



Common and different roles of IL-4 and IL-13 in skin allergy and clinical implications

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Purpose of review

This review summarizes the mode of action of IL-4 and IL-13 in skin allergy, upcoming therapeutics and depicts key outcomes of the latest clinical trials.

Recent findings

Atopic dermatitis is considered to be one of the most common inflammatory skin disease in industrialized countries. Accompanied by strong pruritus, atopic dermatitis has a significant impact on quality of life in severely affected individuals. Aside from unspecific immunosuppressant medications, therapeutics targeting the key cytokines IL-4 and IL-13 and their downstream mediators are under development or have been approved just recently with outstanding potential.

Summary

The recent development of several biologics and small compounds has the potential to revolutionize the treatment of atopic dermatitis, and applying this set of state-of-the-art drugs will provide a unique chance to gain insights into this skin disorder, patient subgroups, and key inflammatory mediators.

Keywords

allergy, atopic dermatitis, baricitinib, biological, dupilumab, lebrikizumab, MEDI-9314, Pf-04965842, skin, tofacitinib, tralokinumab, upadacitinib

INTRODUCTION

Atopic dermatitis, with a prevalence of 10–20% in children and 1–3% in adults, is considered to be one of the most common inflammatory skin disease in western countries. It is believed to be the earliest manifestation of atopic diseases within lifetime and is characterized by specific IgE as well as specific T-cell responses towards common, per se harmless environmental antigens. The numerous factors that predispose for the disease include environmental as well as hereditary, as genetic variants. According the latter, deleterious mutations within skin barrier genes and activating ones in genes of the immune system have been associated with atopic dermatitis. Further it was shown, that the skin inflammation, which appears chronic or relapsing/remitting, contributes significantly to a weakened skin barrier, facilitating allergen penetration (summarized in [1]).

Asides from emollients and topical anti-inflammatory agents that are applied to strengthen the skin barrier, allergen specific immunotherapy (ASIT, SIT, also known as hyposensitization therapy) represents the only treatment directed at the cause of IgE-mediated allergic diseases including atopic dermatitis. In principle, SIT has been demonstrated to

induce immune tolerance by administering allergens to patients with inhalant allergy in repeated, increasing doses. To date, several studies in atopic dermatitis have been performed applying different approaches, allergens, and application routes reporting highly variable effects. Meta-reviews summarizing the results come to different conclusions [2]. But in fact, SIT has been demonstrated not being a risk for deterioration of the disease. Until placebo-controlled trials with longer observation periods and appropriate and harmonized outcome measures for the disease severity are performed, the main indication for SIT remains inhalant allergy. According to the current guideline recommendations, the application of SIT in atopic dermatitis ‘may be considered for selected patients with house dust

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KEY POINTS

- Atopic dermatitis is considered to be one of the most common inflammatory skin diseases in western countries.
- Conventional immunosuppressants bear numerous side effects.
- IL-4 and IL-13 are key players in atopic dermatitis and represent promising target molecules in biological therapy approaches.
- The action of IL-4/IL-13 signaling blockers on the differential expression of the IL-4/IL-13 receptor subtypes has to be taken into account.
- In addition to monoclonal antibodies, directly targeting IL-4 and IL-13 on cytokine or receptor level, small molecule inhibitors targeting JAKs are in clinical trials.

mite, birch or grass pollen sensitization, who have severe AE, and a history of clinical exacerbation after exposure to the causative allergen or a positive corresponding atopy patch test' [3,4].

Therefore, conventional immunosuppressants commonly have been prescribed. Such nontargeted anti-inflammatory therapy approaches, for example, with cyclosporine A, azathioprine, mycophenolate mofetil, and methotrexate bear numerous side effects and rise the probability of infections, since suppressing the immune system in a harsh and global manner.

Medications that target single key players of the immune system, like monoclonal antibodies, are supposed to overcome these problems. In a first approach, several biologicals that have already been approved for the treatment of other chronic inflammatory diseases have also been applied to atopic dermatitis, but did not lead to clear cut results.

Although previous trials [targeting the molecules IL-5 [5], IL-12/IL-23p40 [6,7], CD20 [8,9], prostaglandin D2 receptor 2, and IgE [10]] did not reveal convincing treatment success in atopic dermatitis, intensive scientific progress has identified other target molecules with promising or even proven potential for the main population of atopic dermatitis patients and opened up new possibilities for targeted therapy [11[¶]]. These medications target the molecules that are central in the cascade of the allergic inflammation in atopic dermatitis and are often described as a breakthrough in treating inflammatory skin diseases, and especially atopic dermatitis. To understand their mode of action, an introduction into the underlying mechanisms of the skin inflammation in atopic dermatitis is given in the following paragraphs.

THE KEY CYTOKINES IL-4/IL-13

The allergic inflammation in atopic dermatitis skin is hallmarked by type 2 immune responses, constituting IgE, histamine, the cytokines IL-4, IL-5, IL-13, IL-25, IL-31, IL-33 and thymic stromal lymphopoietin (TSLP) as well as several chemokines as key molecules [12].

IL-4 and its homologous cytokine IL-13 have been studied most intensively throughout the years and a key role in allergic diseases has been assumed ever since. Downstream molecules of the Janus kinase (JAK) and signal transducer and activator of transcription (STAT) families are supposed to be key regulators of the T-cell differentiation and maintenance to T (helper)h2 [13]. In the acute inflammation IL-4 and IL-13 are produced by the same cell types present in lesional atopic dermatitis skin, first of all Th2 T cells, mast cells, and basophils, although being induced by different triggers [12]. Aside from Th2, so-called Tc2 CD8⁺ T cells have been reported to elicit predominantly IL-4, and recently, we described T cells reactive to an atopic dermatitis-specific model antigen to be of this type [14]. Beneath the numerous other cell types that can produce IL-4, NK T cells [15], eosinophils [16], and type II innate lymphoid cells (ILC2) [17] shall be mentioned here.

