

REVIEW

Interleukin-13: Targeting an underestimated cytokine in atopic dermatitis

Thomas Bieber 

Department of Dermatology and Allergy, Christine Kühne—Center for Allergy Research and Education (CK-CARE), University Medical Center, Bonn, Germany

Correspondence

Thomas Bieber, Department of Dermatology and Allergy, Christine Kühne—Center for Allergy Research and Education (CK-CARE), University Hospital Bonn, Bonn, Germany.
Email: thomas.bieber@ukbonn.de

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Abstract

Atopic dermatitis (AD) is a common inflammatory skin condition that has traditionally been considered a paradigmatic type 2 immunity (T2)-driven disease. Interleukin (IL)-4 and IL-13 are both pivotal cytokines involved in the generation of allergic diseases. Currently, besides dupilumab, which blocks the binding of both cytokines to their receptors, a number of new pharmacologic entities have been designed to target both T2 cytokines and/or their receptors and/or receptor-associated signal transduction machinery such as Janus kinases. Recently, IL-13 has been suggested to be the key T2 cytokine driving inflammation in the periphery, while IL-4 may merely have a central effect. There is increasing evidence that this concept holds true for the inflammatory reaction underlying AD, where IL-13 is overexpressed locally and has a significant impact on skin biology, including the recruitment of inflammatory cells, the alteration of the skin microbiome, and the decrease in the epidermal barrier function. This review provides an update on the role of IL-13 in AD and discusses the different strategies aimed at interfering with its biologic activity as well as their potential in a precision medicine approach in the management of AD.

KEYWORDS

atopic dermatitis, biologics, IL-13, precision medicine, T2 cytokines

1 | INTRODUCTION

Atopic dermatitis (AD) is a paradigmatic disease in which complex interactions between the environment and the immune system via the epidermal barrier contribute to the high heterogeneity of the clinical phenotype.^{1–3} Based on the substantial progress made in the last few decades in understanding the epidemiology, genetics, and immunology of AD, it appears that the wide clinical spectrum of AD likely results from the highly complex mechanisms leading to the chronic and, sometimes intermittent, inflammation in AD.⁴

Skin barrier dysfunction combined with an inflammatory micro-environment is regarded as key for immunoglobulin E (IgE) sensitization to environmental allergens in AD.⁴ At least in a subpopulation of children, AD is considered the starting point for the so-called atopic march^{5,6} and atopic comorbidities such as allergic asthma and

rhino-conjunctivitis, where the type 2 (T2) immune response is a pivotal factor. Historically, AD has been considered a T2 disease characterized by interleukin (IL)-4 signaling. This perception stems from the fact that this cytokine was known to be pivotal for the regulation of IgE synthesis, which is classically highly elevated in most patients. However, strong evidence for IL-13 as the primary cytokine involved in AD inflammation has emerged more recently.^{7–9}

Targeting the cytokines involved in AD inflammation represents an important therapeutic strategy.^{10,11} In addition to the recently commercialized biologic dupilumab, which targets the IL-4 receptor alpha (R α) chain and blocks the signaling of both IL-4 and IL-13 cytokines and the downstream inflammatory reaction,¹² a number of other biologics and small molecules such as Janus kinase (JAK) inhibitors¹³ are currently in preclinical and clinical development. However, in light of the potential importance of IL-13 in AD pathogenesis,

biologics specifically targeting the IL-13 cytokine alone may offer an important potential in (a) blocking the mechanisms underlying allergen-induced flare-ups and (b) controlling overall the inflammatory reaction underlying this condition in the long term. This short review paper summarizes the various mechanisms considered to be involved in the inflammatory reaction of AD, briefly reviews the current knowledge on the role of IL-13 in AD, and discusses anti-IL-13 strategies and their potential role in a precision medicine approach for moderate to severe AD.

