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The Decade of AD: Applying Learnings From Psoriasis to AD

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Atopic dermatitis (AD) and psoriasis are two common skin diseases. Current research demonstrates that, as in psoriasis, the cutaneous signs and symptoms of AD are the result of disease-specific immune dysregulation. In psoriasis, we have witnessed a revolution in translating the understanding of immune dysregulation to improvements in managing this disease. This experience may serve as a model for transitioning the understanding of immune-mediated inflammation of AD to improved disease management.

AD is a chronic, inflammatory skin disease affecting an increasing number of individuals in industrialized countries.[1,2] The estimated prevalence of AD in United States adults is 3.2 percent, but the prevalence is severalfold higher in children.[3-6] Evidence suggests that AD can be a life-long illness associated with persistent underlying inflammation punctuated by repeated, intermittant flares. A longitudinal study of children with mild-to-moderate disease found that the majority experienced symptoms into early adulthood.[7]

Psoriasis is an inflammatory disease that affects both the skin and the joints.[8] US prevalence in adults is estimated at 3.2 percent, of whom an estimated 30 percent had pediatric onset.[9,10]

The primary symptoms of AD are pruritus and eczematous lesions in the presence of generally dry skin.[11] The acute lesions associated with AD are characterized by diffuse erythematous patches and oozing papulovesicles. Chronic lesions are poorly demarcated and have scaly patches and plaques with excoriation and lichenification.[11] Pathologic alterations in two physiologic pathways are present in AD: abnormalities of epidermal structure and function, and cutaneous inflammation due to inappropriate immune responses to antigens encountered in the skin.[11] Such responses can profoundly affect the nature of the entire epidermis, as even the nonlesional skin from patients with moderate-to-severe AD is different from the normal skin of healthy individuals.[12]

Two models have been proposed to describe the initiation of AD. The epidermal-based model posits that defects in the permeability barrier are the primary initiators of AD. The extent of this abnormality corresponds to disease severity, and the permeability defects are present even in skin sites without active disease. As the result of sustained barrier abnormalities, antigen entry stimulates an inflammatory cascade.[13,14] In contrast to this model is the immune-based model, which maintains that some forms of AD demonstrate polarized immune pathways

that down-regulate keratinocyte terminal differentiation and lead to a secondary barrier defect. The notion of a secondary barrier defect accommodates the finding that, while genetic sequencing studies demonstrated a robust association between the risk of AD and loss-of-function mutations in the gene encoding filaggrin (*FLG*), a protein important for epidermal barrier function, most patients do not have mutations in *FLG*.[2] One in vitro study demonstrated that differentiation of keratinocytes in the presence of Th2 cytokines, such as interleukin 4 (IL-4) and IL-13, directly down-regulates filaggrin expression, which leads to epidermal barrier dysfunction.[15] The immune-based model of the disease is most prominently supported by evidence that AD disease activity resolves upon treatment with broad-based immunosuppressive therapies.[2,16] Although the primary initiating factor in the disease may still be debated, it has become clear that skin barrier biology and immune mechanisms closely interact in AD, and disease persistence into adulthood supports the chronic nature of the condition (see Figure 1 at right).[11,17]

SIMILARITIES BETWEEN AD AND PSORIASIS

As common inflammatory diseases of the skin, psoriasis and AD share some similarities.[18] The genetics underlying both diseases implicate genes of the adaptive and innate immune systems, as well as those contributing to barrier defects.[18] Both diseases are also subject to environmental triggers, including psychological stress and infections.[19,20] Psoriasis and AD affect broad populations, including children, adults, both sexes, and multiple races.[3,9,21,22] They produce negative impacts on patients' quality of life.[23,24] Their pathophysiologies also share similarities, as both are characterized by chronic inflammation of the skin involving large infiltrates of T cells.[18] Both diseases are also associated with a variety of comorbid conditions. AD is associated with asthma, allergic rhinitis (hay fever), and chronic sinusitis with nasal polyps.[3,25] Comorbid conditions associated with psoriasis include psoriatic arthritis, Crohn's disease, lymphoma, non-alcoholic fatty liver disease, metabolic syndrome or its components, and cardiovascular disorders.[26] Although some population studies suggest that AD also may be associated with an increased risk of cardiovascular disease (CVD),[27] additional epidemiologic studies report no significant association between AD and CVD[28] or suggest that poorer CVD outcomes may be due to an increased burden of comorbidities and negative lifestyle behaviors.[29]

