Review Article

Recent Insights in Atopic Dermatitis Pathogenesis, Treatment, and Disease Impact

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Abstract

Atopic dermatitis (AD) is the most common inflammatory skin condition impacting patient quality of life. Although AD is widely studied, investigators have explored recent advancements in AD pathogenesis, treatment, and disease impact. Therefore, this article summarizes recent advancements in AD pathogenesis, treatments, and disease impact on patient quality of life. A PubMed search was conducted using the keywords: "atopic dermatitis AND pathogenesis," "atopic dermatitis AND microbiota," "atopic dermatitis AND dupilumab," "atopic dermatitis AND JAK$ inhibitors," and "atopic dermatitis AND quality of life." Epidermal barrier dysfunction and immune dysregulation play a key role in the pathogenesis of AD. Although most AD patients express a filaggrin mutation, such mutation alone does not predict disease severity. Immune dysregulation is characterized by T-helper-2 responses in acute AD and Th1 responses in chronic AD. Skin microbiota abnormalities and sweat exacerbate symptomatology. Dupilumab targets the interleukin (IL)-4Rα and is the only Food and Drug Administration-approved biologic that effectively treats AD. Newer alternative agents for AD treatment include IL-12 and IL-23 inhibitors, IL-31R inhibitors, and JAK inhibitors. AD patients have increased anxiety, depression, and sleep disorders ($P < 0.001$) and skin pain ($P = 0.02$) compared to control. AD is influenced by the epidermis, immune system, genetics, microbiota, sweat, and environment. AD has lasting impacts on patients' mental and physical health. Dupilumab is an effective biologic for treating the condition.

Keywords: Baricitinib, comorbidity, dupilumab, pathogenesis

INTRODUCTION

Atopic dermatitis (AD) is a chronic skin condition affecting children and adults.[1-4] While 70% of individuals outgrow AD before adolescence, 30% of cases persist into adulthood.[4,5] AD is characterized by an imperfect cutaneous barrier and dysregulated inflammation.[1] Although the precise role remains unknown, inflammation in acute AD is attributed to T-helper (Th)-2 cells and increased predisposition to skin infections.[6-8] AD patients have higher rates of mood disorders, sleep disorders, and less work productivity.[9] Approximately 50% of children with AD report that their disease negatively impacts their quality of life.[10]

Mild AD is typically managed with topical corticosteroids.[1] More severe cases of AD require additional oral immunosuppression with cyclosporine, methotrexate, azathioprine, and mycophenolate or immunotherapy.[1] Long-term treatment of AD with traditional immunosuppressive agents has adverse side effects that may limit their use.[4] Thus, additional safer treatment options are needed for AD.

Targeted biologic agents are in development to treat AD resistant to systemic immunosuppression. Currently, dupilumab is a Food and Drug Administration (FDA)-approved biologic for moderate-to-severe adult AD. Other biologic agents under study include lebrikizumab, nemolizumab, and Janus kinase (JAK) inhibitors.[1] Since new research in recent years has explored clinical manifestations, social effects, and therapies for AD, the purpose of this review was to gather insight into recent advancements in AD pathogenesis, treatment, and impact on the quality of life.

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METHODS

A PubMed search was conducted using the keywords "atopic dermatitis AND pathogenesis," "atopic dermatitis AND microbiota," "atopic dermatitis AND dupilumab," "atopic dermatitis AND quality of life," and "atopic dermatitis AND JAK$ inhibitors" [Figure 1]. AD pathogenesis articles were selected based on citation frequency and relevance.

RESULTS

Pathogenesis of atopic dermatitis

The pathogenesis of AD is influenced by epidermal barrier dysfunction and immune system dysregulation.[6,11] Epidermal barrier dysfunction initiates the development of AD whereas immune system dysregulation further contributes to disease development.[12] Skin microbiota, sweat, and the environment also contribute.[7,13]

Epidermal barrier dysfunction

AD patients have decreased barrier-stabilizing proteins and lipids.[11] In AD patients, keratinocytes in the stratum corneum are supported with loricrin (LOR), involucrin (IVL), and particles rich in proline.[11] Cells exposed to tumor necrosis factor-alpha and interleukin (IL)-4 are subject to inflammation and downregulation of LOR and filaggrin (FLG).[14,15] Decreased lipid synthesis further contributes to impaired epidermis in AD patients. In AD lesional skin, expression of the enzyme stearoyl-CoA desaturase is upregulated among viable cell layers. This results in increased unsaturated fatty acids and abnormal keratinization in the epidermis.[16]

