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Psoriasis: Ustekinumab and Other Biologics in the Pipeline

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Abstract The improved understanding of the complex immunology and pathogenesis of psoriasis and psoriatic arthritis has established the therapeutic utility of targeted biologic therapies against the pathogenic T cells and the inflammatory cytokines. Particular interest in the interleukin (IL)-23/T helper (Th)17 pathway has led to the development of ustekinumab, which is now approved and widely marketed for the treatment of psoriasis, as well as various investigational biologic agents in current clinical trials. Lack of or improper treatment of psoriasis and psoriatic arthritis can inevitably result in considerable morbidity and quality of life issues for affected patients, emphasizing the continued need for drug research and development to achieve optimal management.

Keywords Dermatopharmacology · Therapy · Psoriasis · Psoriatic arthritis · Comorbidities · Biologics · Immunology · Pathogenesis · Cytokines · T cells · IL-23/Th17 pathway · IL-12 · IL-22 · IL-23 · IL-17 · Tumor necrosis factor-alpha · TNF-α · Ustekinumab · Briakinumab · IL-23 inhibitors · TNF inhibitors · T-cell modulators

Introduction

Psoriasis is a chronic inflammatory skin condition that affects approximately 2 % of the US population [1]. Of this population, an estimated 6 % to 39 % have associated joint disease, which is an inflammatory arthritis that can be progressively destructive and can pose significant limitations on the functional capacity and quality of life of a patient [2–4]. The mounting evidence supporting psoriasis as a systemic disease—including conditions that pose considerable cardiovascular disease risks, such as metabolic syndrome, obesity, hypertension, hyperlipidemia, and diabetes, as well as psychiatric disorders—further justifies the use of systemic therapies [5–8]. The traditional systemic therapies, such as acitretin, methotrexate, and cyclosporine, are still used for the treatment of psoriasis; however, the challenges with long-term management, particularly with the concern for potential serious associated toxicities with these medications, have made biologic therapies an attractive option [9]. In fact, the efficacy of various biologic therapies in psoriasis has been shown in numerous clinical studies, and, importantly, associated with an improved quality of life for the patients [10, 11]. As more detailed information about the complex immunopathology of psoriasis is uncovered, the need for developing targeted therapies to improve upon the efficacy, safety, and durability of available treatment options becomes essential.

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Background: The Interleukin (IL)-23/T Helper (Th)17 Pathway

Although psoriasis is already known as a disease of T-cell mediated chronic inflammation, the increasingly documented evidence that the pathogenesis of psoriasis is through a particular subset of CD4+T helper cells, Th17, has ultimately led to a focus on the development of a new class of biologic therapies [12, 13]. Notably, the Th17 cell lineage is a novel and separate entity from the different arms of cellular immunity, such as Th1 and Th2 cells, that is responsible for the production of cytokines involved in skin inflammation, such as IL-17A, IL-17F, IL-22 [14, 15]. As part of the complex pro-inflammatory cascade in psoriasis, transforming growth factor-beta 1 (TGF-β1) and IL-6 have been shown to be essential in the differentiation of naïve T

cells into Th17 cells [16–18]. TGF- β1, in itself, is elevated in psoriasis and released by keratinocytes upon stress from any injury or infection [19, 20]. The mRNA and protein levels for IL-6 also have been noted to be elevated in psoriatic plaques [21]. IL-23, then, subsequently may provide a stimulus for the proliferation of the Th17 cells [22, 23]. Dendritic cells secrete IL-23—along with IL-12, another key cytokine for Th1 differentiation—but IL-23 also can be produced by keratinocytes and non-dendritic, antigen-presenting cells [24–26]. IL-23, a heterodimeric cytokine in the IL-12 family, is composed of the p19 and p40 subunits that can then bind to the receptor made up of IL-12Rβ1 and IL-23R [27]. IL-12, another heterodimeric cytokine, not only shares the p40 subunit with IL-23 but consists of the p35 subunit [28]. In fact, the pivotal role that the IL-23/Th17 axis plays in psoriasis pathogenesis is reinforced by evidence that the mRNA levels of the subunit p19—unique to IL-23—were elevated in psoriasis lesional skin compared to non-lesional skin, whereas the levels for p35—a subunit distinct to IL-12—were not [29–31]. Importantly, the levels of IL-23 decreased in correlation to skin improvement and efficacy of various therapies—including phototherapy, cyclosporin A, and tumor necrosis factor-alpha (TNF-α) inhibitors—further crediting the role of IL-23 in psoriasis pathology and its utility as a therapeutic target [32–34]. Moreover, specific nucleotide polymorphisms for the IL-23 receptor gene have been associated with psoriasis in large-scale genetic association studies [35–37]. Ultimately, targeting the IL-23/Th17 pathway for the treatment of psoriasis initially led to the development of two biologics, CNTO-1275/ustekinumab and ABT-874/briakinumab.

