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Atopic dermatitis – Recent advances in the management

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ABSTRACT

Atopic dermatitis (AD) is a chronic skin disorder resulting from complex interactions between skin barrier defects and a dysregulated immune system, marked by activation of multiple T cell subsets at different stages of the disease. Until recently, the management of AD rested mainly on the judicious use of emollients, topical steroids, and topical calcineurin inhibitors in the majority of patients and systemic immunosuppressants were advocated in severely diseased. However, in the last few years, new therapeutic strategies were designed and developed to target the various steps in the chain of molecular events that lead to the AD phenotype. This review article will focus on the recent advances in the management of AD.

Keywords: Atopic dermatitis, Recent advances, Management, T cells, Janus kinase inhibitors

INTRODUCTION

Atopic dermatitis (AD) is a chronic skin disorder resulting from complex interactions between skin barrier defects and a dysregulated immune system, marked by activation of multiple T cell subsets at different stages of the disease. Until recently, the management of AD rested mainly on the judicious use of emollients, topical steroids, and topical calcineurin inhibitors in the majority of patients and systemic immunosuppressants were advocated in severely diseased. However, in the last few years, new therapeutic strategies were designed and developed to target the various steps in the chain of molecular events that lead to the AD phenotype. They have been tested in cohorts of AD patients and found to be very effective in controlling the disease process. In this paper, we discuss some of the new therapeutic options [Table 1] that are likely to play a major role in the future management of AD.

INTERLEUKIN (IL)-4 AND IL-13 INHIBITORS

Dupilumab

Dupilumab is a monoclonal antibody that targets IL-4 receptor alpha subunit, eventually blocking the signaling of IL-4 and IL-13, the two cytokines which a play a key role in AD. It is fully human, IgG4-based monoclonal antibody produced by application of VelociGene technology. Earlier studies have shown that inhibiting the signaling of both the two key cytokines IL-4 and IL-13 was a key requirement to block Type 2 inflammation in AD and asthma.[1,2] The efficacy of dupilumab in treating AD is supported by robust clinical data. Pruritus is significantly reduced by week 4 and improvement in investigator global assessment (IGA) scale was noticed by 12 weeks.[3,4] The reduction in clinical severity was sustained throughout the study period and associated with a high

Table 1: New therapeutic options in the future management of atopic dermatitis

No	Name	Target	Route of administration
1	Dupilumab	IL-4 alpha receptor	Subcutaneous
2	Tralokinumab	1L-13	Subcutaneous
3	Lebrikizumab	IL-13	Subcutaneous
4	Nemolizumab	IL-31 receptor A	Subcutaneous
5	Fezakinumab	IL-22	Subcutaneous
6	Abrocitinib	JAK 1	Oral
7	Upadacitinib	JAK 1	Oral
8	Baricitinib	JAK 1 and 2	Oral
9	Tofacitinib	JAK 1 and 3	Oral, topical (ointment)
10	Ruxolitinib	JAK 1 and 2	Topical (cream)
11	Deglocitinib	JAK 1, 2, 3 and TYK 2	Topical (ointment)
12	Crisaborole	PDE 4	Topical (ointment)
13	Tapinarof	Aryl hydrocarbon receptor	Topical(cream)

IL: Interleukin, JAK: Janus kinase, PDE: Phosphodiesterase, TYK: Tyrosine kinase

degree of patient satisfaction.[5,6] A significant decrease in the incidence of skin infections in users of dupilumab was noted in the drug trials.[7] This has been attributed to the positive effects of dupilumab on epidermal barrier functioning. A recent meta analysis concluded that dupilumab is more efficacious in the initial 4 months of therapy in controlling adult AD than methotrexate or azathioprine and is comparable to cyclosporine given at a higher dose of more than 3 mg/kg/day.[8] However, an improvement in EASI (eczema area and severity index) score of over 90% was observed in <40% of AD patients treated with dupilumab.[9]

Known adverse events include head and neck dermatitis, psoriasiform dermatitis, and conjunctivitis (30%). Increased incidence of conjunctivitis was not observed in asthmatics and patients suffering from chronic sinusitis with nasal polyposis who were treated with dupilumab.[10] A immunophenotyping study of AD performed on Asian patients revealed the larger role played by Th17 cells in the immunopathogenesis of Asian AD, showing close resemblance to psoriasis. Further studies on large number of patients would show whether psoriasiform skin changes are replicated in Indian patients treated with dupilumab for AD.[11]

