In Atopic Dermatitis, Looks Can Be Deceiving

During a Science and Innovation Theater presentation at the 2016 Academy of Managed Care Pharmacy annual meeting in San Francisco, California (April 19-22, 2016), Jonathan Silverberg, MD, PhD, MPH, assistant professor of dermatology at Northwestern University Feinberg School of Medicine, uncovered the burdens of atopic dermatitis (AD); communicated the current science, which demonstrates the underlying inflammation in AD; highlighted the association between inflammation and T helper type 2 cell (Th2)-driven immune dysregulation; and described how optimal management can reset expectations of disease control.

This conference presentation and supplement were sponsored by Regeneron Pharmaceuticals, Inc, and Sanofi US.

BURDEN OF AD

AD is a common, chronic, inflammatory skin disease. It is associated with immune dysregulation and skin barrier dysfunction.

Prevalence and Age of Onset

AD affects millions in the United States and it is one of the most common dermatoses. The number of individuals affected has been increasing in industrialized countries. Up to 10% of adults have eczema, and an estimated 3.2%, or 7 to 8 million US adults, have AD. It is estimated that 1.6 million adults who have been diagnosed and treated for moderate-to-severe disease remain uncontrolled. Up to 25% of children experience AD, and it is the top diagnosis at dermatologist visits in children 4 years and younger.

However, AD is not just a pediatric disease. The onset of symptoms spans all ages (Figure 1). AD may be a persistent, life-long disease. The Pediatric Eczema Elective Registry follow-up examined the natural history of children with mild-to-moderate AD (N = 7157). Figure 2 demonstrates the proportion of individuals with at least 5 years of follow-up at a given age who ever reported a 6-month symptom-free and medication-free period (N = 2416). It was not until 20 years of age that 50% of patients experienced at least one 6-month symptom-free interval.

Signs and Symptoms of AD

Patient-reported signs and symptoms of AD can occur on a daily basis. Baseline data for 380 adults with moderate-to-severe AD recruited into a randomized treatment study showed that 91% experienced dry or rough skin 5 to 7 days per week. A total of 78% reported flaking skin, 67% had cracking skin, 51% experienced bleeding, and 34% reported oozing at least 5 days per week (Figure 3).

The presentation of AD differs in its acute, subacute, and chronic forms. Acute and subacute lesions are intensely pruritic and are characterized by erythema, papules, vesicles, excoriations, and serous exudate. Chronic lesions are characterized by lichenification, papules, plaques, and excoriations. Patients with moderate-to-severe AD can experience acute and chronic lesion simultaneously.
In addition to causing dermatologic lesions, patients with AD are susceptible to skin infections and colonization with *Staphylococcus aureus*. In a study of 687 patients with AD, *Staphylococcus aureus* colonization rates of 74% and 38% were reported in acute (n = 97 of 131) and chronic lesions (n = 211 of 556), respectively, versus 3% from the skin of patients with urticaria (n = 8 of 247). Other studies have shown that AD causes exaggerated clinical manifestations of viral infections and an increased susceptibility to dermatophyte fungal infections.

**Effects of Symptoms on Daily Life**

In patients with moderate-to-severe AD, itch is the most common and persistent burden. Eighty-six percent of patients enrolled in one study reported the daily presence of itch, and more than one-third (41.5%) reported itching at least 18 hours per day. In another study, approximately 40% of participants who completed an internet-based questionnaire had more than 10 episodes of itch per day, and 35% had experienced itching for 20 years. In a separate study, more than 50% of participants who completed an internet-based questionnaire reported pain sensation associated with itch.

Sleep disruption is also a problem for patients with moderate-to-severe AD. Nearly 9 of 10 patients with moderate-to-severe AD report disrupted sleep at least 1 night a week and slightly more than half have their sleep disrupted at least 5 nights a week. Sleep disruptions are often doubled in patients with eczema than in those with no disease. In a 2012 US population-based survey (N = 34,613) conducted by the National Health Interview Study, individuals with eczema were more likely than those with no disease to experience fatigue (adjusted OR 2.23; 95% CI, 1.93-2.58), daytime sleepiness (OR 2.04; 95% CI, 1.75-2.38), insomnia overall (OR 1.83; 95% CI, 1.59-2.12), insomnia and fatigue (OR 2.74; 95% CI, 2.28-3.29), and insomnia and daytime sleepiness (OR 2.47; 95% CI, 2.04-2.99) (all significant \( P < .0001 \)).

