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EDITORIAL

Bimekizumab: the new drug in the biologics armamentarium for psoriasis

Egídio Freitas[1], Tiago Torres[1,2,3]

[1]Department of Dermatology, Centro Hospitalar do Porto, Porto, Portugal;
[2]Instituto de Ciências Biomédicas Abel Salazar, University of Porto, Porto, Portugal;
[3]Dermatology Research Unit, Centro Hospitalar do Porto, Porto, Portugal

Abstract

Bimekizumab, a humanized monoclonal IgG1 antibody being currently evaluated for multiple immune-mediated diseases, is mentioned in the recent report by Clarivate, *Drugs to Watch in 2021*, as one of the drugs to be observed in 2021. Due to its novel mechanism of action (dual inhibition of IL-17A and IL-17F), bimekizumab is considered a new therapeutic approach for the treatment of moderate-to-severe psoriasis. Bimekizumab has demonstrated superiority in all direct comparative clinical trials conducted, whether against ustekinumab (IL-12/23 inhibitor), adalimumab (TNF inhibitor) or secukinumab (IL-17A inhibitor), and has shown very encouraging results for the treatment of psoriatic arthritis. Since September 2020, the drug is being reviewed by the EMA and FDA for the treatment of psoriasis. Herein, the current status of bimekizumab is discussed.

Keywords: bimekizumab, IL-17, psoriasis, psoriatic arthritis.

Citation

Freitas E, Torres T. Bimekizumab: the new drug in the biologics armamentarium for psoriasis. Drugs in Context 2021; 10: 2021-4-1. DOI: 10.7573/dic.2021-4-1

In the recent report by Clarivate, *Drugs to Watch in 2021*,[1] bimekizumab is mentioned as one of the drugs to be observed in 2021. Bimekizumab, a humanized monoclonal IgG1 antibody that selectively neutralizes both IL-17A and IL-17F, is currently being evaluated for multiple immune-mediated diseases, including psoriasis and psoriatic arthritis.[2,3] Psoriasis, one of the most common chronic cutaneous immune-mediated diseases, affects between 1% and 3% of adults in western countries. It is associated with numerous comorbidities such as psoriatic arthritis (in 15–30% of psoriasis patients), cardiovascular and metabolic diseases, and depression as well as with an enormous physical and psychological burden.[4]

In the last decades, the increasing understanding on the pathogenesis of psoriasis has led to a shift in the psoriasis treatment paradigm with the advent of biological therapies.[5] The discovery of the IL-23–IL-17 axis, widely considered the most critical immune pathway in the development of psoriasis, led to the development of highly effective and safe drugs targeting this pathway, including IL-23 inhibitors (guselkumab, risankizumab),[6] an IL-17 receptor A inhibitor (brodalumab)[7] and IL-17A inhibitors (secukinumab, ixekizumab).[8] These drugs have led to psoriasis being one of the best-managed chronic inflammatory diseases. However, the choice of appropriate biologic therapy for a patient is very often determined by the presence of comorbidities,[9,10] and there are still some patients that do not respond, lose clinical response, develop adverse events or do not tolerate these treatments.[11] Thus, new drugs are still needed and welcomed. A promising ongoing area is the development of dual inhibitor antibodies, which act simultaneously on two different cytokines, potentially allowing greater disease control.[12]

The IL-17 family consists of five receptors (IL-17RA–E) and six isoforms (IL-17A–F). In addition to IL-17A, IL-17F plays a role in psoriasis pathogenesis. Within the entire IL-17 family, IL-17F is the most structurally homologous (~50%) to IL-17A. Existing both as homodimers (i.e. IL-17A/A or IL-17F/F) or as heterodimers of IL-17A/IL-17F, they share signaling pathways through the same heterodimeric complex of IL-17 receptors A and C (IL-RA/RC) and biologic function. IL-17F is 30 times less biologically potent than IL-17A, yet both cooperate synergistically with IL-6, IL-8 and TNF, amplifying the inflammatory response. In psoriasis, IL-17A and IL-17F are both increased in the blood, skin and synovial samples.[13]

Bimekizumab is a humanized IgG1 monoclonal antibody that simultaneously and selectively inhibits the biological functions of both IL-17A and IL-17F.[14] This new mechanism of action allows a more extensive suppression of disease inflammation, with a greater reduction of gene expression, migration of

inflammatory cells and production of proinflammatory cytokines than the isolated blockade of IL-17A.[15] Additionally, bimekizumab has no activity on IL-17E (thought to have anti-inflammatory properties), unlike the IL-17RA inhibitor brodalumab.[13] In phase I and II clinical trials of psoriasis, bimekizumab has shown promising results leading to the continuation of its development programme. Four phase III studies were conducted to compare bimekizumab with placebo ustekinumab (BE VIVID, NCT03370133[16]), (BE READY, NCT03410992[17]) adalimumab (BE SURE, NCT03412747[18]), and secukinumab (BE RADIANT, NCT03536884[19]). These trials demonstrated the superiority of bimekizumab over placebo and ustekinumab, adalimumab and secukinumab.

