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PSORIASIS (J WU, SECTION EDITOR)

Bimekizumab

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Abstract

Purpose of Review Bimekizumab, a novel monoclonal antibody directed against both interleukin (IL)-17A and IL-17F, is in clinical development as a treatment for psoriasis and psoriatic arthritis. The purpose of this review is to highlight the roles of IL-17A and IL-17F in psoriatic inflammation as well as the clinical data on bimekizumab that has been reported to date.

Recent Findings Phase 2 efficacy results with bimekizumab have demonstrated high levels of rapid skin clearance in psoriasis patients, and high levels of joint disease improvement in psoriatic arthritis patients. Thus far, safety concerns have been limited to cases of mucocutaneous candidiasis, which have been mild-to-moderate and manageable in most instances.

Summary IL-17A and IL-17F are key pro-inflammatory effector cytokines that are over-expressed in psoriatic skin and joints. Bimekizumab, which targets both IL-17A and IL-17F, has shown great promise thus far as a new treatment for patients with psoriasis and psoriatic arthritis. Confirmatory efficacy and safety results in phase 3 studies for these diseases are eagerly anticipated.

Keywords Psoriasis · Psoriatic arthritis · Interleukin-17A · Interluekin-17F · Bimekizumab · Treatment · Biologics

Introduction

Interleukin (IL)-17 consists of a family of cytokines, with IL-17A and IL-17F considered to be the most important IL-17 family members involved in psoriasis pathogenesis. These two pro-inflammatory cytokines are produced by T helper 17 (Th17) and T cytotoxic 17 (Tc17) cells as well as other cells found within skin affected by psoriasis [1•, 2, 3•, 4]. IL-17A/F are central effector cytokines in psoriasis, acting upon keratinocytes, neutrophils, and other cell types to create cellular activation and proliferation. Animal models of pro-inflammatory disease and in vitro cultured cell systems suggest that dual blockade of both IL-17A and IL-17F is superior to single blockade of either cytokine alone. In humans, high rates of complete skin clearance have been demonstrated in psoriasis patients treated with bimekizumab, a novel monoclonal antibody that blocks both IL-17A and IL-17F. Here, we review scientific data on IL-17A and IL-17F as well as clinical data on bimekizumab, which is currently in phase 3 development as a treatment for both psoriasis and psoriatic arthritis.

This article is part of the Topical Collection on *Psoriasis*

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Basic Biology of IL-17A/IL-17F and Roles in Psoriasis Pathogenesis

Psoriasis constitutes an inflammatory skin disease driven by multiple immune cells, belonging to both adaptive and innate immunity (e.g., T cells, dendritic cells, neutrophils, innate lymphoid cells) that, interacting with tissue cells, create positive feedback pro-inflammatory circuits (Fig. 1) [5, 6•]. These cellular interactions are mediated by chemokines (e.g., CCL20, CXCL5, CXCL8, CXCL9), cytokines (principally tumor necrosis factor (TNF)-α, IL-17A, IL-17F, and IL-23), antimicrobial peptides (AMPs), and other inflammatory mediators [5, 6•].

Emerging data from both in vitro and clinical studies indicate that the IL-23/T17 immunologic pathway plays an especially important role in driving changes within affected tissues (Fig. 1) [7, 8]. In particular, IL-23 is a key regulatory cytokine in psoriasis pathogenesis, which promotes differentiation, survival, and proliferation of Th17 and Tc17 cells [9•, 10]. By