FLG mutation is the most common identified genetic factor in AD development.[11] FLG2 mutations within a cohort of 60 African American participants are associated with more persistent AD ($P = 0.004$).[17] Although loss of function mutation in FLG is linked to earlier and more severe AD, patients can develop AD without the mutation.[18] FLG mutations are found in 15%–50% of AD patients whereas 40% of FLG mutation carriers do not develop AD.[19]

Impaired skin barrier predisposes to *Staphylococcus aureus* colonization and herpes simplex virus infection.[1] *S. aureus* adhesion occurs via fibronectin and fibrinogen.[20] S. *aureus*

releases an exotoxin called α-toxin that enhances T-cell proliferation and IL-22 secretion. About 70% of *S. aureus* strains produce staphylococcal enterotoxins (SEs) A, B, and C and toxic shock syndrome toxin-1 (TSST-1). These exotoxins function as superantigens that penetrate the epidermis, increase inflammation, and degrade the already deficient epidermal barrier.[20,21] *S. aureus* strains from AD skin have increased T-cell proliferation, increased IL-2, and decreased interferon-gamma (IFN-γ) compared to non-AD skin.[22]

Immune system dysregulation

AD was widely characterized by cytokine-producing Th2 cells, although recent evidence suggests that AD involves a complex interplay between Th1 and Th2 cells.[14,23] Th2 cells are primarily involved in acute AD whereas Th1 cells are primarily involved in chronic AD.[6] As acute AD begins, Th2, Th17, and Th22 cytokines are released.[6,24] However, as AD progresses to a chronic state, Th1 mounts an additional immune response.[25]

Th2 cells produce pro-inflammatory cytokines and IL-4, IL-5, IL-13, and IL-31.[26] IL-4 induces the differentiation of Th2 cells to produce additional IL-4. Increased Th2 products downregulate Th1 cell production.[26] IL-4 downregulates genes encoding FLG, LOR, and IVL and increases fibronectin, increasing the ability for *S. aureus* to adhere to the skin.[20,26]

IL-4 and IL-13 inhibit keratinocyte differentiation and influence barrier dysfunction in patients with AD.[27] IL-13 induces the migration of CD4+ T-cells, mast cells, eosinophils, and macrophages in the dermis and skin remodeling secondary to inflammation.[28] Both IL-4 and IL-13 induce periostin expression that contributes to additional tissue remodeling in patients with chronic AD.[29]

IL-5 functions as a growth factor for B-cells and supports eosinophil growth and proliferation.[12] In a case–control study of 1120 individuals, IL-5 serum levels were higher in AD lesional skin compared to control ($P < 0.05$).[30] However, a monoclonal antibody against IL-5 was ineffective in AD.[31] IL-31R enhances pruritus in AD.[12,32]

IL-17 and IL-22 are increased in acute and chronic AD.[33] Acute AD is associated with higher amounts of IL-22.[6] In acute AD, IFN-γ production is inhibited by immunoglobulin (IgG).[33]
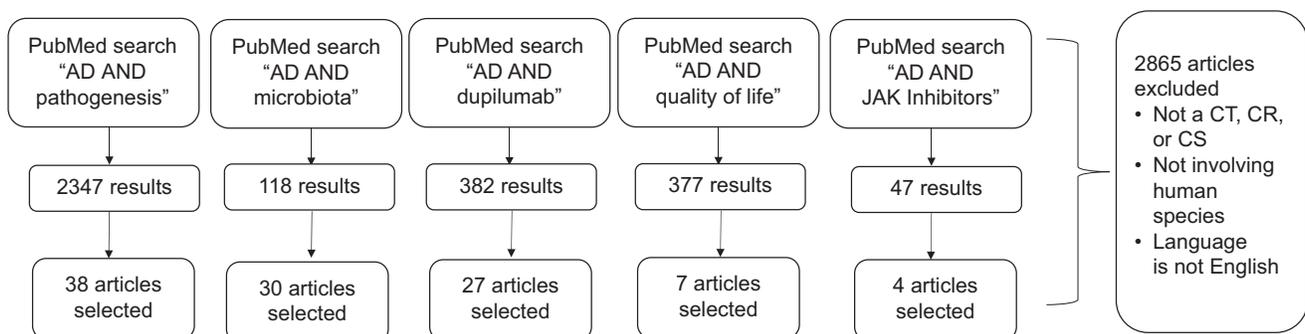
Figure 1: Flowchart of atopic dermatitis PubMed search. AD: Atopic dermatitis, CT: Clinical trial, CR: Case report, CS: Case series

