

# Current and Emerging Therapies for Atopic Dermatitis in the Elderly

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**Abstract:** Atopic dermatitis (AD) in the elderly has recently emerged as a distinct subgroup of AD, garnering widespread concern due to its increasing global incidence rate. Epidermal barrier dysfunction, inflammatory response, and chronic pruritus interact with each other, contributing to the pathogenesis and pathophysiology of AD in the elderly. Although fundamental medications are essential for managing AD in the elderly, older adults often struggle with regular usage of moisturizing emollients, topical medications, and avoidance of environmental triggers, leading to recurrent or even exacerbated disease progression. Therefore, a systematic medication approach is necessary to control pruritus and skin lesions. Traditional systemic treatments may not adequately meet the treatment needs of moderate and severe AD in the elderly and may even pose certain safety risks. Biologics and Janus kinase (JAK) inhibitors, exhibiting excellent clinical efficacy, have made significant breakthroughs in AD treatment. Existing evidence suggests that dupilumab, a human monoclonal IgG4 antibody, has been confirmed as an effective and safe first-line systematic treatment for moderate to severe AD in the elderly, with no notable differences between adults and the elderly. However, the limited inclusion of elderly patients in related clinical studies hinders the generalizability of these findings. As older patients face a higher risk of adverse events with JAK inhibitors, JAK inhibitors are recommended when no other suitable treatment options are available. Obtaining population-specific data is crucial for making evidence-based treatment choices when managing AD in older adults with JAK inhibitors.

**Keywords:** atopic dermatitis in the elderly, treatments, biologics, JAK inhibitors

## Introduction

Atopic dermatitis (AD) is a chronic, relapsing pruritic cutaneous disease characterized by type-2 inflammation and skin barrier dysfunction resulting from environmental stimuli and genetic factors.<sup>1</sup> With societal development and an aging population, AD in the elderly has emerged as a distinct clinical subtype of AD, capturing widespread attention. Unlike the other three types of AD (infantile, childhood, and adult), older adults often experience concurrent pruritic skin diseases with similar clinical manifestations, such as seborrheic dermatitis, geriatric scabies, prurigo, bullous pemphigoid, along with underlying systemic conditions including hypertension, cardiovascular and cerebrovascular diseases, and diabetes. As a result, the diagnosis and treatment of AD in the elderly are more complex than the other types. The treatment of AD in the elderly follows a stepwise approach, which includes basic and systemic treatment, with an emphasis on safety. Compliance with basic treatment is generally poor among elderly patients with AD, and the significance of systemic treatments should be highlighted. Traditional systemic therapies, including systemic corticosteroids and immunosuppressants, have reasonable efficacy but are not well-tolerated in the elderly population. Biologics, particularly dupilumab, have been confirmed as effective and well-tolerated systemic treatments for moderate and severe AD in the elderly. Janus kinase 1 (JAK1) inhibitors, with their advantages of rapid onset and convenient administration, may offer a better treatment option for elderly patients with AD. However, their impact on safety limits their use in the elderly population. This article reviews the epidemiology, clinical

characteristics, diagnosis, and current and emerging therapies for AD in the elderly, providing a new perspective on the diagnosis and treatment of AD in this age group.

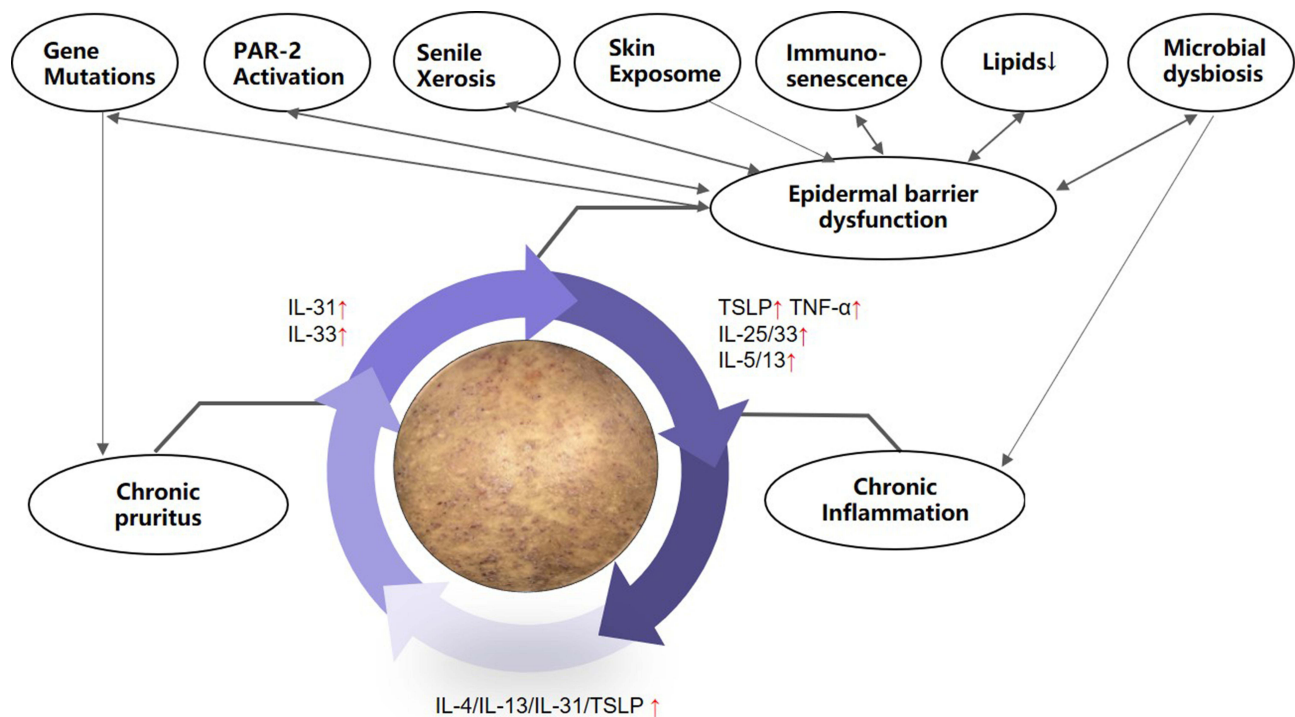
## The Prevalence of AD in the Elderly is Increasing

