Management of Atopic Hand Dermatitis

Lauren R. Port, BA, Patrick M. Brunner, MD, MSc*

KEYWORDS

• Atopic hand dermatitis • Atopic hand eczema • Atopic dermatitis
• Chronic hand eczema

KEY POINTS

- Atopic hand dermatitis is a debilitating skin disease that tends to take a chronic course and is often resistant to conventional treatments.
- A clear history and the identification of potential irritants and allergens are paramount for correct diagnosis and differentiation from other forms of chronic hand eczema.
- In recent years, a better insight into the pathophysiology of atopic dermatitis has helped to develop novel treatment approaches also for atopic hand dermatitis.
- Similar to atopic dermatitis, the treatment of atopic hand dermatitis follows a stepwise approach from topical to systemic therapeutics.

INTRODUCTION

Atopic dermatitis (AD), also known as atopic eczema, is a chronic inflammatory skin disease that is characterized by highly pruritic lesions, commonly triggered by environmental irritants and allergens.[1] Atopic hand dermatitis (AHD) is a specific manifestation of AD in which the aforementioned symptoms are found primarily on the back of the hands, the inner wrists, and the base of the fingers.[2] AHD is considered a multifactorial disease with a complex etiopathogenesis, with genetic predisposition being a major risk factor, but epigenetic modifications and environmental exposures likely also play a key role in its development.[3] Further risk factors include age, pregnancy, geographic location, and environmental exposure,[4] but the exact pathogenesis is still only incompletely understood.

PATHOGENESIS

The pathogenesis of AD most likely involves a combination of many factors, including genetic predisposition, exacerbated immune responses, skin and gut microbiome

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Department of Dermatology, Icahn School of Medicine at Mount Sinai, One Gustave L Levy Place, New York, NY 10029, USA
* Corresponding author.
E-mail address: patrick.brunner@mountsinai.org

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changes, a compromised skin barrier, and environmental triggers.[5,6] A complex combination of inflammatory cells, cytokines, and chemokines is involved in its pathogenesis, resulting particularly in dysregulated Th2, but also Th22 and Th9 immune axes.[6,7] Loss of function mutations in the filaggrin gene are notable for their strong association with AD development.[8] With a loss of integrity to the epidermal barrier, irritants, allergens, and other pathogens can more easily invade the skin, which then mounts a pathologic immune response.[9]

Besides filaggrin, tight junctions play an important role in the defense system of the skin barrier and reduced expression of the claudin-1 protein, for instance, causes skin barrier disruption in AD.[10] Moreover, AD is characterized by insufficient upregulation of antimicrobial peptides due to strong Th2 activation.[11] This combined lack of defense mechanisms increases susceptibility to secondary colonization of organisms like *Staphylococcus aureus*.[11]

Similar to AD, AHD also can arise due to a combination of genetic factors and environmental triggers. Within the broad category of environmental exposures, AHD can be specifically triggered by work environments across various professions, especially those that require the hands to have frequent contact with irritants and allergens.[12] Health care workers, hairdressers, food industry workers, plumbers, and mechanics are some examples.[13] Among nurses, for instance, frequent handwashing has been specifically identified as the primary precipitant of AHD.[14] In this regard, however, it is essential to distinguish between AHD and related conditions such as contact dermatitis, both irritant (ICD) and allergic (ACD).[15] ICD is a response to direct exposure of an irritant to the skin and a resulting inflammatory response, hypothesized to involve activation of the innate immune system. By contrast, ACD is classified as a type IV hypersensitivity response by the adaptive immune system, namely antigen-specific T lymphocytes.[16] For both ACD and ICD, AD is an important risk factor but does not completely explain their development.[17] Compared to both types of contact dermatitis, the pathogenesis behind AHD is generally believedto result from a more complex interaction between genetic predispositions, environmental exposures, and immune pathways.[18]

BURDEN OF DISEASE

Living with a condition as visible as AHD can bring immense physical and emotional discomfort into the patient's everyday life.[19] The unpredictable fluctuation of symptoms and the visibility of AHD can have a profound negative impact on health-related quality of life. AHD can compromise an individual's capacity to execute tasks properly in their workplace or even attend work at all.[20,21] This convergence of physical discomfort and disease visibility helps to emphasize the importance of a correct diagnosis to choose an efficacious treatment modality.

DIAGNOSIS

AD itself is typically a clinical diagnosis. Complementary tests include skin swabs, patch testing, serum IgE measurements, and skin prick or scratch testing.[22] In contrast to other chronic inflammatory conditions, a skin biopsy is not generally beneficial, as histology cannot differentiate between different etiologies of chronic hand eczema.[23–25] Importantly, different ages have shown their unique lesion distribution.[26] While the severity of the disease is usually assessed clinically, some biomarkers can also be used such as serum LDH and CCL17, which are generally increased in patients with moderate-to-severe AD.[27] For AHD, a patient's past medical history plays an important role in the differentiation between AHD and ICD or ACD. Importantly,

patients with AD have higher frequencies of allergies than the general population. On average, 50% of children and 35% of adults suffering from AD are sensitized to common allergens.[28–31] Similarly, chronic hand eczema patients have an increased risk of allergic sensitization, and top ACD allergens haven been shown to include nickel, fragrances, quaternium-15, benzalkonium chloride, and methylisothiazolinone.[32–34] Thus, patch testing is an important diagnostic tool for the differentiation of ICD from ACD.