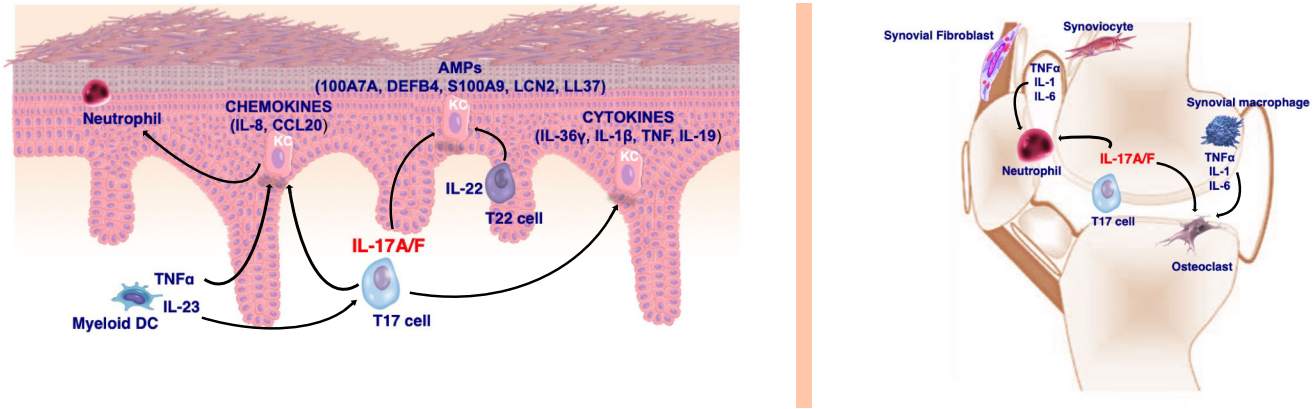

Fig. 1 Overview of psoriatic inflammation in the skin (**a**) and joints (**b**), highlighting key cytokines involved psoriasis and psoriatic arthritis pathogenesis, respectively

contrast, IL-17A and IL-17F are key effector cytokines in psoriasis pathogenesis. These cytokines are normally produced by Th17 and Tc17 cells as well as IL-17+ γδT cells, innate lymphoid cells 3, mast cells, neutrophils, and can be found in serum, tear liquid, lesional, and non-lesional skin of psoriasis patients [11•, 12–15]. In psoriasis, there are increased numbers of IL-17-expressing cells in both lesional psoriasis skin and blood [1•, 2, 3•, 4, 5, 16–18]. Furthermore, upregulation of signature genes downstream of IL-17 signalling is detected in lesional and non-lesional skin of patients with psoriasis [13, 21•]. Notably, therapeutic responses to anti-psoriatic therapies are associated with significant reductions in IL-17A and IL-17F as well as decreased mRNA expression of IL-17-driven genes [19, 20].

In an in vitro study using reconstituted human epidermal sheets, IL-17A stimulated greater transcriptional activation than IL-22 or IFN-γ, which correlated with the gene expression pattern observed in skin affected by psoriasis, i.e., the psoriasis transcriptome [21•]. Among the AMPs, IL-17A induces the expression of LL37, a psoriasis autoantigen that promotes production of pro-inflammatory cytokines, and C-X-C motif chemokine ligand 1 (CXCL1) [14, 15]. This, in turn, drives expansion of ADAMTS-like protein 5 (ADAMTSLP5), another psoriasis autoantigen, causing additional expression of IL-17A and IFN-γ [22–26]. This evidence supports the role of IL-17A as an important effector cytokine that stimulates expression of key downstream molecules in the psoriasis inflammatory cascade.

More recently, resident memory T cells (Trm) have been found in healed psoriasis skin and are believed to be responsible for disease recurrences of psoriasis within the same body areas. Percentages of Trm expressing IL-17A were higher than other Trm cells subpopulations producing other cytokines, namely IL-22 or IFN-γ [27, 28•, 29]. These data highlight the potential role of IL-17A in causing recurrence of psoriasis lesions. Indeed, in patients showing high numbers of IL-17+ Trm cells in resolved lesions, psoriasis recurred more rapidly after stopping UVB therapy [29] compared to patients with more IL-17A- Trm cells.