It appears that IL-4 and IL-13 cooperate in promoting Th2 responses, having both overlapping and additive roles. Regarding overlapping functions, target cells are considered to respond more sensitive and faster to IL-4 compared with IL-13. On the other hand, IL-13 plays a dominant role in the mucosa, especially in airway inflammation and asthma [18] but also parasite clearance during antihelminth immunity [19]. IL-13 is expressed in both acute and chronic lesions of atopic dermatitis. However, there is a selective significant up-regulation of IL-13 mRNA in subacute and chronic atopic dermatitis lesions, which is not seen for IL-4 [20]. The most striking differences in the mode of action between IL-4 and IL-13 occur because of differential expression of their receptor subtypes. To estimate the impact of the action of IL-4R/IL-13R blockers, this complex system of receptors and cellular differences has to be taken into account.

THE IL-4/IL-13/JANUS KINASE/SIGNAL TRANSDUCER AND ACTIVATOR OF TRANSCRIPTION SIGNALING PATHWAY

Three receptors have been discovered that recognize IL-4, IL-13, or both. The type I heterodimer consists of IL-4R α and the γ chain of the IL-2 receptor. It is expressed primarily on hematopoietic lymphoid

and myeloid cells and exclusively described for IL-4 signaling. The γ chain is also shared by receptors for IL-2, IL-7, IL-9, and IL-15. The type II receptor is formed by IL-4R α and IL-13R α 1, and has been shown to bind either IL-4 or IL-13. It is expressed throughout different cell types aside from the hematopoietic lineage, including fibroblasts, endothelial cells, as well as epithelial cells including hair follicles and keratinocytes. Cells of myeloid origin as well as B cells express both type I and II receptors [21].

Interestingly, the formation of the type I and II heterodimers occurs in a different sequential order: IL-4 binds first to IL-4R α followed by recruitment of either γ chain or IL-13R α 1, whereas IL-13 binds first to IL-13R α 1 followed by recruitment of IL-4R α . This tiny difference may also underlie and explain differential functions of the two cytokines.

Further on, IL-13R α 2 has been described to bind IL-13. It has been considered to be a decoy receptor lacking intracellular signaling domains and capable of binding IL-13 with higher affinity compared with IL-13R α 1 and to deplete extracellular IL-13 [22]. However, recently single studies report inflammatory signaling via this pathway [23].

Both type I and II heterodimer receptors signal via the JAK/STAT6 pathways. JAK proteins that belong to the family of protein-tyrosine kinases of the cellular membrane show strong specificity when binding to the IL-4/IL-13 receptors: the IL-4R α chain commonly binds JAK1, whereas the γ c chain associates exclusively with JAK3 and the IL-13R α 1 chain with Tyk2 or Jak2 [24–28]. After receptor phosphorylation, the phosphorylated tyrosine residues serve as a docking platform for STAT6 and other mediators [such as the insulin receptor substrate 2 (IRS-2)], binding via a Src-homology 2 (SH2) domain [29], whereas STAT6 promotes the expression and translocation of the transcription factor GATA-3 to the genomic DNA, licensing the transcription of numerous well known key players of the allergic inflammation, such as IL-4 and IL-13. Moreover, IL-4-mediated and IL-13-mediated phosphorylation of STAT6 is essential for M2 polarization of macrophages [30] and directly induces cytokines and chemokines like TARC and eotaxin. The latter one is produced by dermal fibroblasts and is a potent chemoattractant for human eosinophils. As STAT6 directly upregulates the expression of the IL-4R α , it represents a promising target to interfere the Th2 inflammation [31].

It should be noted that IL-4 is not exclusively signaling through STAT6 but also by IRS [32,33]; its mode of action is nicely reviewed by Keegan *et al.* [34].

EFFECTS OF THE IL-4/IL-13 PATHWAY AND ITS BLOCKADE ON DIFFERENT CELL TYPES IN THE SKIN INFLAMMATION

Although the different distribution of receptor complexes regulates first of all the mode of action of IL-4 and IL-13, a plethora of cell-type specific responses have been described in atopic dermatitis (summarized in Fig. 1).

Keratinocyte–T-cell interactions

Keratinocytes, the cell type that builds the epidermis, have been shown to be key players of the inflammation in atopic dermatitis. Not only the skin barrier and the protection against pathogens, but also a complex cytokine network contributes to the disease. The first discovery of a response to IL-4 by keratinocytes was described in 1996, proposing enhanced reactivity and T-cell interaction [35] and proliferation [36]. On keratinocytes, the receptor system has been reported to be regulated by the cytokines themselves: IL-13 and also IFN- γ upregulate IL-13R α 1 and enhance, therefore, the sensitivity towards IL-4/IL-13 [37], whereas a putatively negative feedback via IL-13R α 2 has been reported upon IL-4 and IL-13 [38]. IL-13R α 2 has a protective role in the pathogenesis of allergic inflammation and loss of skin barrier function in a mouse model of atopic dermatitis, suggesting that it may be an important endogenous regulator of IL-13-induced cutaneous inflammation [39].

Regarding the inflammatory response of keratinocytes, it was shown for IL-4 to enhance the expression of CXCL10, CXCL9, and CXCL11, thereby facilitating the recruitment of T lymphocytes [40]. Both IL-4 and IL-13 are capable to induce expression of TSLP in keratinocytes [41], which subsequently promotes the type 2 inflammatory responses in numerous other cell types.

Effects on epidermal barrier properties

IL-4 and IL-13 negatively affect the innate response to pathogens: several studies detected an inhibitory effect on the antimicrobial peptides hBD-2 and hBD-3 in keratinocytes [42–44], which may explain the observed reduced expression in atopic dermatitis skin. Several reports point to a drastic weakening effect of IL-4 and IL-13 on the expression of the terminal differentiation markers keratin10, filaggrin (FLG), and loricrin (LOR) [45,46]. Keratins and desmogleins were shown to be downregulated in mouse keratinocytes and the human HaCaT cell line [47]. The keratinocyte-derived Th2 cytokine IL-33 further leads to decreased barrier [48] while activating innate lymphoid type II cells (ILC2), which produce