It is not unexpected that a visible skin disease might affect patients' emotional and psychosocial health. AD is associated with stress-related, behavioral, and affective disorders, as well as with symptoms of anxiety and depression.[30-33] Similarly, adult psoriasis patients have reported psychiatric symptoms and diagnoses including depression, anxiety, and suicidality.[34] The psychological distress and diminished social vitality associated with each of these diseases are reflected in assessment scores that indicate a lower health-related quality of life in patients so affected.[35,36]

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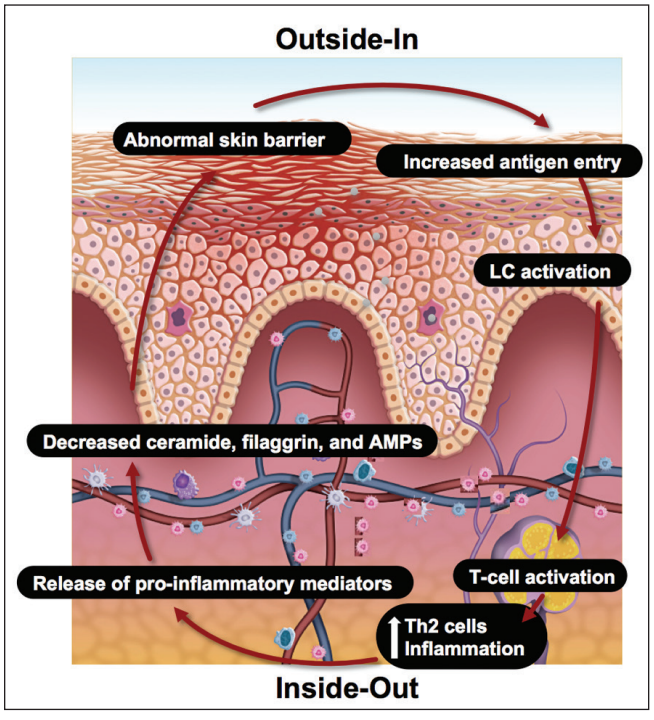

Adapted with permission from Gittler JK, et al.[17]

Figure 1. Models of AD demonstrating the interaction between barrier disruption and immune-mediated inflammation.

DIFFERENCES BETWEEN AD AND PSORIASIS

Probably less understood are the differences between AD and psoriasis, even though they are discrete disease

entities. For example, AD has been associated with a Th2 cell–mediated immune response involving the production of IL-4, IL-5, and IL-13, while psoriasis has been associated with the Th1 cell–mediated immune response that produces interferon-γ (IFN-γ) and IL-2.[18] Genetic studies have added to these differences by showing an association between AD and the genes encoding proteins expressed by Th2 cells, such as *IL-4*, *IL-4RA*, *IL-13*, and *RANTES/CCL5*. Similar studies have demonstrated an association between psoriasis and genes that encode products linked to Th1 and Th17 cells, such as *IL-12B*, *IL-23A*, and *IL-23R*, as well as the innate immune response genes *TNFAIP3* and *TNIP1*, which participate in tumor necrosis factor (TNF) signaling.[18] The types of inflammatory cells that invade the skin in these diseases also differ, as increased eosinophils and mast cells are observed in AD but not psoriasis, and neutrophils accumulate in psoriasis but not AD.[18]

Several other important differences between these two diseases have been noted (see Table below).[18] For example, age of onset differs widely. The majority of people with AD (85 percent) experience onset at five years of age or younger, whereas psoriasis typically begins in adolescence or adulthood.[18] Further, moderate-to-severe AD may be long-lasting: a recent study of adults with moderate-to-severe AD (mean age, 37 years) found that these individuals had lived with AD for a mean duration

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TABLE. DIFFERENCES BETWEEN AD AND PSORIASIS.

