

- 5 Has C, Liu L, Bolling MC et al. Clinical practice guidelines for laboratory diagnosis of epidermolysis bullosa. *Br J Dermatol* 2020; **182**:574–92.
- 6 Weisman A, Chan JM, LaPointe C et al. Physiotherapy for epidermolysis bullosa: clinical practice guidelines. *Orphanet J Rare Dis* 2021; **16**:406.
- 7 Martin K, Geuens S, Asche JK et al. Psychosocial recommendations for the care of children and adults with epidermolysis bullosa and their family: evidence based guidelines. *Orphanet J Rare Dis* 2019; **14**:133.
- 8 Krämer S, Lucas J, Gamboa F et al. Clinical practice guidelines: oral health care for children and adults living with epidermolysis bullosa. *Spec Care Dentist* 2020; **40** (Suppl. 1):3–81.
- 9 King A, Hanley H, Popenhagen M et al. Supporting sexuality for people living with epidermolysis bullosa: clinical practice guidelines. *Orphanet J Rare Dis* 2021; **16**:9.

## Another anti-interleukin (IL)-17 inhibitor: is there an advantage of blocking IL-17A and IL-17F?

DOI: 10.1111/bjd.20959

**Linked Article:** Oliver et al. *Br J Dermatol* 2022; **186**:652–663.

Bimekizumab is the fourth biologic inhibiting interleukin (IL)-17 that has been approved for the treatment of plaque-type psoriasis in Europe.<sup>1</sup> Do we need it?

IL-17 inhibitors are more heterogeneous than the group name implies. Secukinumab and ixekizumab directly inhibit IL-17A, while brodalumab blocks IL-17-receptor alpha and as a consequence inhibits IL-17A, IL-17C, IL-17E and IL-17F.<sup>2</sup> Bimekizumab finds a middle way, and selectively inhibits IL-17A and IL-17F.<sup>1</sup>

One could assume that these marginal differences do not have a clinical impact, but the study by Oliver and colleagues<sup>3</sup> published in this issue of the *BJD* helps us to better understand the molecular mechanisms of bimekizumab. The study preceded the published phase III studies, but gives us insight into the basis on which successful dosing intervals were chosen.

This elegant trial of 49 randomized patients showed nicely that two doses of bimekizumab 4 weeks apart almost normalized the transcriptome of lesional skin to nonlesional levels. The effect was not limited to inflammatory parameters, but the 100% improvement from baseline in Psoriasis Area and Severity Index (PASI 100) peaked at week 12, that is 8 weeks after the second dose. This response, in combination with the transcriptome data, permitted comparison of 4-week and 8-week dosing intervals, while the 12-week dosing interval could be eliminated based on the poor response in this study.<sup>3</sup>

One of the subsequent phase III studies was a head-to-head comparison of secukinumab and bimekizumab.<sup>4</sup> It showed clear clinical superiority of bimekizumab for PASI 100 regardless of the maintenance dosing interval (every 4 weeks vs. every 8 weeks) over time. However, the significantly

increased effectiveness came at the expense of clinical safety. Oral candidiasis was found in 19.3% of the bimekizumab patients while oral candidiasis was found in only 3% of secukinumab patients.<sup>4</sup> Although predominantly mild to moderate in severity, this increase in candida infections is concerning because IL-17A and probably even more in combination with IL-17F is thought to protect skin and mucosa from yeast and fungal infections.<sup>5</sup> So, beyond the clinical effectiveness these mechanistic differences may have implications for clinical safety, particularly as risk factors for candida infections like obesity and diabetes are common in the psoriasis population.<sup>6</sup> At the same time, mucocutaneous candidiasis is often easily treated, and may be more of a nuisance than a threat. A recent review has not found published cases of deep fungal infections in patients on other IL-17 inhibitors.<sup>7</sup>

In conclusion, this elegant study gives us new insight into molecular proof of concept and definition of dosing intervals for psoriasis medications, and is well worth reading. If nothing else it is a beautiful piece of clinical and molecular investigation. The study demonstrates that inhibiting IL-17F increases efficacy and extends dosing intervals. Given the problem of candidiasis, patients and physicians have to decide what they find more important. This is best done based on real-world data.

