

Treatment of Atopic Dermatitis: What's New?

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ABSTRACT

Atopic dermatitis is a common and chronic skin disorder among the children and adults. The treatment guideline that was recently accepted in Europe includes dupilumab, a monoclonal antibody, along with the conventional treatment methods. In addition to dupilumab, other monoclonal antibodies have been developed and their efficacies were evaluated with randomized controlled trials. These antibodies are nemolizumab, lebrikizumab, tralokinumab, fezakinumab, ustekinumab and tezepelumab. Small molecule inhibitors are also being developed and evaluated. These are tofacitinib, upadacitinib, baricitinib, PF-04965842, tradipitant and crisaborole. Thus, the chronic and relapsing course of atopic dermatitis is a driving force for the emergence of new drugs.

INTRODUCTION

Atopic dermatitis is a common and chronic skin disorder that has a prevalence of 17% among the school-age children in the US. The disease usually precedes other allergic disorders of the atopic march i.e., asthma and allergic rhinitis [1]. The pathogenesis of the disease includes altered skin microbiome, skin barrier defects and dysregulated innate immune response along with the shift of the adaptive immune system towards the type-2 pathway. One of the risk factors for the disease is the gene mutations leading to the decreased expression of filaggrin [2]. In addition to the genetic predisposition, environmental factors can also lead to decreased filaggrin expression, which is referred to as the "hygiene hypothesis". As a result, atopic dermatitis has an increasing prevalence among the adults along with the children [3]. The presentation of atopic dermatitis can be acute, subacute or chronic. In the acute phase, erythema, vesicles, bullae, weeping and crusting dominate the clinical picture. In the subacute phase, erosion, crusts, papules and scaly plaques are seen. The chronic phase is characterized by scaling, lichenified plaques and post lesional hypo/hyperpigmentation [2]. In the pediatric population, the disease typically manifest itself either with erythematous plaques or lichenification on the cheeks or flexural sites [1]. (Figure 1) shows one of the typical manifestations of the disease in children: desquamated erythematous plaques on the cheeks. In adults linear excoriations, excoriated papules and lichenified plaques either localized or generalized is seen [1]. (Figure 2) shows an adult patient with widespread excoriations due to atopic dermatitis. (Figure 2a,2b,2c). In adult patients with chronic, severe atopic dermatitis, wide-spread lichenified and excoriated papules may be seen as in prurigo nodularis [1].

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Figure 1: Desquamated erythematous plaques on the cheeks of an infant.



Figure 2a: Widespread excoriations due to atopic dermatitis in the abdominal area.



Figure 2b: Widespread excoriations due to atopic dermatitis in the antecubital region.



Figure 2b: Widespread excoriations due to atopic dermatitis in the antecubital region.

PATHOGENESIS

The inflammation of atopic dermatitis directed by the homing and incoming cells of the skin; and the cytokines, chemokines and immunoglobulins produced by these cells. Interleukin (IL) 4 and 13 are two of the most important of these factors with multiple effects on innate and adaptive immune systems. Together with Tumor Necrosis Factor-Alpha (TNF-alpha), IL4 and IL13 induce the keratinocytes to produce Thymic Stromal Lymphopoeitin (TSLP) and increase the activity of T-helper 2 pathway. IL4 and IL13 also decrease the synthesis of filaggrin, involucrin and loricrin which are structural barrier proteins of the skin; thus leading to barrier dysfunction. IL-13, IL-31, IL-17 and IL-22 are other important mediators of this ongoing inflammation of atopic dermatitis. Janus Kinase (JAK) inhibitors, antimicrobial peptides, Phosphodiesterase (PDE)-4, Aryl Hydrocarbon Receptor (AhR) and Transient Receptor Potential Vanilloid Member 1 (TRPV1) are the other members of this inflammatory pathway [4].

CONVENTIONAL TREATMENT

According to the Atopic Dermatitis 2018 treatment guideline accepted in Europe, the baseline therapeutic interventions include avoidance of clinically relevant allergens, application of emollients and bath oils. For mild disease, with a SCORAD (Scoring Atopic Dermatitis) less than 25, class 2 topical corticosteroids, topical calcineurin inhibitors and topical antiseptics are recommended. For patients with recurrent disease and/or SCORAD between 25 and 50, class 2 or 3 topical corticosteroids, topical calcineurin inhibitors (proactive, twice-weekly use), wet-wrap therapy, phototherapy and psychological counselling are recommended. For patients with severe disease, SCORAD greater than 50 and/or persistent dermatitis, systemic immunosuppression with or without hospitalization, is recommended. Cyclosporine, methotrexate, azathioprine and mycophenolate mofetil can be used both in children and adults. On the other hand, oral corticosteroids are only recommended for adults and it should only be used during flares for a short period of time. Dupilumab, which is also a newly emerging therapeutic option for atopic dermatitis, is also included in the guideline, however, it is only recommended for adults with severe disease. It is important to note that many of the systemic drugs are not licensed for atopic dermatitis and are used off-label in many countries [5].