Ustekinumab, Briakinumab, and Other IL-23 Inhibitors

Ustekinumab is a human monoclonal immunoglobulin G (IgG) antibody that effectively inhibits IL-12 and IL-23 by binding to the shared p40 subunit, and thereby inhibiting the cytokines from binding to the receptors [38]. It is currently marketed in the United States and worldwide for the treatment of moderate-to-severe psoriasis. Phase I and II studies have already established the efficacy of ustekinumab at various doses against placebo by week 12, as measured by a 75 % reduction in the Psoriasis Area and Severity Index score (PASI 75) [39–41]. There were two notable large-scale, phase III, double-blind, placebo-controlled trials with ustekinumab, known as PHOENIX 1 and PHOENIX 2, in which subjects were dosed at either 45 mg or 90 mg at weeks 0, 4, and then every 12 weeks for the treatment of moderate-to-severe plaque psoriasis [42•, 43•]. The PHOENIX 1 trial illustrated that a significantly higher percentage of patients achieved the PASI 75 response by week 12 for both the 45 mg and 90 mg ustekinumab doses compared to placebo, and the response was sustained through week 76 for those patients who remained on a maintenance dose of ustekinumab against the group who had the drug withdrawn [42•]. The PHOENIX 2 study further validated the results of ustekinumab's efficacy, as more patients who received either 45-mg or 90-mg doses of ustekinumab reached at least a PASI 75 score by week 12 as compared to the placebo group (66.7 % and 75.7 % vs 3.7 %, respectively; $p<0.0001$) [43•].

Adjunct to the objective improvements in the PASI scores, the scores of the Dermatology Life Quality Index (DLQI), which reflects the quality of life and indirect costs for each individual, also improved for groups receiving ustekinumab compared to those on placebo [42•, 43•]. Furthermore, the ACCEPT trial, a large-scale comparator study between two doses of ustekinumab, 45 mg and 90 mg, and etanercept at 50 mg twice weekly, showed that more patients on ustekinumab had a PASI 75 score at week 12 compared to those on etanercept [44•].

Ustekinumab has been used in patients with psoriatic arthritis as well, and phase II results from 2009 showed that a greater proportion of patients receiving either 63 mg or 90 mg of ustekinumab achieved 20 % improvements in their joint exam scores (American College of Rheumatology criteria for 20 % improvement [ACR 20]) by week 12 compared to those on placebo (42 % vs 14 %; $p=0.0002$) [45•]. Consequently, phase III clinical trials evaluating the efficacy of ustekinumab for psoriasis arthritis are currently taking place [46]. In addition, a recent open-label trial evaluating the efficacy of ustekinumab in palmoplantar psoriasis provided evidence that the higher dosing of 90 mg may have utility in treating this psoriasis variant that is known to be resistant to many other forms of treatment [47•].

Briakinumab is the recombinant, fully human monoclonal IgG1 antibody also against the p40 subunit that carries out its therapeutic function by binding soluble IL-12 and IL-23 [48, 49]. The therapeutic efficacy of briakinumab was clear across five different doses against placebo for patients with moderate-to-severe plaque psoriasis in a phase II study (63 %–93 % vs 3 %; $p<0.001$) [48]. Subsequent phase III trials continued to show impressive results, with PASI 75 scores achieved for those on briakinumab compared to placebo as well as established treatments such as etanercept and methotrexate and with therapeutic efficacies maintained through week 48 in the open-label extension studies [50•, 51•, 52•]. The safety profile of briakinumab did include an increased number of major adverse cardiovascular events in the treatment group compared to the placebo group. However, despite the marked therapeutic responses seen in the briakinumab-treated groups, the drug's application for approval was withdrawn in 2011, halting further development for briakinumab at this time [53].