Sascha Gerdes <sup>1</sup> and Joerg Albrecht <sup>2,3</sup>

<sup>1</sup>Psoriasis-Center Kiel, Department of Dermatology, University Medical Center Schleswig-Holstein, Campus Kiel, Kiel, Germany; <sup>2</sup>Division of Dermatology, Department of Medicine, John H. Stroger, Jr Hospital of Cook County, Chicago, IL, USA; and <sup>3</sup>Division of Dermatology, Department of Otorhinolaryngology, Rush Medical College, Chicago, IL, USA

Correspondence: Sascha Gerdes

Email: sgerdes@dermatology.uni-kiel.de

Conflicts of interest: S.G. has been an advisor and/or received speaker's honoraria and/or received grants and/or participated in clinical trials of the following companies: AbbVie, Affibody AB, Akari Therapeutics, Almirall Hermal GmbH, Amgen, AnaptysBio, argenx BVBA, AstraZeneca AB, Biogen Idec Ltd, bioskin GmbH, Bristol Myers Squibb, Boehringer Ingelheim, Celgene, Dermira, Inc., Eli Lilly and Company, Foamix Pharmaceuticals Ltd, Forward Pharma, Galderma, Hexal AG, Incyte, Janssen-Cilag, Johnson & Johnson, Klinge Pharma GmbH, Kymab, LEO Pharma, Medac GmbH, MSD, neubourg skin care GmbH, Novartis, Pfizer, Principia Biopharma, Regeneron Pharmaceuticals, Sandoz Biopharmaceuticals, Sanofi-Aventis, Trevi Therapeutics and UCB Pharma. J.A. has participated in clinical trials of AbbVie, Biogen Idec and AiCuris.

## References

- 1 Freitas E, Blauvelt A, Torres T. Bimekizumab for the treatment of psoriasis. *Drugs* 2021; **81**:1751–62.
- 2 Silfvast-Kaiser A, Paek SY, Menter A. Anti-IL17 therapies for psoriasis. *Expert Opin Biol Ther* 2019; **19**:45–54.
- 3 Oliver R, Krueger JG, Glatt S et al. Bimekizumab for the treatment of moderate-to-severe plaque psoriasis: efficacy, safety,

- pharmacokinetics, pharmacodynamics and transcriptomics from a phase IIa, randomized, double-blind multicentre study. *Br J Dermatol* 2022; **186**:652–63.
- 4 Reich K, Warren RB, Lebwohl M et al. Bimekizumab versus secukinumab in plaque psoriasis. *N Engl J Med* 2021; **385**:142–52.
  - 5 Pavlova A, Sharafutdinov I. Recognition of *Candida albicans* and role of innate type 17 immunity in oral candidiasis. *Microorganisms* 2020; **8**:1340.
  - 6 Choudhary S, Pradhan D, Pandey A et al. The association of metabolic syndrome and psoriasis: a systematic review and meta-analysis of observational study. *Endocr Metab Immune Disord Drug Targets* 2020; **20**:703–17.
  - 7 Lee MP, Wu KK, Lee EB, Wu JJ. Risk for deep fungal infections during IL-17 and IL-23 inhibitor therapy for psoriasis. *Cutis* 2020; **106**:199–205.

## Herpesvirus, serious and opportunistic infections associated with atopic dermatitis

DOI: 10.1111/bjd.20982

**Linked Article:** Wan et al. *Br J Dermatol* 2022; **186**:664–672.

Atopic dermatitis (AD) is a chronic inflammatory skin disease characterized by molecular and cellular factors that seem to induce a greater susceptibility to microorganisms that commonly affect the skin as well as microorganisms that produce extracutaneous infections. Previous studies analysing the association of AD with infections were primarily cross-sectional studies that have barely evaluated the impact of AD severity on the risk of infections.<sup>1,2</sup> In this issue of the *BJD*, Wan et al. analyse the risk of herpesvirus, serious and opportunistic infections in paediatric and adult patients with AD.<sup>3</sup> The study utilized a large database of medical records validated for the study of AD and demonstrated that AD was linked with an increased risk of herpesvirus, hospitalized and opportunistic infections, with a higher risk in patients with greater AD severity. The data also suggested that AD itself was a key factor in the susceptibility to infections while other atopic diseases were independent of such association.<sup>3</sup>