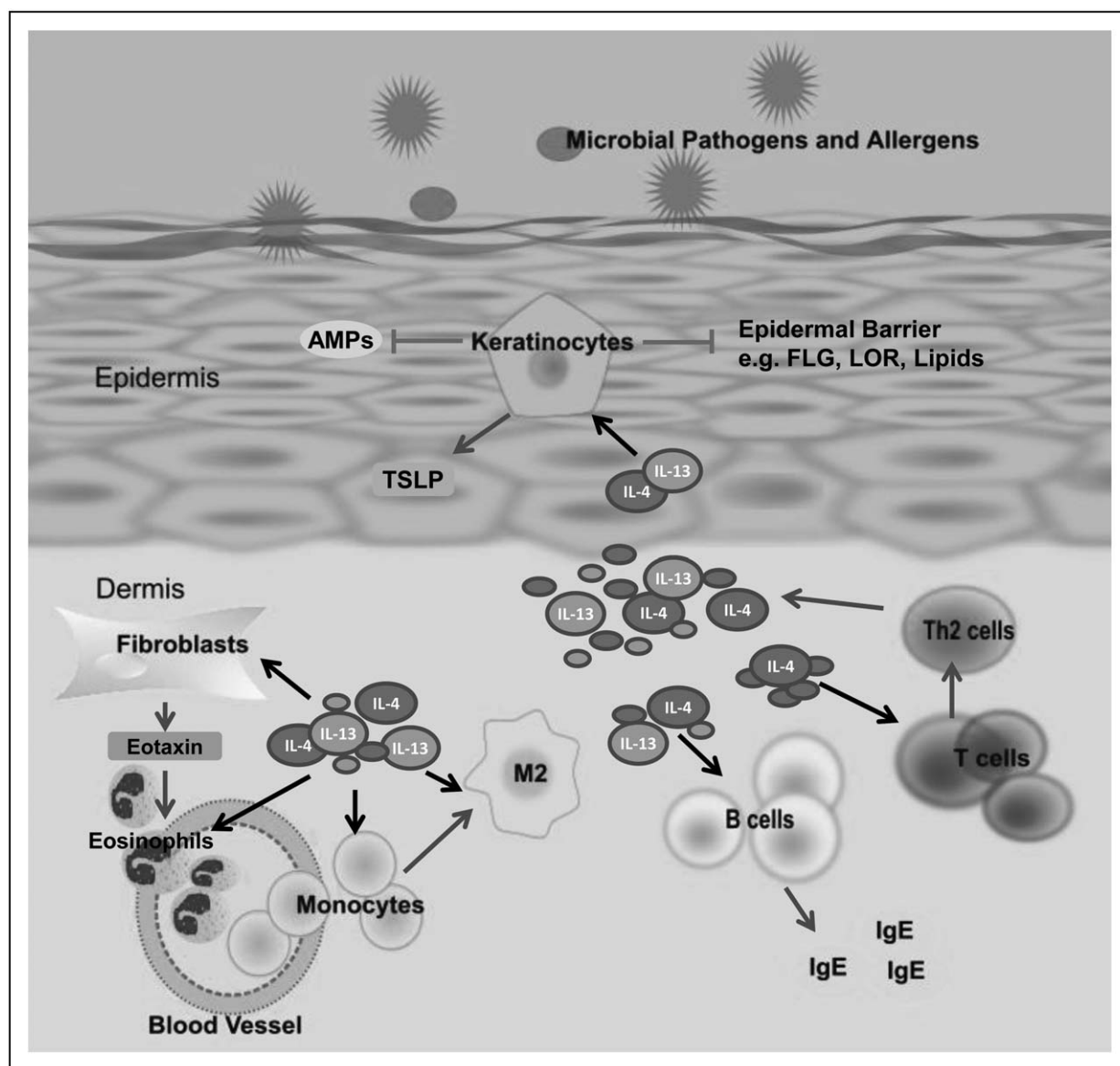


FIGURE 1. Effects of IL-4 and IL-13 on skin inflammation. IL-4 and IL-13 act on keratinocytes, fibroblasts, eosinophils, monocytes and B cells in an overlapping and additive manner. The main differences are because of differences in their expression levels as well as the expression of their receptors. T cells are only able to respond to IL-4 but not IL-13 because of their lack of IL-13 receptor expression.

IL-4 and IL-13. Aside from barrier proteins, it was shown that IL-4/IL-13 signaling leads to lipid abnormalities in atopic dermatitis skin [49[¶]]. In contrast to these negative effects of IL-4/IL-13 on the epidermal barrier, we could recently show that the transcription factor GATA3 is required for FLG expression and epidermal barrier integrity [50].

T cells

T cells infiltrating the skin are hallmarks of atopic dermatitis, driving the inflammation. As explained above, in contrast to IL-13, only IL-4 bears effects on

T-cell activation because of a lack of the type II receptor on T cells. Of interest, one exception was shown for human in-vitro polarized Th17 cells, which can express a functional IL-13 receptor and respond to IL-13 with an impaired IL-17A production [51]. Regulation of virtually every T-cell subset has been reported by IL-4, including Tregs and γ/δ cells. Most prominently, it promotes the growth of activated T cells and represents the central switch inducing differentiation of naive helper T cells towards Th2 cells, by parallel suppression of interferon Th1 cells. T-helper cell-derived IL-4 has been demonstrated to be capable of potentiating B-cell

and CD8⁺ T-cell responses, especially during the priming phase [29]. IL-4 provides long-term survival of memory CD8⁺ T cells following the antigen-specific vast proliferation [52].

Treg development by TGF- β induction is inhibited by IL-4 via STAT6 activation [53], which has been explained by reduced TGF- β 1-induced Foxp3 expression. In contrast, IL-4 had no effect on Foxp3 levels in CD4⁺CD25⁺ natural Tregs [54].

Taken together, IL-4 and IL-13 play key roles in skin inflammation. Although T cells do not react to IL-13 because of lacking receptor expression, myeloid cells as well as keratinocytes become activated by both cytokines, which often results in different responses.

THERAPY TARGETING THE IL-4/IL-13/JAK/STAT PATHWAY

Target IL-4R α : dupilumab

The central role of IL-4, IL-13, and their receptors led to their identification as target molecules decades ago. A biological targeting this pathway, the fully human monoclonal IgG4 antibody dupilumab, has been approved for the treatment of moderate-to-severe atopic dermatitis in the United States and Europe in 2017. Dupilumab acts to the IL-4R α chain, thereby targeting both the type I and type II receptors.