Other IL-23 inhibitors are currently in development, including an antibody that specifically targets the p19 subunit

of IL-23, which has been demonstrated to decrease the mRNA levels of Th17 cytokines in certain mouse models [54]. The hypothesis is that, by directly inhibiting the subunit unique to IL-23, IL-12 and Th1 driven cell-mediated immunity will be preserved, ameliorating the potential infection and cancer risks [55, 56]. Of note, there is one phase II study evaluating the efficacy of an anti-p19 antibody for the treatment of moderate-to-severe plaque psoriasis, SCH 900222 (Merck) [46].

Targeting Th17 Cytokines: IL-17 and IL-22

The importance of the IL-23/Th17 axis in the immunopathogenesis of psoriasis has been highlighted by the efficacy of anti-IL-23 biologic agents for the treatment of psoriasis and has led to the consideration of other downstream components of the pathway as therapeutic targets. In particular, IL-17, one of the effector cytokines of Th17 cells, is a homodimeric cytokine that is secreted by memory T cells and natural killer cells, and involved in activating other key signaling pathways, such as nuclear factor-κB and mitogen-activated protein kinase cascades [57, 58]. IL-17 may support neutrophil recruitment in psoriasis lesions by stimulating keratinocytes to produce CXC chemokines that attract neutrophils and by inhibiting neutrophil apoptosis in inflamed tissues [59–61]. A positive feedback loop for chronic inflammation is maintained in psoriasis by IL-17. IL-17 not only reinforces the effects of TNF-α but induces IL-6 secretion, which directly influences Th17 differentiation [62, 63]. Correspondingly, the gene expression and mRNA levels of IL-17 were, indeed, higher in psoriatic skin compared to noninvolved skin [29, 54].

There are several ongoing clinical trials evaluating the efficacy and safety of anti-IL-17 biologic agents for the treatment of psoriasis. Recently, encouraging evidence from two phase II studies evaluating the efficacy and utility of biologic agents against IL-17 and its receptor was published. Brodalumab (AMG 827) is a fully human monoclonal IgG2 antibody against the IL-17 receptor [64, 65]. For the phase II trial, almost 200 patients with moderate-to-severe plaque psoriasis were randomized to receive either biweekly dosing of brodalumab at 70 mg, 140 mg, or 210 mg; monthly dosing of brodalumab at 280 mg; or placebo. By the end of 12 weeks, a significant proportion of patients achieved improvement in their PASI scores by 75 % (PASI 75) and 90 % (PASI 90) for the 140-mg dose-group (77 % and 72 %, respectively) and the 210-mg dose group (82 % and 75 %, respectively) compared to placebo (0 %; $p<0.001$) [66•]. The second phase II trial was a double-blind, placebo-controlled study of four different monthly doses (10 mg, 25 mg, 75 mg, or 150 mg) of ixekizumab (LY2439821), a humanized monoclonal IgG4 antibody against IL-17 [67•]. For all except the lowest dose, more patients on treatment achieved PASI 75 scores (76.7 %–82.1 % vs. 7.7 %; $p<0.001$) and PASI 90 scores (50 %–71.4 % vs 0 %; $p<0.001$) compared to those on placebo by week 12, again conferring the efficacy of using IL-17 as a therapeutic target [67•]. Another notable upcoming biologic agent against IL-17 in development includes secukinumab (AIN457), a fully human monoclonal IgG1 antibody to IL-17 [68]. In an early phase II study, secukinumab provided a significant therapeutic response compared to placebo after 12 weeks, and is now in phase II and III studies [68].

