

Interleukin 31 and skin diseases: A systematic review

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ABSTRACT

Background: Although the pathophysiology of pruritus has been extensively studied in recent years, with many resultant advancements, management of pruritus is still enigmatic, particularly in chronic cutaneous diseases, such as atopic dermatitis, chronic urticaria, allergic contact dermatitis, cutaneous T-cell lymphoma, and uremic pruritus. The recent finding of the involvement of interleukin (IL) 31 in the pathogenesis of chronic pruritus has provided a novel approach to the management of chronic inflammatory skin disorders. The present report provided an in-depth overview of the role of IL-31 in chronic skin diseases and the possible diagnostic and therapeutic applications in the management of these diseases.

Methods: A systematic review of IL-31 was conducted by using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.

Results: A review of a total of 45 published research articles revealed that the majority of these articles focused on the role of IL-31 in causation of pruritus and in the worsening of the disease in atopic dermatitis. Other publications examined interleukin in other pruritic diseases (cutaneous T-cell lymphoma, uremic pruritus, allergic contact dermatitis, chronic urticaria). In almost every disease, IL-31 levels were reported to be correlated with the pathology and often with pruritus. The cutaneous injection of IL-31 resulted in a long-lasting itching sensation, and the use of monoclonal antibodies that targeted IL-31 led to a reduction in pruritus.

Conclusion: The use of monoclonal antibodies against mediators involved in the pathogenesis of chronic skin diseases has shown promising results. Antibodies that target IL-31, in particular, its receptor A, showed interesting results in atopic dermatitis and decreased pruritus. In subsequent years, the use of these new therapeutic strategies could change the scenario of pruritic skin diseases. However, further studies are needed to more rigorously examine the effects of IL-31 cascade blockage in different chronic skin diseases and to confirm efficacy and the safety of these new therapeutic approaches.

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In 2004, Dillon *et al.*¹ identified a new four-helix bundle cytokine mainly produced by T-helper (Th) type 2 cells, which was named interleukin (IL) 31. Due to its helicoidal structure, IL-31 was grouped with the short chain cytokine family. In studies performed in an experimental mouse model, IL-31 messenger RNA (mRNA) was detected in testicles, bone marrow, skeletal muscle, long and short bowel, thymus, and trachea. IL-31 was found to perform its core functions by interacting with the IL-31 receptor A (IL-31RA) and the oncostatin M receptor (OSMR). Although, the mRNA of these receptors was induced in activated monocytes, epithelial cells also constitutively expressed

this mRNA. Moreover, although IL-31RA mRNA expression was detected in both human and mouse tissues in skin, brain, skeletal muscle, lung, trachea, ovary, prostate, placenta, spleen, thymus, testicle, bone marrow, and leukocytes, OSMR mRNA was detected primarily in trachea, thymus, and skin.

Dillon *et al.*¹ also described the association of overexpression of IL-31 in a transgenic mouse model with intense pruritic skin lesions. Collectively, these research findings stimulated intense interest in the study of the potential role of IL-31 in facilitating dermatitis and epithelial responses, typical of allergic and nonallergic skin diseases.¹ Most recently, a major research effort has been directed to the study of how IL-31 plays a key role in inducing chronic inflammation and in regulating the innate and adaptive immune response.^{1,2} IL-31 serum levels have been detected in different skin diseases as well as in inflammatory diseases and with aging,^{3,4} presumably through its known capacity to promote the secretion of proinflammatory cytokines, chemokines, and matrix metalloproteinases.⁵

Other investigators observed the expression of IL-31RA transcripts in dorsal root ganglia (DRG) of several human tissues specifically located within the cell bodies of primary sensory neurons.⁶ Therefore, it is