AD occurs in relapsing and remitting cycles. In the International Study of Life with Atopic Eczema (ISOLATE), patients (>13 years) and caregivers (of children 2-13 years) underwent in-depth telephone interviews. The study included a minimum of 150 patients recruited from 8 countries; all patients had moderate-to-severe AD. The 1371 patients with moderate AD reported an average of 8.3 episodes of exacerbated symptoms per year, totaling 113 symptomatic days per year and 33 nights of sleep disruption per year (calculated by multiplying the number of flares per year by the number of nights sleep was affected during a flare). For the 631 patients with severe AD, exacerbated symptoms occurred nearly once per month, an average of 11.1 episodes each year. These patients experienced exacerbated symptoms for more than half the year (192 days) and sleep disruption nearly half the nights in a year (162 nights).

Psychosocial dysfunction is increased among patients with AD. Patients of the ISOLATE study reported that the AD flare caused concern about their appearance, affected their self-confidence, and led to feeling unhappy or depressed. Patients with moderate-to-severe AD report feelings of embarrassment and low self-confidence, problems with personal and social relationships, and problems with work. In a study of 102 patients who self-rated their AD as severe, 47% reported being frustrated by the disease, 39% were embarrassed by their appearance, and 35% were angry about their appearance. A cross-sectional study of 266 patients with moderate-to-severe AD and their partners revealed that 38% experienced a decrease in sexual desire.

at least occasionally. In addition, 55% said that the appearance of skin affects their sex life, and 47% said that the disease treatment affects their sex life.

Behavioral, emotional, and psychological disorders are also increased in patients with AD. AD is independently associated with stress-related, behavioral, affective, and schizophrenic disorders. Anxiety, as measured by different clinical scales, is increased in patients with AD. Depressive symptoms are also increased in patients with AD.

Disease Assessment

Disease assessment is largely based on clinical judgment. A plethora of instruments are used to assess severity in clinical trials. However, they are rarely used in clinical practice. Clinicians should ask patients general questions about the impact of AD on daily activity and use available scales mainly when practical. More than 25 disease severity scales are available, including:

- Severity Scoring of Atopic Dermatitis (SCORAD)
- Eczema Area and Severity Index (EASI)
- Investigators’ Global Assessment (IGA)
- Six-Area, Six-Sign Atopic Dermatitis (SASSAD)
- Leicester Sign Score (LSS)

- Total Severity Score (TSS)
- Atopic Dermatitis Severity Index (ADSI)
- Total Body Severity Assessment (TBSA)
- Three-Item Severity Scale (TISS)

Two commonly used quality-of-life scales across AD and other diseases include:

- Dermatology Life Quality Index (DLQI)
- 36-Item Short-Form Health Survey (SF-36)

THE ROLE OF INFLAMMATION IN AD

AD is a systemic, immune-driven disease. Researchers have proposed 2 hypotheses in AD pathogenesis: an epidermal-based model (“outside-in”) and an immune-based model (“inside-out”). Regardless of initiation, in either model, the result is a state of disease.

Epidermal-Based Model

In the epidermal-based model (“outside-in”), AD is initiated by an epidermal barrier defect that occurs either through a genetic or acquired basis, with subsequent systemic immune activation mediated by memory Th2 cells. An abnormal skin barrier leads to antigen penetration and subsequent immune activation. The epidermal-based model is supported by mutations in structural proteins such as filaggrin, envelope precursor proteins, and claudin.

Immune-Based Model

In the immune-based model (“inside-out”), AD is considered an immunologic disorder, with contributing barrier dysfunction. AD is initiated by activated memory Th2 cells that secrete several systemic cytokines, leading to widespread activation of the immune system. Activation of Th2 cells and downstream signaling pathways result in epidermal hyperplasia.

Drivers of Inflammation in AD

Interleukins (ILs) are cytokines secreted by white blood cells that regulate the function of the immune system. IL-4 and IL-13 are key drivers in the underlying inflammatory process that drives itch and lesions. IL-4 and IL-13 represent key upstream drivers in the Th2 pathway that modulate multiple downstream mediators—including IL-5, IL-31, and immunoglobulin E—setting in motion the chronic underlying inflammation of AD.