AD is classified into four stages based on age: infancy (birth–2 years), childhood (>2–12 years), adolescence and adulthood (>12–60 years), and older adult (>60 years).<sup>2</sup> The global prevalence of AD has been rising over the past three decades. In recent years, with the population aging, the prevalence of AD among individuals aged >60 years has been notably high, displaying distinct clinical characteristics compared to AD in children and adults.<sup>3</sup> Currently, there is limited epidemiological data on AD in the elderly, both domestically and internationally. In industrialized countries, the prevalence of AD in the elderly ranges from 1%–3%.<sup>4</sup> In Poland, the incidence rate of AD among the elderly (aged ≥60 years) is 1.86%.<sup>5</sup> In Japan, the incidence rate of AD (age ≥60 years) is approximately 2.6%.<sup>6</sup> Germany reports an incidence rate of AD (age ≥50 years) at 4.3%.<sup>7</sup> An analysis of data from The Health Improvement Network, a database of electronic health records from UK general practitioners, examined the prevalence of AD in different age groups (totaling 9,154,936 cases). The analysis demonstrated a gradual increase in the incidence rate of AD among the elderly over time, possibly attributed to increased senile xerosis and trans-epidermal water loss.<sup>8</sup> Furthermore, while the prevalence of AD in adults is higher among women than among men, the opposite has been observed in the elderly.<sup>9</sup> This difference may be related to the influence of sex hormones in the elderly.<sup>8,10</sup>

## The Pathogenesis of AD in the Elderly Involves the Interaction of Epidermal Barrier Dysfunction, Inflammatory Response, and Chronic Pruritus

AD is a complex and multifactorial skin disorder mainly mediated by type II helper T cells (Th2) to environmental antigens and allergens. In older patients, the aging skin is commonly related to declined physical barrier function, resulting in exacerbation of AD. Aging skin becomes thinner, more translucent, and undergoes elastosis, making it more susceptible to physical damage. Furthermore, older individuals have a diminished ability to restore the skin barrier after irritation.<sup>11</sup> The immune system undergoes dysregulation with aging and is characterized by chronic inflammation, often referred to as “inflamm-ageing”.<sup>12,13</sup> Inflamm-ageing is believed to result from remodeling of both the innate and adaptive immune systems, resulting to the production of chronic inflammatory cytokines.<sup>14</sup> Pruritus, or itching, is a common and distressing symptom experienced by a significant number of elderly patients. In the United States and other regions, approximately a quarter of patients over 65 years old visiting outpatient clinics report pruritus. In the elderly, pruritus is frequently secondary to xerosis (dry skin), often associated with other dermatologic conditions, like AD [Figure 1](#).<sup>11</sup>

