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REVIEW

Targeting IL-4 for the Treatment of Atopic Dermatitis

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Andrea Chiricozzi[1,2]
Martina Maurelli[3]
Ketty Peris[1,2]
Giampiero Girolomoni[3]

[1]Dermatologia, Dipartimento Scienze Mediche e Chirurgiche, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy; [2]Dermatologia, Università Cattolica del Sacro Cuore, Rome, Italy; [3]Department of Medicine, Section of Dermatology, University of Verona, Verona, Italy

Abstract: Atopic dermatitis (AD) is an immune-mediated inflammatory skin disease characterized by a predominant type 2 immune response. Type 2 immunity is driven by multiple cytokines, including interleukin (IL)-4 and IL-13 that are considered central to AD pathogenesis and key therapeutic targets. The dual inhibition of these two cytokines or the selective inhibition of IL-13 proved elevated efficacy in treating AD, whereas the selective inhibition of IL-4 has been poorly investigated as IL-4 inhibiting agents did not show any advance in clinical development programs. This review describes the pathogenic role of IL-4 in AD and briefly resumes the main features of compounds selectively blocking IL-4.

Keywords: atopic dermatitis, IL-4, IL-4 inhibitor, dupilumab, pascolizumab, pitrakinra

Introduction

Atopic dermatitis (AD) is a common inflammatory skin disease resulting from genetic predisposition and environmental factors that cause skin barrier impairment and predominant type 2 immune responses.[1] Genetic susceptibility involves the keratinocyte differentiation process (ie, filaggrin) generating a defective epidermal barrier as well as immune dysregulation with a prevalent Th2 cytokine gene expression.[1] The immune activation can be altered by the dysbiosis of the skin microbiota characterized by the marked colonization of Staphylococcus aureus.[2] Thereby, AD pathogenesis represents a complicated mechanism wherein skin barrier, immune system, microbes, and, lately, the itch-mediating peripheral and central nervous system are interconnected. The pathogenic model has profoundly changed over the last two decades, overcoming the previous hypotheses based on (i) the immunoglobulin E (IgE)-mediated immune response (type 1 hypersensitivity), (ii) the primary role of the epidermal barrier impairment ("outside-in" theory), or (iii) the primary role of the aberrant immune activation ("inside-out" theory).[3–5] The discovery of the role for multiple immune pathways has led to new concepts in AD pathogenesis, and subsequently, to novel therapeutic strategies. It is now clear that the exaggerated immune response and the skin barrier impairment are both necessary for the development of AD, that may be considered a heterogeneous disease, being characterized by different phenotypes/endotypes.[1,6,7] The immune hallmark of AD is the type 2 inflammation that includes the activation of T helper (h) 2 cells, T cytotoxic (c) 2 cells, innate lymphoid cells (ILC)2, γ/δ T cells, eosinophils, and mast cells, B cells, while other immune pathways such as Th22, Th17, Th9 and Th1 contribute to the pathogenic mechanism, particularly in some AD subtypes.[7,8]

Correspondence: Andrea Chiricozzi
Dermatologia, Dipartimento Scienze Mediche e Chirurgiche, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome 00168, Italy
Tel +39-339 5668320
Fax +39-0761-571321
Email chiricozziandrea@gmail.com

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Type 2 immunity is driven by multiple cytokines, including interleukin (IL)-4, IL-5, IL-9, IL-13, IL-25, IL-31, IL-33 and thymic stromal lymphopoietin (TSLP). In particular, IL-4 and IL-13 are considered central to AD pathogenesis and key therapeutic targets.[5,8–10] Because type 2 inflammation also characterizes other atopic disorders, such as food allergies, asthma, allergic rhinitis and conjunctivitis, which are strongly associated with AD, therapeutic strategies blocking type 2 cytokines may be relevant in treating AD and concomitant atopic disorders.-[11] In this review, we provide a brief overview about the pathogenic role of IL-4 and the therapeutic agents blocking this cytokine.