1.1 | Overview of T2 cytokines and their receptors

It is well accepted that the T2 response has evolutionarily developed to protect against parasitic infections. Besides the classic T helper type 2 (Th2) lymphocytes, other cells such as the type 2 innate lymphoid cells (ILC2), mast cells, and basophils are considered a source of the key cytokines involved in this particular response, which are mainly IL-4, IL-13, and IL-5.^{14,15}

IL-5 is recognized as the key mediator in the generation and recruitment of eosinophils in most organs, where they act as important effector cells in allergic reactions.^{16,17} IL-5 binds to a receptor consisting of an IL-5R α subunit and the common beta (β) subunit (β c) of the hematopoietins (ie, IL-3 and granulocyte-macrophage colony-stimulating factor) and activates JAK2.¹⁸

IL-4 and IL-13 share a common receptor subunit, the IL-4R α chain¹⁹ (Figure 1).^{19–21} The primary IL-4 receptor (the so-called type I receptor) consists of the IL-4R α chain and the common gamma chain (γ c) subunit, which was originally discovered as the third receptor

component of the IL-2 receptor IL-2R γ . These receptor subunits are linked to JAK1 and JAK3, respectively, and activate the signal transducer and activation of transcription (STAT) 6 pathway.¹⁹ It is noteworthy that, besides the type I receptor and IL-2 receptor, the common γ chain is shared with other important cytokine receptors, that is, IL-7, IL-9, IL-15, and IL-21.²² Both IL-13 and IL-4 bind to the so-called type II receptor, which comprises the IL-4R α chain and the IL-13R α 1 chain, to activate JAK1 and tyrosine kinase 2 (TYK2), leading to the activation of STAT6.¹⁹

The expression of the type I and type II receptors varies among different cell types. Hematopoietic cells, such as lymphocytes, express only low levels of IL-13R α 1 and relatively large amounts of γ c required for type I receptor formation. By contrast, in nonhematopoietic structural tissue cells such as keratinocytes, γ c expression is low or absent, whereas higher amounts of IL-13R α 1 (required for type II receptor formation) are expressed.²¹ As both IL-4 and IL-13 compete for the binding of the type II receptor, the ratio of IL-4/IL-13 will determine which of the two cytokines will drive the inflammatory response.¹⁹

In addition to IL-13R α 1, IL-13 can also bind with very high affinity to the IL-13R α 2,²³ which has long been assumed to be only a decoy receptor, lacking any intracellular signal transduction machinery. The expression of IL-13R α 2 is induced by several pro-inflammatory cytokines, including IL-13 and IL-4, as well as interferon γ , tumor necrosis factor α , and IL-17.^{24–26} However, recently, it has been shown that IL-13R α 2 can associate with the chitinase-3-like 1 (CH3L1) protein (or YKL-40, encoded by the *CH3L1* gene), which provides alternative machinery involving mitogen-activated