The safety, tolerability, and therapeutic effects of dupilumab have extensively been studied in clinical trials. In two phase III trials (SOLO 1 and SOLO 2), adult patients with moderate-to-severe atopic dermatitis were randomized either into the placebo group or into the treatment groups receiving subcutaneous injections of 300 mg dupilumab weekly and every other week, respectively [55^{***}]. After 16 weeks of treatment with dupilumab 36–38% of patients were ‘clear’ or ‘almost clear’ [investigator global assessment (IGA) 0–1] compared with 8–10% in the placebo groups. Using the Eczema Area Severity Index (EASI), also revealed an improvement of 75% in a significantly higher proportion of patients treated with dupilumab versus placebo ($P < 0.001$). In a further trial (LIBERTY AD CHRONOS) dupilumab was administrated over a period of 1 year in 740 atopic dermatitis patients with concomitant use of topical corticosteroids or calcineurin inhibitors as needed [56^{***}]. The overall efficacy of dupilumab was similar to that observed in the studies mentioned above. Notably, treatment success of dupilumab remained stable over 12 months. Dupilumab therapy has also been demonstrated to be accompanied by a significant improvement of quality of life that correlated with decreasing skin (EASI, SCORAD) and pruritus scores (NRS, SCORAD VAS) [57^{***}].

As an emerging result from these research efforts, treatment with dupilumab (600 mg for first dosing followed by 300 mg every other week) was approved by the US Food and Drug Administration (FDA) in March 2017 [58] and by the European Medicines Agency in September 2017 [59] ‘Dupixent is indicated for the treatment of moderate-to-severe atopic dermatitis in adult patients who are candidates for systemic therapy.’

For the use of dupilumab in clinical routine, further information on possible side effects is relevant. Regarding the mode of action of this antibody, preexisting helminthiasis should be cured before starting treatment with dupilumab. As main possible, clinically relevant side effects local skin reactions at the site of injection and the occurrence or deterioration of noninfectious and mostly mild to moderate conjunctivitis. By contrast, no clinically relevant laboratory abnormalities have been reported [60]. The pathogenesis of conjunctivitis under treatment with dupilumab is still not fully understood and currently under investigation. However, this side effect seems to be specific for atopic dermatitis, since it has not been observed in clinical trials with dupilumab in patients with asthma or polyposis nasi.

Furthermore, in the corresponding professional information on dupilumab, an increased occurrence of oral herpes infection is pointed out [61]. However, in a recently published meta-analysis including data of 2706 patients, the incidence of skin infections including eczema herpeticum, was decreased under treatment with dupilumab in adult with atopic dermatitis [62].

In summary, dupilumab clinical trials have confirmed the key role of both IL-4 and IL-13 in atopic dermatitis. The molecular changes, reduction in clinical signs of atopic dermatitis and subjective symptoms, namely itch, and a reduced incidence of skin infections are suggestive of an overall improvement in skin barrier.

Target IL-13: tralokinumab and lebrikizumab

Another monoclonal antibody, tralokinumab, has previously been studied in phase II studies on asthma [63] and recently been demonstrated to be effective also in atopic dermatitis. It targets the IL-13 molecule binding sites to both IL-13R α 1 and IL-13R α 2 receptor chains, thereby supposed to act on the type II receptor while sparing the type I receptor. In the placebo-controlled phase IIb trial including 204 moderately to severely diseased atopic dermatitis patients tralokinumab was administered in different dose regimen with a maximum dose of 300 mg every other week, a concomitant use of

topical corticosteroids was allowed [64]. This dosage of tralokinumab led to a significant improvement of atopic dermatitis clinical signs (EASI) versus placebo at week 12. Moreover, an improvement of pruritus (NRS) and quality of life could be observed compared with placebo. Common side effects were upper respiratory tract infections occurring as frequently as in the treatment and placebo groups [65]. Following this successful phase II trial, the monoclonal antibody is applied in atopic dermatitis in a phase III trial at the moment.

Whereas tralokinumab binds IL-13 at a site that prevents the ligand from binding both IL-13R α 1 and IL-13R α 2; another monoclonal antibody, lebrikizumab binds IL-13 by blocking the epitope required for IL-4R binding but allowing the ligand to bind IL-13R α 2 [66]. After a successful phase II study, lebrikizumab is currently not further investigated in clinical trials.

To date, isolated blockage of IL-13 effects seems also to be effective in atopic dermatitis and data from ongoing clinical trials remain to be published.

Compared with IL-4R α -targeting drugs described above, these compounds spare to block direct type 2 cytokine effects on T cells because of receptor expression (Fig. 2). Although acting indirectly on the generation of Th2 T cells via antigen-presenting cells, this disparity may result in fine differences regarding the allergic response.

Target Janus kinase: topical and systemic therapy approaches

There are also approaches targeting molecules downstream of the IL-4/IL-13 receptors, namely the Janus kinases. These are especially of interest, as these agents are small molecules that may be applied as an oral treatment, compared with injected antibodies above. Furthermore, many are already approved for treatment of other diseases, for example, rheumatoid arthritis. A drawback may be that these mediators target the immune system at a central and critical point and interfere with the development of several T-cell lineages, not specifically the Th2 axis.