In general, there are two types of AD that have been identified, including IgE anaphylaxis (exogenous) and non-IgE anaphylaxis (intrinsic), where the former refers to elevated serum total IgE (>200 or 400 IU/L, according to facility criteria) and allergen-specific IgE levels are both elevated; The other group refers to normal serum total IgE levels and elevated allergen-specific IgE levels.<sup>15–17</sup> Similar to other age groups, elderly patients with AD experience these two types when the diagnosis of AD is made based on standardized diagnostic criteria.<sup>17,18</sup> Additionally, similar to infantile AD, elderly AD patients may also experience an unspecified allergic type with normal level of serum total IgE and elevated level of allergen-specific IgEs. This indeterminate allergic type represents an intermediate, state between the intrinsic and exogenous types. Unlike infantile AD, these three clinical phenotypes in AD patients often exhibit a discontinuous disease state, possibly indicating different underlying mechanisms. In elderly AD patients with IgE allergies, total IgE levels range from 2500–10,000 IU/mL. The most common environmental allergen in elderly patients with AD is dust mites, followed by pollen. However, the prevalence of allergies to food, fungi, and animal dander is low.<sup>1</sup> Guttman et al<sup>19</sup> analyzed the molecular markers in the skin lesions and peripheral blood of patients with AD across different age groups. They found that levels of Th2-related cytokines such as interleukin (IL)-5, IL-13, and chemokine ligands CCL13, CCL18, and CCL26 decrease with age in the skin lesions of patients with AD. Moreover, levels of Th22 and IL-22 also decrease with age, whereas the expression of Th1/Th17-related cytokines increases. Similar changes in cytokine levels were observed in serum, with downregulation of Th2 cytokines and upregulation of Th1 cytokines in elderly patients with AD. Li et al analyzed the clinical features and molecular profiles of elderly patients with AD in China. They found that serum IgE levels and eosinophil counts in elderly patients with AD were



**Figure 1** The pathogenesis of AD in the elderly that involves epidermal barrier dysfunction, chronic inflammation, and chronic pruritus.

significantly lower than those in other age groups. The serum levels of IL-4, TARC, IL-17A, IL-6, IL-22, IL-33, and thymic stromal lymphopoietin (TSLP) in elderly AD patients than were significantly higher than those in healthy control group, indicating a mixed Th2/Th17/Th22 inflammation.<sup>20</sup> Furthermore, Guttman et al<sup>21</sup> discovered that cardiovascular risk factors (including growth differentiation factor, myeloperoxidase, and serum soluble ST2) and risk factors associated with arterial-pulse cone-like hardening (such as CCL4, CCL7, and sorting protein 1) were higher in elderly patients with AD than those in young patients with AD. This suggests an increased risk of cardiovascular events in older patients with AD, indicating the potential benefits of cardiovascular disease screening and prevention in this population.

## AD in the Elderly Often Presents with a Distinct Clinical Characteristic Known as the “Reverse Sign”

While the skin appearance of elderly AD is generally similar to that of adult AD, there is a difference in the localization of lichenoid eczema. In children and adults with AD, lichen-like lesions commonly appear in the flexural areas of the elbows and knees. However, in elderly AD, these areas are typically unaffected, and the lichen-like lesions appear on the extended sides of the elbows and knees. This reverse sign may be attributed to decreased sweat secretion in the elderly.<sup>2,16,22–24</sup> In addition, elderly AD can manifest with other specific skin manifestations, including intractable facial erythema, lateral eyebrow shedding (Hertoghe’s sign), Dennie-Morgan infraorbital folds, and neck eczema with reticular, rippled, or pigmented skin.<sup>22,25</sup>

## Diagnosis of AD in the Elderly is Difficult

The diagnosis of AD in the elderly can be challenging for several reasons. Firstly, elderly individuals often have other pruritic skin diseases such as contact dermatitis, nummular dermatitis, chronic pruritus, scabies, adverse drug reactions, and skin malignancies. Moreover, the presence of concomitant systemic diseases such as hypertension, cardiovascular and cerebrovascular diseases, gastrointestinal diseases, and diabetes can cause pruritus due to medical conditions or adverse drug-related effects, further complicating the diagnosis of AD in the elderly. The complex immune mechanisms involved in AD and the lack of clear clinical, histopathological, and laboratory diagnostic markers also contribute to the difficulty in diagnosis. Currently, there are no specific diagnostic criteria for AD in the elderly. The Hanifin and Rajka (H&R) diagnostic criteria,

which are widely used for AD diagnosis, can also be applied to the diagnosis of AD in the elderly.<sup>26</sup> Tanei et al<sup>1,4</sup> indicated additional diagnostic points for elderly AD, including lichen eczema on the extremities with the fossa cubitalis and popliteal fossa being unaffected, personal and family history of atopic diseases, increased levels of serum total IgE and allergen-specific IgE, a disease course of >6 months, and exclusion of other pruritic skin diseases.<sup>4</sup> Yue et al<sup>27</sup> conducted a study to validate diagnostic criteria for elderly Chinese populations and proposed the Chinese criteria of atopic dermatitis for children as a diagnostic tool for elderly Chinese patients, particularly for cases of mild and moderate AD, considering the limitations in sensitivity of the H&R and UK Working Party criteria in this population.