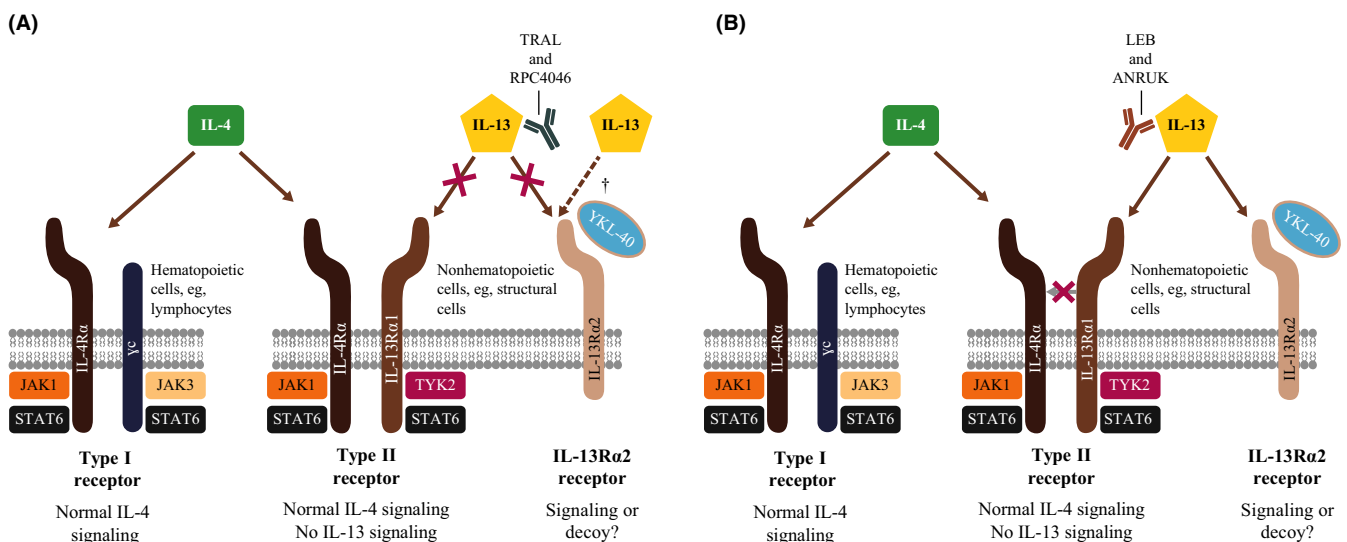


FIGURE 1 IL-4 and IL-13 receptor structure and differential mode of action of anti-IL-13 biologics. Upon binding of its ligand, IL-4R α associates with the common γ chain (type I receptor) to exert signaling through JAK1 and JAK3. IL-13 also binds to IL-13R α 1 (type II receptor) for signaling via JAK1 and JAK2. IL-13 also binds to IL-13R α 2, which associates with YKL40. The signaling transducing machinery linked to this complex has not been completely elucidated.^{19–21} A, Tralokinumab and RPC4046 bind to the IL-13 cytokine at an epitope that overlaps with the binding site of the IL-13R α receptors. This prevents IL-13 from binding to both the IL-13R α 1 and IL-13R α 2 receptors and thus inhibits the subsequent downstream signaling.⁷⁷ ([†]The binding affinity of IL-13 to the IL-13R α 2 receptor is much higher than the affinity for tralokinumab, and therefore, unbound IL-13 can bind to the receptor before being bound by tralokinumab).^{19,77} B, Lebrikizumab and anrukinzumab bind to IL-13, preventing formation of the IL-13R α 1/IL-4R α complex. IL-13 can still bind to IL-13R α 2.⁹¹ (ANRUK, anrukinzumab; IRS, insulin receptor substrate; LEB, lebrikizumab; TRAL, tralokinumab)

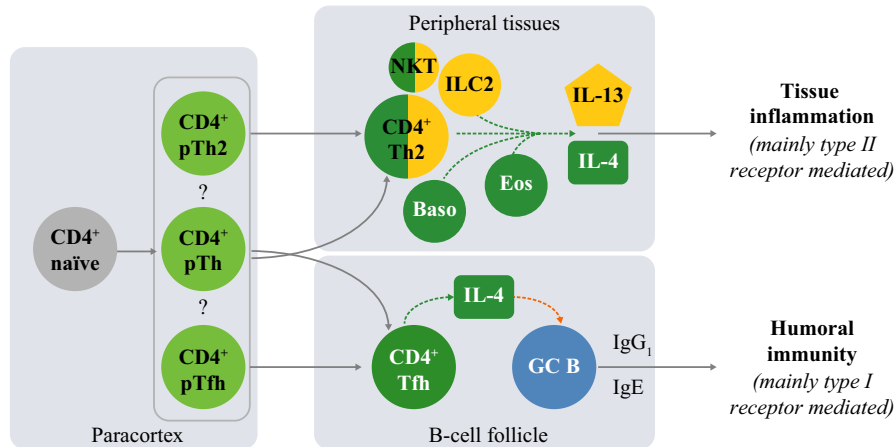


FIGURE 2 Postulated primary roles of IL-4 and IL-13. While IL-4 seems to exert a more central activity (overlapping with the preferential expression of the type I receptor), IL-13 may be the more dominant T2 cytokine in the periphery, where the type II receptor is preferentially expressed by tissue cells.³² Light green = IL-4 mRNA expression; dark green = IL-4 protein expression; yellow = IL-13 protein production. (Adapted from Bao and Reinhardt. *Cytokines* 2015. Baso, basophils; Eos, eosinophils; GC B, germinal center B cells; NKT, natural killer T cells; pTfh, progenitors of T follicular helper cells; pTh, progenitors of T helper cells; pTh2, progenitors of T2 helper cells in the paracortex area)

protein kinases, protein kinase B, and β -catenin.¹⁹ Interestingly, IL-13R α 2 has been reported to attenuate IL-4 signaling by blocking the STAT6 pathway.^{27,28} The serum level of YKL-40 seems to correlate with the severity of AD.²⁹