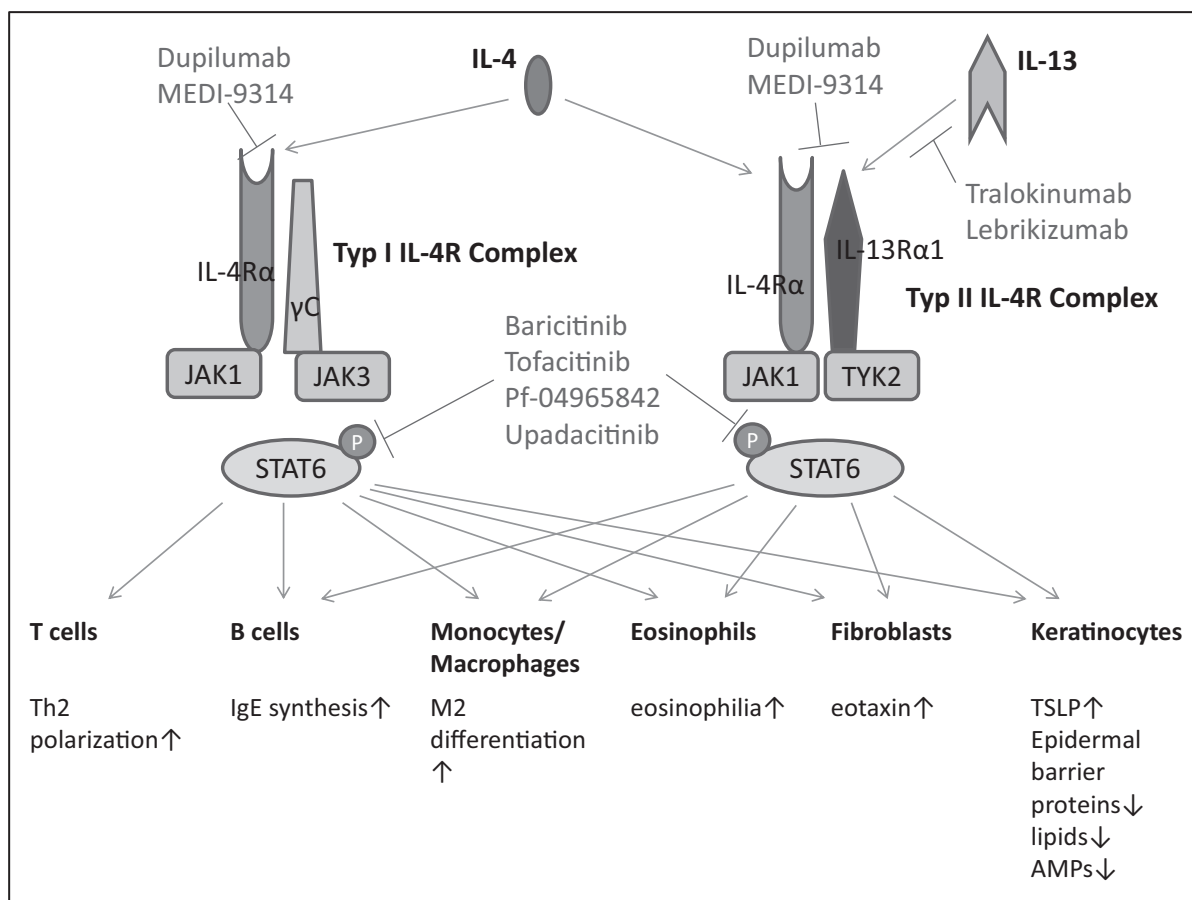


FIGURE 2. IL-4 can bind to both type I and type II IL-4 receptor complex whereas IL-13 can only bind to type II IL-4R complex. Differences in the expression of the receptor subtypes result in differences in the sensitivity of the cells to IL-4 and IL-13, respectively. Upon receptor binding JAK/STAT signaling cascades are activated that leads to proinflammatory, Th2 inflammation favoring effects in the target cells. The different drugs and their blocking mode are depicted in red.

Regarding atopic dermatitis, topical treatment with tofacitinib, a JAK1 and JAK3 inhibitor has been investigated in a phase II trial. After a 4-week treatment period, a significantly higher reduction in disease severity (EASI) compared with the vehicle-control group could be observed. An improvement of pruritus occurred up from treatment day 2 [67]. Similar results were obtained in another phase II trial for topical treatment with the JAK inhibitor JTE-052 [68].

The JAK1/JAK2 inhibitor baricitinib is applied orally. In a placebo-controlled phase II trial including a cohort of 124 moderately to severely diseased atopic dermatitis patients, this agent was administered once daily in a 2 or 4 mg dose, respectively, in combination with topical use of glucocorticosteroids over a period of 16 weeks [69]. Under treatment with 4mg baricitinib daily a significantly higher proportion of patients showed an improvement of clinical signs of 50% (EASI-50) compared with placebo at week 16. Moreover, this effect was accompanied by a reduction of itch and sleep loss.

Taken together, clinical data so far available clearly indicate that targeting this pathway represents a further promising approach.

Further ongoing trials targeting the IL-4/IL-13/Janus kinase/signal transducer and activator of transcription pathway

A phase I trial with another human monoclonal antibody to IL-4R α , MEDI-9314, is completed, and corresponding results remain to be published [70]. Furthermore, a recombinant human IL-4 variant is tested in atopic dermatitis that was termed Pitakinra. This recombinant protein contains two point mutations inhibiting any signaling by preventing the assembly of both type I and type II receptor complexes [71]. However, no results regarding atopic dermatitis are available to date and it appears that the development was discontinued [72]. Therapeutic effects of topical and oral (e.g. upadacitinib) JAK inhibitors in atopic dermatitis are currently intensively investigated in ongoing clinical trials (Table 1).

CONCLUSION

New therapeutic approaches in the treatment of atopic dermatitis aim to be more specific and target directly the IL-4/IL-13 axis. Recent studies and clinical trials are very promising regarding therapeutic effect and safety. It may be hypothesized that therapeutics acting exclusively on the IL-13 signaling may show differences regarding the adaptive immune response compared with IL-4-specific agents, as blocking the IL-13-axis acts only

Table 1. Current status on biologics and small molecules for treatment of atopic dermatitis

Therapeutic	Target	Current status
Dupilumab	Anti-IL-4R α mAb	Approved
Tralokinumab	Anti-IL-13 mAb	Phase III
Baricitinib	JAK1/2 inhibitor	Phase III
Tofacitinib	JAK1/3 inhibitor	Phase II
Pf-04965842	JAK1 inhibitor	Phase III/Breakthr.
Upadacitinib	JAK1 inhibitor	Phase III/Breakthr.
Lebrikizumab	Anti-IL-13 mAb	Phase II
MEDI-9314	Anti-IL-4R α mAb	Phase I

Breakthr, breakthrough therapy status; IL-4R α , interleukin-4 receptor subunit- α ; JAK, Janus kinase.

indirectly on T cells. However, in addition to their role in immunity, Th2 cytokines have been shown to play a critical role in higher functions of the normal brain as memory and learning [73]. Further and especially long-term studies should address this issue to bring certainty regarding implication and safety of these new powerful drugs.

