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New Therapies for Psoriasis and Psoriatic Arthritis

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Abstract

Purpose of review—Over the last several years, novel immunologic pathways pivotal in the development of the pathobiology of psoriasis and psoriatic arthritis have been revealed. These discoveries catalyzed a search for new treatment targets resulting in many new therapies that are now available for patients with psoriatic disease.

Recent findings—Helper T cells that secrete IL-17 (TH17) along with CD8+ cells, innate lymphocyte cells and gamma delta T cells are important in the pathogenesis of psoriasis and psoriatic arthritis (PsA). Recently, agents that target IL-17, the IL-17 receptor, and IL-23 (anti-p19) have been approved or are in clinical trials. Apremilast, a new oral agent, was approved for treatment of psoriasis and PsA.

Summary—Secukinumab, an IL-17A antibody has been approved for treatment of psoriasis and PsA in the US. It is effective with a good safety profile. Ixekizumab, another anti-IL-17A antibody is currently in clinical trials and brodalumab, an IL-17 receptor antagonist, was removed from clinical trials due to safety concerns despite demonstrated efficacy in psoriasis and PsA. Targeting IL-23 with antibodies to p19 is another approach with encouraging results in psoriasis. Apremilast, an oral agent approved to treat psoriasis and PsA demonstrates moderate efficacy with an excellent safety record. The role of tofacitinib in psoriatic disease remains to be determined pending a safety review in psoriasis and completion of PsA trials.

Keywords

psoriasis; psoriatic arthritis; IL-17; IL-23; PDE4

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Conflict of Interest:

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INTRODUCTION

Psoriasis vulgaris is an autoimmune disease of the skin, but it is associated with systemic inflammation and co-morbid conditions that are linked to inflammatory processes, e.g., metabolic syndrome, cardiovascular disease, inflammatory bowel disease and inflammatory arthritis [1]. Psoriatic arthritis (PsA) is an inflammatory joint disease associated with psoriasis characterized by heterogeneous musculoskeletal phenotypes that involve multiple domains including the peripheral joints, axial skeleton, insertion sites (entheses) and digits (dactylitis) [2]. Therapeutic options for the treatment of both psoriasis and PsA have increased dramatically over the past 15 years resulting in markedly improved outcomes for skin and joint disease. Consider that at the turn of the century the main therapies for moderate to severe psoriasis were topical agents, phototherapy, methotrexate and cyclosporine. Therapies for PsA included methotrexate, sulfasalazine and injectable corticosteroids. The arrival of anti-TNF agents represented a major treatment advance because these therapies were very effective for psoriasis and all the musculoskeletal domains of PsA. Despite improved outcomes, approximately 45% of psoriasis and PsA patients did not achieve the PASI 75 skin response or ACR 20 composite joint outcome, respectively.

Advances in our understanding of immunologic pathways revealed that molecules in the IL-23-IL-17 pathway are critical to host defense against staphylococcus, candida and other pathogens and that these molecules also promote skin and joint inflammation[3]. Based on these discoveries, efforts to target molecules in the IL-23-IL-17 and PDE4 pathway to treat psoriasis and inflammatory arthritis commenced resulting in an array of approved therapies for both psoriasis and PsA. In this Review, we will discuss linkage between our revised conceptual understanding of the pathobiology of psoriasis and PsA and the recent therapies that target pathways crucial for the development of skin and joint inflammation. We will also discuss pivotal clinical trials highlighting the efficacy and safety of the new biologic therapies for psoriatic disease.

Psoriasis vulgaris: Pathobiology and therapies are highly linked

Psoriasis vulgaris is an autoimmune disease of the skin, but it is associated with systemic inflammation and co-morbid conditions that are linked to inflammatory processes, e.g., psoriatic arthritis, cardiovascular disease, and inflammatory bowel disease. In the skin, lesions are created primarily by two immune cell types: myeloid (CD11+) dendritic cells (DCs) and T-cells that produce “driver” cytokines of this disease and those cytokines act upon keratinocytes and other skin-resident cell types to create a hyper-proliferative epidermis that is associated with vascular proliferation, vascular dilation, and dermal inflammation. Clinically, these cellular changes produce red, raised plaques that typically have white-to-silver scales on the surface. Usually disease severity is classified by the extent or location of inflammatory lesions, with mild disease defined as <10% affected skin surface and moderate-to-severe disease as >10% skin surface or affecting critical functional regions such as the hands or feet. New therapies have been developed primarily for moderate-to-severe disease, which is judged to be so extensive that it is beyond treatment with topical agents. In turn, these therapies have been developed with a growing understanding of

pathogenic immune cell/cytokine circuits that drive the skin disease and may also contribute to disease co-morbidities.