It should be noted that IL-4 and IL-13, as well as their respective receptors, have been reported to be candidate genes associated with atopic disorders, including AD.³⁰ Most interestingly, genetic variants in the *CH3L1* gene have been reported to be associated with an onset of AD occurring after 8 years of age.³¹

At first glance, it may seem the availability of two different cytokines like IL-4 and IL-13 sharing receptors and biological activities reflects an evolutionarily meaningful redundancy for immune protection. However, more recent investigations have strongly supported a more precise picture in which IL-4 is more relevant for central aspects of the T2 response, for example, for mechanisms localized in the lymph nodes (where type I receptors are mainly expressed) and involved in the generation and regulation of humoral immunity, including IgE (Figure 2).³² In contrast, IL-13 may have a more prominent role in the periphery,³² that is, at the tissue level, where the type II receptor as well as YKL-40 are typically expressed. Translating this knowledge to the skin, one would expect that IL-13 may be a more important mediator for the T2 response in the skin than IL-4.

1.2 | The T2 cytokines in atopic dermatitis

When considering the cellular and soluble factors in the skin under physiological and pathophysiological conditions, one typically distinguishes (a) the elements related to the structural and architectural cells such as keratinocytes, fibroblasts, and endothelial cells and their products; and (b) the hematopoietic cells, which are either considered resident (such as mast cells, resident lymphocytes, and innate lymphoid cells, as well as dendritic cells) or infiltrating cells in the context of an inflammatory reaction.

1.3 | Epidermis-derived mediators contributing to a T2 response

It is assumed that epidermal cells and their mediators play a significant role in the pathogenesis of AD. This may be especially relevant for the first phases of the disease in early infancy, where it has been shown in animal models that the genetically driven barrier dysfunction due to, for example, human filaggrin gene or serine peptidase inhibitor, Kazal-type 5/lympho-epithelial Kazal-type-related inhibitor mutations or variants, may induce the production of keratinocyte-derived mediators in response to nonspecific events such as irritation.³³⁻³⁵ Such mediators are the so-called alarmins, that is, thymic stromal lymphopoietin (TSLP), IL-33, and IL-25, which contribute to the initiation of a local antigen-/allergen-independent inflammatory reaction.³⁶ Interestingly, this particular kind of reaction seems to provide a pro-T2 microenvironment favoring the emergence and propagation of IgE sensitization to allergens when the epidermal barrier is deficient. As another response to irritation or injury, keratinocytes produce a large spectrum of antimicrobial peptides (AMP),³⁷ which may exert other biological properties relevant to the generation of inflammation, as well as the overall immune response. It is assumed that any self-perpetuating inflammatory process in the skin, such as the one occurring in AD, likely has a deep systemic impact and could explain why this disease is now considered a systemic condition rather than purely a skin disease.

1.4 | T2 cytokines produced by hematopoietic cells in the skin

Mast cells, macrophages, dendritic cells, and ILC2 are considered the main resident immune cells in the dermal compartment. Interestingly, ILC2s have been reported to expand and produce IL-13 and IL-5, but not IL-4, when they are activated by the keratinocyte-derived alarmins IL-33 and IL-25.^{38,39}