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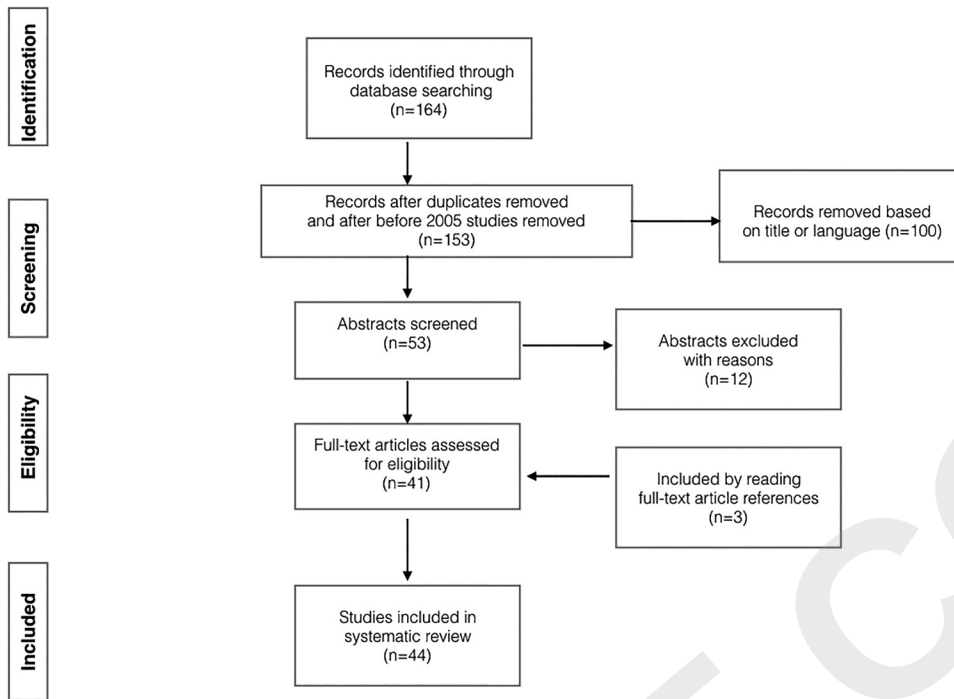


Figure 1. Flowchart of the results of the literature search.

possible that DRG could contribute to the sensation of itch.⁷ The positive trend of published articles that concerned either pruritus or IL-31 during recent years are shown in Fig. 1. The same trend was seen in publications that showed an association of IL-31 with pruritus. The objective of this review was to provide an update of this recently discovered cytokine and an overview of its role in the pathogenesis of pruritic skin diseases.

METHODS

This systematic review was conducted according to the *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* guidelines⁸ by using a PubMed data base. On PubMed website, we searched for articles to March 2017 by using key terms related to IL-31 and skin diseases; a Medical Subject Headings search was performed by using “IL-31 protein, human” and “skin diseases,” followed by a simple search with keywords such as “interleukin 31” and “pruritus” (Table 1). Each of the articles that described in its title a possible role of IL-31 in cutaneous diseases was immediately scanned. The whole article was then read if the abstract indicated that the article potentially met the inclusion criteria. Lastly, we reviewed and searched references of the selected articles.

Articles were included in the present review according to the following inclusion criteria: English language, publication in peer-reviewed journals, research paper. Articles were excluded if the title, abstract, or the full text was not relevant to the topic in question. (Fig. 1). Two authors (M.C., S.Q.) per-

Table 1 List of search terms entered into the PubMed search engine for identification of the studies for this systematic review

No.	Search Term
1	Pruritus [MeSH]
2	Interleukin 31, human [MeSH]
3	Skin diseases [MeSH]
4	Pruritus
5	Interleukin 31
6	Skin diseases
7	Nos. 1 or 2
8	Nos. 2 and 3
9	Nos. 4 and 5
10	Nos. 5 and 6
11	English [language]
12	From inception until March 2017

MeSH = Medical Subject Headings.

formed the initial search and independently reviewed and selected the references based on the inclusion and exclusion criteria. The data derived from our search included the following: study author names, publication dates, study design (*i.e.*, case control, cross-sectional, longitudinal), groups studied, clinical and biologic variables, and the outcome of interest of the study. The main outcome of interest included original studies that concerned IL-31 levels in subjects or animals affected by skin diseases. Given the considerable heterogeneity of the diseases and the difficulty in identifying a common causal

agent, characteristics of the studies and protocols were summarized. The study outcome was reported by using descriptive statistics without conducting any meta-analyses. Results obtained are reported in Supplemental Table 1.

RESULTS

As shown in Supplemental Table 1, a total of 45 research articles were identified from the literature review. These articles were equally divided between animals and humans studies; screening, pathophysiologic, and genetic investigations mainly conducted on human tissues (serum and skin); and therapeutic studies developed on *in vivo* animal models.