Methods

Search of the English-language literature regarding the pathogenic role of IL-4 in AD was carried out, in addition to therapeutic agents targeting IL-4 signaling. Different databases, namely PubMed, Embase, ResearchGate, Google Scholar and Scopus, have been consulted using the following terms: interleukin 4, IL-4, IL-4-inhibitor, IL-4-blocker, atopic dermatitis, atopic eczema, pathogenesis, pathogenic mechanism. Ongoing clinical trials and preliminary results concerning investigational use of IL-4 inhibitors in AD were searched on Clinicaltrial.gov. Data from recent international meetings were also taken into account.

Role of IL-4 in AD Pathogenesis

Gene encoding for IL-4 protein maps on human chromosome 5, clustering with other genes involved in AD pathogenesis such as IL-13 and IL-5, other than IL-3 and granulocyte macrophage colony-stimulating factor (GMCSF).[12,13] IL-4 is a glycosylated, type I cytokine produced by Th2 cells, Tc2 cells, NK T cells, γ/δ T cells, ILC2, eosinophils, mast cells, and activated basophils.[5,14] IL-4 signals through two different receptor complexes: a type I receptor composed by composed of IL-4Rα chain and common γ chain/IL-2 Rγ subunit, and expressed on hematopoietic cells, and a type II receptor consisting of IL-4Rα and IL-13Rα1 subunits, and expressed on nonhematopoietic cells.[15,16] Whilst the type I receptor specifically transduces signals for IL-4, the type II receptor can be activated by either IL-4 or IL-13.[5,15,16] IL-4 acts on both immune and tissue cells, mediating multiple steps of the pathogenic cascade in AD. On the T cell compartment, IL-4 drives the differentiation of naïve CD4+ T cells into Th2 cells, and similarly induces the development of Tc2 and ILC2 cells.[17–20] On the B cell compartment, IL-4 induces IgE production.[21] To amplify type 2 inflammation, IL-4 also modulates dendritic cell activity, reducing their expression of IL-12 and MHC class II and costimulatory molecules, and increasing the production of IL-10, and thus, favoring the differentiation of both naïve CD4+ and CD8+ T cells toward type 2 cells.[22]

The expansion of type 2 T cells results in an elevated frequency of circulating Tc2 and cutaneous lymphocyte-associated antigen (CLA)+ IL-4-producing T cells, detected in AD patients and reflecting a significantly higher number of both Th2 cells infiltrating both AD lesional and nonlesional skin.[23–28] IL-4 also amplifies CCR4+ Th2 cell recruitment to the skin inducing the expression CCR4-binding chemokines, such as CCL22, CCL5, CCL17, CCL2, in monocytes and dendritic cells.[29–31] In addition, it stimulates the expression of CCL26 (eotaxin-3) in keratinocytes, a key chemokine for eosinophil recruitment and, similarly, it induces in fibroblasts the expression of CCL11 (eotaxin-1), another critical cytokine for eosinophil recruitment.[32,33]

Mouse models have defined the centrality of IL-4 in AD pathogenesis, highlighting its capability in inducing all AD histopathological features.[34,35] The overexpression of IL-4 induces IgE production, enhances skin inflammation, favors bacterial skin infection, and mediates pruritus.[34,35] On the contrary, the lack of IL-4 reduces allergen-challenged skin reactivity, and attenuates IgE levels and skin eosinophilia.[36,37] Besides the effect on immune cells, IL-4 also influences keratinocyte differentiation and their innate immune activation. In vitro, IL-4 stimulation alters early and terminal keratinocytes differentiation, suppressing the expression of both terminal keratinocyte differentiation proteins (ie, filaggrin, loricrin and involucrin), and genes related to differentiating keratinocytes at early stages (ie, keratin [Krt]1, Krt5, Krt10, Krt14, desmoglein [Dsg]1a, and desmocollin [Dsc]1).[38–41] In addition, IL-4 alters extracellular lipid content in in vitro AD model similarly to the aberrant stratum corneum lipid structure observed in both AD mice model and human AD skin.[42] IL-4 attenuates antimicrobial peptide (AMP) production, suppressing upregulation of beta defensin (HBD)-2, HBD-3, LCN2, and LL-37, even antagonizing IL-17-induced AMP production in keratinocytes.[43–47] IL-4 also triggers fibroblast production of collagen, fibronectin, and fibrinogen, serving as adhesion molecules for *Staphylococcus aureus*.[48–50] Thereby, IL-4 contributes to skin barrier function impairment and to the increased susceptibility to bacterial