IFN-γ production increases in chronic AD. IFN-γ induces macrophages that secrete pro-inflammatory cytokines and growth factors.[34] Thus, macrophages have a role in chronic AD. Since IFN-γ is a Th1-derived cytokine, this supports evidence for Th1 involvement in chronic AD. Furthermore, IFN-γ reduces IL-4 and IL-13 expression in chronic AD, suggesting a complex interaction between Th1 and Th2 in AD.[34]

Keratinocytes produce antimicrobial peptides (AMPs) including defensins, cathelicidins, calprotectins, and dermcidins.[12] AMPs enhance the innate response resulting in neutrophil, monocyte, and T-cell recruitment in the epidermis.[35] Decreased or absent AMPs contribute to cutaneous infection in AD patients.[36] Calprotectin is comprised of damage-associated molecular pattern (DAMP) molecules S100A8 and S100A9. Upregulation of S100A8 and S100A9 expression in response to IL-17A suggests the involvement of the DAMP-mediated inflammation pathway in AD.[37] Dermcidin peptides are reduced in AD patients, resulting in decreased skin protection and greater susceptibility to bacterial colonization.[38]

Human β-defensins (hBDs) are located on epithelial surfaces and activate upon injury or infection. However, Th2 cytokines downregulate hBD expression as the inflammatory cascade is activated. In AD, impaired hBD expression contributes to bacterial and viral susceptibility.[39] hBD-2 and hBD-3 are located in the upper epidermis and have antibacterial properties against *S. aureus* and herpes simplex virus that commonly colonize AD.[39] IL-4 and IL-13 exacerbate AD by downregulating hBD-2 and hBD-3.[27,40]

The influence of microbiota

AD skin generally expresses low bacterial diversity with greater abundance of *S. aureus* and *Staphylococcus epidermidis* compared to other genera such as *Propionibacterium*. Microbiome diversity is decreased in AD skin compared to non-AD skin in both young children ($P < 0.001$) and adults-teenagers ($P = 0.013$). In children and adults-teenagers, *Staphylococcus* was more abundant in AD skin compared to non-AD healthy skin. However, *Streptococcus* and *Propionibacterium* were decreased in AD skin compared to non-AD and healthy skin in children and adults-teenagers.[5] This suggests skin microbiota changes with age.

S. *aureus* threatens AD patients due to multiple virulence factors. Phenol-soluble modulins (PSMs) are a staphylococcal virulence factor that forms α-helical structures. These structures form cytotoxic pores in keratinocytes. PSMs also enhance *S. aureus* biofilm.[41,42] Additional virulence factors include microbial surface components recognizing adhesive matrix and superantigens. Superantigens include SEs, SE-like superantigens, and *S. aureus* TSST-1. About 57% of AD patients' *S. aureus* skin colonization isolates produced superantigens compared to 33% of control.[43] Furthermore, *S. aureus* penetration through the epidermis directly correlates with increased IL-4, IL-13, and IL-22 and decreased levels of cathelicidin.[44]

In a randomized, placebo-controlled, single-blinded clinical trial of 21 patients with AD and 14 healthy controls, application of topical corticosteroid fluticasone for 4 weeks normalized the microbiome in childhood AD.[45] In children of age 3 months–5 years with moderate-to-severe AD, baseline densities of total bacteria and *Staphylococcus* were higher at the worst AD lesional sites compared to nonlesional ($P = 0.001$) and control ($P < 0.001$) skin. After fluticasone treatment, lesional bacterial communities resembled nonlesional AD skin yet differed from controls ($P < 0.0001$). Normalization of skin microbiome with topical corticosteroid treatment is evident through the restoration of microbial diversity and replacement of *S. aureus* by *Corynebacterium, Prevotella,* and *Acinetobacter.*[45]

Sweat

Substances contained in sweat maintain skin integrity. Sweat contains antimicrobial factors and protease inhibitors.[46] AD patients have abnormal sweat composition and volume.[13]