	AD	Psoriasis
Onset	Early childhood	Adolescence or early adulthood
Plaques	Not well-demarcated	Well-demarcated
	Pink to dull red	Bright red
	Wet	Dry
	Different appearance in acute and chronic phases	Similar appearance in acute and chronic phases
	Frequent impetiginization	Impetigo not evident
Asthma/atopy	Commonly associated	Not associated
Cutaneous infiltrate	No neutrophils in epidermis	Accumulation of neutrophils in epidermis
	Increased eosinophil and mast cell numbers in dermis	No eosinophils and mast cells
Vasodilation	Without angiogenesis	With angiogenesis
Th17 pathway	Attenuated	Increased
Products of inflammatory dendritic cells in epidermis	CCL17, CCL18, and CCL22	Inducible nitric oxide synthase, TNF-α, and IL-23
Leukocytes in circulation	Th2 > Th1 and Th17	Increased Th1, Th17, and Th22
	Increased IgE levels and eosinophil numbers in circulation	Normal IgE levels and eosinophil numbers

IgE=immunoglobulin E.

Adapted with permission from Guttman-Yassky E.[18]

of 27.6 years.[37]

The clinical presentations of the two diseases are also distinct.[18] The plaques associated with AD are highly pruritic, and are wet structures with crusting and serous exudate; they are most likely to be found on flexural areas and the face. In contrast, plaques associated with psoriasis are well-demarcated, dry, and bright-red, and have thick scales that are silvery-white in appearance; these plaques are more likely to be found on the extensor surfaces and the scalp.

An important area of distinction relates to the symptoms and characteristics of itch. Patients with AD are more likely than those with psoriasis to experience itch, especially severe itch, and they may have higher levels of itch over multiple body locations.[38]

In psoriasis, new lesions look similar to chronic lesions, whereas this is not the case in AD. In AD, acute lesions are bright-red, oozing lesions with serous exudate, which, when they become chronic, change to become pink to dull-red, lichenified plaques. Psoriatic lesions are less likely than AD lesions to be associated with bacterial colonization or impetigo. Several histologic differences have also been noted (see Table on previous page).[18]

Genomic profiling has been used to study changes in global gene expression in psoriasis and AD by comparing the profiles from skin of healthy controls and paired lesional and nonlesional samples from patients with disease. In the study of psoriasis patients, the gene expression profile of nonlesional skin was generally similar to that of healthy controls; in contrast, the expression profile from lesional psoriatic skin was completely separate and distinct from nonlesional skin and normal skin.[39] The picture in AD is quite different, in that changes in gene expression show a profile in nonlesional skin of an intermediate phenotype that is actually more similar to lesional skin than to normal skin.[12] This is consistent with the hypothesis that systemic immune abnormalities persist in patients with AD, in spite of the presence of skin regions that do not demonstrate active lesions.[12]

In terms of natural history, AD and psoriasis are also quite different. A majority of individuals with childhood onset AD will undergo spontaneous remission by the time they reach adulthood (only about 10 percent to 30 percent do not).[6] Severe AD in children has been associated with an increased risk for the development of other atopic diseases, such as asthma.[5] In psoriasis, much of the natural history depends on the particular clinical subtype.[40] Accordingly, psoriasis can manifest with chronic, stable plaques that undergo intermittent remissions and exacerbations, or with rapidly progressing, widespread lesions in acute phases.[40] The most common psoriasis subtype, plaque psoriasis, generally manifests as a chronic disease with intermittent remissions. Although periods of complete remission have been known to occur, it is likely that plaques will persist for months to years in the same locations.[40] An appreciable percentage of patients with plaque psoriasis, ranging from 7 percent to 48 percent, are likely to develop concomitant psoriatic arthritis, as well.[41]

Some evidence suggests that there may also be differences in the way patients and clinicians perceive the two diseases. In a cross-sectional survey of physicians and their patients with moderate-to-severe AD (N=678), they showed only moderate agreement in their disease severity ratings; patient-rated severity was higher in 11.2 percent of cases, lower in 20.2 percent, and matched in 68.6 percent.[42] Conversely, in psoriasis, physician ratings of disease severity were found to be consistently lower than those given by the patient in one study of psoriasis severity.[43] In both studies, the investigators speculated that the effects of the disease on the patient's quality of life may contribute to the differences between patient and clinician in their perceptions of disease severity.[42,43]