In the BE VIVID study,[16] the safety and efficacy of bimekizumab were compared, over 52 weeks, with ustekinumab and placebo. At week 16, 85% of patients on bimekizumab achieved a 90% reduction in the Psoriasis Area and Severity Index (PASI90), whilst only 50% of patients taking ustekinumab and 4% of patients on placebo achieved the same result ($p<0.0001$ for both comparisons); an Investigator's Global Assessment (IGA) score of 0/1 was obtained in a significantly higher percentage in patients treated with bimekizumab than with ustekinumab and placebo (84%, 53% and 5%, respectively; $p<0.0001$). Moreover, PASI100 was reached in a significantly higher proportion of patients prescribed with bimekizumab as opposed to those treated with ustekinumab (64% and 38%, respectively; $p<0.001$).

The BE READY study aimed to assess, over 56 weeks, the safety and efficacy of bimekizumab compared to placebo.[17] It had a first therapy period of 16 weeks followed by a randomized withdrawal period; at week 16, PASI90 was achieved by 91% of patients who were treated with bimekizumab *versus* 1% of patients on placebo ($p<0.0001$); 93% of patients with bimekizumab achieved IGA 0/1 *versus* 1% with placebo ($p<0.0001$) and PASI100 was achieved in 68% of patients treated with bimekizumab *versus* 1% with placebo ($p<0.0001$).[17] Additionally, sustained skin clearance was perceived after bimekizumab withdrawal at week 16 (after the last dose of bimekizumab, the median time to failure of PASI75 was 32 weeks). At week 56, PASI90 was maintained in 86.8% of patients treated with bimekizumab 320 mg every 4 weeks (Q4W), in 91% of patients switched to bimekizumab 320 mg every 8 weeks (Q8W) and in 16.2% of patients in whom treatment was suspended.

Regarding the safety profile in both studies, it was found that, in the BE VIVID study, 6% of patients receiving bimekizumab had serious treatment-emergent adverse events (TEAEs) *versus* 8% in the ustekinumab group.[16] In the BE READY study, TEAEs occurred in 74%, 77% and 69% of patients treated with bimekizumab 320 mg Q4W, bimekizumab 320 mg Q8W and placebo, respectively; of these, severe TEAEs were considered in 5%, 3% and 4% of patients with bimekizumab 320 mg Q4W, bimekizumab 320 mg Q8W and placebo, respectively.[17]

Bimekizumab did not show any unexpected safety findings, although the rate of oral candidiasis was higher than with other IL-17 inhibitors (15% in BE VIVID and 10% in BE READY *versus* a rate of 1–4%).[20] However, this 5–10-fold higher rate may not be clinically significant, mainly because most of the cases of candidiasis were limited to the oral cavity and were mild to moderate and responsive to treatment. In addition to candidiasis, it should be noted that, over the duration of the two studies, a patient developed inflammatory bowel disease, probably related to IL-17 inhibition.[21]

The results of the phase III BE SURE study (bimekizumab *versus* adalimumab) and the BE RADIANT study (bimekizumab *versus* secukinumab) were recently published.[18,19]

In the BE SURE study,[18] at week 16, 86% and 85.3% of patients in the bimekizumab group *versus* 47.2% and 57.2% in the adalimumab group achieved PASI90 ($p<0.001$) and IGA 0/1 ($p<0.001$), respectively. The percentage of patients who obtained PASI100 was significantly higher in the bimekizumab group compared to the adalimumab group (60.8% *versus* 23.9% and 66.8% *versus* 29.6%, at weeks 16 and 24, respectively; $p<0.001$ for each comparison). The response rates of IGA 0/1, PASI100 and PASI90, in the two arms of the bimekizumab study (Q4W or Q8W dosing) were maintained until week 56. Patients in the adalimumab group who, at week 24, were switched to bimekizumab Q4W dosing, experienced a rapid increase in their clinical response rates through to week 56. At week 56, the clinical response in these patients was comparable to the arm treated with bimekizumab in the entire study. TEAEs and severe TEAEs were comparable in the groups with bimekizumab (71.5% and 1.6%, respectively) and adalimumab (69.8% and 3.1%). Throughout the study, the most common TEAEs in patients on bimekizumab were upper respiratory tract infection (9.0%), oral candidiasis (16.2%) and nasopharyngitis (20.9%).