Sweat from patients in acute AD has increased glucose concentration compared to sweat from healthy controls and patients with chronic AD ($P = 0.0331$). Sweat glucose concentration positively correlated with severity.[46]

Keratin-plugged sweat pores in AD skin contribute to hypohidrosis, called "sweat retention syndrome."[47,48] Sweat retention may lead to heat retention, xerosis, and increased risk of infection.[49] Histamine can also influence sweating. Since acetylcholine induces perspiration, histamine can suppress perspiration by phosphorylating sweat gland secretory cells consequently inhibiting of acetylcholinergic sweating.

Environment

Children exposed to smoke can absorb harmful metabolites, including nicotine. One specific metabolite of nicotine, called cotinine, was elevated in urine samples of 1669 toddlers exposed to tobacco smoke.[50] Children exposed to environmental tobacco smoke had a greater risk of developing AD compared to controls (odds ratio [OR]: 1.97; 95% confidence interval [CI]: 1.23–3.16). Therefore, tobacco smoke could contribute to the development of AD.

Treatment of atopic dermatitis

Topical corticosteroids and topical calcineurin inhibitors are FDA-approved for the primary treatment of AD.[51-54] Since topical corticosteroids and topical calcineurin inhibitors have been thoroughly studied, this review will discuss novel topical and biologic agents for the treatment of AD.

Phosphodiesterase (PDE) enzymes are targeted by topical AD treatments. PDE-4 is expressed in inflammatory cells.[11] Crisaborole is a topical PDE-4 inhibitor. A study of 1522 participants aged 2 years and older was randomized to crisaborole or vehicle in two identically designed, double-blind, vehicle-controlled studies. More participants in the topical 2% crisaborole group reported a clear score compared to placebo after 28 days of twice-daily application (crisaborole, 51.7%; placebo, 40.6%; $P < 0.001$).[55]

Dupilumab is a human monoclonal antibody against IL-4Rα. It blocks IL-4 and IL-13 signaling pathways.[12] IL-4Rα is found on inflammatory cells such as keratinocytes, T-cells, dendritic cells, and eosinophils.[56] IL-4 and IL-13 induce IgE class switching, promote Th2 survival, recruit eosinophils, and mediate pruritus. IL-4 and IL-13 inhibit keratinocyte terminal differentiation and AMP production.[31] Dupilumab decreases Th2 inflammatory cytokines and reverses epidermal barrier dysfunction. Dupilumab targets products of Th2 cells that are upregulated in chronic AD. These products are IL-5, IL-13, IL-10, and IL-31.[57] The cellular targets of dupilumab include T-cells, B-cells, mast cells, basophils, and dendritic cells.[58] Dupilumab is the first FDA-approved biologic for the treatment of moderate-to-severe AD.[59] The recommended initial dose is 600 mg (two 300 mg subcutaneous injections) followed by 300 mg every other week.[60]

The Eczema Area and Severity Index (EASI) was used in a randomized, placebo-controlled, Phase IIb clinical trial of 379 adult patients with moderate-to-severe AD to evaluate dupilumab efficacy. The largest decrease in EASI was in the group receiving dupilumab once per week (300 mg, 73.7%) and once every 2 weeks compared to placebo (300 mg, 68.2%; placebo, 18.1%) at week 16 ($P < 0.0001$).[61] A dose-dependent relationship was reported.

In two randomized, double-blind, placebo-controlled, Phase III clinical trials, dupilumab improved symptoms in 671 moderate-to-severe AD patients 18 years and older. More participants who received 300 mg subcutaneous dupilumab once per week (38%) or once every 2 weeks (37%) than placebo (10%) had an Investigator Global Assessment Score of 0–1 or at least a 2-point decrease from baseline at week 16 ($P < 0.001$). They also reported improved symptoms of anxiety, depression, and overall quality of life compared to placebo.[62] Clinical improvement with dupilumab was observed in as little as 4 weeks of treatment.[63] Another 12-week randomized study reported that a higher proportion of participants in the dupilumab group achieved EASI-50 compared to the placebo group at week 12 (dupilumab 300 mg, 85%; placebo, 35%; $P < 0.001$).[64] Finally, a 16-week randomized double-blind, placebo-controlled study using dupilumab improved clinical responses in 452 participants.[65] EASI improvement was greater in all dupilumab groups compared to placebo (300 mg once a week, 74%; 300 mg every 2 weeks, 68%; 300 mg every 4 weeks, 64%; 200 mg every 2 weeks, 65%; 100 mg every 4 weeks, 45%; placebo, 18%; $P < 0.0001$) at week 16.[65]