The central immune axis that drives psoriasis vulgaris is created by at least two endogenous autoantigens (cathelicidin/LL-37 and ADAMTS-like protein 5 (ADAMTSL5)), ensuing T-cell activation, and the production of a Type 17 (Th17/Tc17) polar response that releases IL-17 and other associated cytokines [4, 5]. The immune response is shaped by antigen presentation by a large number of cutaneous myeloid DCs that produce the cytokine IL-23, a key “driver” cytokine of Type 17 (T17) T-cell activation and polarization. IL-23 production is stimulated in these dermal DCs by TNF, which may be overproduced in psoriasis lesions by a combination of DCs, T-cells, and other cell types. IL-23 also shapes the immune response towards the activation of Th22 T-cells which release the cytokine IL-22 when activated. IL-17, IL-22, and TNF all act upon keratinocytes, individually and in synergy, to change gene transcription programs in this cell type—the direct response to these cytokines involves hundreds of genes with increased or decreased expression. The induced genes include psoriasin (S100A7), CCL20, cathelicidin/LL-37, CXCL1,2,3 & 8, IL-19, and IL-36 isoforms. Epidermal hyperplasia occurs in response to IL-22, IL-19, IL-36 and other “classic” growth factors such as EGF-family (TGFα, amphiregulin) and FGF-family (KGF, FGF) that are overproduced in lesions, while vascular proliferation is driven by other keratinocyte-produced cytokines such as VEGF and PDGF. CCL20 is a cytokine that “feeds forward” to stimulate dendritic cells and T17 T-cell influx, CXCL 1,2,3 & 8 create neutrophilic influx, and cathelicidin/LL-37 promotes both DC activation and serves as a probable autoantigen in psoriasis [6, 7]. Key therapeutic “nodes” in this inflammatory reaction include TNF, IL-23, and IL-17, as biologic antagonists to each of these cytokines can induce high-grade clinical improvements in psoriasis as measured by the PASI score. A desirable outcome from treatment is at least 75% improvement in the PASI score (a PASI75), although the treatment target is moving towards a PASI90 or even a PASI100 (no residual disease).

Several features differentiate psoriatic from rheumatoid synovium including a lesser degree of lining cell hyperplasia, increased vascularity, infiltration of neutrophils and the absence of a shared epitope [8]. The mechanisms responsible for the divergent histopathologies in PsA and RA were not well understood but reports of an important role for Th17 cells began to emerge [9], [10]. Additional studies identified IL-17 producing CD4- and CD8+ cells in the synovial fluid of PsA but not rheumatoid joints. Moreover, a subset of innate lymphocytes (ILC-3) were also expanded in psoriatic but not RA synovial fluid and these cells also expressed IL-17. These findings in human tissues coupled with mouse models that demonstrated the importance of the IL-23-IL-17 axis in the development of not only arthritis but also enthesitis, dactylitis, axial disease and psoriasiform lesions supported the concept that IL-23, IL-17, IL-22, along with TNF, are key cytokines in PsA pathogenesis (reviewed in [11]). In separate studies, the phosphodiesterase inhibitor (PDE4) was shown to raise cAMP levels in immune cells and lessen the release of inflammatory cytokines [12]. Another oral agent, tofacitinib, a Janus Kinase (JAK) inhibitor blocks multiple pathways in hematopoietic and immune cells and showed efficacy in rheumatoid arthritis [13]. Based on the data outlined on the pathogenesis of psoriasis and psoriatic arthritis outlined above,

clinical trials were undertaken to examine if inhibition of the IL-23-IL-17 cAMP or JAK pathways would prove to be safe and effective in psoriatic disease.