DISCUSSION

The skin is the first line of defense against infectious microorganisms and toxic agents. The epithelium is mainly composed of keratinocytes, Langerhans cells, T lymphocytes, and macrophages.⁹ It is also not only the largest human organ but also a “window” capable of visualizing internal disequilibrium. Pruritus or itch is one of the most frequent symptoms found in skin diseases and is a very disabling condition that entails many complex mechanisms, including pruriceptive nerves, their receptors, and a number of mediators.¹⁰ Chronic inflammatory skin diseases are characterized by an intense and antihistamine-resistant pruritus. Atopic dermatitis (AD) has been studied to a greater extent than contact dermatitis (CD), both in relation to itch. Several molecules are involved in the pathogenesis of pruritus and dermatitis, (IL-4 receptor, IL-18, and IL-31)¹¹ as well as many mediators, such as histamine, leukotrienes, prostaglandins, neuropeptides, protein ligases, muscarinic agonists, and serine proteases.^{12–16}

IL-31 in Chronic Skin Diseases

AD. The majority of the studies were performed by considering AD as a pruritic model. This skin condition can be distinctively designated as the “dermatologic syndrome, which heralds the atopic diathesis,” having pruritus as its cardinal symptom.¹⁷ The study by Dillon *et al.*,¹ in a mouse model, was the first to describe the pathogenic role of IL-31, which, when overexpressed, was associated with an intense itching behavior, alopecia, and dermatitis, and proposed that IL-31 could be involved in promoting skin diseases. Sonkoly *et al.*⁶ indicate that staphylococcal superinfection could induce pruritus in individuals with atopy; this was because of the overexpression of IL-31 mRNA triggered by a staphylococcal superantigen (a known trigger factor for AD). Because there was no difference between IL-31 serum levels in intrinsic and extrinsic AD, Raap *et al.*¹⁸ surmised that IL-31 serum levels correlated with AD disease activity and

not with the AD phenotype. During the flare phase in children with AD, Ezzat *et al.*¹⁹ reported higher IL-31 plasma levels compared with the quiescence phase. Due to the consistent association of high serum IL-31 levels in patients with AD, Lee *et al.*²⁰ indicated its measurement as a disease biomarker. However, results of other studies showed no correlation between IL-31 levels and the pruritus intensity nor to Scoring Atopic Dermatitis 20.^{21,22}

Other Chronic Skin Diseases. Other chronic skin diseases, such as chronic urticaria and CD, have chronic inflammation and pruritus in common. Higher IL-31 levels were found in patients with urticaria compared with healthy controls; however, because urticaria is a fluctuating disease, assessing the score only at the time of blood sampling could not reflect the spectrum of the disease activity.²³ Serum levels of IL-31 in patients affected by allergic CD strongly indicated that targeting IL-31 could be an option to reduce pruritus and to ameliorate chronic skin diseases.²⁴ Studies of IL-31 in mastocytosis, another pruritic disease, showed a direct correlation of high IL-31 serum levels with disease activity.²⁵ Ohmatsu *et al.*²⁶ advanced the research a step further when they decided to investigate IL-31 levels in patients with cutaneous T-cell lymphoma (CTCL); the reason behind this decision was the similarity of many CTCL laboratory markers with AD.

These investigators found augmented IL-31 levels in patients with CTCL and speculated that, as in other chronic skin diseases, this cytokine could play an important role in inflammation and pruritus.²⁶ Both Singer *et al.*²⁷ and Malek *et al.*²⁸ found higher IL-31 levels in patients affected by CTCL. Only the study conducted by Singer *et al.*²⁷ confirmed a correlation with the intensity of pruritus. However, high IL-31 serum levels in CTCL suggest an involvement of the interleukin in the pathogenesis of the disease.^{27,28} Moreover, Ko *et al.*²⁹ confirmed the role of IL-31 in the itching sensation because they found significantly higher IL-31 levels in patients affected by uremic pruritus. A study by Tey *et al.*³⁰ of IL-31RA overexpression in patient's skin with primary localized cutaneous amyloidosis indicated the utility of future IL-31 blockage strategies. Collectively, these studies^{24–30} supported the notion that this controversial interleukin could be involved in the pathogenesis of pruritus both in its initial phase and during the more chronic stages of skin diseases.