A meta-analysis reported a decreased incidence of skin infection in the dupilumab group compared to the placebo group (dupilumab, 6.7%; placebo, 13.3%; $P < 0.00001$). Rates of upper respiratory tract infections were similar between the dupilumab (6.5%) and placebo (5.4%) group ($P = 0.11$). Nasopharyngitis incidence was similar between the dupilumab (15.7%) and placebo (13.9%) groups ($P = 0.55$). There was a higher incidence of conjunctivitis in the dupilumab group (8.0%) compared to the placebo (3.6%) ($P < 0.0001$).[66] Although in one study the rate of herpes virus infection was similar between the dupilumab (6.1%) and placebo groups (5.2%; $P = 0.30$), there was an increased rate of herpes viral infections in dupilumab participants compared to placebo (8% vs. 2%) in a different study.[63,64]

Ustekinumab is a human monoclonal antibody that targets the p40 subunit of IL-12 and IL-23.[1] In two different randomized, placebo-controlled Phase II trials, ustekinumab failed to achieve a significant improvement in the EASI score.[67]

Nemolizumab is a humanized antibody against the IL-31R. IL-31R is found on keratinocytes and monocytes and is associated with AD-associated pruritus. Nemolizumab improved pruritus in 264 moderate-to-severe AD patients in a randomized, double-blind, placebo-controlled Phase II trial. All nemolizumab groups achieved significantly greater EASI improvements compared to placebo (0.1 mg/kg every 4 weeks, 23%; 0.5 mg/kg every 4 weeks, 42.3%; 2.0 mg/kg every 4 weeks, 40.9%; placebo, 26.6%) at week 12.[68] Patients in the highest dosing group also reported a 59%–63% reduction in sleep disturbance.[68]

Omalizumab is a humanized IgG1 monoclonal antibody that binds to IgE, consequently inhibiting mast cell or basophil activation.[1] In a study of adults with severe AD and elevated IgE, omalizumab had a significant EASI improvement in only two of ten patients.[69] Potential for clinical use of omalizumab is restricted by a higher incidence rate of cardiovascular events in AD patients receiving omalizumab (13.4/1000 person-years; 95% CI: 11.6–15.4) compared to controls (8.1/1000 person-years; 95% CI: 6.5–10.1).[70]

JAK/signal transducer and activator of transcription (STAT) signaling is associated with AD pathogenesis.[11] In a study of 69 adult patients with mild-to-moderate AD, adults treated with 2% tofacitinib ointment had greater EASI improvement compared to placebo (tofacitinib twice-daily applications, 81.7%; placebo, 29.9%; $P < 0.001$) at week 4. Participants reported alleviation of itching as early as day 2.[71] JTE-052 is a newer topical ointment that inhibits JAK. JTE-052 targets JAK1, JAK2, JAK3, and tyrosine kinase 2. [Please add citation for PMID: 28960254] Through improvement of skin barrier dysfunction and suppression of IL-31 induced pruritus, JTE-052 consequently restores the skin barrier function and suppresses inflammation. [Please add citation for PMID: 26115905]. In a randomized, vehicle-controlled, Phase II clinical study, 327 participants were randomized (2:2:2:2:1:1) to receive JTE-052 ointment at 0.25%, 0.5%, 1%, 3%, the control ointment, or tacrolimus 0.1% twice daily. All JTE-052 groups had improved EASI scores compared to placebo at week 4 (0.25%, 41.7%; 0.5%, 57.1%; 1%, 54.9%; 3%, 72.9%; placebo, 12.2%; $P < 0.001$).[72] A study of 6 participants treated with oral tofacitinib citrate for 8–29 weeks reported improvement in AD-related pruritus and sleep.[73] Finally, 124 patients with moderate-to-severe AD in a Phase II randomized, double-

blind, placebo-controlled study were instructed to take placebo, baricitinib 2 mg tablets, or baricitinib 4 mg tablets once daily for 16 weeks. All participants were allowed to apply topical triamcinolone. Compared to placebo, 61% of participants receiving 4 mg of baricitinib reported a 50% improvement in EASI at 16 weeks (placebo, 37%; $P = 0.27$). However, 57% of participants receiving 2 mg of baricitinib achieved EASI 50 compared to placebo ($P = 0.65$). One participant receiving baricitinib 2 mg discontinued treatment due to neutropenia, whereas five participants discontinued baricitinib 4 mg due to abnormal leukocyte counts, headache, and eczema. One participant receiving 4 mg of baricitinib reported a serious adverse event of a benign large intestine polyp.[74]