In acute and chronic lesions, the combined effects of IL-4 and IL-13 create a positive feedback loop. Increased expression of IL-4 and IL-13 decreases the production of structural proteins and antimicrobial proteins, resulting in a weakened skin barrier and increased susceptibility to infection. Keratinocytes are also affected, resulting in decreased keratinocyte differentiation. The number of infiltrating immune cells increases, in turn causing increased expression of IL-4 and IL-13. Increases in IL-4 and IL-13 activity correlate with the appearance of acute lesions; expression of these cytokines is also elevated in chronic disease.

Elevated cytokine expression is persistent in skin lesions. In 1 study, expression of IL-4 and IL-13 was measured with reverse transcriptase-polymerase
chain reaction testing of intrapersonal biopsy samples from acute and chronic skin lesions and nonlesional skin of patients with moderate-to-severe AD (N = 17). Expression of IL-4 was significantly higher in acute lesions than in nonlesional skin (P < .05), and expression of IL-13 was significantly higher in chronic lesions than in nonlesional skin (P < .01) (Figure 5).

Abnormalities in Atopic Skin

AD causes genomic, immunologic, and epidermal abnormalities in both lesional and nonlesional skin. In a study, biopsy samples from nonlesional and lesional skin of patients with moderate-to-severe AD (n = 15) were compared with skin from normal, healthy volunteers (n = 10). Genomic profiling revealed that gene expression patterns in nonlesional and lesional skin in patients with AD differ from normal skin. In AD, nonlesional skin and lesional skin have similar differential gene expression in moderate-to-severe disease. In the same study, nonlesional skin in AD demonstrated immune and epidermal abnormalities. The cluster of differentiation 3 cutaneous T-cell population was significantly (86%) higher in nonlesional atopic skin than in normal skin from healthy volunteers (P < .001). Ki-67 cell proliferation was 218% higher in nonlesional atopic skin than in normal skin from healthy volunteers (P < .05). In the histological analysis, hematoxylin and eosin staining revealed differences in both nonlesional and lesional atopic skin compared with non-atopic normal skin (Figure 6).

Management Strategies

Traditional Strategies

Traditional management strategies for AD are reactive, and focus on treating disease flares as they arise. As the intensity of disease increases, therapies are added in a stepwise
fashion. Patients with dry skin only receive basic treatment which focuses on skin hydration and emollients, avoidance of irritants, and identification and addressing of specific trigger factors. Patients with mild-to-moderate AD are prescribed low- to mid-potency topical corticosteroids and topical calcineurin (for patients over 2 years), with higher-potency formulations used as the disease progresses to moderate-to-severe AD. Patients with recalcitrant, severe AD receive systemic or UV therapy (Figure 7).

**Proactive Treatment Strategies**

Improved management strategies focus on reducing the severity and incidence of flares. There is a recent trend toward proactive treatment in AD with topical corticosteroids or topical calcineurin inhibitors. With this strategy, patients receive an induction course of treatment that continues until symptoms are in remission. Twice-weekly maintenance therapy is aimed at keeping symptoms at or below a baseline level.

Opportunities to Optimize Management

Future management of AD can be improved by creating practical, clinically relevant definitions and methods to assess disease severity and control. There is a need for more specific long-term treatments that target the immune-mediated inflammatory nature of AD. During a question-and-answer session with an editor from the American Journal of Managed Care, Dr Silverberg remarked, “I think that for patients who require longer-term control ... there has to be a balance between regulating costs and ensuring that patients have access to these drugs, especially when they are suffering.” Also, increased patient education on the disease course and treatment of AD may optimize management.

SUMMARY

- AD is a common, chronic, inflammatory skin disease that may require continuous, long-term management in moderate-to-severe cases.
- In addition to barrier dysfunction, current understanding of the pathophysiology of AD has identified specific inflammatory mediators, including the Th2 cytokines IL-4 and IL-13, which are central to perpetuating the disease.
- AD has a significant impact on patients’ physical and emotional health, which can affect their quality of life.

REFERENCES


Figure 8 (A). Reactive Treatments: Anti-inflammatory Treatment of Visible Lesions Only

Figure 8 (B). Conceptual Representation of Proactive Therapy