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Conflicts of interest

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REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

1. Werfel T, Allam JP, Biedermann T, *et al.* Cellular and molecular immunologic mechanisms in patients with atopic dermatitis. *J Allergy Clin Immunol* 2016; 138:336–349.
2. Tam H, Calderon MA, Manikam L, *et al.* Specific allergen immunotherapy for the treatment of atopic eczema. *Cochrane Database Syst Rev* 2016; 2:CD008774.
3. European Dermatology Forum (EDF), the European Academy of Dermatology and Venereology (EADV), the European Academy of Allergy and Clinical Immunology (EAACI), the European Task Force on Atopic Dermatitis (ET-FAD), European Federation of Allergy and Airways Diseases Patients' Associations (EFA), the European Society for Dermatology and Psychiatry (ESDaP), the European Society of Pediatric Dermatology (ESPD), Global Allergy and Asthma European Network (GA2LEN) and the European Union of Medical Specialists (UEMS). Wollenberg A, Barbarot S, Bieber T, *et al.* Consensus-based European guidelines for treatment of atopic eczema (atopic dermatitis) in adults and children: part II. *J Eur Acad Dermatol Venereol* 2018; 32:850–878.

4. Werfel T, Heratizadeh A, Aberer W, *et al.* S2k guideline on diagnosis and treatment of atopic dermatitis—short version. *J Dtsch Dermatol Ges* 2016; 14:92–106.
 5. Oldhoff JM, Darsow U, Werfel T, *et al.* Anti-IL-5 recombinant humanized monoclonal antibody (mepolizumab) for the treatment of atopic dermatitis. *Allergy* 2005; 60:693–696.
 6. Khattri S, Brunner PM, Garcet S, *et al.* Efficacy and safety of ustekinumab treatment in adults with moderate-to-severe atopic dermatitis. *Exp Dermatol* 2017; 26:28–35.
 7. Saeki H, Kabashima K, Tokura Y, *et al.* Efficacy and safety of ustekinumab in Japanese patients with severe atopic dermatitis: a randomized, double-blind, placebo-controlled, phase II study. *Br J Dermatol* 2017; 177:419–427.
 8. Simon D, Hosli S, Kostylina G, *et al.* Anti-CD20 (rituximab) treatment improves atopic eczema. *J Allergy Clin Immunol* 2008; 121:122–128.
 9. Sediva A, Kayserova J, Vernerova E, *et al.* Anti-CD20 (rituximab) treatment for atopic eczema. *J Allergy Clin Immunol* 2008; 121:1515–1516.
 10. Heil PM, Maurer D, Klein B, *et al.* Omalizumab therapy in atopic dermatitis: depletion of IgE does not improve the clinical course - a randomized, placebo-controlled and double blind pilot study. *J Dtsch Dermatol Ges* 2010; 8:990–998.
 11. Werfel T. Novel systemic drugs in treatment of atopic dermatitis: results from phase II and phase III studies published in 2017/2018. *Curr Opin Allergy Clin Immunol* 2018; 18:432–437.
- This review summarizes actual and emerging treatment options for atopic dermatitis.
12. Werfel T. The role of leukocytes, keratinocytes, and allergen-specific IgE in the development of atopic dermatitis. *J Invest Dermatol* 2009; 129:1878–1891.
 13. O'Shea JJ, Lahesmaa R, Vahedi G, *et al.* Genomic views of STAT function in CD4+ T helper cell differentiation. *Nat Rev Immunol* 2011; 11:239–250.
 14. Roesner LM, Heratizadeh A, Wieschowski S, *et al.* Alpha-NAC-specific autoreactive CD8+ T cells in atopic dermatitis are of an effector memory type and secrete IL-4 and IFN-gamma. *J Immunol* 2016; 196:3245–3252.
 15. Akbari O, Stock P, Meyer E, *et al.* Essential role of NKT cells producing IL-4 and IL-13 in the development of allergen-induced airway hyperreactivity. *Nat Med* 2003; 9:582–588.
 16. Bjerke T, Gaustadnes M, Nielsen S, *et al.* Human blood eosinophils produce and secrete interleukin 4. *Respir Med* 1996; 90:271–277.
 17. Lund S, Walford HH, Doherty TA. Type 2 innate lymphoid cells in allergic disease. *Curr Immunol Rev* 2013; 9:214–221.
 18. Wills-Karp M, Luyimbazi J, Xu X, *et al.* Interleukin-13: central mediator of allergic asthma. *Science* 1998; 282:2258–2261.
 19. Bancroft AJ, McKenzie AN, Grecis RK. A critical role for IL-13 in resistance to intestinal nematode infection. *J Immunol* 1998; 160:3453–3461.
 20. Tazawa T, Sugiura H, Sugiura Y, Uehara M. Relative importance of IL-4 and IL-13 in lesional skin of atopic dermatitis. *Arch Dermatol Res* 2004; 295:459–464.
 21. LaPorte SL, Juo ZS, Vacklavikova J, *et al.* Molecular and structural basis of cytokine receptor pleiotropy in the interleukin-4/13 system. *Cell* 2008; 132:259–272.
 22. Kasaian MT, Raible D, Marquette K, *et al.* IL-13 antibodies influence IL-13 clearance in humans by modulating scavenger activity of IL-13Ralpha2. *J Immunol* 2011; 187:561–569.
 23. Fujisawa T, Joshi BH, Puri RK. IL-13 regulates cancer invasion and metastasis through IL-13Ralpha2 via ERK/AP-1 pathway in mouse model of human ovarian cancer. *Int J Cancer* 2012; 131:344–356.
 24. Chen M, Cheng A, Chen YQ, *et al.* The amino terminus of JAK3 is necessary and sufficient for binding to the common gamma chain and confers the ability to transmit interleukin 2-mediated signals. *Proc Natl Acad Sci U S A* 1997; 94:6910–6915.
 25. Witthuhn BA, Silvennoinen O, Miura O, *et al.* Involvement of the Jak-3 Janus kinase in signalling by interleukins 2 and 4 in lymphoid and myeloid cells. *Nature* 1994; 370:153–157.
 26. Yin T, Tsang ML, Yang YC. JAK1 kinase forms complexes with interleukin-4 receptor and 4PS/insulin receptor substrate-1-like protein and is activated by interleukin-4 and interleukin-9 in T lymphocytes. *J Biol Chem* 1994; 269:26614–26617.
 27. Murata T, Puri RK. Comparison of IL-13- and IL-4-induced signaling in EBV-immortalized human B cells. *Cell Immunol* 1997; 175:33–40.
 28. Murata T, Taguchi J, Puri RK, Mohri H. Sharing of receptor subunits and signal transduction pathway between the IL-4 and IL-13 receptor system. *Int J Hematol* 1999; 69:13–20.
 29. Silva-Filho JL, Caruso-Neves C, Pinheiro AAS. IL-4: an important cytokine in determining the fate of T cells. *Biophys Rev* 2014; 6:111–118.