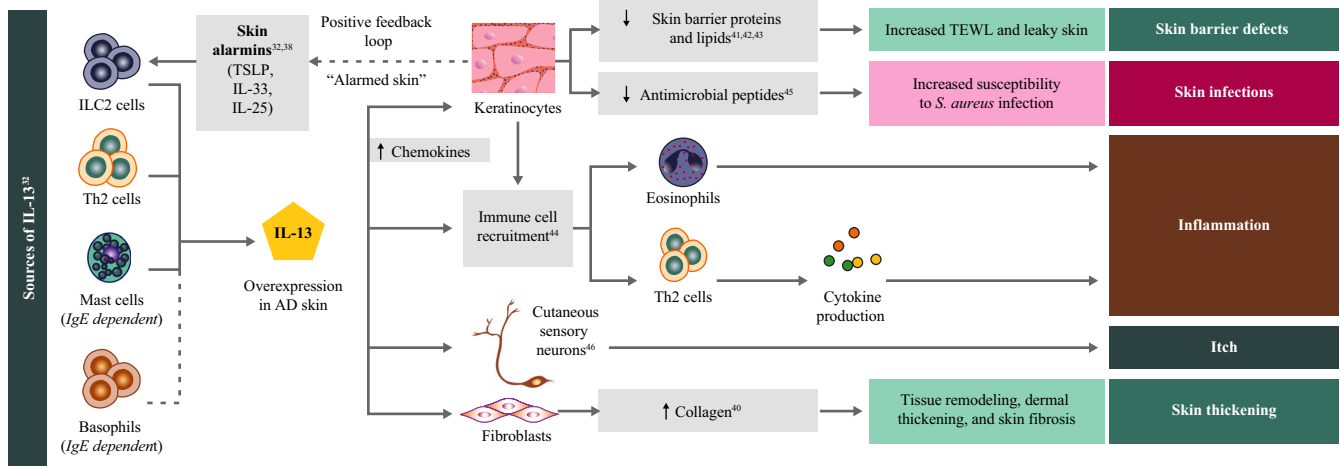


FIGURE 3 Sources and impact of IL-13 in skin. In contrast to IL-4 and in line with the concept that IL-13 is the dominant T2 cytokine in the periphery (Figure 2), IL-13 is overexpressed by different cell types in the skin of atopic dermatitis. There, this T2 cytokine has a wide impact, including the decrease of the barrier function, inducing itch and affecting the microbiome.^{32,38,40–46} (*S.*, *Staphylococcus*)

The “alarmed” keratinocytes are thought to trigger ILC2 activation with increased expression of IL-13, leading to recruitment of activated T cells and resulting in amplified IL-13/IL-4 expression within the skin; this is emerging as a driving pathway of chronic inflammation in AD (Figure 3).^{32,38,40–46}

Additionally, in the context of atopic inflammation in lesional skin, Th2 cells positive for the chemoattractant receptor-homologous molecule expressed on Th2 cells infiltrate the skin and produce IL-13, IL-31, and IL-4.^{47,48} It has also been reported that IL-5-producing eosinophils and IL-4-producing basophils are recruited in AD skin during inflammation.^{47,49}

The concept that AD may be an IL-4-driven disorder emerged from the following observations: (a) IL-4 was initially shown to be crucial in the regulation of the IgE synthesis⁵⁰ and AD is associated with increased IgE levels; (b) a series of reports have emphasized the high response to, and production of IL-4 by, appropriately activated lymphocytes isolated from AD lesional skin⁵¹; (c) reports on an in vivo overstimulation of the IL-4/IL-4R pathway⁵²; (d) IL-4 mediates tissue inflammation⁵³; and (e) first in situ hybridization experiments showed the presence of IL-4 mRNA in AD lesional skin.⁵⁴ However, despite this common perception that AD is an IL-4-driven disease, data have consistently shown that IL-13 is expressed at high levels, whereas IL-4 is expressed at low levels or is undetectable, regardless of the methodology used. Since the binding affinity of IL-4 for the IL-4R α subunit is markedly higher than the binding affinity of IL-13 for the IL-13R α 1 subunit, IL-4 and IL-13 compete for availability of the type II receptor subunits. Consequently, the concentration of IL-4 vs IL-13 in AD skin is an important determinant of signaling through the type II receptor.¹⁹ In 2004, Tazawa et al showed that IL-13 mRNA expression was significantly greater in subacute and chronic lesions compared to nonlesional skin, as well as healthy controls. Further, more IL-13 mRNA could consistently be detected in 27 of 28 samples of AD skin lesions, whereas IL-4 mRNA was only detected in three of 28 samples.⁵⁵ A recent study by Tsoi et al⁷ confirms the dominance of IL-13 mRNA expression in lesional skin with near undetectable

IL-4 expression. In addition, recent studies have shown the same relationship looking at protein levels in lesional skin, confirming high levels of IL-13 in all skin samples, while IL-4 levels were low and only detected in a minority of patients.^{8,9} Additionally, expression levels of IL-13 in lesional skin have been strongly correlated with disease severity, as measured by the SCORing Atopic Dermatitis tool.^{9,56} Overall, this growing body of evidence suggests that AD is an IL-13-, rather than IL-4-, driven disease.

