

The Changing Paradigm of Atopic Dermatitis Therapy

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■ Abstract

The pathophysiology of atopic dermatitis (AD) is complex, and future treatment options will likely be incorporated in a multimodal approach to management. The new, directed therapies that have been developed will likely be used in conjunction with concomitant continuous or intermittent use of standard therapies; the goal is to optimize therapeutic outcomes while minimizing adverse impacts on safety and cost. Current data regarding disease course and expression throughout life suggest that treatment strategies also will need to be adjusted as a patient grows. Research also indicates that interventions begun in infancy—such as the use of emollients—may mitigate or prevent AD signs and symptoms in children at high risk for the disease.

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■ Keywords

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Within the past 2 decades, ongoing research regarding the pathophysiology of atopic dermatitis (AD) and other conditions associated with immunoglobulin E (IgE) sensitization has resulted in an expanded and more

comprehensive understanding of the genetic, immunologic, and environmental factors involved in the onset and expression of atopic diseases.

This evidence has generated interest in multiple clinical care pathways. The importance—and possibility—of identifying and preventing disease in at-risk infants is an area of major interest. The care of patients with established disease can now include the use of new agents that are often more clearly targeted at a specific biologic pathway. Given risk-benefit ratios that include not only toxicity but also cost, better use of existing and widely used topical and systemic treatments remains an area of active investigation. New information has led to an increased ability to provide optimal management, and to meet public expectations for better disease control and quality of life for patients and their families.

However, our better understanding of both the complexity of atopic disease and the multiple therapeutic choices available increases the need for health care providers to understand the myriad options now available for both preventive and therapeutic interventions. Providers must be aware of safety and cost issues for available agents and be prepared to inform families about the range of treatment choices available as well as the evidence available to date regarding the safety of these various agents.

Considering Long-Term Treatment Safety in AD

Medications that are approved by the US Food and Drug Administration (FDA) have undergone rigorous testing for efficacy and safety, but the experience with a new medication prior to FDA approval often is relatively short-term and, compared to the anticipated, real-world experience, consists of exposure to relatively few subjects. Postmarketing surveillance over time can reveal safety signals that bear watching and, in some instances, the FDA has mandated the collection of such information in a more structured fashion, as in the case of topical calcineurin inhibitors (TCIs).

The TCIs tacrolimus and pimecrolimus were approved by the FDA—in 2000 and 2001, respectively—for the second-line treatment of patients with AD 2 years of age and older. In 2006, the FDA issued a requirement that both TCIs carry a boxed warning on their labels, cautioning prescribers and consumers about a theoretical risk for malignancy associated with these agents.

Following a meeting of the FDA Pediatric Advisory Committee in 2003, two 10-year prospective patient registries were created to track malignancies in patients with AD treated with TCIs: A Prospective Pediatric Longitudinal Evaluation to Assess the Long-Term Safety (APPLES) of tacrolimus, initiated in 2005, and the Pediatric Eczema Elective Registry (PEER), initiated in 2004. In the protocols for both registries, each patient is assessed every 6 months over a period of 10 years for any serious adverse events, including systemic and

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cutaneous malignancies. In the APPLES registry, the last among 8,037 patients was enrolled in 2012; the estimated date of completion is August 2022.¹ In the PEER registry, recruitment is ongoing until 2017, with an estimated total enrollment of 8,000 patients; the estimated completion date is December 2021.² The interim data from the APPLES registry are expected to be published in the first quarter of 2017.

In the decade since this warning was instituted, numerous epidemiologic and clinical studies have been published that fail to support a clear association between TCIs and malignancy, including lymphoma. Among these was an update published in 2013 by Siegfried and colleagues,³ who evaluated the preclinical, clinical, and epidemiologic evidence available to that point and concluded that an association between TCIs and malignancies was unsubstantiated. An analysis of data from the The Health Improvement Network database in the United Kingdom also have failed to detect an increased risk for malignancies with the use of TCIs.⁴

Finally, Sigurgeirsson and colleagues⁵ reported the results of their 5-year randomized, open-label trial involving 2,418 infants with AD between 3 and 12 months of age. The infants were randomized to receive pimecrolimus (with a short-term topical corticosteroid allowed to manage disease flares) or topical corticosteroids alone; 1,205 infants were in pimecrolimus group, and 1,213 were in the corticosteroid group. The study had two objectives: primarily, to compare the safety of pimecrolimus and topical corticosteroids, and secondarily, to document the long-term efficacy—treatment success being defined as a clear or almost-clear score on the Investigator's Global Assessment.

The investigators reported that treatment success was achieved in more than 50% of patients by week 3 in both groups. After 5 years of treatment, overall treatment success in both groups was greater than 85%, and facial treatment success was 95% in both groups. The safety profile in both groups was similar, and no evidence of impairment of humoral or cellular immunity was seen in either group. The authors concluded that these findings support the use of pimecrolimus as a first-line therapy of mild to moderate AD in infants as young as 3 months of age.