MANAGEMENT AND TREATMENT

Due to a better understanding of AD pathogenesis, there has been a revolution in treatment options for AHD, particularly due to the advent of biologics and small molecules that have recently become available.[35] Nevertheless, patient counseling about proper skin care practices and topical treatment modalities including moisturizers, corticosteroids, and calcineurin inhibitors are particularly important aspects of the treatment plan for AHD patients.[36]

Similar to AD, the approach for AHD treatment is directly proportional to the severity of the condition. Topical corticosteroids and calcineurin inhibitors are generally prescribed first, followed by higher potency topical corticosteroids and UV therapy, and, if not sufficient, systemic therapeutic modalities.[37] Wet wrap therapy has long been used to boost the efficacy of topical treatments and is still an important treatment strategy.[38] Calcipotriol, a derivative of vitamin D3, has efficacy for chronic hand eczema patients.[39] Crisaborole, a PDE-4 inhibitor, has been approved for patients with AD and can also improve AHD symptoms.[40,41]

The topical application of JAK inhibitors is currently being investigated in several trials for chronic hand eczema. Delgocitinib is a pan-JAK inhibitor that has shown overall improvement in hand eczema,[42] and ruxolitinib, a JAK1 and JAK2 inhibitor, also showed positive data for its improvement of pruritic symptoms in hand eczema patients, and has been approved for the treatment of AD.[39,43,44] Importantly, these topical treatments have only been investigated short term, and their long-term safety still needs to be established.

Regarding the use of phototherapy, psoralen and ultraviolet A (PUVA) and narrowband ultraviolet B (NB-UVB) have been proven to reduce symptoms of AHD. Using a 308 nm excimer laser is another treatment option for chronic hand eczema that could potentially serve as a replacement for other UV therapies due to its ability to target smaller areas at a lower dose of UV radiation.[45]

There are now several recently approved systemic therapies available for AD. IL-4 and/or IL-13 inhibitors (dupilumab, tralokinumab, and lebrikizumab) target type 2 inflammatory immune pathways.[46,47] JAK inhibitors (abrocitinib, upadacitinib, and baricitinib) have also proven effective treatments for AD, which more broadly target cytokine pathways.[42] While most of these agents are approved for the treatment of moderate-to-severe AD, their impact specifically on AHD is less clear.

Dupilumab has specifically demonstrated positive results in trials for AD patients with chronic hand eczema.[48,49] While tralokinumab and lebrikizumab showed improved symptoms and overall quality of life for patients with AD, their impact on hand manifestations has not been analyzed as robustly as dupilumab.[42,46,50] Alitretinoin is a vitamin A derivative and has been approved in various countries for chronic hand eczema. It works by targeting retinoic acid receptors, improving symptoms of inflammation. However, there are side effects that arise after prolonged use, including but not limited to headaches, teratogenicity, alopecia, and myalgias.[39,51] Systemic immunosuppressants such as cyclosporine, azathioprine, methotrexate, and mycophenolate mofetil

have also been explored as a possible treatment option for patients with chronic hand eczema.[37] However, these oral immunosuppressants can have a wide range of adverse effects and patient monitoring is necessary.[2,39]

As for systemic JAK inhibitors, there has been recent research addressing their treatment specifically for hand eczema patients, particularly with atopic predispositions.[42,43] Gusacitinib has been shown to suppress the underlying inflammatory response in patients with hand eczema.[52] Baricitinib is another systemic JAK inhibitor that has displayed improvement for patients with AD but has not been profoundly researched for patients with hand eczema specifically,[43] but a case series showed improvement in patients with chronic hand eczema.[53] Upadacitinib, a small molecule JAK inhibitor, has exhibited positive signs of improvement in the treatment of AD patients with atopic hand eczema in 2 randomized phase-3 trials.[54] Abrocitinib has also been approved for the treatment of moderate-to-severe AD and showed efficacy for AHD.[55] Overall, the rapidly increasing group of JAK inhibitors show promising results for various forms of eczema; however, their efficacy will need to be weighted in light of their long-term safety data, which are often not yet available.

SUMMARY

Recent developments in AD treatment also have a profound impact on treatment modalities of AHD. While many patients can now be treated with better efficacy, more research is still needed to identify optimal care for the patient with AHD.

CLINICS CARE POINTS

- AHD can be a debilitating skin disease, that needs to be distinguished from allergic and irritant contact dermatitis.
- Novel treatment approaches are currently revolutionizing the care of patients with AD, including those with AHD.

DISCLOSURES

P.M. Brunner has received personal fees from Almirall, Sanofi, Janssen, LEO Pharma, AbbVie, Pfizer, Boehringer Ingelheim, GSK, Regeneron, Eli Lilly, Celgene, Novartis, UCB, Merck, RAPT Therapeutics, Galderma, and BMS. P.M. Brunner has received research support from Pfizer, United States (grant paid to his institution). L.R. Port declares no relevant conflicts of interest.

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