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A REVIEW OF MANAGEMENT OF ATOPIC DERMATITIS

***Dr. Babitha M., Radhika B.[1], Jincy Mary S. O.[2] and Reshma V. H.[3]**

*Assisstant Professor, Department of Pharmacy Practice, Sree Krishna College of Pharmacy and Research Centre.
[1,2,3]Pharm D Students, Sreekrishna College of Pharmacy and Research Centre.

***Corresponding Author: Dr. Babitha M.**

Assisstant Professor, Department of Pharmacy Practice, SreeKrishna College of Pharmacy and Research Centre.

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ABSTRACT

Atopic dermatitis (AD) is a chronic, relapsing skin disease characterized by itching, redness, edema, papulovesicles, scaling and dry lichenified skin which affects up to 20% of children and 1-3% of adult population. The main treatment regimen of atopic dermatitis include topical corticosteroids (betamethasone valerate), calcineurin inhibitors (tacrolimus, pimecrolimus), phototherapy and immunosuppressives (ciclosporin A, mycophenolate mofetil). Topical corticosteroids were considered as the first line agents. Calcineurin inhibitors were used in corticosteroid tolerated patients. New topical therapies like Phosphodiesterase inhibitors, Janus Associated Kinase-Signal Transducer and Activator of Transcription inhibitors and systemic therapies with Dupilumab, Lebrikizumab/Tralokinumab, Apremilast were also approved for the treatment of AD.

KEYWORDS: Atopic dermatitis (AD), Topical corticosteroids (TCS), Topical calcineurin inhibitors, Immunosuppressives.

INTRODUCTION

Atopic dermatitis (AD) is a chronic, relapsing disease predominantly affecting infants, children and adolescents aged ≤ 16 years.[1] It is characterized by itching, redness, edema, papulovesicles in the acute stage; edema and scaling in the subacute stage; and dry lichenified skin in the chronic stage. AD is one of the most common skin disease, which affects up to 20% of children and 1-3% of adults in most countries of the world.[2] The recurrent eczematous lesions with age-specific morphology and distribution usually occur for the first time in infancy or early childhood and may persist throughout life in up to 60% of the cases of moderate or severe childhood eczema.[8] The prevalence of atopic dermatitis is rising in many developing countries. Atopic dermatitis is the first step in the development of other allergic diseases such as rhinitis and/or asthma.

Atopic dermatitis is normally accompanied by the cutaneous physiological dysfunction of drug and barrier-disrupted skin due to abnormalities of the epidermic especially the horny cell layers. The corticosteroids and tacrolimus ointments are the mainstay of treatment for inflammation. AD can be managed by avoidance of triggering factors and treatment with corticosteroids. Emollients are considered as the first line agent in the management of inflammation. In moderate-to-severe AD, potent topical corticosteroids (TCS), calcineurin inhibitors, phototherapy and conventional immunosuppressive medications (eg, cyclosporine) are often required. However, efficacy of topical therapies can be limited, and their frequent use is cumbersome and carries the risk for side effects.[3]

Topical corticosteroids

Topical steroids are currently the main stay of treatment for AD. Initial therapy consist of hydrocortisone and mild strength steroid ointment like triamcinolone or betamethasone valerate. Several treatment regimens with corticosteroids are used. Options include intermittent use of corticosteroids or initial therapy with a highly potent corticosteroid followed by a time-dependent dose reduction or change to a less potent preparation.[4,5] Methylprednisolone aceponate (MPA) is a corticosteroid with strong vasoconstrictive and potent glucocorticoid receptor-binding properties and have rapid metabolic clearance. It can be applied once daily to the affected skin, topical MPA is rapidly effective and safe in the treatment of acute, moderate and severe atopic dermatitis. Lower potency corticosterods may be sufficient for the treatment in younger children.