Numerous severity scales are available to measure the severity of AD. However, they are typically used only in clinical trials, as they were not designed for clinical practice.[6] The most commonly used instruments are the Severity Scoring of Atopic Dermatitis (SCORAD), the Eczema Area and Severity Index (EASI), the Investigator's Global Assessment (IGA), and the Six Area, Six Sign Atopic Dermatitis (SASSAD) scale.[44] In practice, clinicians should ask general questions about itch, sleep, impact on daily activity, and persistence of disease; they should use the currently available rating scales mainly when practical.[6]

Rating scales for psoriasis disease severity also abound, although they differ from those used for AD. Despite the use of dozens of scoring systems,[45] no single instrument has been found to capture all dimensions of psoriasis severity.[41] The Psoriasis Area and Severity Index (PASI) has been described as the most thoroughly validated score for quantitative evaluation of the clinical severity of psoriasis.[41] Overall, neither disease has a severity assessment method that is considered to be all-encompassing.[6,41]

PASI and EASI are empirically similar, as each is designed to assess the area and severity of disease. However, they assess different characteristics of two different diseases. PASI assesses redness, thickness, and scaling of psoriasis on a 5-point scale (0 to 4) for each

characteristic.[46] EASI assesses erythema, edema, excoriation, and lichenification of AD on a 4-point scale (0 to 3).[47] Formulas have been designed to accommodate the scores for all four regions of the body; the head/neck, trunk, upper extremities, and lower extremities. Both scoring tools can be too unwieldy to use outside of a clinical trial setting.

MANAGEMENT OF AD AND PSORIASIS

Both AD and psoriasis are chronic inflammatory diseases with inflamed, hyperkeratotic lesions on the skin.[18] For both diseases, patients with mild-to-moderate symptoms rely on topical therapy. This consists largely of anti-inflammatory, topical corticosteroids, with the addition of topical vitamin D analogs for psoriasis, and the addition of topical calcineurin inhibitors for AD.[48,49] When the disease is not controlled by topical therapy, systemic agents may be considered.[8,50] The evolution of new treatments for psoriasis over the past decade has been guided by the growth in knowledge of the immune circuits that influence specific cellular changes in the skin. Biologic agents that treat specific immune dysregulation in psoriasis are now available. In contrast, AD has only recently been linked to specific T-cell pathways. Successes in treating psoriasis suggest that therapies directed to disease-specific inflammation offer new avenues for disease control.

Currently, management of AD includes optimal skin care, addressing the skin barrier defect with regular use of emollients and skin hydration. Avoiding specific and nonspecific trigger factors is also helpful.[51,52] Further treatment, based on disease severity, can include the addition of various therapeutic agents in a step-wise fashion.[52]

In cases of AD that cannot be controlled by an optimized topical treatment plan and adherence, systemic treatment options of limited duration might need to be considered.[50,53] The management strategy for AD has traditionally focused on treating visible lesions.[54,55] In this scenario, patients administer treatment only when they experience visible signs and symptoms. When symptoms resolve, they stop treatment, and when symptoms reappear, they re-treat the symptomatic areas. A more forward-looking approach to AD management is to strive to reduce the severity and incidence of flares and is reflected in the recent trend toward using topical corticosteroids or topical calcineurin inhibitors as proactive treatments.[51,54-56]

CONCLUSION

AD is a common, chronic, inflammatory disease that may require continuous, long-term management in moderate-to-severe cases. The impact of AD on patients' physical and emotional health can negatively affect their quality of life. Current understanding of the pathophysiology of AD recognizes the role of specific inflammatory mediators, including the Th2 cytokines IL-4 and IL-13, in perpetuating the disease. As recently demonstrated with the success of immunologically based treatments for psoriasis, the translation of knowledge about the biologic basis of AD may have the potential to lead to more effective therapies. ■

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