Advantages of dupilumab include a lack of need for close laboratory monitoring, and an established long-term efficacy for over 52 weeks in conventional doses and for up to 148 weeks in adults who were put on at 300 mg weekly dose.[5] Notably, dupilumab does not activate latent tuberculosis. Indeed, blocking IL-4 may have a protective effect against tuberculosis.[12] In 2016, the Food and Drug Administration (FDA) granted dupilumab "breakthrough therapy" designation for the treatment of severe AD in children 6 months to 11 years of age and later, in March 2019, FDA approved the drug for treatment of adolescents.[13] Infants diagnosed with AD have shown poor response to vaccination. However, immune responses to vaccination with tetanus toxoid and meningococcal serogroup C were not affected by dupilumab usage in adult patients with AD.[14]

Tralokinumab

Tralokinumab targets IL-13, a cytokine which is preferentially expressed in keratinocytes. Upregulation of IL-13 has been consistently documented in the lesional skin of AD patients. A phase 2a trial showed promising results in adults aged 12 years and above. Tralokinumab decreased the pruritus score within a week and the improvement in the disease burden was sustained till the end of the study period.[15]

Lebrikizumab

Lebrikizumab is a more selective inhibitor of IL-13 and the results from recently published trials are convincing.[16]

TREATMENT OF AD: BEYOND TARGETING OF IL-4/IL-13

Besides IL-4/IL-13 blockade, other means to inhibit Th2 axis such as Janus kinase (JAK) inhibition and interference with IL-31 activity have been recently explored in recent studies in AD patients. IL-31 is produced by Th2 cells and is a key driver of pruritus in AD through action on sensory neurons and keratinocytes. When tested in healthy individuals and AD patients, IL-31, induced itch after a mean delay of 143 minutes. Nemolizumab, an anti-IL-31 receptor A antibody showed demonstrable reduction in the severity of pruritus in two recently concluded trials.[17,18] Reduction in pruritus was evident within the 1st week of commencing therapy.[18] The efficacy was not dose dependent in the study reported by Ruzicka *et al*.[17] Exacerbation of AD necessitated rescue therapy in 27.8% of patients in the group receiving 0.5 mg/kg, which achieved the best results. Nasopharyngitis, upper respiratory tract infection, peripheral edema, exacerbation of preexisting asthma, and increased creatine kinase levels were the other common adverse events associated with nemolizumab.[17] The safety profile and tolerability of nemolizumab were deemed appropriate on the basis of a subsequent study done for a longer period of 64 weeks.[19]

Fezakinumab, a IL-22 monoclonal antibody, showed a favorable safety profile in a recently conducted phase 2a trial on AD patients. The clinical improvement was consistent throughout the study period. Superior results were obtained in patients who suffered from severe AD.[20]

Omalizumab worked at a dosage of 1200 mg/month in a study done on AD patients.[21] Earlier studies using omalizumab did not show satisfactory response.[2] IgE may not be a desirable target for treating AD. The reduction in severity of AD obtained using dupilumab and fezakinumab were independent of the levels of IgE.

JAK INHIBITORS; ROLE IN THE MANAGEMENT OF AD

JAK inhibitors can be administered by mouth in comparison to biologicals which are administered parenterally. Maintenance of cold chain from manufacturer to the recipient is an absolute requirement for retaining the efficacy of monoclonal antibodies such as dupilumab and others which were discussed in the previous sections. This could be a disadvantage in resource poor locations.

TOFACITINIB

The impact of tofacitinib goes beyond Th2 cells and it also suppresses the generation of pathogenic Th17 cells and the activity of the itch cytokine IL-31. It also modulates IL-6 and IL-23 signaling. Oral tofacitinib was tested in patients older than 18 years with AD. An improvement was noticed from week 4 onward. SCORAD (SCORing atopic dermatitis) index was reduced by 58% at week 14. This was accompanied by a significant decrease in pruritus score by 69.9%.[22]

BARICITINIB

Baricitinib is 100 times more potent in inhibiting the activity of JAK1 and JAK2 than JAK3. This blocks the generation of IL-23 which sustains Th17 axis and interferon γ, the chief cytokine produced by Th1 cells. Baricitinib may have more inhibitory effect on eosinophils through blockade of JAK2. The broad ranging activity of baricitinib was effective in relieving pruritus, which was noticeable within 2 days of use in adult AD patients. The improvement was dose dependent with 4 mg of baricitinib showing superior efficacy when compared to 2 mg in relieving AD.[23] The improvement was sustained till the end of the study period of 16 weeks. However, moderate or low potency topical steroids were applied by the participants and may be a contributing factor. Acne, nasopharyngitis, and folliculitis were noted in a few patients. However, the incidence of adverse events did not increase in patients who were on long-term therapy with baricitinib for rheumatoid arthritis.[24]