In addition to IL-17A, IL-17F has increasingly been studied and is also emerging as key effector cytokine in psoriatic inflammation. It is expressed at high levels within lesional and non-lesional psoriatic skin, and has been demonstrated to have overlapping biologic functions with IL-17A, although IL-17F is approximately 30-fold less biologically active than IL-17A [13, 30]. IL-17F shows greater than 50% structural homology and it is produced by Th17 cells upon stimulation with IL-23. IL-17F also can form heterodimers with IL-17A, with intermediate biologic potency compared to IL-17A and IL-17F homodimers. IL-17F is thought to potentiate IL-17A activity, as its effects in inducing keratinocyte gene expression are similar. In vitro studies assessing the effects of IL-17 family cytokines in monolayer keratinocytes have confirmed the overlapping effects of IL-17A and IL17F in stimulating the expression of AMPs (e.g., DEFB4, LCN2, S100A9, S100A7A), chemokines (e.g., CCL20, CXCL8), and cytokines (e.g., IL-36γ) [31]. Additionally, keratinocyte transcriptomes induced by either IL-17A or IL-17F significantly correlated with the psoriasis transcriptome, highlighting the potential contribution of both cytokines to psoriasis pathogenesis [31]. Similar to psoriasis skin lesions, inflamed synovial tissues from psoriatic arthritis patients showed increased expression of IL-17A and IL-17F [32•].

Microarray studies proved that the in vitro effects of IL-17A are potentiated by the synergism with other pro-inflammatory cytokines such as IL-1β or TNF-α, and, likewise, IL-17F showed synergistic and additive effects with TNF-α and IL-1β, respectively, in inducing pro-inflammatory cytokine secretion in cultured rheumatoid arthritis-derived synoviocytes, psoriasis skin fibroblasts, myoblasts, and hepatocytes [33, 34, 35•, 36•, 37, 38]. To elucidate the pathogenic role of IL-17A and IL-17F in psoriatic arthritis, in vitro studies investigated the effects of both cytokines on primary normal human dermal fibroblasts and synoviocytes

obtained from patients with psoriatic arthritis [39–41, 42••]. Combined stimulation with IL-17F and TNF-α induced the expression of pro-inflammatory genes such as IL-6 and IL-8, although to a lesser extent compared to dual stimulation with IL-17A and TNF-α [39–41, 42••]. In addition, concomitant inhibition of both IL-17A and IL-17F was investigated in synoviocytes from psoriatic arthritis patients and dermal fibroblasts cultured with pro-inflammatory mediators derived from supernatant of flow-sorted Th17 cells [39, 41, 42••]. Cultured cells were then exposed to anti-IL17A monoclonal antibodies, anti-IL17F monoclonal antibodies, or bimekizumab, a humanized monoclonal IgG1 antibody neutralizing IL-17A, IL-17F homodimers, and IL-17A/IL-17F heterodimers [39, 41, 42••]. Inhibition induced by bimekizumab led to greater reductions of IL-6, IL-8, and other inflammatory genes (i.e., CXCL1, CXCL2, CXCL3, and IL-15RA) expression than IL-17A blockade alone [39, 41, 42••]. This study also assessed chemotactic potential of neutrophils towards Th17-stimulated dermal fibroblasts, and showed a greater suppression of neutrophil migration through transwell permeable membranes using bimekizumab, compared to either IL-17A or IL-17F blockade alone [39, 41, 42••].

Overall, these experiments provided evidence for the use of bimekizumab to treat both psoriasis and psoriatic arthritis.

Bimekizumab Efficacy

Psoriasis

Bimekizumab is a novel IgG monoclonal antibody that binds to a peptide region that is shared by IL-17A and IL-17F (Fig. 2). The first-in-human phase 1 bimekizumab study was performed in 39 patients with mild plaque psoriasis [43]. Study subjects received either a single intravenous dose (8–640 mg) of bimekizumab or placebo in a randomized, double-blinded manner. In all 18 patients receiving 160 mg, 480 mg, or 640 mg ($n = 6$ for each group), 100% clearance or near 100% clearance was achieved 8–12 weeks after dosing [43]. Durations of responses after these single doses in these 18 patients ranged from 12 to 20 weeks.