Does IL-31 Cause Only Pruritus or Does It Take Part in Disease Activity?

Dermatitis Pathogenesis. The involvement of genetic factors in the development of hand dermatitis has been extensively demonstrated.^{31,32} At the same time, there is strong evidence that supports the pathogenetic role

of IL-31 gene polymorphism in AD^{22,33} and in the pathogenesis of mastocytosis.²⁵ Kasraie *et al.*³⁴ clarified the proinflammatory effect of IL-31 on monocytes and macrophages, fundamental to the chronification of eczema. Later, Wong *et al.*,³⁵ in a studies in which IL-31 and IL-33 were simultaneously cocultured with eosinophils and fibroblasts, reached the conclusion that these immune system cells could produce high levels of proinflammatory cytokine (IL-6) and AD-related chemokines (C-X-C motif chemokine ligands CXCL1, CXCL8, CXCL10; C-C motif chemokine ligands CCL2 and CCL5). Consequently, Wong *et al.*,³⁵ speculated that eosinophils and fibroblasts play a major role in the pathogenesis of chronic skin pruritic diseases.³⁵ The role of DRG neurons in AD was first hypothesized by Arai *et al.*³⁶ and then confirmed by Kato *et al.*³⁷ In contrast to the results of studies obtained by Cevikbas *et al.*,³⁸ they individuated IL-31RA in AD nerve fiber and in normal human DRG.^{36–38}

Pruritus Mechanisms. The intradermic injection of IL-31 into mice skin, performed by Arai *et al.*,³⁶ resulted in long-lasting itching and IL-31RA overexpression in DRG. Hawro *et al.*,³⁹ by skin-prick testing humans with IL-31, confirmed what was previously reported in animals that related to the late spread of the itching sensation. This effect was indicated once more to be related to an indirect mechanism of IL-31 in causing pruritus through the release of pruritogenic mediators from keratinocytes.³⁹ Another hypothesized mechanism that leads to pruritus was the increase of β -endorphin. Lee *et al.*²⁰ reported that calcium-cell influx, stimulated by the interaction between IL-31 and its receptor, activated signal transducer and activator of transcription 3, and, subsequently, increased β -endorphin level. In previous work carried out by Lee *et al.*,⁴⁰ β -endorphin was associated to a subjective itch sensation in patients with AD. Although some data were provided by these studies, the precise mechanisms that generate pruritus still remain unclear.

Pruritus Model

IL-31 is overexpressed in different disease conditions and in many itch-correlated disorders. Viral and bacterial infections, as well as IL-4 induced by immune diseases, have been shown to increase tissue and serum IL-31 levels.⁴¹ In patients affected by immune-related diseases, IL-31 is mainly secreted locally by Th2 and Th1 lymphocytes. This increased production begins in a subacute phase and continues during the chronic stages.¹ As previously described, there are high IL-31 levels in many pruritic skin diseases (AD, allergic CD, CTCL, urticaria, primary localized cutaneous amyloidosis, uremic pruritus, prurigo). The reported studies were unable to assess whether or not IL-31 levels are

related to pruritus intensity or to disease activity; certainly, IL-31 is increased in the previously described chronic pruritic skin diseases. However, it seems quite clear that IL-31 levels are not significantly augmented in nonitching chronic skin pathologies.

One of the prime distinguishing aspects of IL-31 is that the cytokine induces late onset pruritus, which differentiates it from the histamine-induced pruritus. IL-31 injection in animal or human skin caused scratching behavior or at least a long-lasting pruritus.^{1,39,42} This kind of itching stimulus indicates the involvement of a skin-receptorial compound through a peripheral nerve fiber.^{43,44} It is known that IL-31 has two receptors: OSMR and IL-31RA. OSMR is mostly expressed on keratinocytes, whereas IL-31RA is in peripheral sensory nerve fibers.^{1,43,44} However, in malignant pruritus, both receptors are increased in the epidermis.⁴⁵