Calcineurin inhibitors

Topical calcineurin inhibitors (TCI) are new class of drugs in the treatment of AD. The two drug forms available are: tacrolimus 0.03% ointment and 1.0% pimecrolimus cream. The studies shows that pimecrolimus cream 1%, used at the first signs or symptoms of AD, reduces or eliminates the need for topical corticosteroids in adult patients. Tacrolimus 0.1% ointment can be used for adult and 0.03% for children. The proportion of patients experiencing no flares in 6

months in pimecrolimus treatment group was 67.6% in infants (aged 3-23 months) and 61.0% in children (aged 2-17 years), compared to 45% adult patients.[6] Pimecrolimus can be used in milder cases of AD, or in long-term maintenance for prevention of flares of the disease and for its assumed steroid-sparing effect. Tacrolimus can be reserved for moderate to severe cases of AD, and can be used as first line therapy instead of topical corticosteroids.[7]

Phototherapy

Nowadays, artificial UV radiation is frequently employed in the treatment of atopic dermatitis. The mechanism of action targets immunomodulation through apoptosis of inflammatory cells, inhibition of Langerhans cells and alteration of cytokine production.[9] UV rays also has an antimicrobial effect reducing the colonization of *S. aureus*, due to its anti-inflammatory effect. Phototherapy is a second-level treatment used in adults and much less in children. It should not be applied in children younger than 12 years.

Immunosuppressive medications

Ciclosporin A

Ciclosporin inhibits the production of NF-AT dependent proinflammatory cytokines in T cells and used in the treatment of AD. An initial daily dose of 2.5-3.5 mg/kg/day and a maximal daily dose of 5 mg/kg/day. A dose reduction of 0.5-1.0 mg/kg/day every 2 weeks is recommended in the treatment regimen.

Mycophenolate mofetil (MMF)

Mycophenolate mofetil (MMF) is an immunosuppressant drug for the treatment of systemic lupus erythematosus and prevention of transplant rejection. MMF 40-50 mg/kg/day in younger children and 30-40 mg/kg/day in adolescents were used in the treatment of AD.

New topical therapies for atopic dermatitis

Phosphodiesterase (PDE) inhibitors (Crisaborole)

Patients with AD showed significantly elevated leukocyte PDE activity compared to non-atopic normal individuals or to patients with allergic contact dermatitis.[10] Clinical consequences of these abnormality included elevations in histamine release and IgE synthesis. Crisaborole ointment has been approved by FDA for topical use in AD patients as young as 2 years of age. Paller AS et al, found that the drug was effective in lessening inflammation and appears to relieve skin itching fairly early during therapy. It is now used as an alternative therapy to TCS.

Janus Associated Kinase-Signal Transducer and Activator of Transcription (JAK-STAT) inhibitors (Tofacitinib)

The JAK inhibitor tofacitinib has been shown to inhibit cytokines such as interleukin (IL) 4 directly, leading to reduced inflammation.[11]

New and emerging systemic therapies of atopic dermatitis

Anti IL-4 and IL-3 (Dupilumab)

Dupilumab is a monoclonal antibody effective in improving the symptoms of adult patients with AD in a dose dependent manner. Simpson EL et al, found that this drug was approved for the treatment of adult with moderate-to-severe AD who are not adequately controlled with topical therapies. The initial dose is 600 mg (two 300 mg subcutaneous injections) followed by 300 mg given every other week.

Anti IL-13 (Lebrikizumab / Tralokinumab)

Eichenfield L et al, found that Lebrikizumab act by blocking IL-13 and used in the treatment of moderate to severe AD. Tralokinumab is a human monoclonal antibody, used in the treatment of AD.

PDE4 inhibitor (Apremilast)

Apremilast is an oral PDE4 inhibitor approved for the treatment of obstructive pulmonary disease, plaque psoriasis, and psoriatic arthritis. Samrao A et al, found that it was effective in reducing pruritus.

Anti-IL31 (Nemolizumab)

Nemolizumab is a humanized monoclonal antibody used in the treatment of moderate to severe AD with improvement in pruritus. Nemolizumab subcutaneous injections were well-tolerated with adverse effects mostly in AD exacerbations.

CONCLUSION

Mild atopic dermatitis can be managed with a combination of topical corticosteroids and general recommendations like moisturizers and moderate condition requires TCS supplemented with topical calcineurin inhibitors and also phototherapy is effective. In the case of severe atopic dermatitis, traditional immunosuppressive medications including ciclosporin, mycophenoate mofetil are used. Newer topical and systemic agents are also effective to treat moderate to severe AD.

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