These promising results led to a randomized, double-blinded, placebo-controlled phase 2b study in moderate-to-severe plaque psoriasis (BE ABLE 1) [44••]. Two-hundred fifty patients received either placebo or varying doses of bimekizumab (64 mg, 160 mg, 320 mg, or 480 mg) subcutaneously every 4 weeks for 12 weeks [44••]. As expected, a dose-response was observed, except that the 480-mg dose group did slightly less well than the 320-mg dose group; indeed, the best overall clinical responses at week 12 were observed in the 320-mg dose group ($n = 43$): PASI 75 of 93.0%, PASI 90 of 79.1%, PASI 100 of 55.8%, and IGA 0/1 of 86.0% [44••].

More recently, long-term results from this phase 2b study were presented (BE ABLE 2) [45••]. PASI 90 responders at week 12 were continued on 320 mg of bimekizumab every 4 weeks for a total of 60 weeks. Clinical responses were PASI 90 of 80–100% (non-responder imputation [NRI]) and 93–100% (observed), PASI 100 of 70–83% (NRI) and 80–96% (observed), and IGA 0/1 of 78–100% (NRI) and 97–100% (observed) at week 60, indicating high levels of clearance/near clearance in psoriasis patients on 320 mg of bimekizumab every 4 weeks over the course of 1 year [45••]. Long-term phase 3 studies, which are ongoing, are testing bimekizumab doses of 320 mg given subcutaneously every 4 or 8 weeks [45••].

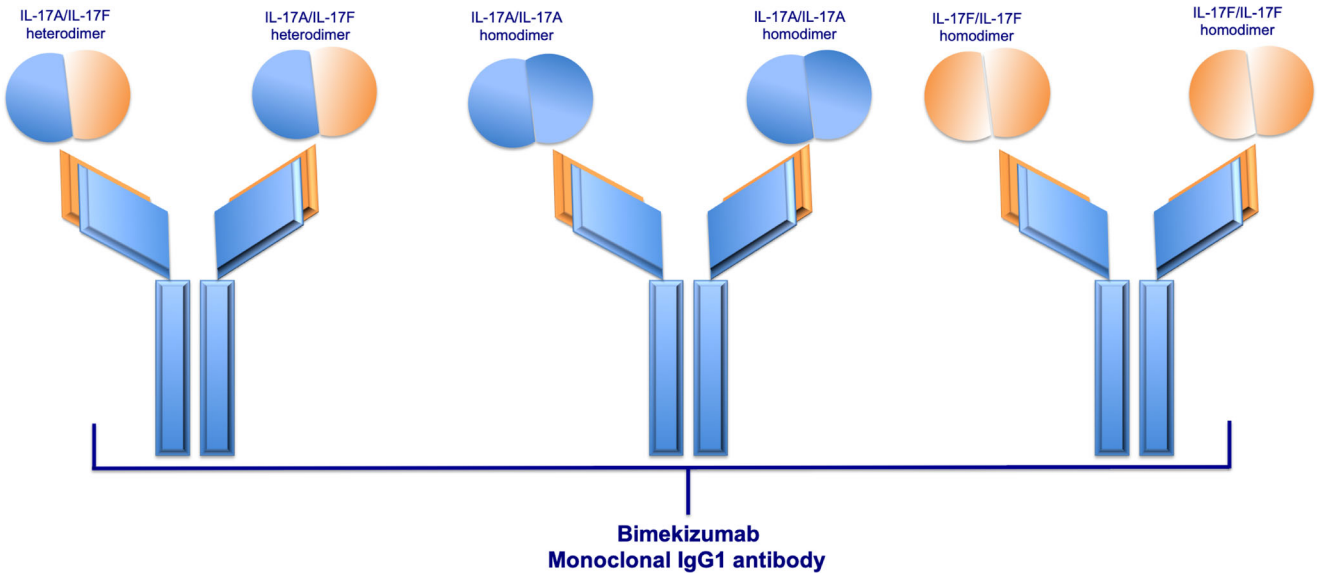

Fig. 2 Schematic structure of bimekizumab and its binding sites: IL-17A/IL-17F heterodimers, IL-17A/IL-17A homodimers, and IL-17F-IL-17F homodimers

