

## UPDATE OF TREATMENT OPTIONS IN ATOPIC DERMATITIS: A NARRATIVE REVIEW

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### **Abstract**

Atopic dermatitis (AD) is a chronic, inflammatory skin disease characterized by pruritus, inflammatory skin lesions. It causes severe impairment of quality of life along with the impairment of physical well-being of the patient. The management of AD has been always challenging due to its chronic and recurrent course with periods of remission. As the medical science progresses many modalities of treatment have been introduced, beginning from bathing methodology, topical and systemic. This study tries to give a narrative review of the different management options, which clinical dermatologists can use for the management of atopic dermatitis. These options need to be evaluated and matched according to the age, sex and severity of atopic dermatitis.

**Key Words -** Atopic dermatitis, Treatment, Pruritus

### **Introduction**

Atopic dermatitis is a type of endogenous eczema. It is a common chronic and pruritic skin condition characterised multiple remission and relapse during its course. Itch or pruritus is the hallmark of atopic dermatitis. It has been estimated that around 10-20% of children and 1-3% of adults suffer from this disease.<sup>1</sup> It may be associated with other diseases like food allergy, bronchial asthma and allergic rhinitis.<sup>2</sup> Genetic and environmental factors resulting in, epidermal barrier dysfunction, immune dysregulation and alteration of the cutaneous microflora has been found as the main factors causing atopic dermatitis.<sup>3-5</sup> Atopic dermatitis due to its chronic course it is associated with psychological stress not only in patients but also in the parents, and resulting in impaired Quality of Life (QoL).<sup>6</sup> Many modalities of treatment are available for the treatment of atopic dermatitis but the treatment of atopic dermatitis is always challenging. This review tries to accumulate the various modalities available for the management of atopic dermatitis.

### **Management of atopic dermatitis**

1. Education and counselling of patients, parents and guardians.
2. Proper bathing.
3. Appropriate use of moisturizers.
4. Use of immunomodulators: phototherapy, topical and systemic medications.
5. Other miscellaneous interventions.
6. Management of coexisting allergies in a patient with atopic diathesis.<sup>7,8</sup>

### **Baths**

The patient should be advised to have a bath of around five to 10 minutes. It should not be prolonged one as it can remove the skin surface lipids. The water should be just warm not hot.<sup>9</sup> For the bath, the patient should be asked to use a cleanser that is

fragrance free and the cleanser should be at neutral to low PH. Syndet bars are preferred than soaps or combars. The syndet bars or the synthetic detergent bars contain a synthetic surfactant, which is soap free. The synthetic surfactants may consist of fatty acid isothionates, sulfosuccinic acid esters as their principal ingredient. They have the capacity to preserve the skin surface lipids, which is important for maintaining the barrier function of the skin.<sup>10</sup>

**Bleach Bath:** The bleach bath has the property of prevention of infection and inflammatory cascade, which is an aggravating factor for atopic dermatitis. It is usually advised to have a bleach bath for 2-3 times a week. For the preparation of bleach bath, around 118 ml of household bleach whose active ingredient is NaOCl (Sodium Hypochlorite) is added to 151 litres of water. The patient's body or the affected areas are soaked for around ten minutes and then using a dry towel the body is patted dry. Immediately, the appropriate moisturiser needs to be applied.<sup>11,12</sup>

**Oatmeal Bath:** The oatmeal bath can soothe the skin, maintain the barrier function and reduce the inflammation. For an oatmeal bath one cup, which is 236ml, of finely powdered colloidal oatmeal is slowly added to the bathtub slowly so that the colloidal oatmeal dissolves evenly. The water of the bathtub should be just warm. The body should be soaked in the bathtub for 10-15 minutes and then dried by just patting.<sup>13,14</sup>

