

2007 Treatment Update—Treatment Options for Atopic Dermatitis

a report by

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Atopic dermatitis is a chronic inflammatory pruritic skin disease that affects approximately 15% of children in industrialized countries. It is the most common skin disease of young children, but may affect patients of any age.¹

Its origin is multifactorial and includes many commonly encountered triggers. In 1892, Besnier used the term neurodermatitis to describe a chronic pruritic skin condition seen in patients suffering from a nervous disorder.² This familial disorder was termed prurigo Besnier because of its intensely pruritic nature. In the early 1900s, Coca noted the occurrence of a similar disorder with other diseases such as asthma and hayfever and used the term atopy to refer to the allergic constellation of these diseases.³ The term atopic dermatitis was coined by Wise and Sulzberger in 1933 to comprehensively describe this inheritable skin disorder.⁴ Since its earliest description, atopic dermatitis has had one primary feature recognized by clinicians and patients alike—intense pruritus triggered by a variety of stimuli.

More than half of the patients with atopic dermatitis develop asthma and seasonal allergies.² Patients with atopic dermatitis have increased transepidermal water loss and xerotic skin. This abnormal barrier contributes to the cutaneous hyperreactivity which is an essential feature of atopic dermatitis.³

Therapy of atopic dermatitis should begin with optimal skin care, addressing the skin barrier defect with regular use of emollients and skin hydration, along with the avoidance of trigger irritants. The severe skin dryness of the skin is often accompanied by intense pruritus and inflammation. The regular use of emollients is paramount for addressing these issues and remains essential in the management of atopic dermatitis.⁴ Another important area of treatment is patient education. Patients should be educated to avoid common irritants and to use agents like soaps and hot water temperatures during showering or bathing with caution.⁵

Patient and Care Giver Education

Probiotics are orally administered micro-organisms that have been used for atopic diseases because they may

have anti-inflammatory and anti-allergic properties through promoting helper Th1 cell responses and by restoring intestinal permeability and gut flora.⁶

Lactobacillus spp., *Bifidobacterium* spp., and *Saccharomyces* spp.—particularly *L. casei*, *L. rhamnosus*, *L. acidophilus*, *L. plantarum*, *B. longum*, *B. bifidum*, and *S. cerevisiae boulardii*—are the most commonly used probiotics and actively researched organisms at the basic level and in clinical trials.⁷ However, to date six randomized controlled trials have now been performed that, based on their data, do not show a clinically useful effect of probiotics for treating established AD.

Chinese medicines have produced impressive responses in cases of atopic eczema that have proved resistant to conventional treatment. However, physicians should realize their potential toxicity as well as the uncertainty of their ingredients. Although the constituents and amounts of plant material may differ in many of these remedies, placebo controlled trials have been performed with a specific formulation.⁸ They have shown a beneficial response in children and adults with atopic eczema. Nevertheless, the effect is usually temporary, with relapse after treatment is stopped. Even if the treatment is continued its effectiveness often wears off after a variable period, usually around six to 12 months.⁹

Atopic dermatitis is a common, potentially debilitating condition that can compromise quality of life. Although for many patients the symptoms of atopic dermatitis resolve by adolescence, the condition can persist into adulthood. It is for this reason that it is important to have new treatment strategies and an updated practice parameter.

Atopiclair was US Food and Drug Administration (FDA) approved to relieve the symptoms of atopic dermatitis and irritant contact dermatitis in July 2003. Atopiclair is a hydrophilic cream developed for the management of atopic dermatitis; it is a non-steroidal hydrophilic cream comprised of glycyrrhetic acid, hyaluronic acid, telmestaine, and extracts from *Vitis vinifera*, which have been combined with a moisturizing, emollient base.¹⁰ Glycyrrhetic acid has

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both anti-inflammatory and antipruritic effects. The product contains shea butter, and patients with a known allergy to nuts or nut oil should exercise caution. Atopiclair seems devoid of significant local side effects such as irritation and contact dermatitis; burning on application is rarely reported.¹¹

MimyX was FDA approved for the treatment of radiation dermatitis, atopic dermatitis and allergic contact dermatitis in July 2005. MimyX cream for the treatment of atopic dermatitis. Unlike traditional topical treatments for atopic dermatitis that target the inflammatory pathway, MimyX cream works by restoring the natural components of the stratum corneum and re-establishing barrier function of the outer layers of the epidermis. MimyX cream contains palmitoylethanolamide (PEA), an endogenous bioactive fatty acid that is deficient in atopic skin. There is evidence that MimyX cream replenishes PEA levels in atopic skin, restores the disrupted skin barrier of AD, and promotes skin barrier repair. PEA has been implicated in various pharmacologic pathways. It is believed to have activity as an analgesic, anti-inflammatory, antiproliferative, anti-anaphylactic, and antiserotonergic agent. PEA is found in most mammalian tissues and is a natural constituent of skin, including the stratum granulosum of the epidermis. It is produced by cells to downregulate the inflammatory response. MimyX cream is approved for patients of all ages and provides a non-steroidal alternative to treating atopic dermatitis.¹²

Topical corticosteroids have been the mainstay of therapy for atopic dermatitis. They reduce inflammation and pruritus by inhibiting the transcriptional activity of several pro-inflammatory genes.¹³ Therapy with these agents should not replace the frequent use of moisturizers. The local and systemic effects of topical steroids are well recognized. Local effects include skin atrophy, striae, telangiectasias, hypopigmentation, rosacea, perioral dermatitis and acne. Systemic side effects include adrenal suppression, cataracts, glaucoma, and growth retardation in children.¹⁴