Outcome Measures in Psoriasis and Psoriatic Arthritis Clinical Trials

Outcome measures of the skin and joints that are commonly performed in clinical trials are summarized in the reference by Mease [14]. The Psoriasis and Severity Index (PASI) is a composite measure of erythema, scaling, and induration in different body parts. It is measured on a scale from 1-64 but commonly expressed as the percent of patients who demonstrate a 50, 75, 90 or 100% (PASI 50, 75, 90 or 100) improvement following treatment. The primary arthritis endpoint is the percentage of patients meeting criteria for 20% improvement in the American College of Rheumatology response criteria (ACR 20). Individual ACR components include the number or tender and swollen joints, patient's global assessment of disease activity, physician's global assessment of disease activity and responses on the Health Assessment Questionnaire-Disability Index (HAQ-DI) Secondary outcomes are often the ACR 50 and 70. The change in enthesitis can be assessed with the Leeds Enthesitis Index and dactylitis by a simple count or the Leeds Dactylitis Index.

Recently Approved and Emerging Therapies

IL-17 antagonists

Three biologic IL-17 antagonists—secukinumab, ixekizumab, and brodalumab—have been studied in large (phase 3) trials in psoriasis vulgaris. Results for psoriasis and PsA trials discussed in the following sections can be found in Table 1. Secukinumab is an IL-17A monoclonal antibody that has recent FDA approval for treatment of psoriasis. Treatment with secukinumab has induced a PASI75 response in 87% of patients in the JUNCTURE study [16] and it was shown to be superior to ustekinumab (anti-IL-12/23 p40 subunit) in the CLEAR study based on PASI90 and PASI100 outcomes. [17] In general, this agent is well tolerated with only a small risk of increasing infections that include a few cases of mucocutaneous candidiasis, a recognized disease of IL-17 deficiency states in humans. Ixekizumab is another IL-17A monoclonal antibody. Ixekizumab induced a PASI75 response in 90% of patients in the best-performing cohort in the UNCOVER studies and it too shows a good tolerability profile. [18] Within 2 weeks of starting ixekizumab, there is a strong reduction in IL-17-induced genes in keratinocytes that includes reduced expression of S100A7, CCL20, IL-19, IL-36, cathelicidin/LL-37, and CXCL1,2,3&8 chemokines [19] and also reduced expression of IL-17-regulated genes in circulating monocytes that are associated with cardiovascular disease risk. [20] Brodalumab is a monoclonal antibody to the IL-17 receptor A subunit. It blocks binding of IL-17 to cognate receptors that are prominently expressed on keratinocytes and other cell types, including some types of leukocytes. It also blocks signaling by other cytokines that use the IL-17 receptor A subunit, e.g., IL-25. In the AMAGINE-2 study, brodalumab induced an 86% PASI75 response in the best performing cohort and it was shown to be superior to ustekinumab treatment in the AMAGINE-3 study [21]. Side effects have included mild-to-moderate candida infections, infrequent neutropenia, and some cases of serious infections. An increase in suicidal ideation and completed suicides, observed in a small subset (<1%) of brodalumab treated

patients, has delayed its FDA approval and led to sale of the product to another pharmaceutical company that is continuing to pursue FDA approval. From the standpoint of treating psoriasis, treatment with brodalumab had led to very rapid and nearly complete reversal of psoriasis-related genes that are modulated by IL-17 and other inflammatory cytokines. [22]