## Basic Treatments for AD in the Elderly

To date, there are no guidelines published on the treatment of AD in the elderly. However, proper treatment and management of senile AD can help alleviate symptoms and improve patients' quality of life. The management and treatment of AD in the elderly typically involve basic and systemic approaches. Basic treatments focus on identifying and avoiding exacerbating factors, maintaining the skin barrier through the use of moisturizers and emollients, implementing anti-inflammatory measures with topical corticosteroids, topical calcineurin inhibitors, PDE4 inhibitors, and providing oral antihistamines to relieve pruritus.<sup>28–32</sup>

## Use of Topical Moisturizers and Emollients to Maintain the Skin Barrier

AD occurs due to potential skin barrier dysfunction, which is further aggravated in the elderly due to skin inflammation. This is characterized by an imbalance of skin flora colonization, reduced sweating, and a relative lack of ceramide in the epidermal stratum corneum.<sup>33,34</sup> Therefore, proper bathing practices and regular application of moisturizers are particularly crucial for the AD in the elderly and form the foundation of any treatment plan. It is advisable for elderly individuals with poor compliance to moisturizers to avoid hot water and reduce the frequency of baths to minimize damage to the skin barrier. Fragrance-free and allergen-free non-soapy cleansers with a neutral to low pH can be used. Taking a warm bath (32°C–37 °C) for 5–10 min once a day or every other day is recommended. Elderly patients with AD should choose suitable moisturizing emollients and apply them multiple times a day immediately after bathing to minimize water evaporation and help restore and maintain the skin barrier function.<sup>35</sup>

## Anti-Inflammatory Measures Including Topical Corticosteroids, Topical Calcineurin Inhibitors, and Topical PDE4 Inhibitors

Topical corticosteroids are the first-line anti-inflammatory treatment for AD, which can effectively reduce inflammation and preventing disease progression.<sup>36</sup> When initiating topical corticosteroid treatment, factors such as potency, formulation, severity, and body area to be treated should be considered. Clinicians should be alert to local skin adverse reactions (such as skin atrophy, telangiectasia, and purpura) related to long-term topical corticosteroids, particularly in the elderly with fragile skin.<sup>37</sup> Elderly patients with AD may face challenges when applying various topical medications due to lower self-care ability.<sup>38</sup> It may be necessary to prescribe a combined preparation of topical corticosteroids and moisturizers to enhance the treatment compliance in older patients with AD, even though the stability of the drugs in such formulations might be compromised.<sup>39</sup>

Topical calcineurin inhibitors (tacrolimus and pimecrolimus) act by inhibiting cytokine production in T cells through intracellular calcineurin inhibition, which is different from the mechanism underlying topical corticosteroids. Topical calcineurin inhibitors are suitable for treating AD that involve with the face, neck, forearms, and hands of older patients. The most common adverse event is irritative symptoms (such as transient burning sensation and hot flushes) at the site of application during the first few days of treatment. The AD in the elderly may discontinue use of topical tacrolimus due to these adverse effects, highlighting the importance of prior explanation to improve treatment compliance. Low dose of tacrolimus ointment mixed with an emollient can minimize the irritation, which can be beneficial during the initial stage of treatment. Currently, there is no existing evidence indicating increased risk of cutaneous malignancies, lymphoma, or other malignancies with appropriate application of topical tacrolimus.<sup>28,31</sup>

Crisaborole is the firstly topical phosphodiesterase 4 (PDE4) inhibitor approved for treating mild to moderate AD. It is considered a second-line option, similar to the topical calcineurin inhibitors, for patients who are unresponsive to topical corticosteroids.<sup>40</sup> Crisaborole has demonstrated safety and efficacy in the treatment of mild to moderate AD in patients aged 2 years and older,<sup>41,42</sup> with improvement in symptoms such as pruritus, erythema, exudation, excoriation, induration/papulation, and lichenification. The results of two large clinical trials showed a treatment success rate of approximately 32%.<sup>43,44</sup> While it is an effective treatment option with a low incidence of adverse effects, it may be expensive for elderly patients with AD. The elderly population often prefers topical corticosteroids due to their rapid efficacy and lower cost.