Prior to the appearance of the boxed warning on TCI labeling, many clinicians were liberally—and successfully—prescribing these medications, as indicated, as a second-line, short-term agent for managing mild to moderate flares of AD in patients 2 years of age and older, particularly in treating facial and intertriginous areas. Health care providers often were prescribing TCIs off-label as longer-term, maintenance therapy to prevent flares and to treat AD in children less than 2 years of age. The institution of the boxed warning caused many clinicians to avoid TCIs and resume more frequent use of topical corticosteroids. This was detrimental to those patients who had achieved control of AD with the TCIs, particularly those with involvement of skin areas (such as the face and intertriginous areas) for which topical corticosteroids cannot be used on a prolonged basis.

Luger and colleagues⁶ recently published a consensus article that reviewed the literature on TCIs (most of which addressed pimecrolimus, specifically) and concluded that these agents are safe and effective for treating AD in infants as young as 3 months of age. They further recommended that the labeling

in the United States and Europe restricting TCI use to patients 2 years of age and older be changed. In addition, they advised that the boxed warnings be removed.

Scientific Advances and Drug Development for AD

The advent of biologics greatly expanded the treatment options for immune-mediated diseases. The discovery of the role of inflammatory cytokines in rheumatoid and psoriatic arthritis as well as cutaneous psoriasis and the introduction of tumor necrosis factor inhibitors for these diseases provided a much-needed alternative to standard therapies. However, they also introduced new concerns regarding both safety and cost. Since that time, treatment options have been introduced that target other inflammatory mediators, such as interleukins (ILs), which play key roles in many inflammatory dermatologic diseases.

Targeted treatments for AD based on pathophysiologic processes involved in AD have been developed, including the IL-4R α receptor blocker dupilumab and small-molecule phosphodiesterase-4 (PDE-4) inhibitors such as crisaborole.

However, therapeutic strategies using biologic agents and small molecules that have been successful in treating psoriasis may not work with equal efficacy in AD. Psoriasis has specific, identified molecular pathophysiologic pathways that the newer medications have targeted, whereas AD is a more heterogeneous disease with multiple genetic, immunologic, and environmental components and complex pathophysiologic pathways, all of which have been shown to vary among ethnic and geographic populations. Therefore, although newer biologic agents are welcome additional options for treating AD and, it is hoped, will lead to improved outcomes in many patients, it is unlikely that any single agent, class of agents, or therapeutic approach can be expected to be universally applicable treatments for all forms of AD. Instead, the choice of agents used in subsets of patients may be best guided by techniques that could include patient stratification based on biomarkers such as transcriptome analysis, immunohistochemistry, and serum cytokine profiling. This is a key area for future study in AD.

Renewed Attention to Existing Agents

In the current and future treatment of AD it is likely that safety and economic considerations will favor the development of better stratagems that use currently existing, traditional modalities. Such a strategy was used to improve the treatment of acute lymphoblastic leukemia (ALL): only one new medication has been developed for ALL in the last 35 years, but the patient survival rate has increased over that time from 60% to 95%, the result of optimization of existing treatments.

Traditional therapeutics that are candidates for future optimization in selected patients with AD include methotrexate, cyclosporine,⁷ and coal tar.^{8,9} The use of newer agents such as systemic biologic agents initially, with subsequent “pulsed” dosing of topical corticosteroids, in tandem or in concert with TCIs or topical PDE inhibitors, could provide patients with a therapeutic plan that maximizes response and minimizes cost and toxicity. Topical bleach baths have been found to have both anti-inflammatory as well as anti-infective properties, identifying their utility in both preventing infection and decreasing inflammation.¹⁰

In addition, newer evidence indicates that the traditional intervention of petrolatum, in an attempt to protect the skin barrier, appears also to have beneficial immunologic effects.^{11,12} Identification of at-risk infants and intervention with topical emollients and other dry skin care could prove to be an effective public health intervention, leading to the decreased incidence of disease. In addition, interventions that might be optimal in infancy may need to be modified with age and in light of changing manifestations of AD.

Conclusion

Current evidence indicates that the complex pathophysiology of AD requires a multimodal approach to management and a view toward changing strategies as a child grows. Allergen avoidance, skin barrier protection, and long-term treatment plans will necessitate ongoing patient education and skill development as patients become increasingly able to participate in the management of their disease. Therapeutic education of parents—and, in the long term, patients themselves—must include attention to AD comorbidities as more information becomes available on the effects of AD and its treatments on cardiovascular, musculoskeletal, and neurologic systems.

In addition, as new classes of therapies are presented for possible inclusion in the roster of potential treatments for AD, changes will be needed in the algorithms of care that we now use, including interventions in infancy—such as emollient use—that may prevent the manifestation of AD symptoms in children who are at risk for the disease. Judicious use of the multiple, new, directed therapies that have been developed—likely employed in conjunction with continuing or intermittent use of standard therapies—will allow practitioners to provide optimal therapy while minimizing adverse impacts on safety and cost.

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