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Thomas Bieber, MD, PhD, MDRA

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Editorial for the Journal of Allergy and Clinical Immunology

In search of the holy grail in atopic dermatitis:

Will dupilumab become the first Disease Modifying Atopic Dermatitis Drug (DMADD)?

Thomas Bieber, MD, PhD, MDRA^{1,2,3}

¹ Department of Dermatology and Allergy, University Hospital, Bonn, Germany

² Christine Kühne-Center for Allergy Research and Education, Davos, Switzerland

³ Davos Biosciences, Davos, Switzerland

Correspondence:

Thomas Bieber

Department of Dermatology and Allergy

and Christine Kühne-Center for Allergy Research and Education (CK-CARE), University

Hospital of Bonn, Venusberg Campus 1

D-53127 Bonn, Germany

Tel.: +49-228-287-14388, Fax: +49-228-287-14881

E-mail: Thomas.Bieber@ukbonn.de

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Declaration of interest

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Atopic dermatitis (AD) is a highly heterogeneous disorder which has been assumed to be the port of entry for IgE sensitization during early infancy and to be the first step in the atopic march being followed by food allergy, allergic rhinitis and allergic asthma¹. The atopic march is far from being a general phenomenon but only occurring in an ill-defined subgroup of patients². A decade ago, AD has been considered as candidate for disease modification by applying either preventative or therapeutic interventions to better control the emergence of AD and its associated comorbidities potentially developing in the context of an atopic march³. Insights into the mechanisms underlying the chronic inflammation in the skin have highlighted the primary roles of the genetically driven epidermal barrier function and the role of the Th2 (T2) cytokines IL-4 and IL-13 in the generation of IgE and as drivers for the skin inflammation⁴. More recently, besides IL-4 and IL-13, a widening of the adaptive immune response with e.g. IL-22 and IL-17 have been reported to be detectable in the skin as well as in the periphery of patients with AD leading to a kind of immunological march⁵. However, clear clinical correlates between the distinct steps of the atopic march and the immunological march are still lacking. Moreover, it has been postulated that the main steps of the atopic march – and the opportunities to intervene for potential disease modification – are operative during childhood. In a paper published in this issue of the *Journal of Allergy and Clinical Immunology*, Geba *et al.* report on the attenuating effect of dupilumab on the atopic march in a meta-analysis of the database from 12 clinical trials⁶. They assessed the incidence rate ratios of new or worsened allergic events from baseline compared to patients in the placebo arms. They found an overall reduction of the risk of developing new allergies of 37% while this improved to 54% when including IgE as a category. Most importantly, the best response was reached in patients with following profile: adolescents (<18 years) with Caucasian ethnic background, early onset of AD (<2 years), severe AD and asthma at base line.

A number of lessons and questions can be associated with this report. At least in a subgroup of mainly adolescent patients with a particular clinical phenotype, a targeted therapy with a biologic directed against the T2 cytokines IL-4 and IL-13 has the potential to at least reduce the further development of atopic comorbidities during the observation time of these studies. This strongly suggests some plasticity of the T2 immune response in the atopic march until adolescence during which it seems still receptive for this kind of intervention. Assuming that the role of the T2 immune response may be even more dominant in younger patients⁷, one

may speculate that the attenuation effect reported in this study may be more significant when starting dupilumab in an earlier stage of the disease, i.e. in early childhood or even in infancy. Similarly to the lessons learned so far from the results of the clinical development programs and real world data with dupilumab as well as other targeted therapies in AD, not surprisingly there is no “one-size-fits-all” in terms of impact on the atopic march. This report therefore further supports the need of a precision medicine approach ideally based on predictive biomarkers enabling to identify such patients with a good clinical response for AD combined to attenuation of the ongoing atopic march. While the authors provide some evidence for a reduction in the incidence rate of new allergies in phase 3 studies extending up to 52 weeks of the clinical development program of dupilumab, they did not explore in such detail the potential long-term effect of dupilumab on AD itself. There are currently two mutually excluding concepts with regards to the issue of AD and systemic inflammation with significant implications for our understanding of the atopic march: some authors argue that AD is primarily a systemic disease⁸ while others favor the hypothesis that the inflammatory burden in the skin has an impact on the overall immune system and on further organs potentially affected by atopic and non-atopic comorbidities⁹. The fact that patients who are receptive for attenuation of the atopic march in the present study are younger individuals with early onset and more severe forms of AD would support the concept that severe skin inflammation is an important driving force in the mechanisms underlying the progress of the atopic march. Thus, efficiently reducing this inflammatory burden would be a crucial strategy to impact on the development of comorbidities. If this hypothesis is valid, further studies should confirm that attenuation of the atopic march in this subpopulation is associated with a long-term remission of AD after stopping the therapy. Another possible scenario would be a complete stop of the atopic march without significant long-term remission of AD. This dissociation would seemingly question the primary role of the skin-derived inflammation for the atopic march. In the same line, a retrospective analysis of the data base from the clinical trials with dupilumab for asthma with consideration to the concomitant presence of AD could at least partially answer the question of the role of skin-derived inflammation in the atopic march.