Vigorous rubbing after a bath should be avoided as it can irritate the skin. After the bath the soak and smear, technique can be used to apply the anti-inflammatory medications and/or moisturizers. In this technique the moisturizer is applied liberally shortly after the bath, usually within three minutes. The topical anti-inflammatory agents if indicated should be applied before the application of the moisturizer.<sup>15</sup>

### **Moisturizers**

The cornerstone and agent of choice for management of atopic dermatitis are moisturizers. Moisturizers are available over the counters as well. Before choosing appropriate moisturizer or

before prescribing one, certain characteristics need to be taken care of. An emollient for a patient of atopic dermatitis should be free of fragrance, preservatives or other additives, which can act as triggering factor for exacerbation of atopic dermatitis. It should have an occlusive property by which it blocks trans-epidermal water loss, humectant property by which it binds water molecules and emollient property by which it maintains skin barrier function. Certain additives in moisturizers contain substances like parabens, fragrances, tocopherol or other biological additives, which can trigger the inflammatory process and aggravate the disease. The emollient can be topped up with certain additives like aloe vera, coconut oil, ceramide, natural moisturizing factor sand anti-microbial peptides for their better efficacy. Moisturizing creams are preferred over lotions in atopic dermatitis due to their higher proportion of oil in creams than lotions.<sup>16-19</sup> The moisturizers should be applied using the soak and smear technique for better outcome.<sup>15</sup>

### **IMMUNOMODULATORY THERAPY:**

#### **Phototherapy**

Natural sunlight is considered useful for atopic patient. However, sunlight and high temperature can induce pruritus start and itch scratch cycle and can be harmful to patient. UV-B, or UB-A or combined UV-AB phototherapy can be beneficial. The UV rays act by inducing apoptosis of the T-Cells, reduction of Th2 cytokines and reduction of the antigen-presenting cell in the skin. It also reduced microbial colonisation in the skin (like *Staphylococcus aureus*).<sup>20-23</sup>

#### **Topical anti-inflammatory agents**

**Topical Corticosteroids:** Topical corticosteroids is FDA approved for management of atopic eczema and is the first line pharmacologic therapy. The corticosteroids are immunosuppressive, anti-inflammatory, ant proliferative and vasoconstrictive. It also retards the T cell, macrophage and dendritic cell proliferation. Nevertheless, the corticosteroids always remains to be a double-edged sword and proper potency and formulation should be prescribed by the clinician and the adverse effects should be kept in mind. The common side effects consist of skin atrophy, striae, steroid acne, perioral dermatitis, purpura, hypertrichosis, and hypopigmentation. Topical corticosteroids under occlusion can lead to gram-negative folliculitis. Systemic absorption can lead to HPA suppression.<sup>15,24,25</sup>

**Topical calcineurin inhibitors:** Topical calcineurin inhibitors are FDA approved for the management of atopic dermatitis. Pimecrolimus 1% cream can be used for the management of mild to moderate disease and tacrolimus 0.03% to 0.1% can be used for moderate to severe disease. They work by supressing the T cell activation, reducing the secretion of the Th2 profile cytokines and by inhibiting release of other proinflammatory mediators. They reduce the mast cell and dendritic cell activity as well. The topical calcineurin inhibitors are particularly useful for skin of face and intertriginous area, which have higher chances of atrophy after prolonged application of topical corticosteroids. The side of topical calcineurin inhibitors include local stinging and burning sensation.<sup>26-28</sup>

**Crisaborole:** Crisaborole is a phosphodiesterase 4 inhibitor which is FDA approved for the management of mild to moderate atopic dermatitis. Phosphodiesterase 4 leads to degradation of cyclic AMP and results in increased production of pro-

inflammatory cytokines.<sup>29-31</sup>

Topical antimicrobials and antihistamines are other topical agents, which can be used for the management of atopic dermatitis. Topical antibiotics like fusidic acid 2%, or mupirocin 2% might be required where secondary infection has taken place and for the staphylococcal carrier sites, nasal or extra nasal.<sup>32,33</sup> Topical antihistamines like doxepin can be used for itch relief.<sup>34,35</sup>