## Systemic Treatments for AD in the Elderly

Due to age-related physical limitations and reduced mobility, elderly patients often struggle with adhering to treatment plans involving moisturizing emollients, avoiding triggers, and applying topical medications such as glucocorticoids and calcineurin inhibitors. This can lead to persistent or worsening symptoms, necessitating systemic medications to control pruritus and skin lesions. Traditional systemic therapies for AD include oral antihistamines/anti-allergic drugs, systemic corticosteroids, oral immunosuppressants, and light therapy (narrow-band ultraviolet UVB), etc. However, these treatments have limitations when it comes to elderly patients with AD. Oral antihistamines/anti-allergic drugs are only applied to alleviate the AD-related pruritus temporarily but with limited efficacy for long-term disease control. Oral corticosteroids require careful monitoring and carry the risk of adverse events including hypertension, diabetes, infections, peptic ulcer disease, cataracts, osteoporosis, adrenal dysfunction, and steroid purpura. Long-term use of oral immunosuppressants like cyclosporine increases the risk of malignancies (such as non-melanoma skin cancer or lymphoma) and organ toxicity, particularly in the cardiovascular system and kidneys. Regular visits to the hospital every week or every other week to receive continuous UVB exposure can be burdensome for elderly patients with AD. Lam et al<sup>45</sup> reported a systematic review highlighting the underrepresentation of the older group in randomized clinical trials (RCTs) of systemic immunomodulatory treatments for AD, causing no sufficient evidence to support their safe clinical application in this population.

## Oral Antihistamines/Anti-Allergic Drugs

The use of antihistamines in AD remains controversial, but many studies support their role in alleviating AD-related pruritus, especially in patients with comorbid allergies such as urticaria and allergic rhinitis.<sup>1,46,47</sup> For elderly patients with AD, taking first-generation antihistamines before bedtime can improve sleep quality and control itching due to their sedative effect on the central nervous system.<sup>48</sup> However, it is important to be aware of the potential side effects of first-generation antihistamines in the elderly, including dizziness, drowsiness, cognitive dysfunction, urinary retention, constipation, and postural hypotension.<sup>49</sup> Second-generation antihistamines have fewer side effects than first-generation ones, but caution should still be exercised, considering the elderly population's underlying health conditions, such as cardiac and renal issues. Adjusting the dosage may be necessary due to age-related metabolic changes.<sup>50</sup>

## Systemic Corticosteroids

Systemic corticosteroids can be used for patients with moderate to severe AD at a dose of 5–15 mg/day or 0.1–0.2 mg/(kg·d). Retrospective studies have shown that combining systemic glucocorticoid therapy with basic treatments is relatively effective for elderly AD.<sup>4,16</sup> However, systemic use of glucocorticoids in elderly patients can lead to electrolyte imbalances, hypertension, osteoporosis, and other adverse reactions. Additionally, their long-term efficacy is limited, and relapse or rebound may occur after discontinuation. Clinicians should monitor and prevent the occurrence of these adverse events.

## Oral Immunosuppressants

Cyclosporine inhibits the production of T cell-dependent cytokine and activates the immune pathway by blocking nuclear factors in T cells. Oral cyclosporine is effective in treating severe AD in elderly patients when administered at optimal and full doses (eg, 3 mg/kg/day).<sup>28</sup> However, clinicians need to be cautious about the potential increased risk of malignancies



including non-melanoma skin malignancies or lymphoma, as well as organ toxicity, especially in the cardiovascular system and kidneys, related to long-term use of cyclosporine for the AD in the elderly. The course of oral cyclosporine treatment for AD in the elderly should not exceed 12 weeks, although intermittent restarts of >2 weeks can be considered. Elderly individuals may be more concerned about the adverse effects of cyclosporine due to the increased risk of cancer and higher prevalence of renal insufficiency in this age group. Discontinuation of oral cyclosporine often leads to the recurrence of symptoms in elderly patients with AD. Moreover, the cost of cyclosporine is significantly higher than that of oral corticosteroids, which limits its application to treat the AD in the elderly. Methotrexate is primarily used for refractory elderly AD at relatively low doses of 10–15 mg per week. Azathioprine is mostly prescribed for severe or refractory cases in elderly patients with AD at a daily dose of 50–100 mg, with mercaptopurine methyltransferase genotyping recommended prior to medication. Tripterygium vine may be an important option to treat the elderly patients with moderate to severe AD, as it does not have adverse effects on fertility and can be administered at a daily dose of 1.0–1.5 mg/kg. When using immunosuppressants such as cyclosporine, methotrexate, azathioprine, and tripterygium, careful attention should be given to potential adverse reactions, including bone marrow suppression and hepatic and renal insufficiency in elderly patients.

## Phototherapy

Ultraviolet light is beneficial for AD, particularly for patients with moderate to severe symptoms.<sup>51</sup> Narrow-band UVB phototherapy exerts immunomodulatory effects by suppressing the immune pathways of Th2, Th22, and Th1 cells, as well as their associated cytokines in the affected skin of individuals with AD. As an adjuvant therapy, narrow-spectrum UVB treatment with an irradiation dose ranging from ~0.35–0.70 J/cm<sup>2</sup> can be beneficial for elderly patients with AD.<sup>52</sup> However, it is important to note that narrow-spectrum UVB therapy may not effectively address acute episodes of AD and excessive exposure can potentially trigger eczema flare-ups. Additionally, narrow-band UVB phototherapy should not be used in combination with oral cyclosporine or topical calcineurin inhibitors, as this will increase the risk of skin malignancies. Adverse events of phototherapy may consist of mild irritation, diffuse pigmentation, or solar lentigo.