NEW TREATMENT MODALITIES

Biologic agents

The chronic and relapsing course of the disease has led physicians to the search of newer and more effective treatment modalities for atopic dermatitis. The monoclonal antibodies that were previously used for other diseases were tried in the treatment of atopic dermatitis as well; however, none of these were successful in treating the disease [6]. These agents include: omalizumab (anti-IgE), infliximab (anti-TNF), efalizumab and alefacept (anti-T-cell), pitrakinra (anti-IL(interleukin)4/13), mepolizumab (anti-IL5) and rituximab (anti-CD20) [7]. Newer biologic agents are being developed for atopic dermatitis [6]. Currently, only Dupilumab, a monoclonal antibody against IL-4R-alpha, is approved for atopic dermatitis in Europe and US [8].

Dupilumab: Dupilumab is a monoclonal antibody which has an affinity towards the alpha chains of IL-4 and IL-13, both of which have a role in inducing the activation of T-helper 2 cells and production of cytokines [8]. Thus, dupilumab has a double action in the inhibition of inflammatory pathways of atopic dermatitis [9]. In a study performed by Beck et al., compared to the patients treated with placebo, patients treated with dupilumab had a significantly higher reduction in the Eczema Area And Severity Index (EASI) scores, significantly higher near-clearance rate according to the investigator's global assessment scores and a significantly decreased pruritus scores. Furthermore, skin infections were found to be more frequent in the placebo group, whereas nasopharyngitis and headache were more common with dupilumab [10]. Simpson et al., have conducted two independent phase 3 studies, enrolling over a thousand patients, evaluating the efficacy of dupilumab in patients with moderate to severe atopic dermatitis: SOLO 1 and SOLO 2. They have concluded that, dupilumab was more efficacious in clearing atopic dermatitis according to the investigator's global assessment index with a p-value less than 0.001 in both studies; the improvement in EASI score was significantly higher with dupilumab in both studies and dupilumab was more successful in reducing of pruritus, anxiety and depression compared to placebo in both studies. The most frequently encountered side effects of dupilumab were injection site reactions and conjunctivitis [11]. Food and Drug Association (FDA) has approved dupilumab in the treatment of

atopic dermatitis in the year 2017, as a result of these studies [5]. In a meta-analysis about the adverse effects of dupilumab, it was concluded that, dupilumab moderately increases the risk of conjunctivitis and injection site reactions, it slightly increases headache and back pain and has a little effect on increasing the risk of upper respiratory tract infections. On the contrary, dupilumab decreases the risk of exacerbation of atopic dermatitis and superinfection [12].

The recommended dosing regimen for dupilumab is 600 mg injected subcutaneously on day 0 and then 300 mg injected subcutaneously every 2 weeks. As with other biologic agents, immunogenicity is an important concern with the use of dupilumab as well. For the patients who received dupilumab treatment with the regimen mentioned above, 7% have developed anti-drug antibodies in SOLO 1/ SOLO2 and CHRONOS studies, which were conducted for 16 weeks and 52 weeks respectively. Studies concerning the use of dupilumab in children and adolescent atopic dermatitis patients are being conducted as well, which will further expand our scope about this novel drug [13].

Nemolizumab: IL-31 is a cytokine that has a major role in inflammation and pruritus. Nemolizumab targets IL-31 receptors [2]. A phase-two trial for nemolizumab was performed by Ruzicka et al., in [14]. It was concluded that after 12 weeks of treatment with patients receiving nemolizumab every 4 weeks, there was a statistically significant decrease in pruritus, EASI and body surface area affected with atopic dermatitis. The most frequent adverse effects reported due to nemolizumab use were nasopharyngitis, upper respiratory tract infections, exacerbation of atopic dermatitis, peripheral edema and increased creatinine kinase levels [14]. It was further concluded that, nemolizumab was successful in the treatment of moderate-to-severe atopic dermatitis up to 64 weeks. The adverse effects due to nemolizumab were similar to those reported in the previous study [15].