IL-22 is another effector cytokine of Th17 cells that is crucial to the proliferation of keratinocytes, and the maintenance and remodeling of epithelial tissues [69, 70]. Levels of IL-22 mRNA have been found to be upregulated in psoriatic skin lesions compared to normal skin, and, importantly, correlate to the severity of disease involvement and decrease with treatment efficacy [70, 71]. Interestingly, intradermal injections of IL-23 in mouse models led to psoriasis-like skin changes while no such change was induced in IL-22 knockout mice, suggesting the essential role of IL-22 in psoriasis hyperkeratosis and making it an attractive therapeutic target [72].

New Tumor Necrosis Factor Inhibitors

TNF has been well documented to be involved in the immunopathology of psoriasis, and, in fact, is a well-known target for many of the currently approved biologic therapies for the treatment of psoriasis and psoriatic arthritis [73]. The efficacy and safety of several TNF inhibitors have been shown for adalimumab [74, 75], infliximab [76, 77], etanercept [78, 79], and golimumab [80]. Certolizumab pegol (CZP), a new TNF inhibitor with a completely different structure than the preceding anti-TNF biologic agents, is based on the pegylated Fab' portion of an anti-TNF antibody [81]. By omitting the antibody Fc fragment, this particular TNF inhibitor does not activate the complement cascade or antibody-dependent cellular toxicity [81]. CZP has already been shown to be useful in the treatment of other inflammatory diseases, including rheumatoid arthritis and Crohn's disease [82, 83]. A recent phase II randomized, placebo-controlled, double-blind study of 176 patients with moderate-to-severe plaque psoriasis used two different biweekly doses of CZP (200 mg and 400 mg) for a total treatment period of 12 weeks [84•]. At the end of 12 weeks, more patients receiving either 200 mg or 400 mg of CZP achieved a PASI 75 score compared to patients on placebo (74.6 % and 82.8 % vs 6.8 %, respectively; $p<0.001$) [84•]. In addition, a greater proportion of CZP-treated patients on both doses improved to a Physician's Global Assessment (PGA) score of clear or almost clear compared to the

placebo group (52.5 % and 72.4 % vs 1.7 %; $p<0.001$) [84•]. CZP provides an example of the utility of modifying treatments against already established targets for future drug development.

T-cell Modulators

Upstream to the cytokines that are targeted for the current and upcoming biologics are the T cells that are key to the immunopathology of psoriasis and psoriatic arthritis [73, 85]. Abatacept is a T-cell modulating biologic currently approved for the use in patients with rheumatoid arthritis and juvenile idiopathic arthritis [86, 87]. It is a soluble, fully human fusion protein comprised of the CTLA-4 domain that can bind CD80, or CD86 that was shown to improve psoriasis skin lesions in phase I studies and joint disease in a phase II trial [88, 89]. The recent phase II multicenter, randomized, double-blind, placebo-controlled study evaluated the efficacy and safety of three monthly doses (three doses of 3 mg/kg, three doses of 10 mg/kg, or two doses of 30 mg/kg followed by 10 mg/kg) of abatacept in patients with psoriatic arthritis [89]. By day 169, a significant percentage of patients who received either the 10 mg/kg or the 30/10 mg/kg doses achieved an ACR 20 response compared to those patients on placebo (48 % and 42 % vs 19 %, respectively; $p<0.05$) [89].

Other notable T-cell modulators in development include a humanized IgG4k antibody against P-selectin glycoprotein ligand-1, which participates in the T-cell response during inflammation (AbGn-168; Boehringer Ingelheim, Ingelheim am Rhein, Germany) and a monoclonal antibody for CD4 (BT-061; Biotest, Dreieich, Germany), which functions as a co-receptor on CD4+ T helper cells [90, 91].

Conclusion

The initiation of the appropriate treatment and management strategy for psoriasis is vital to the prevention of disease progression and comorbidities, as well as significant financial expenses that can correlate with disease severity [92]. Although the spectrum of psoriasis treatment options has substantially increased and diversified, the average annual incremental indirect and direct costs is $1500 per psoriasis patient per year [93]. Strikingly, a recent analysis of the costs of work loss and productivity, which are determinants of indirect costs, for psoriasis patients was estimated at $8.6 and $9.9 billion a year, respectively [94]. This calculation is a product of a multitude of factors, one of which may include those patients with inadequate treatment response, thereby making drug development and research an important factor to successful management of this chronic, debilitating condition.

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