiesterase 4 inhibitor, in patients with moderate to severe psoriasis: 16-week results of a phase 3, randomized, controlled trial (ESTEEM 1). Presented at: 71st Annual Meeting of the American Academy of Dermatology; March 1-5, 2013; Miami Beach, FL.
17. Schett G, Wollenhaupt J, Papp K, et al. Oral apremilast in the treatment of active psoriatic arthritis: Results of a multicenter, randomized, double-blind, placebo-controlled trial. *Arthritis Rheum*. 2012;64:3156-3167.
18. Antoni C, Krueger GG, de Vlam K, et al. Infliximab improves signs and symptoms of psoriatic arthritis: Results of the IMPACT 2 trial. *Ann Rheum Dis*. 2005;64:1150-1157.
19. Bachmann F, Nast A, Sterry W, Philipp S. Safety and efficacy of the tumor necrosis factor antagonists. *Semin Cutan Med Surg*. 2010;29:35-47.
20. Papp KA, Menter A, Strober B, et al. Efficacy and safety of tofacitinib, an oral Janus kinase inhibitor, in the treatment of psoriasis: A phase 2b randomized placebo-controlled dose-ranging study. *Br J Dermatol*. 2012;167:668-677.
21. Mamolo C, Harness J, Tan H, Menter A. Tofacitinib (CP-690,550), an oral Janus kinase inhibitor, improves patient-reported outcomes in a phase 2b, randomized, double-blind, placebo-controlled study in patients with moderate-to-severe psoriasis. *J Eur Acad Dermatol Venereol*. 2013 Jan 7. doi: 10.1111/jdv.12081. [Epub ahead of print]
22. Curtis JR, Mariette X, Lee EB, et al. Tofacitinib, an oral Janus kinase inhibitor: Analysis of malignancies across the rheumatoid arthritis clinical program. Presented at: American College of Rheumatology/Association of Rheumatology Health Professionals Annual Meeting; October 26-30, 2013; San Diego, CA. Abstract 802.
23. Arthritis Advisory Committee Meeting, May 9, 2012. NDA 203214: Tofacitinib for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had inadequate response to one or more disease-modifying anti-rheumatic drugs. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ArthritisAdvisoryCommittee/UCM302958.pdf. Accessed June 13, 2014.