

Therapeutic perspectives in atopic dermatitis

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Atopic dermatitis (AD) is a chronic inflammatory skin disorder found in patients with a history of respiratory allergy (1, 2). Recent studies of atopic skin inflammation reveal a Th2-driven process in acute skin lesions followed by a Th1-driven process in the chronic AD lesion (3). Treatment is primarily directed at symptom relief and reduction of this complex skin inflammation. With an increased understanding of the immune dysregulation associated with AD, therapy directed at correcting specific immune abnormalities has been attempted. This paper will review an approach to the management of "difficult-to-treat" patients with AD. Particular emphasis will be placed on the development of newer anti-inflammatory therapies that go beyond corticosteroids.

General principles

Understanding the individual patient's disease pattern, as well as identifying and reducing exacerbating factors where possible, is essential for effective management of AD. The role of such factors as allergens, infectious agents, irritants, physical environment, and emotional stressors needs to be considered. Therapeutic intervention must be modified to the special needs of each patient. Patients should understand that therapy is not curative, but that avoidance of exacerbating factors, in conjunction with daily topical skin care – particularly skin hydration and topical corticosteroids – can relieve acute symptoms and improve long-term outcome. Hydration is not only important for skin moisturization but also enhances the penetration of topical corticosteroids.

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Corticosteroids

Topical corticosteroids reduce inflammation and pruritus and are useful in controlling acute flares of AD. Use of a

particular drug will depend on the severity and distribution of the skin lesions. As a general rule, the lowest potency corticosteroid that is effective should be used. Inadequate prescription size often contributes to suboptimally controlled AD, especially when treating patients with widespread, chronic disease. The average patient requires at least 840 g of a moisturizer or topical medication to cover the body once a day for a month. Patients often become frustrated by the inconvenience of refilling prescriptions, resulting in noncompliance with the treatment regimen. In addition, dispensing the prescribed medication in larger quantities can result in substantial savings for the patient.

In addition to their anti-inflammatory properties, topical corticosteroids may have an effect on bacterial colonization in AD. Nilsson et al. found that the density of *Staphylococcus aureus* on the skin could be reduced by topical corticosteroid therapy (4). Furthermore, in a double-blind, randomized trial, the bacteriologic and clinical effects of desonide were compared with its excipient in 40 children with AD (5). After 7 days of once-daily topical treatment, the clinical score improved in the desonide group, and *S. aureus* density decreased dramatically. In the excipient group, no significant differences in clinical score or *S. aureus* density were noted. These results show the efficacy of topical corticosteroid treatment alone on *S. aureus* colonization in atopic skin, and suggest a role for inflammation in bacterial colonization.

Identification and elimination of exacerbating factors

Infection

Infection can reduce response to corticosteroid therapy. Patients with AD have an increased susceptibility to viral infections such as herpes simplex, molluscum contagiosum and verrucae; to superficial dermatophytosis, particularly that caused by *Trichophyton rubra* and *Malassezia furfur*; and to *S. aureus* infections. *S. aureus* may exacerbate AD by secreting toxins that can act as superantigens which directly activate T cells and HLA-DR + cell types (6). Furthermore, a subset of patients with AD can mount an IgE response to the specific toxin isolated from their skin. In such patients, toxins may exacerbate AD by activating mast cells, basophils, and/or other Fc epsilon-receptor-bearing cells armed with the relevant IgE antitoxin. Superantigens have also been found to induce steroid resistance. This may account for the clinical observation that patients respond

better to a combination of antibiotics and topical corticosteroids than to either therapy alone (7).

Irritants

Patients with AD have a lowered threshold of irritant responsiveness. Identifying and avoiding irritants is integral to successful management of this disease. These include soaps, detergents, chemicals, smoke, abrasive clothing, extremes of temperature, and humidity. Alcohol and astringents found in toiletries can be dehydrating, and the use of soaps, solvents, and similar compounds should be minimized.

Allergens

Foods and aeroallergens such as dust mites, animal danders, and pollens may exacerbate AD in a subset of patients (8). Exposure to allergens has been found to reduce the glucocorticoid receptor-binding affinity of T cells and thereby alter response to corticosteroid therapy (9). Identification of allergens may be approached by taking a careful history and doing selective immediate hypersensitivity skin tests. Negative skin tests with proper controls have a high predictive value for ruling out a suspected allergen. Positive skin tests, on the other hand, have a lower correlation with clinical symptoms and should be confirmed with a double-blind, placebo-controlled challenge for suspected food allergens, unless there is a history of anaphylaxis to the food. Avoidance of foods implicated in controlled challenges results in clinical improvement. Environmental control measures, particularly decreasing dust-mite load, have also been shown to improve skin symptoms in patients with chronic AD (10).

Experimental immunomodulatory therapy

For patients who are resistant to therapy, alternative therapies should be considered, as long-term treatment with oral or high potency topical corticosteroids can lead to significant adverse events. Ultraviolet light (UVB or PUVA) therapy may be a useful adjunctive modality in the treatment of chronic recalcitrant AD. Therapeutic trials using several experimental immunomodulators/immunosuppressive agents have also been reported.