#### **Systemic anti-inflammatory agents**

The American Academy of Dermatology (AAD) has laid down certain guidelines for the use of systemic immunomodulatory therapy for a patient of atopic dermatitis. According to AAD, systemic immunomodulatory therapy in a case of atopic dermatitis is given for patients in whom optimised topical regimens do not adequately control signs and symptoms of disease and for the patients whose medical, physical and/or psychological states are greatly affected by their skin disease.<sup>36</sup>

The systemic anti-inflammatory agents for management of atopic dermatitis include:

**Corticosteroids:** Corticosteroid has multiple mechanism of action leading to final immunosuppression. It leads to NFkB and AP-1 transcription factor inhibition. It also causes apoptosis of lymphocytes and eosinophils. Corticosteroids act on the arachidonic acid pathway by phospholipase A2 and cyclooxygenase inhibition. The resultant effect is reduced activity of inflammatory cells and inhibition of proinflammatory cytokines. The corticosteroids also have effects on the dermal vasculature. They inhibit angiogenesis, causes vasoconstriction and reduced vascular smooth muscle response to histamine and bradykinin.<sup>37,38</sup>

The dose of corticosteroid in atopic dermatitis is subjective and depends on clinicians' assessment of the patient. The important side effects of systemic corticosteroids include reactivation of tuberculosis and other infection, impaired wound healing, gastritis and gastric ulcer, electrolyte imbalance, fluid retention and hypertension, iatrogenic diabetes, osteoporosis, myopathy, glaucoma, menstrual irregularities, Cushing syndrome, suppression of HPA axis and Addisonian crisis, even psychosis in rare cases. While prescribing a systemic steroid to a child it should be kept in mind that steroid causes growth retardation. While the patient is on systemic corticosteroid therapy proper monitoring needs to be done including weight and growth chart monitoring, blood counts, infection screening, serum electrolyte levels, blood glucose levels, serum triglyceride levels, cardiac monitoring, bone x-rays, routine ophthalmologic examination and others. After a long course of corticosteroid therapy, serum cortisol level should be checked ideally before steroid withdrawal.<sup>39,40</sup>

**Alitretinoin:** Alitretinoin or 9-cis retinoic acid is a non-aromatic retinoid. Its special characteristic is that it binds to all the retinoic acid receptors and retinoid X receptors. Upon binding with RAR and RXR it causes reduction in cytokines and chemokines which causes inflammation and mediate apoptotic activity and resulting in antiproliferative effect. Although very less reporting has been done regarding the use of alitretinoin for atopic dermatitis, it can be used in adult with atopic dermatitis at a dose of 30 mg per day. The common side effect include headache, dyslipidaemia, photosensitivity and teratogenicity. It is pregnancy category X drug. If alitretinoin is planned in a case of atopic dermatitis then preliminary investigations must be done

like blood counts, liver function tests, fasting lipid profile, renal function tests and most importantly pregnancy test in a female of reproductive age group.<sup>41-43</sup>

**Azathioprine:** Azathioprine is an immunosuppressant and immunomodulatory substance. After administration of azathioprine it is rapidly converted to 6-mercaptopurine. The active metabolites of azathioprine, 6-thioguanine monophosphate and other 6-thioguanine metabolites are structurally similar to the endogenous purines. They get incorporated into the DNA and RNA and inhibit purine metabolism and cell replication. As a result, they also effect the T cell and B cell and antigen presenting cell function. The empirical dose of azathioprine is 2-3 mg/kg daily but the dose may be needed to adjust according to the thiopurine methyltransferase levels. Thiopurine methyltransferase (TPMT) converts 6-mercaptopurine to inactive metabolites. In case of reduced TPMT levels there can be azathioprine toxicity resulting in myelosuppression. Azathioprine is pregnancy category D drug. The important side effects of azathioprine include leucopenia, opportunistic infections, reactivation of latent infections and occasionally lymphoma on long-term usage. Before starting a patient of atopic dermatitis on azathioprine proper risk benefit ratio should be discussed. TPMT levels, pregnancy test, routine blood count, serum biochemistry tests and screening of latent infection should be done.<sup>44-50</sup>

