Ann Natl Acad Med Sci (India), **54(2):** 78-89, 2018

Review Article

Atopic Dermatitis: Drug Delivery (Management) and Approaches (Strategies) in Perspective

Virendra N. Sehgal
Dermato-Venereology (Skin/VD) Center, Sehgal Nursing Home,
Panchwati, Delhi.

ABSTRACT

Age-related cutaneous manifestations are definitive pointer to the diagnosis of atopic dermatitis, the confirmation of which is solicited by 3 major and 3 minor criteria. Its unpredictable course is punctuated by exacerbations and remissions. Several treatment options, namely: 1st, 2nd and 3rd line are in vogue ever since. The 1st line envisages general measures, 2nd encompasses topical applications, while the 3rd take into account drug therapy comprising, systemic Corticosteroids, Cyclosporin, Azathioprine, Thymopentin, Interferon–therapy, Topical Calcineurin inhibitors: Tacrolimus and Pimecrolimus. The mode of action, their dosages and adverse drug reaction (ADR), in particular, have been focused in this paper with special attention to refresh their drug delivery (management) approaches (strategies) in perspective. An endeavor to focus attention to emerging etio-pathogenesis, and its application in the contemporary context has also been made.

Keywords: Atopic dermatitis, Immunoglobulins E, Cyclosporin, Azathioprine, Thymopentin, Interferon-therapy.

Introduction

Atopic dermatitis (AD) is a non-contagious, intensely pruritic, inflammatory, chronic skin disorder having a course of exacerbations and remissions, occurring in infancy and childhood running in families with a history of atopy. It is frequently associated with an elevated immunoglobulins E (IgE) levels in serum. Disease has an intricate immunological basis influenced by genetic/ familial predisposition, and certain environmental, life style and dietary factors. Recent trends suggest a continuous rise in the prevalence of atopic dermatitis in developed nations and in countries undergoing rapid urbanization and industrialization. The clinical phenotype that characterizes AD as the product of complex interactions among susceptibility genes, the host's environment, defects in skin barrier function, and systemic and local immunologic responses (1-4). IgE discovered in 1966 by the Japanese scientist couple Teruka and Kimishige Ishizaka (5), plays an important role in allergy, and is especially associated with type 1 hypersensitivity.

Serum IgE levels in a normal, non-atopic individual are only 0.05 percent of the IgG concentration, the isotype responsible for most of the classical adaptive immune response (6). Although IgE is typically the least abundant

Correspondence : Dir. Prof. (Dr.) Virendra N Sehgal, Dermato Venerology (Skin/VD) Centre, Sehgal Nursing Home, A/6 Panchwati, Delhi-110 033 (India). Ph: 011-27675363, 9810182241. Email: drsehgal@ndf.vsnl.net.in.

isotype, it is capable of triggering the most powerful immune reactions. Increased serum levels of IgE have subsequently been reported in patients with asthma, hay fever, atopic dermatitis (7-9) and also in patients infested with intestinal parasites (7). In several studies the concentrations of other immunoglobulin classes have been investigated in atopic subjects. Varelzidis *et al* (10) found a significant rise in the level of IgG in a study of adults and children with atopic eczema. High serum levels of IgA in atopic subjects have been described by Ortiz (11). Drug delivery approaches (12), in particular, are adopted for largely it takes into account formulations, technologies, and systems for transporting a pharmaceutical compound in the body as needed to safely achieve its desired therapeutic effect.

Drug Delivery (Management) Approaches (Strategies)

Due to variations in presentation in different age groups and severity of the disorder, the therapy has to be individualized. The treatment of AD envisages reducing symptoms, preventing exacerbations and recurrences, and minimizing side-effects from medications. The use of emollients, wet dressings, topical corticosteroids, antibiotics for infections, antihistamines, stress management, counseling and avoidance of allergens or triggers (1) are its main stay, the brief of treatment modalities (13) are recounted below:

A. First (1st) Line Therapy

a. General advice - decreasing scratching, improving family interaction, correcting sleep disturbances, and avoidance of trigger factors.

b. Reduction of trigger factors
   i. Curtail use of Soap and detergent
   ii. Avoid contact with wool
   iii. A central or room humidifier may help in obviating xerosis
   iv. Eliminate air borne allergens
   v. Avoid house pets
   vi. Alleviate patient and/or family stress

c. Topical therapy
   I. Bathing followed by emollients, moisturizing creams and emollients are useful and important treatment adjuncts for the daily skin care of patients with dry and inflamed skin
   ii. Initial administration of mild/mid potent topical steroids
   iii. Maintenance by ichthammol /coal tar

d. Systemic therapy
   i. Oral antihistaminic therapy comprising hydroxyzin hydrochloride / dihydrochloride at bed time, and antibiotics when impetigo develops.