## Biologics

In recent years, several biologic medications have been developed and approved or are undergoing clinical trials under the supervision of regulatory agencies such as the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) (refer to Table 1 for an overview). These biologics have demonstrated high efficacy in patients with AD. Dupilumab, as a human monoclonal IgG4 antibody, targets the alpha subunit of the IL-4 receptor. By suppressing the IL-4 and IL-13 signaling pathways, it effectively controls the Th2 response, leading to reduced levels of CCL17, a key regulator of Th2 response and an AD biomarker. Dupilumab was approved in 2017 for the treatment of moderate to severe AD in adults, demonstrating significant improvements in pruritus and inflammation without dose-limiting toxicity.<sup>53–56</sup> Studies have also investigated the efficacy and safety of dupilumab in elderly patients with severe AD.

**Table 1** Biologics Therapies for AD

Target	Name of Drug	Mechanism	Administration Route	Development Stage
IL-4 $\alpha$	Dupilumab	Inhibits the IL-4/IL-13 signaling pathway by blocking the shared IL-4 receptor- $\alpha$ subunit	Subcutaneous injections	Approved by FDA in 2017
IL-13	Lebrikizumab	Inhibits IL-13 by preventing the formation of the IL-13R $\alpha$ 1/IL-4R $\alpha$ heterodimer	Subcutaneous injections	Phase III Clinical Trial Completed
IL-13	Tralokinumab	Binds with high affinity to IL-13, preventing its interaction with its receptors and succeeding signaling pathways	Subcutaneous injections	Approved by EMA in 2021
IL-31	Nemolizumab	Inhibits IL-31 by binding to its receptor $\alpha$ subunit (IL-31 $\alpha$ )	Subcutaneous injections	Approved by Japan in 2022

(Continued)

**Table I** (Continued).

Target	Name of Drug	Mechanism	Administration Route	Development Stage
IL-22	Fezakinumab	Blocks IL-22 involved in skin hyperplasia and skin barrier dysfunction.	Intravenous injections	Phase II Clinical Trial Completed
IL-12/IL-23	Ustekinumab	Blocks IL-12 and IL-23 by targeting their common p40 subunit, thus inhibiting the Th1 and Th17/Th22 responses	Subcutaneous injections	Phase II Clinical Trial Completed
IL-33	Etokimab	Blocks IL-33 and hence effectively inhibits neutrophil migration.	Intravenous injections	Ongoing
IgE	Omalizumab	Binds to the Fc (CH3 domain) of IgE molecules and prevents its interaction with its high affinity receptor FcεRI on mast cells and basophils, inhibiting the process of mast degranulation and release of inflammatory mediators.	Subcutaneous injections	Phase II Clinical Trial Completed
OX40	ISB 830	Binds to OX40 (CD135), a co-stimulatory molecule expressed on T cells, and prevents its interaction with OX40L (CD252) expressed on activated antigen presenting cells, thus failing to potentiate the T cell responses triggered through T cell receptors.	Intravenous injections	Phase IIb Clinical Trial Completed
TSLP	Tezepelumab	Binds to TSLP and prevents its interaction with its receptor hence blocking all downstream events associated with immune-modulating proteins and Th2 cytokines.	Intravenous injections	Phase IIb Clinical Trial Completed

A multicenter retrospective observational study evaluated 276 patients aged  $\geq 65$  years and revealed significant improvements in Eczema Area and Severity Index (EASI) scores, pruritus, sleep quality, and overall quality of life after 16 weeks of treatment with dupilumab. The efficacy of dupilumab in older AD patients was comparable to that in younger patients. Adverse reactions were observed in 22.51% of elderly AD patients treated with dupilumab, with conjunctivitis being the most common adverse event, although it was often pre-existing and did not worsen significantly during treatment. Only 1 patient (0.36%) stopped taking the drug due to adverse reactions.<sup>57</sup> Silverberg et al<sup>58</sup> pooled the data from four RCTs on dupilumab<sup>59–61</sup> and based on age-related stratifications ( $<60$  [N = 2261] and  $\geq 60$  [N = 183] years), dupilumab efficacy and safety were noted in patients aged  $\geq 60$  years with moderate to severe AD. The results revealed that dupilumab improved the signs and symptoms in AD in patients aged  $\geq 60$  years, and this improvement was comparable to that observed in patients aged  $<60$  years. The safety was noted to be consistent with the known dupilumab safety profile. However, the generalizability of these findings is limited by the small number of patients in the  $\geq 60$ -year-old group. This limitation can be attributed to the pain of injections and regular treatment visits every 2 weeks.<sup>62</sup> Future studies should explore the safety of dupilumab in patients aged  $\geq 70$  years. In 2021, tralokinumab was approved by EMA for the treatment of moderate to severe AD in adults, becoming the world's first monoclonal antibody targeting IL-13 approved for the treatment of AD.<sup>63–65</sup> Several other biologics are still being examined in clinical trials, exhibiting good efficacy and safety data.