**Cyclosporine:** This immunosuppressant and immunomodulatory substance was originally isolated from the fungus *Tolyphocladium inflatum*. Cyclosporine causes inhibition of the intracellular enzyme calcineurin. As a result, it leads to reduction in pro-inflammatory factors and reduces the langerhans cell function. It leads to suppression of cellular and humoral immunity, mainly T cell function. Cyclosporine A (CsA) is not cytotoxic, does not suppress bone marrow, and is not teratogenic. Cyclosporine is available as two formulations, the original sandimmune and the neoral form. The neoral formulation is more absorbed and more bioavailable. The dermatologic dosage of cyclosporine is usually 2.5-5 mg per kilograms of body weight per day. It has the propensity to cause renal dysfunction, hypertension and dyslipidaemia. Other side effects of cyclosporine include tremors, headache, GI intolerance, electrolyte abnormalities and even hypertrichosis and hyperplasia of gums. Cyclosporine is contraindicated in extremes of ages, usually in less than 18 years and more than 65 years of age. It is pregnancy category C drug. Before starting a patient on cyclosporine pre-existing renal function, hypertension, malignancy, presence of any active infection should be screened for. A patient on cyclosporine needs to be regularly monitored for alteration in blood pressure and serum creatinine levels. Other relevant investigations like routine blood counts and blood biochemistry tests should always be done at regular intervals and monitored. Intake of grape juice is contraindicated with cyclosporine as it can cause elevation of cyclosporine levels in blood.<sup>5,50-52</sup>

**Methotrexate:** Methotrexate also known as amethopterin causes inhibition of dihydrofolic acid reductase resulting interference with DNA synthesis, repair, and cellular replication. Methotrexate is specific for S phase of cell cycle. It can be administered orally, intramuscularly or intravenously. The dose and route of administration is subjective to the severity of atopic dermatitis and needs evaluation by the treating doctor. Before

administration of methotrexate baseline evaluation for immunosuppressants needs to be done with special emphasis on blood counts and liver status. Since methotrexate is a pregnancy category X drug, pregnancy must be ruled out before starting a female of reproductive age group on methotrexate. The tests needs to be repeated at regular intervals for proper monitoring. The important adverse effects of methotrexate include hepatotoxicity like liver fibrosis and cirrhosis, pancytopenia, pneumonitis, pulmonary fibrosis a gastrointestinal upset and teratogenicity. At high doses, methotrexate can cause nephrotoxicity and at long-term usage, lymphoma can occur. Methotrexate overdose can cause toxicity which is manifested as mucositis, stomatitis, oesophagitis, acute renal failure, pancytopenia, neurological dysfunction and diarrhoea. Leucovorin glucarpidase and thymidine are the antidotes, which can be used as an antidote for methotrexate toxicity.<sup>53-57</sup>

**Mycophenolic acid:** Mycophenolic acid (MPA) was originally isolated as a fermentation product of *Penicillium stoloniferum* in 1986 is a class of immunosuppressant. MMA inhibits the de novo pathway of purine biosynthesis, the only mechanism of purine biosynthesis that exists in lymphocytes. It also causes reduced recruitment of pro inflammatory cytokines, reduced expression of adhesion molecules and inhibits ant presenting cells and B cells. The adult dose of MPA for atopic dermatitis varies from 100 to 200 mg per day. MPA is notorious to cause hyperglycemia, hypercholesterolemia, electrolyte imbalance, gastrointestinal complaints, haematological abnormalities, pulmonary toxicities and occasionally flu like syndrome. Before starting MPA baseline investigations must be done to avoid the side effects. MPA has been categorised as pregnancy category D drug.<sup>58-60</sup>