The efficacy and safety of secukinumab was examined in 2 phase III trials, FUTURE 1 and FUTURE 2 [23, 24]. In Future 1, 606 PsA patients were randomized to receive and intravenous dose of secukinumab at weeks 0,2 and 4 followed my monthly administration at 75, 150 mg or secukinumab or placebo. Approximately 30% of patients had prior exposure to anti-TNF therapy. At week 24, those patients on secukimumab 75 or 150 mg had a significantly higher ACR20 response vs placebo (50.0%, 50.5% vs 17.3%). Improvements in enthesitis and dactylitis were also noted. In Future 2, 397 PsA patients (65% no prior anti-TNF exposure) were randomized to receive 75, 150 or 300 mg of secukinumab or placebo weekly subcutaneously for 4 weeks and then every 4 weeks. The ACR 20 was the primary outcome at 24 weeks and revealed 54% of patients on 300 mg achieved this outcome compared to 51% of patients on 150 mg, 29% on 75 mg and 15% on placebo. The treatment response was lower with 75 and 150 mg compared with 300 mg per day in patients with prior TNF exposure. Adverse events in both studies were rare and included a numerically but not statistically higher rate of candida infections with no deaths in either trial but longer term data are required to adequately assess risk. The efficacy and safety of ixekizumab in PsA was examined in the RHAP phase III clinical trial presented at the ACR meeting in November 2016[25]. In a phase III trial, 417 PsA patients were randomized to adalimumab, placebo or ixekizumab 80 mg every 2 weeks or 160 mg every 4 weeks and the ACR20 endpoint was assessed at 24 weeks. A significantly greater percentage of patients treated with ixekizumab 80 mg Q2W or Q4W achieved ACR 20, ACR50, ACR70 and PASI 75/90/100 responses than with placebo at 12 and 24 weeks ($p<.01$). Both ixekizumab groups experienced significantly greater reductions than placebo for measures of dactylitis (LDI-B) at 12 and 24 weeks but not for enthesitis (LEI). Efficacy results with adalimumab versus placebo were also significant on most measures and both agents inhibited radiographic progression. The incidence of serious adverse events was numerically greater in the ixekizumab and adalimumab groups than placebo ($p>0.27$). Lastly, a phase II trial of brodalumab in PsA randomized 168 patients receive 140 or 280 mg of brodalumab weekly vs placebo [26]. At week 12, 37 and 39% of patients achieved the ACR endpoint vs. 18% of patients on placebo. Results were similar between patients who received prior biologic therapy and those who were biologic naïve. All brodalumab studies were halted as outlined above due to concerns about suicidal ideation and completed suicides and the future of this medication is not known.

IL-23 antagonists

IL-23 is a cytokine composed of p19 and p40 protein subunits, but the same p40 subunit is combined with another protein, p35, to form IL-12. Ustekinumab is a monoclonal antibody to the p40 subunit and thus a dual antagonist of IL-12 and IL-23. Ustekinumab was approved by the FDA in 2009 based on ability of this agent to induce PASI75 responses in ~70% of treated patients vs. <5% placebo-treated patients. Since approval, ustekinumab has

established a record of being well tolerated and of having the ability to maintain PASI75 responses for many years of treatment in most patients. Ustekinumab is also effective in PsA for arthritis, dactylitis, enthesitis and this agent inhibits radiographic progression [27, 28]. More recent work with specific IL-23 antagonists (monoclonal antibodies to the p19 subunit) has led to the conclusion that ustekinumab likely improves psoriasis and PsA by IL-23 blockade, but with the possibility that co-blockade of IL-12 might decrease effectiveness of this agent to a small degree. Three p19 monoclonal antibodies—guselkumab, BI655066 and tildrakizumab—are now in Phase 3 studies in psoriasis vulgaris, after showing very impressive effects in Phase 2 studies. Guselkumab induced a PASI75 response in >90% of treated patients and with superiority to the TNF antagonist adalimumab in a randomized study [29]. Molecular profiling showed a striking ability to reverse the psoriasis tissue phenotype and most disease-defining mRNA products, including the “driver” cytokine IL-17. [30] BI655066 also induced a PASI75 response in >90% treated patients and it was superior to ustekinumab in this randomized trial (personal communication). In a smaller prior study, BI655066 was shown to down-regulate IL-17 production in skin lesions and thus modulate downstream IL-17 regulated genes in keratinocytes and other cell types. Interestingly, a single dose of this antibody induced clearing of psoriasis for 1 year in some treated patients, suggesting that disease remission might be possible by targeting IL-23 in psoriasis. [31] Tildrakizumab was shown to induce a PASI75 response in 74% of patients in the highest dose cohort, but it was not tested against an active comparator in Phase 2 [32]. Phase II trials designed to study the efficacy and safety of IL-23 inhibition in PsA are underway or in the planning stages but no data are available at this time.