However, since there may be significant differences in the profile of the adaptive immune response depending on factors such as age, acute vs chronic AD, severity, ethnic background, or individual natural history of the disease, it remains to be explored whether IL-13 plays the same pivotal role under all conditions. Although the common phenotypes described share robust T2 activations, the overall T2 response may decrease in dominance with age and the Th1/Th17 response may become increasingly important.⁵⁷

1.5 | Impact of IL-13 on skin inflammation

T2 cytokines have a strong impact on the skin immune response and barrier function. It has been shown that both IL-4 and IL-13, by virtue of STAT6 activation, significantly decrease the expression of key structural proteins like filaggrin, filaggrin 2, loricrin, involucrin, keratin 1, keratin 10, hornerin, desmoglein, and desmocollin 1, as well as the lipid composition important for normal skin barrier function.^{42,43,58–65} This contributes to the increased transepidermal water loss (TEWL) typically measured and may even predict AD.^{66,67} Additionally, both IL-4 and IL-13 have been reported to decrease the production of AMP by keratinocytes⁶⁸ and thereby play a role in the dysbiosis of the skin typically characterized by a strong colonization with *Staphylococcus aureus*, which has recently been shown to precede the appearance of AD lesions.⁶⁹ IL-13 induces keratinocytes to attract CD4⁺/CCR4⁺ T cells by virtue of C-C motif chemokine 22 production.⁴⁴ Through its high-affinity binding to the IL-13R α 2/YKL-40 receptor complex, IL-13 potentially induces, either directly or indirectly via TSLP, an

increased collagen deposition and fibrotic tissue remodeling,^{19,20,70,71} which is clinically more often observed in long-lasting chronic lichenified lesions.⁷² In addition, IL-13 induces expression of matrix metalloproteinase (MMP)-9 in human keratinocytes, which mediates cell migration and tissue remodeling through action on collagen IV of the basement membrane.^{56,72} Furthermore, IL-13 was shown to down-regulate MMP-13 expression in human dermal fibroblasts and may thereby decrease collagen degradation, resulting in fibrosis with excess collagen deposition, as found in the thickened dermis of chronic lichenified AD skin lesions.⁴⁰ Moreover, besides IL-31, peripheral itch-sensory neurons can be stimulated by IL-4 and IL-13, which are considered pruritogenic.⁴⁶ The mechanistic involvement of IL-13 in skin inflammation, as outlined previously, in combination with data showing the overexpression of IL-13 in the skin compared to IL-4, further supports that AD is likely an IL-13-driven disease (Figure 3).

1.6 | Targeting IL-13: rationale and current strategies

Our understanding of AD pathophysiology has made major advances over the last few decades. With regard to the assumed role of IL-13 in the generation and maintenance of the inflammatory reaction and the significant impact of this cytokine on skin, in particular epidermal barrier function, pharmacological therapies that inhibit its biological activity are in development. In general, at least three distinct pharmacological approaches targeting the IL-13-induced pathways are considered: (a) small molecules interfering with interactions between the cytokine and its receptor, known as protein-protein interaction modulators (PPIMs)⁷³⁻⁷⁵; (b) small molecules interacting with intracellular signaling pathways such as kinase inhibitors⁷⁶; and (c) biologics blocking the binding of IL-13 to its receptor site.⁷⁷

2 | PPIMs

Recently, small molecules able to affect PPIMs have been designed⁷³⁻⁷⁵ based on data obtained from small-molecule libraries and dynamic simulations. This *in silico* approach in drug design allows for the development of new active compounds, particularly in the growing field of strategies targeting interleukins and their receptors. It is expected that PPIMs will be tested for T2 cytokines such as IL-4 and IL-13 in the context of allergic diseases.