Selective JAK1 inhibitors such as abrocitinib and upadacitinib have been tried in recently conducted trials done on adult AD patients.[25] Abrocitinib is equivalent to dupilumab in reducing the severity of AD, besides providing immediate itch relief.[26] Up to 44% of patients achieved significant improvement reaching a IGA scale 0–1 with abrocitinib. Itch was relieved within 24 hours. 200 mg of abrocitinib provided itch relief in a higher proportion of patients than dupilumab and the improvement from baseline disease activity was satisfactory.[26] Thrombocytopenia is a notable adverse event due to impact on both megakaryopoiesis and thrombopoiesis.[26] However, thromboembolic events may be less common than in users of other JAK inhibitors such as ruxolitinib, tofacitinib, and baricitinib. Upadacitinib reduced the levels of thymus and activation regulated chemokine (TARC) and IL-22 levels within 2 weeks of initiation of therapy in AD patients, as reported in a recent publication.[27] Acne and worsening of AD were noticed in a section of participants (>10%).[27]

TOPICAL JAK INHIBITORS IN AD

JAK inhibitors are used in topical formulations. Smaller size of the molecule is an advantage, allowing penetration through the epidermal barrier. Deglocitinib formulated in an ointment base was studied in Japanese patients.[28] Deglocitinib is an inhibitor of all the 4 JAKS. Japanese children aged 2–15 years, who were on a 4-week treatment, did not develop irritation or atrophic changes. Patient reported pruritus score declined steadily during the study period. The efficacy was dose dependent with 0.5% ointment twice daily showing superior effect compared to 0.25%.The incidence of impetigo and folliculitis was comparable to vehicle group.

Significant reduction in pruritus was observed as early as day 1 after the application of 2% tofacitinib ointment twice daily in adults.[29] About 73% of the tofacitinib treated versus 22% in the vehicle group showed reduction in the severity of AD as defined by the physician global assessment scale.

Itch relief was obtained within 36 hours of twice daily application of ruxolitinib 1.5% as a cream in adults older than 18 years and the effect remained till the end of the study period of 12 weeks.[30] It was superior to triamcinolone in reducing the severity of AD and was well tolerated over the flexural skin.

PHOSPHODIESTERASE INHIBITORS–ROLE IN AD MANAGEMENT

Crisaborole

Crisaborole is a low molecular weight molecule which permeates the skin and is well tolerated in adults and children with AD.[31] It is an inhibitor of phosphodiesterase (PDE) 4, a cyclic AMP degrading enzyme expressed in monocytes, lymphocytes, endothelial cells, and smooth muscle cells. Crisaborole may have a broader range of activity than topical calcineurin inhibitors. The systemic absorption is negligible and the absorbed drug is quickly transformed to inactive metabolites.[32] Skin atrophy was not seen during the study

period of 4 weeks. Improvement in disease severity was seen as early as day 8 of therapy with crisaborole. Application site pain following crisaborole was uncommon (4.4%). However, in a subsequent report, application site pain developed in 5 out of 10 adults who applied crisaborole over face.[33]

Apremilast

Apremilast is an oral PDE inhibitor which failed to show a clinically meaningful response in a recently conducted phase 2 trial in AD patients, when used at a dose of 30 mg twice a day.[34] Apremilast may be more effective in chronic AD where Th1 and Th17 cells play a significant role. Future trials done on larger number of patients would throw more light on the place of apremilast in the management of AD.

Tapinarof

Tapinorof is an aryl hydrocarbon receptor modulator. It also has antioxidant activity. In a study done on patients aged 12 years and above, improvement was seen in 52% of patients using 1% of tapinorof cream twice a day in comparison to 24% in the group applying vehicle alone.[35] A higher incidence of minor adverse events was noticed in the tapinarof group.

CONCLUSION

There have been noteworthy changes in the treatment landscape of AD in the recent years. Dupilumab has been approved by the US FDA for use in children down to 6 years of age. Topical therapeutic options that have shown satisfactory results in children include deglocitinib, a Pan JAK inhibitor and crisaborole, a PDE 4 inhibitor. Oral JAK inhibitors have shown promising results in studies done on adult AD and represent valuable additions to the treatment options for moderate to severe AD in the near future.

Declaration of patient consent

Not required as there are no patients in this article.

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Conflicts of interest

There are no conflicts of interest.

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