New Oral Therapies

Two small molecule drugs, apremilast and tofacitinib, have now completed phase 3 trials in psoriasis and the former is now FDA approved for treatment of psoriasis vulgaris. Apremilast is an inhibitor of phosphodiesterase E4 (PDE4), which is an enzyme that metabolizes cAMP, so this inhibitor raises cAMP levels within cells. Within T-cells, high levels of cAMP act as a brake, but not a complete inhibitor, of T-cell activation through the TCR complex and associated signal transduction, so levels of cytokines produced by activated T-cells will be reduced. Thus treatment of psoriasis is associated with reduced production of IL-17, IL-22, and TNF in patients that respond well to it, as well as an increase in the anti-inflammatory cytokine IL-10. [33] Other immune cell types are also affected by higher cAMP levels—the general response is lower levels of cellular activation/inflammation with treatment. Thus, apremilast should be viewed as relatively broad-acting immune modulator, but producing less blockade of T-cell activation that some well characterized immune suppressants such as cyclosporine at clinically relevant doses. The effects of apremilast are thus more variable on immune pathways in individual patients than cyclosporine (or biologic antagonists of IL-17 or IL-23), with responding patients tending to have more reductions in cellular immune infiltrates and associated cytokines [33] and with a PASI75 response induced in 33.1% of apremilast-treated patients vs. 5.3% of placebo-treated patients in the ESTEEM1 study. [34] While fewer patients respond to this agent compared to biologics targeting IL-17 or IL-23, few adverse events (other than GI intolerance) have been associated with apremilast use and routine monitoring of hematologic or metabolic parameters is not required, unlike methotrexate which has more defined

toxicity in psoriasis patients. As a consequence, apremilast is now used a first-line targeted therapy by many dermatologists.

The impact of apremilast on musculoskeletal inflammation parallels the magnitude of the response observed in psoriasis with no major safety signals. In the phase III Psoriatic Arthritis Long-Term Assessment of Clinical Efficacy (PALACE) 1 trial, 504 patients were randomized to placebo, apremilast 20 mg or 40 mg per day in a 1:1:1 ratio [35]. At week 16, significantly more apremilast - 20 mg BID (30%) and 30 mg BID (30%) compared to placebo (19%), achieved the ACR 20 measure at 16 weeks. The most common GI events were nausea and diarrhea and generally occurred early in the treatment course. Similar ACR responses were reported in the PALACE 3 study and responses were maintained at 52 weeks. A numerical but not statistical improvement was observed for dactylitis and enthesitis [36]. Radiographic endpoints have not been examined in apremilast trials to date. The approved dose of apremilast is 20 mg BID and it is prescribed as monotherapy.

Tofacitinib is an inhibitor of select Janus kinases (JAKs) with JAK1 and JAK3 being strongly inhibited at therapeutically relevant doses and with JAK2 being weakly inhibited. JAKs 1 and 3 are key signal-transducing kinases for cellular responses to a broad range of immune cytokines, so like apremilast, tofacitinib should be viewed as broad-acting immune modulator, but with stronger and more consistent immune suppression and thus clinical efficacy. In a phase 3 trial, 63.6% of patients treated with 10mg of tofacitinib bid had a PASI75 response vs. 5.6% of placebo-treated patients and the response was roughly of the same magnitude (statistically not inferior) to etanercept[37]. Both clinical efficacy and immune suppression are highly dose-dependent and clear signals of immune-suppression, e.g., herpes zoster activation and bacterial infections, were seen in rheumatoid arthritis (RA) patients treated with tofacitinib 10mg bid, whereas lower rates were observed with use of 5mg bid (the FDA approved dose in RA). However, used as monotherapy in psoriasis patients 10 mg bid of tofacitinib is much better tolerated and rates of serious AEs, infections, malignancies and discontinuations due to AEs have been low across Phase 3 studies. [38] Still, in response to a new drug application for use in psoriasis, the FDA has asked for additional safety information and approval is pending evaluation of that data.