According to our model (Fig. 2), these receptors may sustain and/or worsen the itching sensation through different pathways. Th2 and Th1 lymphocytes initiate an *in situ* production of IL-31, only after a repetitive and long-lasting skin process. Once IL-31 reaches a sufficient concentration, IL-31 could exert its action through the two pathways described in Fig. 2. In the first cascade, IL-31 directly stimulates OSMR, which is mainly present on keratinocytes and less present on cutaneous sensory nerve fiber. IL-31RA has also been individuated in eosinophils, which participate in the production of proinflammatory cytokines (AD-related chemokines CXCL1, CXCL8, CCL2, and CCL18).⁴⁶ Keratinocytes and skin IL-31 then stimulate peripheral sensitive nerve fiber; once the stimulus reaches DRG, through the sensitive path (classic itching way), it initiates the scratching reflex (direct way). The other cascade might be activated by serum IL-31. In this model, the interleukin links DRG to IL-31RA by blood flow. By following the second pathway, IL-31 might also initiate the scratching reflex (indirect way). As described above, the scratching behavior seems to be triggered by a spinal unconscious reflex. This reflex leads, in turn, to a vicious spiral facilitated by new skin lesions, a further local IL-31 relapse, and additional scratching lesions.

IL-31–IL-33 Axis

Wong *et al.*³⁵ reported the expression of IL-31RA and IL-1 receptor-like 1 (also known as ST2, the IL-33 receptor) on dermal fibroblasts. They also demonstrated that IL-31 and IL-33 together could stimulate the coculture of eosinophils and fibroblasts to secrete high levels of IL-6 and AD-related chemokines.³⁶ However, Metz *et al.*⁴⁷ did not find any correlation between IL-31, IL-33, and other itch biomarkers in patients affected by chronic spontaneous urticaria. IL-33, a Th2 proinflammatory cytokine, induces IL-31 secretion by interaction

Figure 2. Interaction between interleukin (IL) 31 and oncostatin M receptor (OSMR) and IL-31 receptor A (IL-31RA). IL-31 exerts its action by two pathways. In the first pathway, IL-31 directly stimulates OSMR. The keratinocytes and the cutaneous IL-31 (red dots) stimulate peripheral sensitive nerve fiber; once that stimulus reaches dorsal root ganglia (blue dot), through the sensitive path (classic itching way), it initiates the scratching reflex (direct way, black arrows). The second pathway might be activated by plasmatic IL-31. In this model, the interleukin reaches dorsal root ganglia IL-31RA by blood torrent. Accordingly, in this second way, IL-31 might also initiate the scratching reflex (indirect way, blue arrows).