2.1 | Kinase inhibitors

Depending on whether IL-13 binds to the type II receptor and/or to the IL-13R α 2/YKL-40 heterodimer, different target kinases can be considered. Molecules impacting the signaling pathway of YKL-40-associated signaling machinery are currently not in development or being tested clinically in AD.

Signaling of IL-13 through IL-4R α and IL-13R α 1 (type II) is linked to JAK1 and TYK2, respectively, and several JAK inhibitors (JAKis)

with different JAK selectivity profiles are in development in a variety of conditions, including AD.⁷⁸ These first-generation JAKis are less selective and block predominantly JAK1 and JAK2 (ruxolitinib and baricitinib), JAK1 and TYK2 (PF-06700841), or all JAKs (delgocitinib, tofacitinib, peficitinib, and oclacitinib).⁷⁹

The second generation of JAKis of interest for blocking IL-13 activity displays a more selective inhibition of either JAK1 (abrocitinib, filgotinib, upadacitinib, and itacitinib) or TYK2 (BMS-986165). Some of these molecules are currently in clinical development for the treatment of AD, such as abrocitinib, baricitinib, upadacitinib (oral), and delgocitinib (topical).⁷⁶

2.2 | Biologics

2.2.1 | Dupilumab

Dupilumab is a first-in-class biologic that binds to the IL-4R α subunit of the type I and type II receptors, preventing both IL-4- and IL-13-mediated signaling.^{14,15} It is now approved in several countries for moderate to severe forms of AD in adults.^{80,81} Pediatric development programs are not yet completed, but data for the adolescent population are available,⁸² and there is a large body of evidence for the clinical efficacy and safety of dupilumab in AD.⁸³⁻⁸⁷ In the pivotal phase III studies, dupilumab as monotherapy provided a good clinical response, witnessed by 50% Eczema Area and Severity Index (EASI) responses (EASI 50) in about 69% and 65% of the SOLO-1 and SOLO-2 patients, respectively, compared to 25% and 22% in the placebo groups.⁸⁷ The US Food and Drug Administration-required primary endpoint of Investigator's Global Assessment (IGA) of 0 or 1 (clear or almost clear and reduction of 2 grades or more from baseline) was reached in 37% of the patients receiving weekly dupilumab, compared to 10% receiving placebo. Common adverse events reported more frequently in the treatment arm than in the placebo arm included injection site reactions and conjunctivitis. In contrast to the increased incidence of conjunctivitis reported in the AD studies, studies of dupilumab in asthma⁸⁸ or chronic sinusitis with nasal polyposis⁸⁹ did not report the emergence of conjunctivitis or blepharitis.⁹⁰ Further studies are required to explain this observation.

2.2.2 | Lebrikizumab

Lebrikizumab exerts its activity by binding to the IL-13 cytokine at an epitope that overlaps with the binding site of the IL-4R α receptor, preventing heterodimerization of the IL-4R α /IL-13R α 1 subunits^{11,91} (Figure 1).^{19,77,91} The clinical development program was initially set for the therapy of allergic asthma⁹² and subsequently for AD. In a proof-of-concept (PoC) phase II study, lebrikizumab was tested in moderate to severe AD patients who had been subjected to a run-in period with the medium-potency topical steroid (TCS) triamcinolone acetonide (0.1%).⁹³ The safety profile was good, with only mild and moderate side effects. At the primary endpoint at week 12, EASI 50

was reached in 82% of patients, while a 62% response was observed in the placebo group, which was also treated with TCSs. IGA 0/1 was observed in 33% of patients in the lebrikizumab group and in 19% of patients in the placebo group.