Scientific rationale for the potential efficacy of tofacitinib in PsA was reported in a study that examined the effect of this agent on protein expression in synovial fibroblast cultures and explant tissues [37]. They demonstrated that tofacitinib significantly decreased Signal Transducer and Activator of Transcription (STAT)3, pSTAT1, Nuclear Factor (NF)κBp65 and induced Suppressor of Cytokine Signaling (SOCS)53 and Protein Inhibitor Of Activated STAT (PIAS)3 expression in the cells and explant cultures. In addition, Interleukin (IL)-6, IL-8, Monocyte Chemoattractant Protein (MCP)-1, Matrix Metalloproteinase (MMP)9/ MMP2 and MMP3 levels also decreased in explant tissues. Unfortunately, data on treatment response in PsA is not available at this time but clinical trials are in progress.

Conclusion

The array of treatment options for psoriasis and psoriatic arthritis unveiled over the past several years offer new hope for patients with psoriatic disease. The tremendous impact on

therapeutic response is most evident in psoriasis where agents in the IL-23-IL-17 pathway induce marked plaque clearance. The results in PsA for these agents are similar to those observed with anti-TNF agents, however, the safety signals from these compounds are not concerning and may offer an advantage for many patients. IL-17 blockade is also effective for axial disease and inhibits radiographic progression. The reports of suicidal behavior with the IL-17 receptor antagonist was not anticipated and no plausible mechanism has been identified. These reports point to the complexity of the IL-23-IL-17 signaling pathway. In regards to oral agents, apremilast offers a modest response in the skin and joints with few safety signals and routine safety monitoring is not required- a major advantage for many patients. Apremilast is not indicated in patients who demonstrate radiographic damage or axial involvement. The role of tofacitinib in psoriasis remains to be established based largely on potential safety concerns and we await data on efficacy in PsA. The rapid development of successful targeted strategies for treatment of psoriasis and PsA illustrate overlapping disease pathways and underscore the tremendous value and impact of translational immunology research.

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Key Points

1. Psoriasis vulgaris and psoriatic arthritis are immune-driven inflammatory diseases of skin and joint-related connective tissues, respectively
2. Although many different inflammatory molecules likely create the complex tissue phenotypes in these diseases, cytokines such as TNF, IL-23, and IL-17 drive cellular responses that create cascading inflammation and these cytokines are inhibited by specific biologic therapeutics that are emerging as therapeutic options for both psoriasis and psoriatic arthritis
3. The increasing understanding of cellular and molecular mechanisms of tissue inflammation in these diseases is also opening the door to treatment with new small molecule antagonists of inflammation-related signal transduction.

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Table 1

Comparison of treatment response of biologic agents and small molecules in psoriasis and psoriatic arthritis

Agent	Psoriasis			Psoriatic Arthritis					
	Study	N	PASI 75/pbo (%)	Study	N	ACR 20/pbo (%)	D/E +/-	Axial +/-	X-ray +/-
Secukinumab	Juncture	676	87/3.3	Future 2	397	54/7	-	ND	ND *
Ixekizumab	Uncover 2	1224	90/48	RHAP	417	60/31	+/-	ND	+
Brodalumab	Amagine 2	1831	86/8	Phase II	168	39/18	-	-	-
Tildrakizumab	Phase IIb	**355**	74/4	ND	ND	ND	ND	ND	ND
Guselkumab	Phase II	293	81/5	ND	ND	ND	ND	ND	ND
Apremilast	Esteem 1	844	33/5	PALACE 1	504	31/19	-	-	-

Results from phase II and phase III studies in psoriasis and PsA are enumerated in the table. The data are derived from the trials and should not be used to compare agents since the study populations differ. The results for the most responsive cohorts are shown. Abbreviations: pbo-placebo; PASI Psoriasis Activity Skin Index ;(D/E)- Dactylitis/Enthesitis, only significant changes listed as +; (ACR)American College of Rheumatology 20 response; Axial-response of axial disease to treatment; documented improvement in pre-defined radiographic endpoints (X-ray).

* Inhibition of radiographic damage was presented in the FUTURE2 trial [15].