B. Second (2nd) Line Therapy

a. Intensive topical potent corticosteroids for short periods
b. Wet-wrap techniques: affected parts covered with emollient followed by a wet inner and dry outer dressing used over night
c. Contact allergy to medicaments is possible, change to different preparations or patch test to topical agents.
d. Phototherapy, a useful treatment option in moderate to severe, resistant disease which frequently needs systemic immunosuppressive.

PUVA is recognized to be beneficial in the management of adult AD, and children over 12 years of age. Narrowband UVB (14) is preferred in pediatric age group. Limitations are visits to treatment center and risk of premature skin aging and cutaneous malignancies.

C. Third (3rd) Line Therapy Drugs

Systemic corticosteroid

Acute flare-up, in patients of AD may benefit from a short course of systemic therapy with corticosteroids (15, 16), but long-term use in adults and any use in children should be avoided.

Cyclosporin

Cyclosporin (CSA) is an immuno-suppressant drug widely used in organ transplantation to prevent rejection (17, 18). It reduces the activity of the immune system by interfering with the activity and growth of T cells (19). T-cell receptor activation causes release of intracellular calcium that in turn binds to calmodulin, and activates calcineurin. The calcineurin complex then dephosphorylates the nuclear factor of activated T cells (NFATc), which migrate into the nucleus and make a complex that is a transcription factor for inflammatory cytokines, (e.g., IL-2). Cyclosporin binds to cyclophilin (intracytoplasmic proteins–immunophylin), which blocks the dephosphorylation of NFAT, resulting in a decrease of T-helper cells (CD4), and cytotoxic (CD8) in the epidermis. Cyclosporin A (CyA) inhibits calcineurin-dependent pathways, resulting in reduced levels of pro-inflammatory cytokines, such as IL-2 and IFN-g. CyA is effective in treatment for both adult and childhood AD (20). It is an isolate from Tolypocladium inflatum, the fungus found in a soil samples (21). It is a cyclic non-ribosomal peptide of 11 amino acids, and contains a single D-amino acid, rarely encountered in nature (22).

Dosage schedule

Unresponsive atopic dermatitis to topical therapy may require high-dose comprising 5 mg/kg/day divided into two doses of CSA as an acute management strategy for a period of 6 weeks, followed by randomization to receive maintenance treatment with either CSA 3 mg/kg/day or enteric-coated mycophenolate sodium (1440 mg/day) for 30 weeks, followed by a 12-week follow-up period (23, 24). However, for long term treatment lowest effective dose is recommended (25).

Adverse drug reactions (ADRs) of CSA are (26)

- Enlargement of the gums
- Convulsions
- Peptic ulcers
- Pancreatitis
- Fever,
- Vomiting
- Diarrhea
- Confusion
- Hypercholesterolemia,
- Dyspnea
- Numbness and tingling particularly of the lips
- Pruritus
- High blood pressure, potassium retention possibly leading to hyperkalemia
- Kidney and liver dysfunction (nephrotoxicity) and hepatotoxicity

Azathioprine

Azathioprine (AZA) Imuran, is an immuno supressive drug used in organ transplantation, and autoimmune diseases including atopic dermatitis (27-29). It belongs to the chemical class of purine analogues (29).

Dosage schedule

Usual pediatric dose for atopic dermatitis in patients greater than 17 years: 2.5 mg/kg orally once a day, in the morning, for 3 months.

Adverse drug reactions (ADRs)

It has several side-effects including myelo suppression, hepatotoxicity, and susceptibility for infection (30).