Another issue of particular interest is whether other therapies targeting only IL-13 such as tralokinumab and lebrikizumab may have the same disease modifying ability as dupilumab. Due to its dual mode of action on both T2 cytokines, dupilumab has the potential to block the biologic activity of IL-13 as the most important driving force of the skin inflammation¹⁰ as well

as the more centrally acting IL-4 which could be more relevant for the generation of IgE sensitization (Figure 1). Blocking IL-13 in the skin has several effects: a reduction of the inflammation, a reduction of the pruritus and an improvement of the skin barrier function, thereby reducing the permeability which allows the penetration of allergens and the IgE sensitization mechanisms related to this phenomenon. While the value of total IgE as a reliable biomarker has always been questioned in AD, according to the present study, measuring IgE could be of interest to appreciate the disease modifying effect of dupilumab and potentially other preventative or therapeutic interventions. If further prospective studies, particularly in the pediatric population, confirm the impact of dupilumab on AD and the atopic march, it could become the first medicinal product to qualify as Disease Modifying Atopic Dermatitis Drug (DMAAD) or as Disease Modifying Atopic March Drug (DMAMD). It cannot be excluded that therapies addressing very early events in the immunological march such as those targeting OX40/OX40L have a similar potential to be disease modifying for AD and the atopic march. It will be of great interest to explore whether the rather broad acting JAK inhibitors exhibit similar properties.

With the paper from Geba *et al.* a new era in the therapeutic landscape of AD has been initiated. Not only efficiently treating the chronic skin inflammation but developing strategies aiming at true disease modification should be the new focus of drug development. There are a number of prerequisites which need to be addressed in the context of such strategies (Bieber T., *submitted*) including at least consensual definitions of e.g. (i) the atopic march, (ii) the successful disease modification in AD, (iii) the windows of opportunities for intervention, (v) the length, designs and endpoints of clinical trials as well as (iv) the biomarker programs for patient stratification to be included in prospective approaches exploring the disease modifying potential of already approved drugs or those currently in development. These new developments will be challenging and require a new mindset for the stakeholders involved in this process, i.e. the scientific community, the pharmaceutical industry, the regulators, the third party payers and the patients organizations.

References

1. Davidson WF, Leung DYM, Beck LA, Berin CM, Boguniewicz M, Busse WW, et al. Report from the National Institute of Allergy and Infectious Diseases workshop on "Atopic dermatitis and the atopic march: Mechanisms and interventions". *J Allergy Clin Immunol* 2019; 143:894-913.
2. Belgrave DC, Granell R, Simpson A, Guiver J, Bishop C, Buchan I, et al. Developmental profiles of eczema, wheeze, and rhinitis: two population-based birth cohort studies. *PLoS Med* 2014; 11:e1001748.
3. Bieber T, Cork M, Reitamo S. Atopic dermatitis: a candidate for disease-modifying strategy. *Allergy* 2012; 67:969-75.
4. Weidinger S, Beck LA, Bieber T, Kabashima K, Irvine AD. Atopic dermatitis. *Nat Rev Dis Primers* 2018; 4:1.
5. Bieber T. Atopic dermatitis: an expanding therapeutic pipeline for a complex disease. *Nat Rev Drug Discov* 2022; 21:21-40.
6. Geba GP, Li D, Xu DQ, Mohammadi K, Attre R, Ardeleanu M, et al. Attenuating the atopic march: Meta-analysis of the dupilumab atopic dermatitis database for incident allergic events. *Journal of Allergy and Clinical Immunology* 2023.
7. Brunner PM, Israel A, Leonard A, Pavel AB, Kim HJ, Zhang N, et al. Distinct transcriptomic profiles of early-onset atopic dermatitis in blood and skin of pediatric patients. *Ann Allergy Asthma Immunol* 2019; 122:318-30 e3.
8. Brunner PM, Suarez-Farinas M, He H, Malik K, Wen HC, Gonzalez J, et al. The atopic dermatitis blood signature is characterized by increases in inflammatory and cardiovascular risk proteins. *Sci Rep* 2017; 7:8707.
9. Maintz L, Bieber T, Simpson HD, Demessant-Flavigny AL. From Skin Barrier Dysfunction to Systemic Impact of Atopic Dermatitis: Implications for a Precision Approach in Dermocosmetics and Medicine. *J Pers Med* 2022; 12.
10. Bieber T. Interleukin-13: Targeting an underestimated cytokine in atopic dermatitis. *Allergy* 2020; 75:54-62.

Figure 1: Schematic mode of action of dupilumab in attenuating the atopic march.

Due to its dual mode of action, dupilumab can act on the level of the skin inflammation by blocking the biological activity of IL-13 locally produced by Th2 cells as well as IL-4 produced by ILC2 cells. This reduces the systemic impact of IL-13 and numerous other cytokines and chemokines produced locally and measurable in the circulation. A reduced skin inflammation will also hamper the skin-derived sensitization mechanisms initiated by epidermal Langerhans cells (LC) which have captured allergens ultimately leading to increased allergen-specific IgE contributing to new allergies as described in the atopic march. By blocking the biological activity of IL-4, dupilumab should also directly hamper the widening of the IgE-synthesis generated by the skin-derived sensitization. (KC: keratinocytes; LC: Langerhans cells; ILC2: innate lymphoid cells type 2).