Lebrikizumab and tralokinumab: IL-13 is a cytokine produced by T-helper 2 cells and has a role in allergen sensitization, barrier dysfunction, defects in innate immune system and the inflammation of atopic dermatitis. Lebrikizumab and Tralokinumab are both monoclonal antibodies targeting IL-13 [16]. Simpson et al., evaluated the efficacy and safety of

lebrikizumab with a randomized, placebo controlled phase-two trial incorporating 209 patients. It was concluded that, in patients receiving 125 mg lebrikizumab every 4 weeks, the proportion of those achieving EASI-50 were significantly higher compared to placebo, after 12 weeks of therapy. Furthermore, the adverse effects were similar between two groups [17]. Wollenberg et al., have evaluated the efficacy of tralokinumab with a phase-two study incorporating 204 patients. They have concluded that, 300 mg tralokinumab, every 2 weeks, after 12 weeks of treatment, has led to a significant improvement in the EASI scores and a significantly greater number of patients have achieved clearance according to the investigator's global assessment when compared to placebo. Furthermore, the responses were greater in those patients with higher IL-13 levels. Improvements in SCORAD and Dermatology Quality of Life Index (DLQI) were also significant. The most frequently encountered adverse events were headache and upper respiratory tract infections. Unlike dupilumab, the risk of conjunctivitis was not increased [18].

Fezakinumab: Fezakinumab is a monoclonal antibody against IL-22, which is a cytokine that is responsible for epidermal hyperplasia and the inhibition of skin barrier function [19]. Guttman-Yassky et al., have performed a phase-two trial evaluating the efficacy and safety of fezakinumab in atopic dermatitis patients. The patients received intravenous fezakinumab monotherapy of a loading dose of 600 mg on day 0 followed by 300 mg every 2 weeks for a total of 10 weeks. It was concluded that, compared to placebo, fezakinumab therapy produced a significant decline in SCORAD, the body surface area involving atopic dermatitis and the investigator's global assessment. The most commonly encountered adverse effects were upper respiratory tract infections [20].

Ustekinumab: Ustekinumab is a monoclonal antibody that targets the p-40 subunits of IL-12 and IL-23. It is already licensed for Chron's Disease, plaque psoriasis and psoriatic arthritis. Pan et al., have reviewed 10 studies incorporating a total of 107 patients receiving ustekinumab treatment for atopic dermatitis and have concluded that only 54 percent of the patients have benefited from treatment. Although there were little to no adverse effects, the efficacy of ustekinumab in

treating atopic dermatitis is not significant compared to placebo and further studies should be performed [21].

Tezepelumab: Tezepelumab is a monoclonal antibody targeting thymic stromal lymphopoietin. Simpson et al. conducted a phase-two trial evaluating the efficacy of tezepelumab in adult patients with moderate to severe atopic dermatitis. 113 patients, all applying class 3 topical corticosteroids in adjunct with tezepelumab treatment, were randomized into two groups: 280 mg tezepelumab or placebo was applied subcutaneously every 2 weeks for a total of 16 weeks. At the end of the study, the percentage of patients achieving an EASI-50 score by week 12 was significantly higher in the treatment group than in the placebo group. Furthermore, the decline in SCORAD, investigator's global assessment score, pruritus numerical rating and 5-D itch scales were higher in the treatment group compared to placebo. Additionally, the adverse effects reported were similar in both groups [22].

Small molecules

Tofacitinib: Tofacitinib is a JAK inhibitor that interferes with the signaling of IL-4, IL-5, IL-13, IL-31, IL-33 and thymic stromal lymphopoietin [2]. Bissonette et al., have conducted a phase-two trial assessing the safety and efficacy of 2% topical tofacitinib applied twice daily for 4 weeks, in the treatment of mild-to-moderate atopic dermatitis. They concluded that patients treated with topical tofacitinib experienced a significant reduction in pruritus starting from day 2 and that a significant improvement was observed in EASI, physicians global assessment and the body surface area involved, starting from week 1 of treatment. Most frequently observed adverse effects were infections and infestations; however, no serious adverse effects were observed with topical tofacitinib therapy [23].

Upadacitinib: Similar to Tofacitinib, Upadacitinib is also a JAK inhibitor; however it is specific to JAK-1. A drug company has performed a randomized controlled trial in order to evaluate the efficacy of upadacitinib in the treatment of atopic dermatitis. Patients received either 7.5 or 15 or 30 mg of the drug once daily for 16 weeks. At the end of the treatment, all three doses were significant in improving EASI and investigator's global assessment scores, when compared to placebo. The reduction in pruritus was seen as early as 7 days

and improvement in EASI was seen as early as week 2. The most frequently reported adverse effects were acne and upper respiratory tract infections [2].