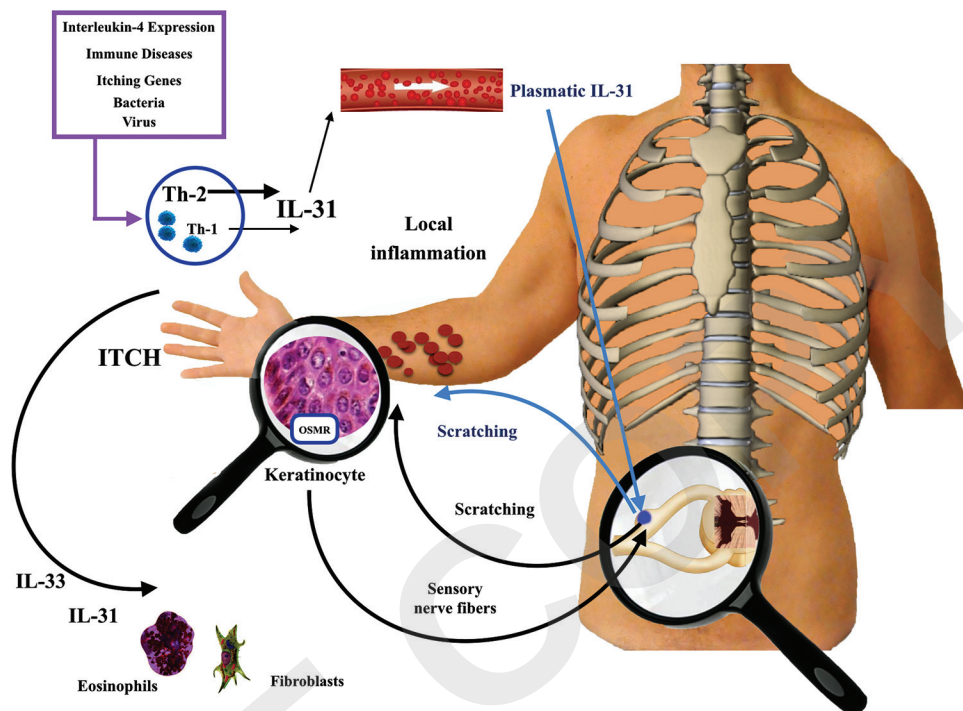
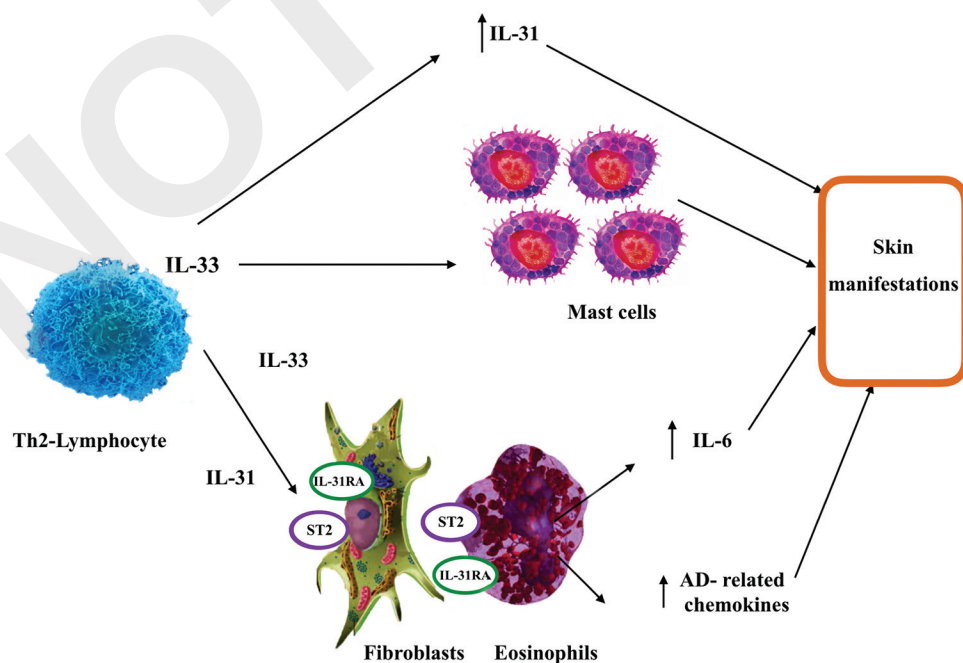


Figure 3. Interleukin (IL) 33, a T-helper (Th) type 2 proinflammatory cytokine, by interacting with IL-4 induces IL-31 secretion. IL-33 interacts with its receptor on mast cells, which leads to the secretion of several factors capable of causing skin manifestations, including IL-31. IL-31 and IL-33 together could stimulate eosinophils and fibroblasts (by interacting with their receptors IL-31 receptor A [IL-31RA] and IL-33 receptor [ST2]) to secrete high levels of IL-6 and atopic dermatitis (AD) related chemokines.



with IL-4. Maier *et al.*⁴⁸ reported that a nuclear factor kappa B-binding element enhanced the effects of IL-33 on IL-4 in inducing IL-31 expression in Th2 cells. They also found that Th2 cells were able to release IL-31; the same effect could not be obtained by using Th9 cells.⁴⁸ Two case reports are described in the literature of pruritic skin lesions in patients undergoing antineoplastic drugs treatments, which had elevated serum levels of both IL-31 and IL-33. We suggest the involvement of keratinocytes toxicity with a subsequent re-

lease of IL-33 (Fig. 3). The interaction of IL-33 with its receptor on mast cells could lead to the secretion of several factors, including IL-31, which are capable of causing skin manifestations.⁴⁹ The close link between these two cytokines was further demonstrated in other diseases that involve the immune system. A positive correlation was observed between IL-31 and IL-33 plasma levels and between both IL-31-IL-33 and soluble ST2 in patients with allergic airway diseases. This indicates an important role of the IL-33-