Thymopentin (31-38)

Thymopentin (31) an immuno-stimulant (32), is a thymic polypeptide (33), which interacts with T cells (34, 35), causing T – helper cell activation resulting in enhanced interleukin-2 production with subsequent proliferation of cytotoxic T lymphocytes and natural killer cells which are capable of producing immune interferon (36), thus helps to improve

immunological condition(s) including atopic dermatitis (37).

Dosage schedule

Thymopentin therapy reduces the clinical severity of atopic dermatitis at a dose of 1 mg/kg, three times per week for 8 weeks (38, 39).

Adverse drug reactions (ADRs)

No significant adverse drug reactions are noticed, except for an increase in the T-helper/ T-suppressor ratio.

Interferon –therapy (40-48)

Interferons (IFNs) (40) are a group of signaling proteins (41), the cytokines, molecules used for communication between cells to trigger the protective defenses of the immune system that help eradicate pathogens such as viruses, bacteria, and parasites. Interferons are named for their ability to interfere with viral replication by protecting cells from virus infections (42). Their other functions are to activate immune cells, such as natural killer cells and macrophages; they increase host defenses by up-regulating antigen presentation by virtue of increasing the expression of major histocompatibility complex (MHC) antigens. Certain symptoms of infections; fever, muscle pain and flu-like symptoms, are also caused by the production of IFNs and other cytokines. Currently, AD is classified into Extrinsic atopic dermatitis (eAD) (43), IgE associated allergic atopic dermatitis, and Intrinsic atopic dermatitis (iAD), non-allergic atopic eczema/dermatitis syndrome (AEDS) (44). eAD has elevated Th2- and decreased Thl-expressing cells in the peripheral blood, with elevated interleukin (IL-4 and IL-13) expression, increased, IgE levels and decreased IFN-gamma production. Accordingly, it is imperative to highlight the role of recombinant interferon-gamma therapy in severe atopic dermatitis (45-47).

Dosage schedule

50 micrograms/m2 rIFN-gamma (n = 40) or placebo (n = 43) by daily subcutaneous injection for 12 weeks.

Adverse drug reactions (48, 49)

· Early: Flu-like syndrome : Fever, chills, generalized aches and pains, headache, poor appetite.
· Fatigue, drowsiness.
· Low blood counts

Topical immunosuppressant (50-64)

Calcineurin inhibitors

- **Tacrolimus** (50)

Tacrolimus (FK506), a macrolide lactone produced by soil fungus Streptomyces tsukubaensis. It was originally used intravenously or orally for prevention of organ rejection after transplant. Tacrolimus, especially through the topical route of administration, gained entry into therapy for inflammatory dermatoses (51), such as atopic dermatitis, without significant risk of toxicity (47). The use of tacrolimus (53, 54) (Prograf) and pimecrolimus (55) (Elidel) ointments has been licensed in the UK since 2001 subject to National Institute for Health and Clinical Excellence guidance. Tacrolimus ointment is restricted to use in adults (0.1%) and children over 2 years of age (0.03%) with moderate to severe atopic dermatitis not controlled by topical corticosteroids. Pimecrolimus cream is for use in corticosteroid resistant facial dermatitis. They are perceived as second-line agents, but conditions of use vary.

Many studies have demonstrated their efficacy, and their attraction is the absence of the cutaneous side-effects, atrophy of skin, striae, telangiectasia and bruising that may be seen with prolonged or inappropriate corticosteroid use (56). The US Food and Drug Administration

(FDA), however, has warned of their injudicious use due to theoretic side-effects (57) related to immuno-suppressant, including cutaneous or internal malignancies children.

A pilot study (58) was initiated to evaluate the efficacy of tacrolimus 0.1% ointment in the treatment of atopic hand eczema (AHE). The study was an open-label non-comparative using tacrolimus 0.1% ointment in 10 patients with AHE. Inclusion criteria included patients with hand eczema, known history of atopy, AD, hay fever and/or asthma. Patients had to stop topical application of steroids and systemic use of steroids or antihistamines for 4 weeks. Patients applied tacrolimus 0.1% ointment twice daily for 4 weeks. Evaluation was performed before treatment, after 4 weeks of treatment, and after a follow-up period of 4 weeks. During follow-up, the patients used emollients. Treatment efficacy was established at each visit based on the following parameters: itch and/or burning sensation, dryness, erythema, lichenification, erosions and fissures. Of the 10 patients, four had marked or complete improvement at the end of treatment, four other cases had partial improvement, while in one patient the treatment failed. One patient left the study due to side-effects.