Baricitinib: Baricitinib is an orally administered drug that modulates the pro-inflammatory cytokines via the inhibition JAK1 and JAK2. In a phase-two study performed by Guttman-Yassky et al., 124 moderate to severe atopic dermatitis patients received topical corticosteroid therapy for 4 weeks prior to being divided into three random groups: one receiving 2 mg/day baricitinib, others receiving 4 mg/day baricitinib and placebo for a total of 16 weeks. Patients receiving 4 mg/day and 2 mg/day baricitinib therapies had a significant reduction in EASI score as early as week 4, when compared to placebo. Baricitinib was also effective in improving sleep-loss and pruritus. Adverse effects due to the drug were similar to those of placebo, which were headache, nasopharyngitis and increased creatinine kinase levels [24].

PF-04965842: Similar to Upadacitinib, PF-04965842 is also a newly emerging oral JAK-1 inhibitor for the treatment of moderate to severe atopic dermatitis. A phase-two randomized controlled trial is being performed by a drug company currently in order to evaluate the efficacy of the drug in comparison to placebo. Until now, a significant improvement was seen in the patients receiving 200 mg/day after 12 weeks of treatment. Moreover, compared to the placebo group, a significant reduction in EASI scores was seen in patients receiving 100 mg/day and 200 mg/day for 12 weeks. Most frequently encountered adverse events were nausea, diarrhea, upper respiratory tract infections and headache [2].

Tradipitant: Tradipitant is a small molecule that targets the Neurokinin (NK)-1 receptor with the aim of reducing pruritus in atopic dermatitis patients. In a phase-two trial that incorporated 69 patients with moderate to severe atopic dermatitis, receiving either 100 mg/day tradipitant or placebo once daily for 4 weeks, it was shown that tradipitant reduced pruritus significantly; however the reduction in SCORAD and EASI were insignificant when the treatment group is compared to placebo [25].

Crisaborole: Topical crisaborole has been used for atopic dermatitis for a couple of years; however, it was approved for the treatment of mild-to-moderate atopic dermatitis only recently in the US. Crisaborole increases Cyclic Adenosine

Monophosphate (c-AMP) levels via the inhibition of phosphodiesterase-4 enzyme. Increased c-AMP levels, in turn, inhibit the production of inflammatory mediators [6]. Pallor et al have conducted a phase-three trial comparing the efficacy of topical crisaborole in the treatment of mild-to-moderate atopic dermatitis. Patients older than 2 years of age, applied topical crisaborole twice daily to all affected areas for 28 days. The treatment group had a significantly higher percentage of patients achieving clearance by the end of 28 days, compared to placebo. Furthermore, pruritus resolved earlier in the treatment group. The adverse effects related to crisaborole were insignificant [26].

Other modalities

There are several newly emerging modalities for which the clinical efficacy and safety trials are going on. JTE-052/LEO124249 is a JAK1, JAK2, JAK 3 and Tyrosine Kinase 2 (TYK2) inhibitor which is applied topically. DRM-02, Roflumilast, E6005/RVT-501 and Leo-29102 are topically applied PDE4 inhibitors. PAC-14028 is a TRPV1 inhibitor that is applied topically as well. CT327 (Creabilis) is a topically applied newly emerging atopic dermatitis drug as well, it is a tropomyosin receptor kinase A inhibitor. Q301 is a topically applied 5-lipoxygenase inhibitor, Omiganan pentahydrochloride is a synthetic cationic peptide with wide-spectrum antimicrobial activity and Tapinarof (GSK2894512) is an Aryl Hydrocarbon Receptor (AhR) agonist which induces filaggrin expression. All of these drugs are under further investigation. As the pathogenesis of atopic dermatitis is understood better, many new drugs will be emerging as well [4].

CONCLUSION

Atopic dermatitis is a chronic inflammatory skin disease that affects the quality of life of the patients tremendously. According to the "hygiene hypothesis", there was a shift in the adaptive immune system towards the T-helper 2 pathway, leading to the increased prevalence of atopic dermatitis, especially among adults. The chronic and relapsing course of moderate-to-severe atopic dermatitis is not only a treatment challenge but also a driving force for the emergence of new drugs.

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