The Role of Interleukins 4 and/or 13 in the Pathophysiology and Treatment of Atopic Dermatitis

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KEYWORDS

• Atopic dermatitis • Eczema • Inflammation • T helper 2 • Interleukin 4 • Interleukin 13 • Biologic

KEY POINTS

- Atopic dermatitis is an inflammatory skin disease mediated by increased T helper 2 inflammation in the skin and blood.
- Novel biologics targeting the T helper 2 cytokines, interleukins 4 and 13, show promise for the treatment of moderate to severe atopic dermatitis.

INTRODUCTION

Atopic dermatitis (AD) is a chronic, pruritic, inflammatory skin and potentially multisystem disorder that is associated with considerable morbidity. The most common morbidity, severe itch, in AD may result in difficulty falling asleep, staying asleep, more frequent nighttime awakenings, nocturnal scratching, and poor sleep efficiency, ultimately leading to daytime fatigue and impairment of instrumental activities of daily living.[1–3] AD is also associated with increased symptoms of anxiety and depression and higher rates of diagnosed depression, anxiety, attention-deficit (hyperactivity) disorder, and other mental health disorders in both children and adults.[4–6] Moreover, chronic itch and AD are associated with impaired productivity at school and work, social and relationship problems, and poor health-related quality of life.[3,7,8]

AD is commonly associated with several atopic disorders in children and adults, including asthma, hay fever, and food allergy.[1,9] The overlap of these disorders suggests potentially overlapping disease mechanisms and/or triggers that extend beyond the skin. Recent studies have identified several previously unrecognized comorbidities of AD, including cardiovascular disease, myocardial infarction, stroke, obesity, osteoporosis, injury and fracture, alopecia areata, and vitiligo.[5,10–15] Taken together, the comorbid health conditions occurring in patients with AD suggest that AD is a systemic disease, with widespread harmful effects.

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There are currently several unmet needs in the management of AD, particularly pruritus.[16,17] First, AD is typically managed by treating flares after activity has become full blown. Although this approach is reasonable in patients with only occasional flares, it is inadequate in patients with frequent flares or persistent disease with daily symptoms. In fact, moderate AD may be associated with symptoms 1 out of every 3 days in perpetuity.[18] Second, AD is typically managed using topical therapies, including emollients, corticosteroids (TCS), and calcineurin inhibitors. Topical therapies are typically effective for treating mild disease, but may not be effective in more severe disease and do not address underlying systemic inflammation.[19] Moreover, they are impractical and difficult to apply for patients with extensive disease. Several systemic immunosuppressants have been shown to be effective for treating AD, including intramuscular or oral corticosteroids, cyclosporine, methotrexate, azathioprine, and to a lesser extent, mycophenolate mofetil.[20] Each of these agents has a poor adverse-effect and/or tolerability profile, which limits their use in the clinical dermatology setting and requires laboratory monitoring for adverse effects. For example, systemic corticosteroids can cause glucose intolerance, weight gain, insomnia, depression, psychosis, and adrenal and immune suppression. Cyclosporine can cause, among other side effects, headaches, anemia, nephrotoxicity, hypertension, hirsutism, and electrolyte abnormalities. Methotrexate can cause anemia, leukopenia, gastrointestinal discomfort, weakness, and hepatotoxicity. Even when these agents are successfully used for treating AD, their potential toxicity precludes them from being used long term. The US Food and Drug Administration (FDA) has recommended that cyclosporine not be used in other disorders more than 1 year. Moreover, none of these agents are approved by the FDA for the treatment of AD. Only cyclosporine is approved for the treatment of AD in Europe.

Improved understanding of the immune basis of disease has allowed for the development of multiple novel targeted therapies in the AD pipeline. The principal benefit of more targeted therapy is the combination of improved efficacy and safety. The treatment of moderate to severe psoriasis has been revolutionized by the advent of multiple biologic therapies.[21] This review focuses on the roles of interleukin 4 (IL-4) and/or -13 in the pathophysiology of and development of targeted biologics for AD.

PATHOGENESIS

AD pathophysiology involves the interaction of epidermal barrier dysfunction with systemic inflammation and immune dysregulation. However, a fundamental debate exists as to whether AD is driven primarily by barrier dysfunction (outside-inside hypothesis) or primarily by an inflammatory response to irritants and environmental allergens (inside-outside hypothesis).[22]

Outside-In Hypothesis

The "outside-in" hypothesis posits that epidermal barrier dysfunction precedes AD and is required for the disease to manifest.[23] The outside-in hypothesis is supported by previous studies demonstrating loss-of-function mutations in the filaggrin gene (FLG).[24] Suboptimal filaggrin proteins may alter epidermal corneocyte shape and change the organization of lamellar bodies, resulting in impaired barrier function of the epidermis.[25] Poor epidermal barrier function leads to increased transepidermal water loss, decreased skin hydration, and vulnerability to exogenous insults.[26] Skin barrier dysfunction might also be acquired secondary to irritants and mechanical disruption.[27] Damaged keratinocytes from the disrupted epidermal barrier may then trigger the recruitment and/or expansion of inflammatory cells via release of thymic stromal lymphopoietin and other cytokines.[28,29] Epidermal barrier breakdown also permits allergen penetration and binding to Langerhans cells, resulting in increased Th2 inflammation in the skin and systemically; this may also predispose toward atopic diseases, for example, asthma and food allergy.[22,23]

Inside-Out Hypothesis

The "inside-out" hypothesis posits that inflammation precedes and even causes barrier dysfunction in AD. Recent studies identified multiple polymorphisms of inflammatory genes in patients with AD, including IL-4 receptor-α (IL4Rα), IL-4, IL-13, IL-31, cluster of differentiation 14 (CD14), serine peptidase inhibitor, Kazal type 5, chemokine (C-C motif) ligand 5 (RANTES).[23,30–33] These polymorphisms may lead to (a) immune dysregulation and cutaneous inflammation, resulting in (b) impaired keratinocyte differentiation and function, followed by (c) downregulation of filaggrin and antimicrobial peptides (AMPs), thereby (d) allowing penetration of exogenous allergens.[23,25]

In summary, the outside-in and inside-out hypotheses differ on the sequence of events leading to disease manifestation. It may be that the outside-in hypothesis applies to a subset of patients, such as those with FLG polymorphisms, whereas the inside-out hypothesis applies in patients with polymorphisms of immune-related genes.[23] Regardless of "the chicken or the egg,"