Psoriatic Arthritis and Other Conditions

In a randomized, double-blinded, placebo-controlled, proof-of-concept phase 1b trial of psoriatic arthritis, 53 patients received either intravenous placebo or intravenous doses of bimekizumab that ranged from 40 to 560 mg at weeks 0, 3, and 6 [42••]. At week 8, clinical responses were ACR 20 of 80%, ACR 50 of 40%, and ACR 70 of 23.3%, notably higher (and in a shorter time period) than clinical responses observed with both anti-TNF-α blockers and IL-17A blockers [42••]. At week 20, ACR 20 responses were maintained and ACR 50 and ACR 70 responses increased to 57% and 37%, respectively [42••]. Maximal responses were seen as early as week 4 and sustained for 12–20 weeks [42••]. Of note, all patients were on concomitant anti-inflammatory or anti-rheumatologic drugs during this trial.

This study was followed by a randomized, double-blinded, placebo-controlled, dose-ranging phase 2b (BE ACTIVE) trial in 206 patients with psoriatic arthritis [46••]. Patients received 16 mg, 160 mg, or 320 mg subcutaneously every 4 weeks for 12 weeks. At week 12 (the primary endpoint), the ACR 50 ranged from 24.4 to 46.3% [46••]. Dosing was extended out to 48 weeks, with clinical responses of 76% (ACR 20), 63% (ACR 50), and 39% (ACR 70) at this time point for patients in the highest dosing group (320 mg every 4 weeks) [46••]. Phase 3 psoriatic arthritis trials are ongoing.

Bimekizumab has also been tested in patients with ankylosing spondylitis [47] and rheumatoid arthritis [48], with the latter proof-of-concept study utilizing bimekizumab as an add-on drug in patients with inadequate responses to the TNF-α-blocker certolizumab pegol [48]. The ankylosing spondylitis trial (BE AGILE) was a 48-week, randomized, double-blinded, placebo-controlled trial that enrolled 303 patients [47]. At week 12 (the primary endpoint), 45.9% of patients receiving bimekizumab 320 mg every 4 weeks versus 13% receiving placebo achieved ASAS 40, which are promising results that are likely to lead to further development of bimekizumab for ankylosing spondylitis.

In the rheumatoid arthritis trial, patients who demonstrated inadequate responses to certolizumab pegol after 8 weeks were continued on certolizumab and randomized to receive either bimekizumab ($n = 52$) or placebo ($n = 27$) thereafter [48]. At week 20 (after 12 weeks of dual therapy versus single drug therapy), patients on certolizumab pegol plus bimekizumab had better DAS28(CRP) responses than patients on certolizumab pegol alone [48]. This study is novel in that it highlights a possible role for IL-17A/IL-17F inhibition in combination with anti-TNF-α therapy in patients with rheumatoid arthritis.

Bimekizumab Tolerability and Safety

In the early phases of clinical development of bimekizumab across disease states, patients have tolerated the medication well with no unexpected safety signals. In the single-dose intravenous phase I study for psoriasis, adverse events (AE) were seen in 84.6% of patients receiving bimekizumab and 76.9% of placebo-treated patients, the majority of which were mild, with only 1 serious AE (SAE) of vomiting reported in a subject receiving bimekizumab that the investigators deemed unrelated to the treatment [43]. AE considered related to the drug were also non-serious, occurring in 46.2% and 30.8% of subjects receiving bimekizumab and placebo, respectively [43]. The most common AE reported were headache, nasopharyngitis, oropharyngeal pain, and local reactions to the ECG machine leads.