Interferons (IFN)

It is well established that IFN- γ inhibits Th2 responses. Treatment with rIFN- γ has been shown to reduce clinical severity and decrease total circulating eosinophil counts in patients with AD (11). In one study, a small subset of patients showed persistent improvement 3 months after treatment was discontinued (12). Although a few reports suggest some clinical benefit from using rIFN- α , other studies have not confirmed this finding. A single study of two patients suggests improvement in their AD when rIFN- α and rIFN- γ were used sequentially (13).

Intravenous immunoglobulin (IVIG)

IVIG has been reported to be an effective therapy in steroid-dependent asthma (14). Since chronic inflammation and T-cell activation appear to play a critical role in the pathogenesis of both asthma and AD, IVIG could have immunomodulatory effects in AD. Furthermore, IVIG may directly neutralize microbial toxins and reduce tissue colonization with infectious agents involved in the pathogenesis of AD (15). In an open study of high-dose IVIG in two children with severe AD unresponsive to topical corticosteroids, 5 days of treatment with 400 mg/kg per day resulted in significant improvement with almost complete clearing 28 days after treatment (16). IVIG treatment decreased both serum IgE levels and spontaneous IgE production *in vitro*. In an alternative approach, Burek-Kozłowska et al. (17) applied IVIG topically to an affected area of AD on one extremity and a halogenated corticosteroid to a corresponding control area on the opposite extremity in six patients. After once-daily treatment for 9 days, the IVIG-treated areas showed significant improvement in 5/6 patients and was superior to topical corticosteroids in two of these patients and equivalent in three.

Phosphodiesterase inhibitors

AD leukocytes have been shown to have a genetically determined increased cAMP-phosphodiesterase (PDE) enzyme activity (18). PDE inhibitors such as Ro 20-1724 have been found *in vitro* to normalize the elevated IgE synthesis, IL-4 production, and basophil histamine release in AD cells. Ro 20-1724 has also been reported to suppress IL-5 secretion by Th-2 cell lines (19). Importantly, preliminary clinical studies using topical application of high-potency PDE inhibitors have demonstrated them to be of clinical benefit in AD (20).

Cyclosporin (Cs)A

CsA is a potent immunosuppressive drug which acts primarily on T cells by suppressing cytokine transcription. The drug binds to an intracellular protein, cyclophilin, and this complex in turn inhibits calcineurin, a Ca^{2+} -calmodulin-dependent protein phosphatase involved in the initiation of cytokine gene transcription. In an 8-week double-blind, placebo-controlled, crossover study, patients receiving CsA had a significant improvement in their AD (21). Thirty-three patients treated with 5 mg/kg per day CsA for 8 weeks showed significant improvement in the extent and activity of dermatitis ($P < 0.001$). Several other short-term, blinded, placebo-controlled studies confirm the clinical benefit of oral CsA in severe refractory AD (22). Due to concerns regarding systemic toxicity, topically administered CsA has also been used in AD. These studies have demonstrated inconsistent efficacy of local CSA applications on lesions of AD.

FK506

Tacrolimus, or FK506, a macrolide lactone isolated from *Streptomyces tsukubaensis*, is a potent immunosuppressive agent with a spectrum of activity similar to cyclosporin. Its smaller molecular size and higher potency compared to cyclosporin suggested it could be effective as a topical agent. Although it is structurally unrelated to CsA, tacrolimus also interacts with a cyclophilin-like cytoplasmic protein, FK506-binding protein, and this complex in turn inhibits calcineurin, interfering with gene transcription of multiple cytokines including IL-2 (23). Two multicenter, well-controlled studies reported that FK506 in ointment form (tacrolimus) can effectively reduce the clinical symptoms of AD, with markedly diminished pruritus often within 3 days of initiating therapy (24, 25). In these studies, no significant systemic side-effects were noted. A sensation of skin burning at the site of application was the only adverse event that was significantly more frequent with tacrolimus than with vehicle alone. This adverse event generally resolved within 1 week, accompanying the resolution of skin lesions.

The mechanism by which tacrolimus exerts its beneficial effects remains to be elucidated, although it probably includes the inhibition of IL-4 and IL-5 gene transcription (22). Indeed, skin biopsies obtained after 3 and 7 days of treatment with topical tacrolimus have revealed markedly diminished T-cell and eosinophilic infiltrates. Tacrolimus also inhibits the transcription and release of other cytokines, such as IL-3, IFN- γ , TNF- α , and GM-CSF, which contribute

to allergic inflammation. Of note, various cell types important in allergic skin inflammation including mast cells, basophils, eosinophils, keratinocytes, and Langerhans' cells have tacrolimus (FK506)-binding proteins and down-regulate their mediator or cytokine gene expression after treatment with tacrolimus. Since recent studies suggest that

the T-cell activation in AD is biphasic with activation of Th2-like cytokines during the acute phase and increased expression of Th1-cytokines in chronic lesions, the capacity of tacrolimus to inhibit the activation of multiple cell types and cytokines may account for its ability to reduce skin inflammation effectively in AD.

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