· **Pimecrolimus** (59)

Pimecrolimus is an ascomycin macrolactam derivative, which has a potential to bind to macrophilin-12 (FKBP-12) *in vitro* and inhibits calcineurin. Thus it inhibits T-cell activation by inhibiting the synthesis, and release of cytokines from T-cells. It also prevents the release of inflammatory cytokines and mediators from mast cells (60-64).

Azathioprine and Betamethasone *versus* Betamethasone Therapy (65)

Efficacy of combine topical emollients containing azathioprine (AZT) and betamethasone (BM), and betamethasone alone was used in two groups of moderate-to-severe atopic dermatitis, twice a day for a period of 8 weeks. The recurrence, and presence of side-effects were evaluated, the former was found to be superior in contrast to betamethasone, suggesting usefulness of AZT in the future dispensation (65).

Topical Therapy, Evolving Scenario (66-76)

Although, several treatment options are in vogue, its treatment continues to loom large, because its etio-pathogenesis is largely seem to be enigmatic (66, 67) nevertheless, the endeavors to unfold it are relentlessly continuing. The advent of stratum corneum (66, 68), the impeccable skin barrier has taken the central stage. Accordingly, its micro-anatomy (structure) and physiology (function) has added refreshing dimensions. The alterations in its patho-physiology have been a definitive step forward, enshrining the role of flaggrin (69) and serine proteases (70) in particular. The changing pattern in the former may impede its physical strength, hydration status, skin pH, and buffering capacity amongst other physio-chemical properties. Filaggrin (71, 72), the epidermal barrier protein is, therefore, a major pre-disposing factor in the pathogenesis of AD. In addition, up-regulation of serine protease activity may cause adverse structural changes due to degradation of certain proteins, the part component of epidermal structure and its functions, thus interfering in the formation of the stratum corneum intercellular lipid membrane, regulating epidermal water flux and gradient, resulting in induction of TH2 (Subset Type pattern) of inflammation. Simultaneous, immune system (73) and its dysfunction through IgE mediated sequence of events capped by genetic (74) undertones may initiate and/or perpetuate the clinical expression of AD. Hence, the preceding rumblings responsible for the clinical connotation of AD, may bring to the fore

newer modalities to counter the intricate often difficult to treat condition. Thus, atopic dermatitis treatment envisages (75).

- Eliminating inflammation and infection
- Hydrating the skin
- Controlling pruritus, and
- Avoiding exacerbative factors

Addition of moisturizer to a low-potency corticosteroid lotion in separate regimens is effective in treating the signs and symptoms of mild-to-moderate atopic dermatitis (75, 76).

Bathing and Emollients (77-80)

Foaming detergents and soaps should be avoided. A soap substitute should be used for cleansing (77-78). A regular use of emollient(s) may even protect against inflammation provoked by irritants, thus increasing the benefit obtained from topical corticosteroid therapy (79). Indeed, ceramide-rich emollients may lead to improvements in childhood atopic dermatitis through a specific barrier repair mechanism (80).

Topical Suppression of Inflammation (81)

Topical steroids are the predominant treatment for the inflammation of atopic dermatitis, and are very safe. The strength and mode of application of the topical steroids may depend on the severity of the dermatitis, the site(s) and the age of the patient. Less potent topical steroids should be used on the eyelid, face, axillae, groins and inner thighs. Less potent topical steroids are used in less than 1 year old children. Systemic absorption may occur, even with 1% hydrocortisone ointment. It is therefore recommended to apply the ointment once daily in the evening, morning application of emollients, may be effective. There appear to be no differences in efficacy or side-effects between pulsed potent corticosteroid creams and the continuous use of mild topical corticosteroids in patients with mild to moderate disease (81).