The phase IIIb BE RADIANT study was the first head-to-head study with a IL-17 inhibitor.[19] All primary and secondary endpoints have been achieved. At week 16, the group treated with bimekizumab reached PASI100 in a significantly higher proportion than the group treated with secukinumab (61.7% *versus* 48.9%, respectively; $p<0.001$).[19] Additionally, bimekizumab showed superiority in both monthly and bimonthly dosing, compared to secukinumab in reaching PASI75 at week 4 (71.0% *versus* 47.3%, respectively; $p<0.001$) and complete skin clearance at week 48 ($p<0.001$).[19] The oral candidiasis frequency was higher with bimekizumab compared to secukinumab (19.3% *versus* 3.0%, respectively).[19]

Concerning psoriatic arthritis, the results of the BE ACTIVE study, a phase IIb dose-ranging, placebo-controlled trial, have recently been published.[22] The primary endpoint was a 50% improvement in ACR response criteria at 12 weeks, which consists of a much more rigorous endpoint than commonly used. Bimekizumab exhibited a relatively fast action time. At week 8, the initial improvements were verified and, at week 12, the improvements were well established. It was

shown that bimekizumab can maintain the response level in a large percentage of patients for at least 2 years, at a dose of 160 mg every 4 weeks. These results were independent of previous exposure to TNF inhibitors.

Conclusion

Bimekizumab, due to its different mechanisms of action (dual inhibition of IL-17A and IL-17F), is considered a novel therapeutic approach for the treatment of moderate-to-severe psoriasis. Bimekizumab demonstrated superiority in all direct comparative clinical trials conducted, whether against ustekinumab (IL-12/23 inhibitor), adalimumab (TNF inhibitor) or secukinumab (IL-17A inhibitor; press release data only), and has shown very encouraging results for the treatment of psoriatic arthritis. Bimekizumab is highly effective, extremely fast to act and appears to have a safety profile similar to other anti-IL-17 biological therapies, although there are still limited data regarding its long-term safety and efficacy and its use in a real-world population.

Since September 2020, the drug is being reviewed by the EMA and FDA for the treatment of chronic moderate-to-severe plaque psoriasis, based on the results of three phase III trials that showed superiority over ustekinumab (BE VIVID), adalimumab (BE SURE) and placebo (BE READY).

It will be interesting to elucidate the position of bimekizumab in the highly crowded market of psoriasis treatment.

Contributions: All the authors contributed equally to the preparation of this review. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole and have given their approval for this version to be published.

Disclosure and potential conflicts of interest: EF has no conflicts of interest. TT is a scientific consultant/speaker/clinical study investigator for AbbVie, Almirall, Amgen, Arena Pharmaceuticals, Biocad, Biogen, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Eli Lilly, Fresenius Kabi Pharma, Janssen, Leo Pharma, MSD, Mylan, Novartis, Pfizer, Samsung-Bioepis, Sandoz, Sanofi, UCB, Viatris. He is also an Associate Editor for *Drugs in Context*. The International Committee of Medical Journal Editors (ICMJE) Potential Conflicts of Interests form for the authors is available for download at: https://www.drugsincontext.com/wp-content/uploads/2021/05/dic.2021-4-1-COI.pdf

Acknowledgements: None.

Funding declaration: There was no funding associated with the preparation of this article.

Article URL: https://www.drugsincontext.com/bimekizumab:-the-new-drug-in-the-biologics-armamentarium-for-psoriasis

Correspondence: Tiago Torres, Department of Dermatology, Centro Hospitalar do Porto, Rua D Manuel II, S/N, 4050-344, Porto, Portugal. Email: torres.tiago@outlook.com

Provenance: Invited; externally peer reviewed.

Submitted: 6 April 2021; **Accepted:** 11 May 2021; **Publication date:** 8 June 2021.

Drugs in Context is published by BioExcel Publishing Ltd. Registered office: Plaza Building, Lee High Road, London, England, SE13 5PT.

BioExcel Publishing Limited is registered in England Number 10038393. VAT GB 252 7720 07.

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