Latest updates on atopic dermatitis
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Atopic dermatitis (AD), or atopic eczema is a chronic, itchy inflammatory condition that starts in childhood usually before 2 years of age. Clinically it is characterized by erythema, papules/ papulovesicles with excoriations or lichenification, typically involving the flexures. It is associated with other atopic conditions in the individual or other family members. AD is a common dermatosis seen in children and adolescents. Management of AD had always proven to be challenging with its recurrent remissions and exacerbations. In the continuously evolving scientific world, newer therapies are emerging for the management of AD.

The pathogenesis of AD involves dysregulation of epidermal and immune functions besides genetic factors. From outside in, the pathophysiology of AD depends upon:Barrier defects, triggers and immune dysfunction. Loss of function in filaggrin and deficiencies in loricrin, involucrin and claudins lead to epidermal barrier disruption causing transepidermal water loss and xerosis. Environmental and other stressors cause precipitation or aggravation of the disease. T cell-mediated inflammation plays an important role. Activation of immune cells and production of cytokines cause changes in keratinocytes and barrier defects. The pathogenesis involves a dysfunctional innate and adaptive immune response, including an unbalanced increase in T helper type 2 (Th2) cells and hyperimmunoglobulinemia E. The increased numbers of Th2 cells are involved in stimulating the production of immunoglobulin E and eosinophilia by releasing interleukin-4, -5, and -13, as well as, in decreasing protection against bacterial superinfection by releasing interleukin-10.

AD has a patient centric management, which takes into account the severity of AD, quality of life, sleep pattern, age and work/school environment. Topical treatment consists of emollients, corticosteroids and calcineurin inhibitors. Systemic agents include oral corticosteroids, immunosuppressants and biologics.

Emerging therapies for AD subsume both topical and systemic therapies. Crisabole (phosphodiesterase [PDE] 4 inhibitor) was approved by FDA in 2016 as a topical therapy. It is the first new topical agent developed during last 15 years. It can be used by adults and pediatric patient aged >2 years with mild to moderate atopic eczema. Open label extension trial with >500 patients from phase 3 trials were conducted in adults and pediatrics. The adverse effects included application site pain and infection. The Janus kinase (JAK)-signal transducer and activator of transcription (STAT) pathway is utilized by numerous cytokines and growth factors for signal transduction. Tofacitinib is a small-molecule JAK inhibitor. It has been shown to inhibit cytokines such as IL-4 directly and leads to rapid attenuation of JAK-STAT signalling in keratinocytes. In a phase Ila clinical trial tofacitinib 2% ointment has shown greater efficacy against vehicle with comparable

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safety in the treatment of mild to moderate AE.\textsuperscript{5} It is a promising new treatment for AD.

New systemic pipeline treatments for AD are different drugs and biologics. Apremilast, a PDE4 inhibitor, is an oral agent approved for psoriasis. It has been reported in phase 2 clinical trial in adult patients with moderate and severe atopic dermatitis. Its higher dose had greater efficacy but more adverse effects have been reported.\textsuperscript{5} JAK inhibitors like baricitinib (oral) and tofacitinib (oral) stop JAK1, JAK2 and JAK3 activity are being used in rheumatoid arthritis.\textsuperscript{6} They have been tried in adults aged >18 year with moderate to severe AD, cell lines suppression is their main side effect.\textsuperscript{6}

A number of biologicals have also been used in AD. Dupilumab, an IL-4 receptor alpha inhibitor, was approved by FDA in 2017.\textsuperscript{7} It is used in adults aged >18 year with moderate to severe AD. It is directed against IL-4 receptors and blocks signaling from IL-4 and IL-13. It is administered in weekly dose regimen. Pediatric studies in patients aged 12 to <18 year with moderate to severe disease have been carried out. Its adverse effects include injection site reaction and conjunctivitis.\textsuperscript{7} Lebrikizumab and tralokinumab (IL-13 inhibitors) are in phase 2 trials. These have been used in >18y old adults with moderate to severe AD in combination with topical steroids. The reported adverse effect was conjunctivitis.\textsuperscript{8} Nemolizumab is IL-31 receptor inhibitor, monoclonal antibody, used in phase 2 trial in adults with moderate to severe disease. Peripheral edema and exacerbation of atopic dermatitis are its adverse effects.\textsuperscript{9} Omalizumab, an IgE inhibitor, is also being used in the treatment of AD with high IgE levels.\textsuperscript{8} Mepolizumab is an anti-IL-5 biologic, which has been approved recently in the United States and European Union for severe eosinophilic asthma. This compound did not fulfil expectations in a short-term pilot study in patients with AD, but given the improvement for eosinophilic asthma, new studies have been initiated to address the long-term risk/benefit ratio of mepolizumab in a subset of patients of AD with eosinophilia.\textsuperscript{9}

Some biologicals like ustekinumab,\textsuperscript{7} a fully human monoclonal antibody against IL-12/23 and TNF alpha inhibitors,\textsuperscript{10} like etanercept and infliximab, which are effective in psoriasis may have therapeutic potential in AD, as well.

This is an exciting time in treatment of AD. We can change the expectations of patients. Patient care can be improved with well-controlled itch and rash, and minimal disease over time.

References