Previous studies have suggested that the molecular and cellular mechanisms that underlie AD can have a negative impact on the protection against microbial infections.<sup>4</sup> Defects in the epithelial barrier, dysregulation in expression of antimicrobial proteins, and altered adaptive and innate immune responses in AD potentially make patients with this disease more prone to infections.<sup>4–6</sup> In that respect, T-helper (Th) 2 inflammatory predominance, which is a hallmark in a significant group of patients with AD, prevents effective immune responses against microorganisms by specific mechanisms.<sup>7</sup> In that sense, it has been found that Th2 inflammation has an inhibitory role in the production of the major antiviral cytokines type I interferons (IFN- $\alpha$ /IFN- $\beta$ ) by cross-regulation mechanisms between the high-affinity receptor for IgE and Toll-like receptors (TLRs).<sup>6,8</sup> Th2 cytokines can also have an inhibitory function on the

expression of TLRs and their signalling, as well as in the expression of epithelial barrier proteins and antimicrobial proteins.<sup>5</sup> Collectively, a relevant body of evidence suggests that the numerous factors associated with AD predispose the immune system in those individuals to be more permissive to microbial infections.<sup>4–8</sup>

Previously it has been suggested that infections induced by herpesvirus, such as herpes simplex virus or varicella zoster virus, were more frequent in individuals with severe AD.<sup>9,10</sup> Extracutaneous infections were also found to be frequent in patients with AD.<sup>1</sup> However, most of the studies that analysed the impact of AD on the risk of different infections were carried out in a cross-sectional manner. In that sense, the study presented by Wan et al. in this issue of the *BJD* allowed the analysis of the temporal association of AD and different infections and is one of the first studies to analyse the influence of AD severity on infectious comorbidities.<sup>3</sup>

In conclusion, the study by Wan et al.<sup>3</sup> represents a relevant contribution in the understanding of the clinical association between AD and different infectious diseases. The data presented would potentially contribute to further deepening exploration into the complex interplay that exists between chronic inflammatory skin diseases such as AD and infectious agents.

Natalija Novak<sup>1</sup> and Beatriz Cabanillas <sup>2</sup>

<sup>1</sup>Department of Dermatology and Allergy, University Hospital Bonn, Venusberg Campus 1, Bonn, 53127, Germany and <sup>2</sup>Department of Allergy, Research Institute Hospital 12 de Octubre (imas12), Avenida de Córdoba s/n, Madrid, 28041, Spain

### Correspondence:

Beatriz Cabanillas.

Email: bcabanillas.imas12@h12o.es

Conflicts of interest: the authors declare they have no conflicts of interest.

## References

- 1 Strom MA, Silverberg JL. Association between atopic dermatitis and extracutaneous infections in US adults. *Br J Dermatol* 2017; **176**:495–7. <https://doi.org/10.1111/bjd.14708>.
- 2 Seegreber M, Worm M, Werfel T et al. Recurrent eczema herpeticum – a retrospective European multicenter study evaluating the clinical characteristics of eczema herpeticum cases in atopic dermatitis patients. *J Eur Acad Dermatol Venereol* 2020; **34**:1074–9. <https://doi.org/10.1111/jdv.16090>.
- 3 Wan J, Shin DB, Syed MN et al. Risk of herpesvirus, serious and opportunistic infections in atopic dermatitis: a population-based cohort study. *Br J Dermatol* 2022; **186**:664–72.
- 4 Weidinger S, Novak N. Atopic dermatitis. *Lancet* 2016; **387**:1109–22. [https://doi.org/10.1016/S0140-6736\(15\)00149-X](https://doi.org/10.1016/S0140-6736(15)00149-X).
- 5 Bussmann C, Peng WM, Bieber T, Novak N. Molecular pathogenesis and clinical implications of eczema herpeticum. *Expert Rev Mol Med* 2008; **10**:e21. <https://doi.org/10.1017/S1462399408000756>.
- 6 Peng WM, Jenneck C, Bussmann C et al. Risk factors of atopic dermatitis patients for eczema herpeticum. *J Invest Dermatol* 2007; **127**:1261–3. <https://doi.org/10.1038/sj.jid.5700657>.