## JAK Inhibitors

The JAK-STAT signaling pathway plays an essential role to mediate the effects of various key cytokines that bind to keratinocytes, immune cells, and peripheral sensory neurons to exacerbate the inflammation and itching, such as IL-4, IL-5, IL-13, IL-31, IL-22, and TSLP, which are implicated in the pathogenesis of AD. The therapeutic potential of JAK inhibitors was initially recognized in researches of autoimmune and autoinflammatory diseases characterized by JAK-STAT polymorphisms or heightened JAK-STAT signaling. Recently, JAK inhibitors have emerged as a novel treatment approach for AD due to the significance of JAK-STAT signaling, particularly JAK1, in regulating Th2 cytokines including IL-4, IL-13, and IL-31 (refer to Table 2 for an overview).<sup>66–68</sup> Baricitinib, upadacitinib, and abrocitinib have

**Table 2** JAK Inhibitors Therapies for AD

Target	Name of Drug	Mechanism	Administration Route	Stage
JAK1/2	Baricitinib	Inhibits JAK1 and JAK2 in the JAK-STAT signaling pathway, thus exerting an immunomodulatory and anti-proliferative effect	Oral	Approved by European Union in 2020
JAK1	Upadacitinib	Selectively inhibits JAK1 of the JAK-STAT pathway, thus blocking downstream cellular processes contributing to inflammatory conditions	Oral	Approved by FDA in 2022
JAK1	Abrocitinib	Selectively inhibits JAK1 of the JAK-STAT signaling pathway, thus preventing activation of JAK1 containing heterodimeric receptors and thereby inhibiting downstream Th2 differentiation and itch while avoiding undesirable effects of JAK2 inhibition such as neutropenia and anemia	Oral	Approved by FDA in 2022
JAK/SYK	Gusacitinib (ASN002)	Targets a broad range of cytokine axes through dual inhibition of JAK and SYK, a non-receptor tyrosine kinase that inhibits terminal differentiation of keratinocytes and is involved in regulation of B cell and dendritic cell differentiation and Th17/IL-17 signaling	Oral	Phase IIb Clinical Trial Completed
JAK1/2	Ruxolitinib	Selectively inhibits JAK1 and JAK2 to optimally deliver drug directly to the affected skin to accelerate the onset of action and reduce the potential of AEs typically observed with oral administration	Topical	Approved by FDA in 2022
JAK1/2/3/TYK2	Delgocitinib	Broadly inhibits signaling of inflammatory cytokines involved in the pathophysiology of AD and can improve skin barrier function by promoting the production of terminal differentiation proteins, such as filaggrin	Topical	Approved by Japan in 2020

received FDA or EMA approval for the oral treatment of moderate to severe AD.<sup>69–74</sup> In three randomized Phase III trials (Measure Up1, Measure Up2, and AD Up) evaluating the efficacy and safety of upadacitinib in moderate-to-severe AD, elderly patients ( $\geq 65$  years and  $\leq 75$  years) treated with upadacitinib 15 mg and 30 mg QD achieved comparable or higher percentages of EASI 75 and vIGA-AD 0/1 (a validated Investigator's Global Assessment of AD 0/1 score) at week 52 compared to the placebo group. The incidence of adverse events (AEs) adjusted for exposure was higher in patients aged  $\geq 65$  years receiving upadacitinib 30 mg than in patients aged  $\geq 65$  years receiving upadacitinib 15 mg or patients aged  $< 65$  years receiving upadacitinib 15 mg or 30 mg.<sup>75,76</sup> Cork et al,<sup>77</sup> analyzed data from one phase IIB study and six phase III studies of abrocitinib in the treatment of moderate to severe AD.<sup>69,78–82</sup> The study investigated the long-term safety of abrocitinib in a large sample of patients across different age groups, with data collected up to July 24, 2020. The analysis was conducted in two cohorts: a placebo-control cohort comprising adolescent patients aged 12–17 years and a full analysis cohort consisting of patients who received at least one dose of abrocitinib (100 mg or 200mg). The patients were divided into four groups based on age: 12–17 years old, 18–39 years old, 40–64 years old, and  $\geq 65$  years old. In the full analysis cohort, approximately 5% of patients were aged  $\geq 65$  years. Overall, a higher proportion of patients aged  $\geq 65$  years reported serious AEs, severe AEs, and AEs leading to treatment discontinuation compared to other age groups. The analysis also observed an increased incidence of low platelet counts ( $< 75 \times 10^3/\text{mm}^3$ ), low absolute lymphocyte counts ( $< 0.5 \times 10^3/\text{mm}^3$ ), and opportunistic shingles infection with age and dose. Consequently, patients aged  $\geq 65$  years may require closer monitoring when treated with abrocitinib. Ruxolitinib cream, approved by the FDA in 2022 for the treatment of moderate to severe AD, selectively inhibits JAK1 and JAK2 to deliver the drug directly to the affected skin, resulting in faster onset of action and reduced potential for AEs typically associated with oral administration.<sup>83</sup> Delgocitinib ointment, which was approved by Japan in 2020 for the treatment of mild and moderate AD, exhibits broad inhibition of signaling pathways associated with inflammatory cytokines related to the pathogenesis of AD. It also