In the larger phase 2b study of 250 psoriasis patients, AE reported through week 12 occurred more commonly in bimekizumab-treated patients than in those on placebo (60.6% and 35.7% of patients, respectively), but only 1.6% were considered severe [44••]. More treatment discontinuations due to AEs also occurred in patients receiving bimekizumab compared to placebo (4.8% and 2.4%, respectively), but these numbers were small [44••]. No dose relationship was seen between the incident AE and bimekizumab. There was 1 SAE in the placebo group (viral meningitis) and 2 SAE reported by one patient in the bimekizumab group (large intestinal polyp and colon cancer), which occurred 15 days after the first dose of drug [44••]. None of these SAE were considered treatment-related. The most common AE were nasopharyngitis, upper respiratory tract infection, and arthralgia. Bimekizumab-treated patients had 9 fungal infections (oral candidiasis, oral fungal infections, vulvovaginal candidiasis, and tinea pedis), which did not lead to treatment discontinuation, consistent with the known protective effect of IL-17 against mucosal yeast pathogens. There were no cases of inflammatory bowel disease, major cardiac events, suicide, or serious infections. This safety profile was maintained at week 60 in the extension phase of the trial [45••]. The most common AE through this time point were oral candidiasis and nasopharyngitis [45••].

In the phase 1b psoriatic arthritis trial [42••], which included patients on concomitant anti-inflammatory and anti-rheumatologic drugs, a similar safety profile was seen with no new signals. Similar numbers of AE occurred in patients who received a single intravenous dose of bimekizumab as those receiving placebo (68.4 vs. 71.4%), with only 3 rated as severe (5.3% on bimekizumab and 7.1% on placebo), and none of these events were considered to be treatment-related [42••]. No patients discontinued the study because of an AE. Only 1 patient reported an SAE (3 events related to a fall and not considered treatment-related). Two cases of mild candidiasis occurred (oral and vulvovaginal), which resolved with antifungal therapy [42••]. As seen in the psoriasis trials, no cases of inflammatory bowel disease, major cardiac events, suicide, or serious infections were seen. Again, no relationship to the dose of the drug was seen in terms of AE incidence. A

similar safety profile was evident in the larger phase 2 48-week psoriatic arthritis trial again with no unexpected events, major cardiac issues, inflammatory bowel disease, or suicide [46••]. Nasopharyngitis (12.1%) was the most common AE, and oral candidiasis was seen in a few bimekizumab-treated patients (4.9%), all of which were mild-to-moderate in severity and did not lead to study dropout [46••].

Similar safety results were found in the phase 2b trial of 303 patients with ankylosing spondylitis [47]. Treatment emergent AE through week 12 were similar between bimekizumab and placebo groups (35.4% and 36.7%, respectively), with the most frequent AE found to be nasopharyngitis and headache. Finally, results in the rheumatoid arthritis trials using bimekizumab as add-on therapy with certolizumab pegol also found a safety profile similar to bimekizumab alone [48].

Conclusion

Bimekizumab, a monoclonal antibody that binds to and blocks function of both IL-17A and IL-17F (key effector cytokines in psoriatic inflammation), has shown great promise in early stages of clinical development for patients with psoriasis, psoriatic arthritis, and ankylosing spondylitis. In particular, striking numbers of treated psoriasis patients experience complete skin clearance (over 80%) and up to 80% of psoriatic arthritis patients have demonstrated ACR20 responses. The main side effect of this drug thus far has been oral candidiasis, which has been mild and manageable in most affected patients. If phase 3 clinical studies confirm these early phase efficacy and safety results as outlined here, bimekizumab will be an important new addition for treating patients with psoriasis and psoriatic arthritis.

Compliance with Ethical Standards

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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