infections. In addition, IL-4 both directly and indirectly, stimulates itch sensory neurons. Indeed, IL-4 is capable of directly activating itch sensory neurons in vitro, and, in mice, intradermal injections of IL-4 induced rapid and significant increase of scratching.[51,52] It has been shown, by employing sensory neuron-specific genetic deletion of IL-4Rα, that chronic itch is dependent on neuronal IL-4Rα and Janus kinase 1 signaling.[52] Rather than triggering acute itch, activation of neuronal IL-4Rα sensitizes sensory neurons to multiple other pruritogens. IL-4 significantly amplifies scratching behavior to low doses of known pruritogens like histamine.[52] The indirect effects of IL-4 in potentiating itch signal may be also due to its capability to enhance the interaction between IL-31, identified as key pruritogen cytokine, and its receptor (IL-31Rα), and increasing the expression of IL-31 receptor, in a dose-dependent manner, in bone marrow-derived dendritic cells.[53] The presence of IL-4 increases CCL-17 and CCL-22 production regulated by IL-31, conversely to IL-31 stimulation alone.[53] Finally, IL-4, together with granulocyte/macrophage colony stimulating factor, supports the differentiation of monocytes into monocyte-derived dendritic cells, which are abundantly present in AD lesional skin and potently contribute to sustain T cell activation in AD skin.[54]

Therapeutic Relevance of Targeting IL-4

Inhibition of type 2 inflammation proved elevated efficacy in treating AD. The first approved monoclonal antibody, dupilumab, which blocks IL-4Rα and thus the activity of both IL-13 and IL-4, primed the therapeutic strategy of blocking type 2 cytokines, their receptors, or their coupled intracellular signal transducers such as Janus kinases (JAK) - signal transducer and activator of transcription (STAT) pathway.[55,56] Notwithstanding IL-4 signaling is considered a very interesting potential therapeutic target for the treatment of AD, a few attempts in neutralizing soluble IL-4 have been previously performed, but no pharmacologic entity blocking IL-4 is apparently in the current treatment pipeline for AD. The pharmaceutical development of monoclonal antibodies blocking the IL-4Rα subunit, is predominant.[57] The therapeutic advantage of blocking this receptor subunit is to contemporarily neutralize the signaling of both IL-4 and IL-13 that show overlapping, but not redundant functions in potentiating type 2 inflammation. Indeed, IL-4, driving T cell differentiation, is thought to have a key pathogenic role in the early steps of AD pathogenesis, whereas IL-13 does not promote Th2 differentiation and its effects seem to be more focused on peripheral tissue cells and the effector phase of the immune response.[56,58] Thereby, T cells respond to IL-4 stimulation only as they do not express IL-13 receptors with the exception of Th17 cells that are reported to express a functional IL-13 receptor lessening IL-17 production.[59] The hypothesis of an early relevant intervention of IL-4 in the pathogenesis of AD is in line with other findings describing an elevated IL-4 expression in acute lesional skin, which further increase in chronic AD lesions.[60,61] Because IL-4 mainly acts on both T cell and ILC differentiation towards a type 2 response, but tissue cell activation in AD is suggested to be preferentially driven by IL-13, the dual blockade of these cytokines has the advantage of blocking multiple steps of the pathogenic cascade, reflecting a both rapid and maintained therapeutic response. The neutralization of IL-4 signaling alone may not directly suppress tissue cell response, which might translate therapeutically into a late-onset response, compared to simultaneous IL-4/IL-13 blockade.