ST2 interaction in Th2-IL-31 immunity during an allergic response.⁵⁰

Evidences and Future Treatment Approaches

Monoclonal Antibodies. The first attempt to interfere with IL-31 was conducted by Grimstad *et al.*⁵¹ in a mouse model in 2009. The use of anti-IL-31 antibody showed an improvement in the itching sensation but did not improve the AD condition; this finding indicated an unclear role in the pathogenesis of the disease.⁵¹ Also, in nonhuman primates (cynomolgus), the treatment with anti-IL-31 monoclonal antibody suppressed the itching sensation induced by IL-31 injection.⁵² Promising results have also been obtained by using nemolizumab, a humanized anti-IL-31RA monoclonal antibody. The administration of this antibody inhibited IL-31-induced pruritus in cynomolgus monkeys.⁵³ The first use of anti-IL-31RA antibody in humans showed excellent results in patients affected by AD, decreasing pruritus, sleep disturbance, and topical use of cortisone.⁵⁴

These results were recently confirmed by Ruzicka *et al.*⁵⁵ in a phase II randomized trial on patients with moderate-to-severe AD. The administration of nemolizumab at three different doses significantly improved pruritus. Although all the doses led to the itch suppression, the 0.5 mg/kg dose administered every 4 weeks showed the best benefit-to-risk profile.⁵⁵ Another therapeutic strategy came from the study by Cedeno-Laurent *et al.*⁵⁶ The investigators demonstrated that IL-31-producing malignant T cells in CTCL expressed chemokine receptor type 4; they also reported that the administration of mogamulizumab, a fully humanized anti-chemokine receptor type 4 monoclonal antibody led to pruritus improvement and IL-31-positive T-cell reduction.⁵⁶ However, a study on the IL-1 and IL-31 cascade indicated that interfering with IL-31 could not be completely useful (due to the blockage of skin differentiation). Therefore, the investigators suggested maintaining low levels of IL-31 to promote the antimicrobial barrier.⁵⁷

Other Therapeutic Strategies. Other types of therapies have shown effects on IL-31. Gonzales *et al.*⁵⁸ reported the capacity of prednisolone, dexamethasone, and oclacitinib to equally suppress an IL-31-induced itching sensation in dogs. Park *et al.*⁵⁹ treated mice affected by AD with an herbal preparation, gamisasangja-tang, used in the traditional medicine. They achieved a reduction of the dermatitis index and a significant decrease of IL-31 mRNA expression and production, and hypothesized a herbal-interfering effect on IL-31 production, although no evidence was found.⁵⁹ Otsuka *et al.*⁶⁰ described a reduction of pruritus in patients with

AD who were treated with epinastine (histamine H₁ receptor antagonist) with a concomitant reduction of the IL-31 serum level, possibly related to cross-reactivity of the histamine H₁ receptor with the H₄-histamine receptor. It is known that H₄ receptors are upregulated under a Th2 response and that the stimulation of these receptors leads to augmented IL-31 circulating levels.^{60–62}

CONCLUSION

Scratching behavior is an archaic defense mechanism aimed to remove possible dangerous substances from the skin. In many diseases, it becomes a distressing stimulus that worsens preexisting skin lesions. The reported studies mentioned herein could partially explain the role of IL-31 in causing itch and skin lesions in chronic inflammatory diseases. The use of monoclonal antibodies against mediators involved in the pathogenesis of chronic skin diseases has shown promising results. For example, the treatment with dupilumab, an antibody against IL-4 receptor alpha, has resulted in a clear reduction of signs and symptoms of AD (pruritus, sleep disturbance) and improved the quality of life in adults with moderate-to-severe AD.^{63,64} The encouraging results of anti-IL-31RA antibody in moderate-to-severe AD⁵⁵ open up new perspectives not only in AD but also in other pruritic skin diseases. Therefore, these new therapeutic strategies should be integrated in the approach to chronic skin disorders, which are inadequately controlled by conventional therapies.⁶⁵ The use of monoclonal antibodies that target IL-31 and/or its receptor A could change the scenario of pruritic skin diseases. However, more studies are necessary to further examine the effects of IL-31 cascade blockage in different chronic skin diseases and to confirm the efficacy and the safety of these new therapeutic approaches.

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