**Apremilast:** Apremilast is a small molecule, which exerts its mechanism by inhibiting phosphodiesterase-4, and resultant increase of cyclic AMP levels of pro-inflammatory cytokines such as tumour necrosis factor- $\alpha$ , interleukin-23 and Interleukin-12. For adults with atopic dermatitis the dose is 20-30 mg twice daily. Apremilast is comparatively safer drug when compared to other immunosuppressive agents. It is a pregnancy C category drug. The most important side effects include diarrhoea and nausea, which may warrant withdrawal of drug. It is advisable to start with 10 mg once daily dose and gradually increasing the dose to the upper limit.<sup>61-63</sup>

**Dupilumab:** Dupilumab is a monoclonal antibody, which got FDA approval for moderate to severe atopic dermatitis in 2017. Dupilumab is fully human-derived monoclonal antibody. Dupilumab binds to the alpha subunit of IL-4 Receptor which is common between IL-4 and IL-13. IL-4 and IL-13 induces differentiation of naïve T cells to Th2 cell line, which is the cornerstone of pathogenesis of atopic dermatitis. Dupilumab is administered subcutaneously. It is available in the market as 200 mg/1.14 ml syringe and 300mg/2ml syringe. The dose of atopic dermatitis is 600mg SC initially followed by 300 mg SC every other week. Dupilumab can cause ocular side effects like conjunctivitis, blepharitis dry eye and keratitis. Injection site reaction and immunosuppression are other side effects. Proper screening should be done before starting Dupilumab as done with every biologics.<sup>64-68</sup>

Other non-immunomodulatory systemic agents for the management of atopic dermatitis include antimicrobials,

antihistamines and oral Vitamin D3.

**Systemic antimicrobials:** The use of short course of antibiotics can suppress the Staphylococcal colonization. It is also indicated in a case of a flare of a case of atopic dermatitis.<sup>69,70</sup>

Systemic antihistamines: Antihistamines control pruritus and hence break the itch scratch cycle. It induces sedation and sleep as well.<sup>71,72</sup>

**Systemic Vitamin D:** Vitamin D has immunomodulatory effects both in the innate and adaptive immune systems, and there is increasing data showing its relevance in inflammatory processes such as AD. In combination with standard therapy, vitamin D is sufficient to achieve a reduction in severity of AD.<sup>73-76</sup>

## OTHER THERAPIES

They include interferon gamma which suppresses and downregulates Th2 and IgE function, immunotherapy with aeroallergen, passing of psoralen treated WBCs through extracorporeal UV-A light system and Chinese herbal medications.<sup>77-81</sup>

## MANAGEMENT OF COEXISTING ALLERGIES

Around 20-30% of atopic dermatitis is associated with food hypersensitivity and it forms a component of atopic march. Eggs, milk, peanuts, soy, wheat and fish cause around 85-90% of food allergy. Although they mostly cause immediate hypersensitivity, they have the propensity to cause acute flare of atopic dermatitis and such components might need exclusion from diet. Skin prick test can help in finding the agent of exclusion.<sup>82-84</sup> Dust mites, pollen grains, animal dander can cause aeroallergen allergy resulting in AD exacerbation. Use of vacuum cleaners, avoidance of furry toys and pets can avoid aeroallergen reactivity.<sup>85-88</sup> Components of topical medications and skin care products can cause an aggravation of AD.<sup>89</sup> Proper patch tests can be done to find the offending agent.<sup>90-92</sup>

## Conclusion

Atopic dermatitis has a chronic course and causes a significant distress to the patients and parents in all aspects. Many modalities of treatment and management are available for controlling the acute phase and prevention of exacerbation of atopic dermatitis. Appropriate methods should be selected alone or in combination assessing the status of the patient and calculating the risk and benefits of each modality of management.

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