 30. Rahal OM, Wolfe AR, Mandal PK, *et al.* Blocking interleukin (IL) 4- and IL13-mediated phosphorylation of STAT6 (Tyr641) decreases M2 polarization of macrophages and protects against macrophage-mediated radioresistance of inflammatory breast cancer. *Int J Radiat Oncol Biol Phys* 2018; 100:1034–1043.
 31. Hebenstreit D, Wirmsberger G, Horejs-Hoeck J, Duschl A. Signaling mechanisms, interaction partners, and target genes of STAT6. *Cytokine Growth Factor Rev* 2006; 17:173–188.
 32. Chen Z, Lund R, Aittokallio T, *et al.* Identification of novel IL-4/Stat6-regulated genes in T lymphocytes. *J Immunol* 2003; 171:3627–3635.
 33. Serezani APM, Bozdogan G, Sehra S, *et al.* IL-4 impairs wound healing potential in the skin by repressing fibronectin expression. *J Allergy Clin Immunol* 2017; 139:142.e5–151.e5.
 34. Keegan AD, Zamorano J, Keselman A, Heller NM. IL-4 and IL-13 receptor signaling from 4PS to insulin receptor substrate 2: there and back again, a historical view. *Front Immunol* 2018; 9:1037.
 35. Junghans V, Jung T, Neumann C. Human keratinocytes constitutively express IL-4 receptor molecules and respond to IL-4 with an increase in B7/BB1 expression. *Exp Dermatol* 1996; 5:316–324.
 36. Yang Y, Yoo HM, Choi I, *et al.* Interleukin 4-induced proliferation in normal human keratinocytes is associated with c-myc gene expression and inhibited by genistein. *J Invest Dermatol* 1996; 107:367–372.
 37. Wongpiyakorn J, Suto H, Ushio H, *et al.* Up-regulation of interleukin-13 receptor alpha1 on human keratinocytes in the skin of psoriasis and atopic dermatitis. *J Dermatol Sci* 2003; 33:31–40.
 38. David M, Ford D, Bertoglio J, *et al.* Induction of the IL-13 receptor alpha2-chain by IL-4 and IL-13 in human keratinocytes: involvement of STAT6, ERK and p38 MAPK pathways. *Oncogene* 2001; 20:6660–6668.
 39. Sivaprasad U, Warrier MR, Gibson AM, *et al.* IL-13Ralpha2 has a protective role in a mouse model of cutaneous inflammation. *J Immunol* 2010; 185:6802–6808.
 40. Albanesi C, Scarponi C, Sebastiani S, *et al.* IL-4 enhances keratinocyte expression of CXCR3 agonistic chemokines. *J Immunol* 2000; 165:1395–1402.
 41. Bogiatzi SI, Fernandez I, Bichet JC, *et al.* Cutting edge: proinflammatory and Th2 cytokines synergize to induce thymic stromal lymphopoietin production by human skin keratinocytes. *J Immunol* 2007; 178:3373–3377.
 42. Nomura I, Goleva E, Howell MD, *et al.* Cytokine milieu of atopic dermatitis, as compared to psoriasis, skin prevents induction of innate immune response genes. *J Immunol* 2003; 171:3262–3269.
 43. Ong PY, Ohtake T, Brandt C, *et al.* Endogenous antimicrobial peptides and skin infections in atopic dermatitis. *N Engl J Med* 2002; 347:1151–1160.
 44. Albanesi C, Fairchild HR, Madonna S, *et al.* IL-4 and IL-13 negatively regulate TNF-alpha- and IFN-gamma-induced beta-defensin expression through STAT-6, suppressor of cytokine signaling (SOCS)-1, and SOCS-3. *J Immunol* 2007; 179:984–992.
 45. Howell MD, Kim BE, Gao P, *et al.* Cytokine modulation of atopic dermatitis filaggrin skin expression. *J Allergy Clin Immunol* 2007; 120:150–155.
 46. Danso MO, van Drongelen V, Mulder A, *et al.* TNF-alpha and Th2 cytokines induce atopic dermatitis-like features on epidermal differentiation proteins and stratum corneum lipids in human skin equivalents. *J Invest Dermatol* 2014; 134:1941–1950.
 47. Omori-Miyake M, Yamashita M, Tsunemi Y, *et al.* In vitro assessment of IL-4- or IL-13-mediated changes in the structural components of keratinocytes in mice and humans. *J Invest Dermatol* 2014; 134:1342–1350.
 48. Seltmann J, Roesner LM, von Hesler FW, *et al.* IL-33 impacts on the skin barrier by downregulating the expression of filaggrin. *J Allergy Clin Immunol* 2015; 135:1659.e4–1661.e4.
 49. Berdyshev E, Goleva E, Bronova I, *et al.* Lipid abnormalities in atopic skin are driven by type 2 cytokines. *JCI Insight* 2018; 3; pii: 98006.
- This work addresses the impact of the allergic inflammation on lipids of the skin by state-of-the-art techniques.
50. Zeitvogel J, Jokmin N, Rieker S, *et al.* GATA3 regulates FLG and FLG2 expression in human primary keratinocytes. *Sci Rep* 2017; 7:11847.
 51. Newcomb DC, Boswell MG, Zhou W, *et al.* Human TH17 cells express a functional IL-13 receptor and IL-13 attenuates IL-17A production. *J Allergy Clin Immunol* 2011; 127:1006.e13–1013.e4.
 52. Huang LR, Chen FL, Chen YT, *et al.* Potent induction of long-term CD8+ T cell memory by short-term IL-4 exposure during T cell receptor stimulation. *Proc Natl Acad Sci U S A* 2000; 97:3406–3411.
 53. Takaki H, Ichiyama K, Koga K, *et al.* STAT6 Inhibits TGF-beta1-mediated Foxp3 induction through direct binding to the Foxp3 promoter, which is reverted by retinoic acid receptor. *J Biol Chem* 2008; 283:14955–14962.
 54. Baron U, Floess S, Wiczorek G, *et al.* DNA demethylation in the human FOXP3 locus discriminates regulatory T cells from activated FOXP3(+) conventional T cells. *Eur J Immunol* 2007; 37:2378–2389.
 55. Simpson EL, Bieber T, Guttman-Yassky E, *et al.* Two phase 3 trials of dupilumab versus placebo in atopic dermatitis. *N Engl J Med* 2016; 375:2335–2348.
- In two randomized, placebo-controlled, phase 3 trials of identical design Dupilumab improved the signs and symptoms of atopic dermatitis, including pruritus, symptoms of anxiety and depression, and quality of life, as compared with placebo.
56. Blauvelt A, de Bruin-Weller M, Gooderham M, *et al.* Long-term management of moderate-to-severe atopic dermatitis with dupilumab and concomitant topical corticosteroids (LIBERTY AD CHRONOS): a 1-year, randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet* 2017; 389:2287–2303.
- This phase 3 trial points out that treatment success of dupilumab remained stable over 12 months.
57. Tsianakas A, Luger TA, Radin A. Dupilumab treatment improves quality of life in adult patients with moderate-to-severe atopic dermatitis: Results from a randomized, placebo-controlled clinical trial. *Br J Dermatol* 2017; 178:406–414.
- This study connects treatment success by the biological Dupilumab with a significant improvement of quality of life, correlated with decreasing pruritus.