has the potential to restore the skin barrier function by increasing the production of proteins involved in terminal differentiation, like filaggrin.<sup>84</sup> Daniel et al<sup>85</sup> analyzed 32 Phase II and phase III clinical trials involving five JAK inhibitors (abrocitinib, baricitinib, upadacitinib, ruxolitinib, and delgocitinib) in adult patients.<sup>83,84,86,87</sup> Among these trials, the proportion of participants aged over 65 years ranged from 2.1%–8.0%. In the majority of trials (7 of 9), older adults constituted 5% of the study population. Several trials established upper age limits (65, 70, or 75 years), and most trials (87.5%) included statements indicating that certain unspecified laboratory abnormalities or medical conditions could lead to exclusion at the discretion of the researchers. These criteria may inadvertently exclude many older adults. While majority of trials did not explicitly exclude older patients based on age, the limited representation of individuals aged >65 suggests that indefinite exclusion criteria or challenges in recruiting and retaining older patients might contribute to the underrepresentation. Since the prevalence of exclusionary diseases tends to increase with age, a number of older adults may be excluded from trials even when there is no specified upper age limit. While it is important to avoid unnecessary risks for patients in clinical trials, the use of common comorbidities and low age thresholds can be overly cautious. Furthermore, JAK inhibitors have been associated with black box warnings for serious infections, malignancies, thrombosis, major cardiovascular events, and death.<sup>88</sup> The elderly population is particularly susceptible to these disorders. As a result, the EMA recommends that patients aged 65 and older, who have an increased risk of major cardiovascular problems and cancer, and who smoke, should only be considered for JAK inhibitors if no suitable alternative treatment options exist. To establish the safety and efficacy of JAK inhibitors, aggressive efforts are needed to recruit and retain older adults in clinical studies. Without such studies, oral JAK inhibitors may not become the first-line therapies for AD in the elderly.

## Conclusion and Future Perspectives

The incidence of AD is gradually increasing among the elderly population. Although type 2 inflammation still plays a crucial role involved into the pathogenesis of AD in the elderly, it exhibits unique features known as inflamm-ageing. Elderly patients with AD often have other concurrent pruritic skin conditions, and there are no specific clinical, histopathological, or laboratory diagnostic markers. Thus, clinicians need to exercise caution to ensure an accurate diagnosis and exclude various differential diagnoses. The management and treatment of AD in the elderly primarily involve basic and systemic therapies. Elderly individuals often exhibit reduced adherence to basic treatments, especially topical drugs, which can result in delayed relief or even worsening of the disease. Additionally, the elderly population has a higher incidence of cardiovascular diseases, malignant tumors, and other systemic conditions. Therefore, it is crucial to select an effective, safe, and well-tolerated therapeutic approach for AD in the elderly. Early initiation of systemic therapy is critical, even in cases of mild to moderate AD in the elderly, to alleviate symptoms and improve their quality of life. Traditional systemic therapies have limitations due to adverse events or the need for continuous monitoring of laboratory indicators. Novel systemic therapies, particularly biologics and JAK inhibitors, play significant roles in the treatment of AD in the elderly. Dupilumab, the first biologic approved by the FDA for AD, has demonstrated efficacy and safety across all age groups. Despite limited evidence, the efficacy and safety of dupilumab in treating AD in the elderly are comparable to those in younger patients. However, JAK inhibitors cannot be considered first-line therapy for AD in the elderly due to the risk of certain adverse events such as infection and cardiovascular issues, despite their good and rapid efficacy. Importantly, there is limited clinical data available on the application of JAK inhibitors in elderly patients with AD, similar to biologics. Overall, despite the increasing evidence of rising AD incidence among older adults, the development of effective and safe treatment guidelines for AD in the elderly is still underestimated. More population-specific data is necessary to establish evidence-based treatments tailored to this age group.

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## Disclosure

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