Impact of atopic dermatitis

AD is a detrimental disease that significantly impacts the quality of life. It affects mental and physical functioning due to disease chronicity and sleep deprivation from pruritus.[1,75] To explore the psychiatric impact from AD, a study of 380 AD patients reported anxiety symptoms more often than depression symptoms. Furthermore, 50% of participants lived with AD for more than 27 years, and 40% were diagnosed in adulthood.[75]

In a study of 354,416 AD patients aged 2–17 years, AD was associated with increased rates of attention-deficit hyperactivity disorder diagnoses.[76] In a study of AD patients aged 6–12 years, AD patients had higher levels of ADHD symptoms compared to control (OR: 1.88; 95% CI: 1.04–3.39).[77] Pruritus is associated with sleep disturbances, psychological distress, and nocturnal scratching which causes daytime fatigue and impairment of daily activities.[60,78,79]

Another study investigated the impact of AD on health-related quality of life and productivity in 349 AD patients and 698 controls. Among AD patients, 29.8% reported anxiety, 31.2% reported depression, and 33.2% reported sleep disorders compared to 16.1%, 17.3%, and 19.2% in the placebo group, respectively (all $P < 0.001$). Participants' responses to the standardized Short Form 36 questionnaire were used to measure their mental and physical health, reflected by the mental and physical component scores. Higher scores equated to better health status. The average mental component score in AD patients (44.5) was lower than controls (48.0; $P < 0.001$). The average Physical Component Score in AD patients (47.6) was lower than controls (49.5; $P = 0.004$). About 25.6% of AD patients self-reported an overall work impairment compared to 18.1% of controls ($P = 0.004$).[9]

A prospective birth cohort study of 2916 participants reported AD patients with resolved AD in early childhood continued to have emotional and behavioral problems at 10 years of age. Based on the Strengths and Difficulties Questionnaire at 10 years of age, AD patients reported exacerbated mental health problems (OR: 1.49) and emotional symptoms (OR: 1.62).[80]

Discussion

Epidermal dysfunction and immune dysregulation play key roles in the pathogenesis of AD. Other factors that contribute to AD pathogenesis include skin microbiota, sweat, and environment. Proteins that contribute to the epidermal barrier are downregulated in AD patients predisposing to inflammation and eczema formation.[11,14,15] AD patients' susceptibility to *S. aureus* colonization and infection further decreases the integrity of the epidermal barrier. The FLG gene plays a role in AD pathogenesis. Loss of function in the FLG gene predisposes patients to more severe and persistent AD.[18,19]

Dupilumab is a promising new treatment option for AD patients who have exhausted topical medications. Phase II and Phase III trials demonstrated excellent improvement in AD skin and were well tolerated by patients.[64,66]

The JAK/STAT pathway is a promising therapeutic target in both topical and oral formulations. A 2% tofacitinib ointment applied twice daily improved EASI in 4 weeks.[71] Furthermore, a Phase II study reported baricitinib as an effective treatment in adult participants with moderate-to-severe AD compared to placebo.[74] Baricitinib and future JAK inhibitors are a promising treatment option in resistant AD cases limited to systemic therapy.

Research has demonstrated the impact of AD on quality of life. AD patients reported lower mental and physical scores compared to healthy controls ($P < 0.001$; $P = 0.004$).[9] Adolescents diagnosed with AD and followed up at age 10 had increased mental health and emotional problems (OR: 1.49 and 1.62, respectively).[80] Such findings increase the necessity for safe, effective, and affordable treatments.[81]

Conclusion

Recent developments have increased understanding of the complexity and pathogenesis of AD. Newly approved medications have expanded the therapeutic options for patients and providers.

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Conflicts of interest

There are no conflicts of interest.

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