58. U.S. Food and Drug Administration: FDA approves new eczema drug Dupixent. 2017. Available at: <https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm549078.htm>. [Accessed 7 March 2019]
 59. European Medicines Agency: Dupixent. Available at: <https://www.ema.europa.eu/en/medicines/human/EPAR/dupixent#authorisation-details-section>. [Accessed 12 March 2019]
 60. Han Y, Chen Y, Liu X, *et al.* Efficacy and safety of dupilumab for the treatment of adult atopic dermatitis: a meta-analysis of randomized clinical trials. *J Allergy Clin Immunol* 2017; 140:888.e6–891.e6.
 61. Rote Liste: Dupixent 300 mg injektionslösung 2018. Available at: <https://online.rote-liste.de/suche/p/26905/Dupixent%20300%20mg%20Injektions%C3%B6sung%20in%20einer%20Fertigspritze%20%20Fertigspritzen%20mit%20automatischem%20Sicherheitssystem>. [Accessed 7 March 2019]
 62. Fleming P, Drucker AM. Risk of infection in patients with atopic dermatitis treated with dupilumab: a meta-analysis of randomized controlled trials. *J Am Acad Dermatol* 2018; 78:62.e1–69.e1.
 63. Brightling CE, Chanez P, Leigh R, *et al.* Efficacy and safety of tralokinumab in patients with severe uncontrolled asthma: a randomised, double-blind, placebo-controlled, phase 2b trial. *Lancet Respir Med* 2015; 3:692–701.
 64. Wollenberg A, Birrel C, Dawson M, *et al.* A phase 2b dose-ranging efficacy and safety study of tralokinumab in adult patients with moderate to severe atopic dermatitis (AD). *AAD* 2017; Poster #4496.
 65. Wollenberg A, Howell MD, Guttman-Yassky E, *et al.* Treatment of atopic dermatitis with tralokinumab, an anti-IL-13 mAb. *J Allergy Clin Immunol* 2019; 143:135–141.
 66. Popovic B, Breed J, Rees DG, *et al.* Structural characterisation reveals mechanism of IL-13-neutralising monoclonal antibody tralokinumab as inhibition of binding to IL-13Ralpha1 and IL-13Ralpha2. *J Mol Biol* 2017; 429:208–219.
- By analyzing the crystal structure of therapeutic antibodies to Interleukin-13, this work reveals crucial differences between the working mechanisms of two biologicals.
67. Bissonnette R, Papp KA, Poulin Y, *et al.* Topical tofacitinib for atopic dermatitis: a phase IIa randomized trial. *Br J Dermatol* 2016; 175:902–911.
 68. Nakagawa H, Nemoto O, Igarashi A, Nagata T. Efficacy and safety of topical JTE-052, a Janus kinase inhibitor, in Japanese adult patients with moderate-to-severe atopic dermatitis: a phase II, multicentre, randomized, vehicle-controlled clinical study. *Br J Dermatol* 2018; 178:424–432.
 69. Guttman-Yassky E, Silverberg JI, Nemoto O, *et al.* Baricitinib in adult patients with moderate-to-severe atopic dermatitis: a phase 2 parallel, double-blinded, randomized placebo-controlled multiple-dose study. *J Am Acad Dermatol* 2018; 80:913.e9–921.e9.
 70. U.S. National Library of Medicine: MEDI9314. Available at: <https://clinicaltrials.gov/ct2/show/NCT02669667>.
 71. Wenzel S, Wilbraham D, Fuller R, *et al.* Effect of an interleukin-4 variant on late phase asthmatic response to allergen challenge in asthmatic patients: results of two phase 2a studies. *Lancet* 2007; 370:1422–1431.
 72. U.S. National Library of Medicine: Pitakinra. Available at: <https://clinicaltrials.gov/ct2/show/NCT00676884>.
 73. Gadani SP, Cronk JC, Norris GT, Kipnis J. IL-4 in the brain: a cytokine to remember. *J Immunol* 2012; 189:4213–4219.