Selective Inhibitors of IL-4 Signaling

In 2017, both the European Medicines Agency and the US Food and Drug Administration approved dupilumab for the treatment of moderate to severe AD. Clinical outcomes derived from Phase 3 trials have been confirmed by a large number of real-life studies, demonstrating high clinical effectiveness and very favorable safety profile.[62,63] Targeting the same receptor subunit, other drugs, namely CBP 201 (manufacturer: Suzhou Connect Biopharmaceuticals), AK 120 (manufacturer: Akeso Biopharma), are now tested in Phase II and Phase I trials, respectively (Table 1).[64,65] With a different mechanism-of-action, pitrakinra, is able to block both IL-4 and IL-13. It represents an IL-4 double mutein, recombinant protein that binds to IL-4Rα receptor subunit without signaling through, thus not determining receptor activation.[66] So far, pascolizumab (SB 240683), is the only humanized monoclonal antibody neutralizing IL-4 that was developed for the treatment of asthma.[67] A pilot study, a phase I/II, randomized, double-blind, placebo controlled, parallel-group trial, enrolling 120 patients with symptomatic steroid-naïve asthma, was conducted but results are

Table 1 Therapeutic Agents Targeting IL-4 That are Marketed or Under Clinical Development for the Treatment of AD

Compound	Type of Molecule	Target	Phase of Development
Pitrakinra	Inactive human recombinant protein similar to IL-4 (also a PEGylated variant of subcutaneous pitrakinra was investigated)	IL-4 alpha receptor subunit	Phase IIb in AD - unknown future development program
Dupilumab	Fully human monoclonal IgG4 antibody	IL-4 alpha receptor subunit	FDA and EMA approved
CBP 201	Monoclonal antibody	IL-4 alpha receptor subunit	Phase II
AK 120	Monoclonal antibody	IL-4 alpha receptor subunit	Phase I
Pascolizumab (SB 240683)	Humanized monoclonal IgG1 antibody	IL-4	Phase II in asthma - unknown future development program

Abbreviations: EMA, European Medicines Agency; FDA, Food and Drug Administration; IL-, interleukin.

not reported and no further development has been planned.[68]

Conclusions

The role of IL-4 in AD is well established and multiple lines of evidence support its relevant contribution in mediating multiple clinical features, including skin inflammation and pruritus. Nevertheless, its therapeutic relevance is still debated as it is usually considered a valid target for AD in conjunction with IL-13 neutralization. Conversely to IL-13 alone that constitutes a target for various compounds currently tested in clinical trials, the selective inhibition of IL-4 is not considered an advantageous therapeutic intervention for type 2 mediated disorders. However, further investigations on developing new IL-4 targeting agents will be worthy to expand and diversify the therapeutic armamentarium in AD and other type 2 inflammation mediated itchy skin disorders.

Disclosure

Andrea Chiricozzi served as advisory board member and consultant, and has received fees and speaker's honoraria or has participated in clinical trials for Abbvie, Biogen, Fresenius Kabi, Leo Pharma, Lilly, Janssen, Novartis, Sanofi Genzyme, and UCB-Pharma

Ketty Peris reports grants and personal fees for advisory Board meeting from Almirall, AbbVie, Biogen, Lilly, Celgene, Galderma, Leo Pharma, Novartis, Pierre Fabre, Sanofi, Sandoz, Sun Pharma and Janssen, outside of the submitted work.

Giampiero Girolomoni has been principal investigator in clinical trials sponsored by and/or and has received personal fees from AbbVie, Abiogen, Almirall, Amgen, Biogen, Boehringer-Ingelheim, Bristol-Meyers Squibb, Celgene, Celltrion, Eli-Lilly, Genzyme, Leo Pharma, Menlo therapeutics, Novartis, OM Pharma, Pfizer, Regeneron, Samsung, Sandoz and UCB Pharma.

The authors report no conflicts of interest for this work.

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