Antipruritic Agents (82-84)

1. Antihistamines (82-84)

H1-receptor antagonists (82) are used predominantly for their sedative effect. Agents such as promethazine or trimeprazine given 1 h before bedtime can be useful when there is severe nocturnal itching. However, they can cause drowsiness and lack of concentration the next morning. In infants, these preparations may occasionally cause paradoxical excitation. They are best used in short courses, for example 10–14 days, as tachyphylaxis can occur with prolonged use (83). Most studies (84) concluded that non-sedating antihistamines are of little value for the pruritus of atopic dermatitis

2. Antibiotics (85-87)

Systemic antibiotic treatment is indicated for widespread bacterial secondary infection, primarily *S. aureus*. First- or second-generation cephalosporins or semi-synthetic penicillins administered for 7 to 10 days are usually effective. Clindamycin or oral fusidic acid (85) are possible alternatives in cases of penicillin or cephalosporin allergy. Besides, heavy colonization of klebsiella pneumonia (86) may also be recovered, requiring administration of metronidazole specific for anaerobic gram negative bacteria (87).

3. Leukotriene Antagonists (88)

Leukotriene antagonists (montelukast and zafirlukast) are useful for the treatment of asthma and allergic rhinitis. In AD therapy they are not fully elucidated. Zafirlukast (Accolate) is approved in AD and asthma for adolescents, and adult. In chronic AD montelukast (Singulair) achieved little success. It is administered in the doses of 5mg daily for 4 weeks in a clinical double-blind study (88) of moderate to severe AD in young patients between 6 to 16 years showed a significant decrease in disclosed severity, but in another study with severe AD and different doses of 5 mg, 10 mg, 20 mg, a partial

improvement comprising relief of pruritus; and erythema, in a few patients. AD patients *per se* failed to show any benefit from leukotriene receptor antagonist therapy.

Phototherapy

Phototherapy options namely:

- broad-band UVB (280 to 320 nm)
- narrowband UVB (311 to 313 nm),
- UVA (320 to 400 nm), UVA1 (340 to 400 nm)
- PUVA, and PUVA bath
- Combinations of UVB, TCs and UVB with UVA as well as UVA1

Medium- and high dose therapy are useful in AD. In the pediatric population, UV therapy should be restricted to children older than 12 (89)

Bioengineered Immuno-modulators (90)

Most of the new approaches aim at inhibiting components of the allergic inflammatory response, including cytokine modulation, the tumor necrosis factor [TNF] inhibitors, blockade of inflammatory cell recruitment, the chemokine receptor antagonists, cutaneous lymphocyte antigen inhibitors, and inhibition of T-cell activation (alefacept and efalizumab). Currently, bioengineered immune- modulators are in a clinical trial phase for AD treatment (90).

IgE-blocking Antibody (91)

IgE-blocking antibody omalizumab is a recombinant human monoclonal antibody that targets specific antihuman IgE drugs, which binds free serum IgE and avoids binding to Fc3RI receptors as well as Fc3RII [CD23] receptors on mast cells, basophiles, and antigen-presenting cell surfaces, which stops release of pro-inflammatory mediators.

Omalizumab is for use in adults and children older than 12 years with asthma and AD for 3 months; subcutaneous injections of 0.015 mg/kg IgE and 0.03 mg/kg each 2 weeks or 4 weeks. The role of omalizumab in dermatology and for AD is probably best directed towards patients who have high levels of IgE, and in whom the IgE is an etiologic factor for their disease (91).

Probiotics (92, 93)

They have also been tried in AD. Probiotics are cultures of potentially beneficial bacteria that positively affect hosts with adverse reactions to certain foods, as may be the case in AD. Many interventional studies have reported variable outcomes with manipulation of diet and environment in pregnant women, the primary prevention, and children with established AD, the secondary prevention. However, more work is required to determine the effect of such measures on the long-term outlook of patients with AD. Early treatment with microbial probiotics may be beneficial by boosting Th1 immune responses in AD (92, 93).

It is difficult to predict the outcome of the disease. It is found to be more persistent and prevalent in young children, the episodes of remission become more frequent and of longer duration in an aging child. A spontaneous remission after the age of 5 may be observed in 40 to 60 percent of patients who develop the disease in infancy. A poor prognosis is seen in individuals who have widespread disease in childhood, associated rhinitis/asthma, a positive family history, and/or very high serum IgE levels (1).

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