2.2.3 | Tralokinumab

The mode of action of the fully human IgG4 monoclonal antibody tralokinumab is different from lebrikizumab in that tralokinumab binds to the IL-13 cytokine at an epitope that overlaps with the binding site of the IL-13R α receptors, preventing IL-13 from binding to both IL-13R α 1 and IL-13R α 2^{11,77} (Figure 1). Interestingly, this strategy has been postulated to be potentially more efficacious than blocking the binding to IL-13R α 1 alone.⁹⁴ Similar to lebrikizumab, the PoC phase II trial has been performed in moderate to severe patients having first been exposed to class III (potent steroids, according to European classification) TCSs in a run-in period and with continuous application as a background therapy for both placebo and active arms.⁹⁵ The adverse effects were similar in both groups and classified as mild to moderate. The IGA 0/1 response was about 27% and 12% in the active and placebo groups, respectively. EASI 50 was reached in 73% of the active group vs 52% of the placebo group when compared to baseline after the 2-week run-in period with potent TCSs.

As for the results obtained with lebrikizumab, due to the run-in period and continuous treatment with TCSs, it is difficult to appreciate the real efficacy of this biologic and to compare the data to those obtained with dupilumab. The pivotal phase III trials with tralokinumab as monotherapy should provide a better assessment of the therapeutic potential of this new compound.

2.2.4 | Others

Other biologics targeting IL-13 are in development. ASLAN004, a fully human monoclonal antibody that targets the IL-13R α 1 receptor, is currently in clinical trials for the treatment of AD.⁹⁶ Biologics targeting IL-13 for use in other indications (eg, asthma and irritable bowel disease) are also in development. Anrukizumab (IMA-638)^{97,98} is an anti-IL-13 with an analogous mode of action to lebrikizumab. In contrast, similar to tralokinumab, RPC4046 (ABT-308)^{73,94} and CNTO 5825⁹⁹ block the binding of IL-13 to both IL-13R α 1 and IL-13R α 2.

3 | PERSPECTIVE: IS THERE A PLACE FOR IL-13 IN PRECISION MEDICINE FOR ATOPIC DERMATITIS?

Atopic dermatitis is characterized by a large and heterogeneous clinical phenotype.⁴ There is increasing evidence that the variation in underlying genetic background and immunologic mechanisms could explain this broad phenotypic spectrum. As a correlate, the lack of a single immunologic mechanism may also explain the

variability in the clinical response to more targeted therapeutic approaches, such as biologics aiming to specifically block certain cytokines and/or their receptors classically assumed to be pivotal in the generation of inflammation. An attempt to respond to this phenomenon would be a more tailored precision medicine approach based on biomarkers³ predictive for the therapeutic response to a distinct targeted therapy, potentially leading to a disease-modifying effect.¹⁰⁰ Since IL-13 has been reported to be linked with a phenotype prone to the development of bronchial hyperresponsiveness,¹⁰¹ targeting this cytokine in a very early phase of the natural history could hamper the emergence of this comorbidity.

With regard to the role of IL-13 in AD, it would, therefore, be of great interest to further explore the possibility that this cytokine is crucial for some particular subtypes of AD that could be identified by an appropriate biomarker-based stratification. This kind of approach has been done in an exploratory way in the tralokinumab phase II trial mentioned previously.⁹⁵ It is interesting to note that, as observed in asthma with lebrikizumab, when compared to the placebo group, the clinical response in both AD subgroups, defined by an increased level of dipeptidyl peptidase-4 and periostin (both markers that are induced by IL-13 *in vitro* and *in vivo*), was significantly better than in the intent-to-treat population. Due to the limited number of patients in these subgroups, it is too early to make any final interpretation from this particular study.

4 | CONCLUSION

There is currently strong evidence that in AD, IL-13 is significantly more expressed than IL-4 in lesional skin and is therefore one of the key drivers in this condition. IL-13 has a large impact on the epidermal barrier function and the local immune response. Hence, a number of new strategies, including targeting this cytokine and its receptors, are currently in development. JAKis and anti-IL-13 biologics are now in the pivotal phases of their clinical development programs, and these studies will hopefully confirm that targeting IL-13 is a new option to treat patients with moderate to severe AD. The approach of an IL-13-related, biomarker-based stratification of the complex phenotype of AD seems promising and worth consideration in further clinical development programs, ultimately paving the way for a precision medicine strategy in the management of AD.

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CONFLICTS OF INTEREST

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ORCID

Thomas Bieber  <https://orcid.org/0000-0002-8800-3817>

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