Topical corticosteroids are grouped into seven potency categories, with class 1 containing the most potent agents and class 7 containing the least. A general principle in treating atopic patients with topical steroids is to use the least potent agent possible and to limit the frequency of application. In comparison with adults, children are at higher risk for the local and systemic side effects of corticosteroids. In children, only mild to moderately potent steroid preparations should be utilized.¹⁵ Class 1 steroids should generally be avoided in children younger than twelve years of age. In children with atopic dermatitis,

the fingertip unit (FTU) is defined as the amount of medication extending from the tip of the first joint on the palmar aspect of the index finger, and is described as a measure for the application of corticosteroids.¹⁷ In general, one FTU is required to cover the hand or groin, two FTU for the foot or face, three FTU for an arm, six FTU for the leg, and fourteen for the trunk. In acute flares of disease, steroids should be used in combination with emollients and skin care regimens in order to avoid steroid overuse and steroid-related side effects.

Although topical corticosteroids have long been used as the mainstay of therapy in atopic dermatitis, the development of topical immunomodulators has enabled a steroid free anti-inflammatory topical treatment.¹⁶

In the US and Europe, pimecrolimus cream (1%) and tacrolimus ointment (0.03%) are approved for the treatment of atopic dermatitis in children aged two or older and in adults.¹⁷ Tacrolimus ointment (0.1%) is only approved for use in adults. Side effects with topical calcineurin inhibitors (TCIs) include a transient burning sensation of the skin. In a study comparing the local side effects in children of 0.03% tacrolimus ointment versus 1% pimecrolimus cream, pimecrolimus demonstrated better local tolerability.¹⁸

TCIs are not associated with skin atrophy and were hailed as a useful alternative in the treatment of sensitive areas such as the face.¹⁹ On January 19, 2006 the US FDA announced the approval of updated labeling for both pimecrolimus (Elidel® cream) and tacrolimus (Protopic® ointment). The labeling now includes a boxed warning about possible cancer and a patient medication guide. The new labeling also identifies these treatments as second-line treatments.

TCIs have been compared with topical corticosteroids in a limited number of studies. Compared with a low-potency corticosteroid, 0.03% and 0.1% tacrolimus ointments were shown to be more effective in children with moderate to severe atopic dermatitis.²⁰ In addition, a multicenter European trial demonstrated that 0.03% tacrolimus applied twice or once daily in children with moderate to severe atopic dermatitis was more effective than twice-daily treatment with 1% hydrocortisone acetate ointment. Based on these findings the two classes of drugs may provide a more clinically useful approach if utilized in a complementary manner. Although the optimal approach has yet to be identified, Pimecrolimus cream 1% (Elidel) with as-needed pulses of moderate topical corticosteroids has been proven to be an effective treatment regimen. However, both physicians and parents of children with atopic dermatitis are hesitant to use TCIs. As a result many

physicians and patients have discontinued the use of TCIs and have sought alternative, often very potent interventions, with varying degrees of success.

Leukotriene Inhibitors

The FDA has labeled leukotriene inhibitors such as zileuton, zafirlukast, and montelukast for the treatment of asthma. Because asthma and atopic dermatitis have a similar pathogenesis, these agents may have a role in the treatment of atopic dermatitis. It should be noted that montelukast should not be used in children under six years of age, and zafirlukast should not be given to children under twelve years of age.

As with TCIs, cyclosporine A inhibits calcineurin-dependent pathways, resulting in reduced levels of pro-inflammatory cytokines such as interleukin (IL)-2 and interferon (IFN). Clinical trials to date have demonstrated cyclosporine as an effective treatment for adult and childhood AD.²¹ In children it is especially important to note that vaccinations may not be effective during immunosuppressive therapy.

Omalizumab (Xolair) is a recombinant DNA-derived humanized immunoglobulin (Ig)G16-kappa monoclonal antibody to human IgE. Omalizumab is approved for the treatment of asthma in patients 12 years and older with serum IgE levels not exceeding 700IU/ml.²² The efficacy of omalizumab in patients with refractory atopic dermatitis and IgE levels far exceeding those of patients with asthma has been reported with mixed results.²⁵ Acute atopic dermatitis

is characterized by a Th2 immune response (IL-4, IL-5), whereas chronic atopic dermatitis is more encompassed by a Th1 immune profile (IL-2, tumor necrosis factor alfa (TNF)- α). The Th2 immune response in atopic dermatitis is marked by eczematous cutaneous lesions, eosinophilia, and elevated serum IgE levels. High-affinity IgE receptors (Fc ϵ RI) are prominent in atopic dermatitis. The significance of this high-affinity receptor for IgE has been demonstrated by studies in which blockade of the Fc ϵ RI receptor site by anti-Fc ϵ RI antibodies results in a paucity of allergen binding. Fc ϵ RI-bound allergen-specific IgE has been unequivocally detected in patients who are allergic.

Omalizumab has warnings for both malignancy and anaphylaxis; however, their incidence appears to be remote. Omalizumab only binds free IgE without crosslinking IgE that is already bound to Fc ϵ RI receptors, minimizing the risk of anaphylaxis.²³ Optimal candidates with atopic dermatitis are those with severe, refractory disease in which other systemic therapies were not successful. Omalizumab may provide a safer alternative to traditional therapies when treating patients with severe atopy who are persistently unresponsive to other therapeutic measures.

The treatment of atopic dermatitis with phototherapy is well established and represents a standard second-line therapy of choice in adults.²⁴ In children, UV therapy should be restricted to adolescents greater than twelve years of age, except in severe cases. To date, the long-term side effects of UV therapy are still unknown. ■

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