Current and Emerging Biologics for the Treatment of Pediatric Atopic Dermatitis

Rima I. Ghamrawi, Katheryn A. Bell, Esther A. Balogh, Lindsay C. Strowd & Steven R. Feldman

To cite this article: Rima I. Ghamrawi, Katheryn A. Bell, Esther A. Balogh, Lindsay C. Strowd & Steven R. Feldman (2020): Current and Emerging Biologics for the Treatment of Pediatric Atopic Dermatitis, Expert Opinion on Biological Therapy, DOI: 10.1080/14712598.2021.1840548

To link to this article: https://doi.org/10.1080/14712598.2021.1840548

Accepted author version posted online: 20 Oct 2020.

Submit your article to this journal

View related articles

View Crossmark data
Abstract

Introduction: Atopic dermatitis (AD) is a chronic inflammatory skin condition characterized by erythematous lesions, pruritus, and a skin barrier defect. Long-term treatment in children is challenging, as there is only one Food and Drug Administration-approved systemic medication. Current treatments may have limited efficacy or serious side effects in children. With a deeper understanding of AD pathogenesis and the advent of target-specific medications, several biologics are undergoing clinical trials for future use in pediatric AD.

Areas covered: This article reviews the current and emerging biologic therapies for the treatment of pediatric AD. It allows for a comprehensive comparison of medications and their
clinical trials to help providers optimize patient treatment plans while providing expert insight into upcoming advancements in the treatment of pediatric AD.

**Expert opinion:** Treating pediatric AD is complicated given the variety of disease severity, the psychosocial impact, and the relative lack of approved medications for severe disease. Given the amount of safety data on dupilumab, newer biologics will likely be second-line. We do not yet understand the long-term impact of newer biologics on an immature immune system, nor do we fully understand their risks and toxicities. We should proceed optimistically, yet cautiously, with the study of biologics in children.

**Keywords:** atopic dermatitis, atopic eczema, biologics, clinical trials, dupilumab, lebrikizumab, nemolizumab, pediatric, risankizumab, tralokinumab

---

**Article Highlights**

- AD is a common chronic skin condition with continuously increasing incidence among children.
- Mild-to-moderate pediatric AD is treated with emollients and topical therapies, although chronicity and necessity for multiple treatment vehicles may add to the complexity of treatment and barriers to adherence. Moderate-to-severe disease requires phototherapy, systemic immunosuppressants, or biologics.
- Current FDA-approved biologic therapies for pediatric AD include: dupilumab (anti-IL-4Rα monoclonal antibody).
- Other emerging biologic therapies undergoing clinical trials include: lebrikizumab (anti-IL-13 monoclonal antibody), tralokinumab (anti-IL-13 monoclonal antibody), nemolizumab (anti-IL-31Rα monoclonal antibody), and risankizumab (anti-IL-23 monoclonal antibody).
- The advent of new biologic therapies will likely allow for improved treatment of pediatric AD and attempt to address the unmet needs of AD treatment in this population.

This box summarizes key points outlined in the article.
1. Introduction

1.1 Epidemiology

Atopic dermatitis (AD) is a chronic inflammatory skin condition affecting between 6% and 13% of pediatric patients in the United States.[1,2] AD often presents in early childhood, with the majority of patients experiencing onset before the age of five years old.[3] Nearly half of all affected children will experience symptoms that persist through adolescence, beginning with AD in infancy and subsequently developing allergic rhinitis and asthma later in childhood, a sequence known as the “atopic march.”[4,5]

1.2 Etiology

The pathogenesis of AD is complex and multifactorial, resulting from a culmination of defects in genetic factors, the natural skin barrier, microbiome, and innate and adaptive immune systems.[6] Defects in the skin barrier can be due to loss-of-function mutations in genes that encode for proteins such as filaggrin, transglutaminases, desmoglein, claudins, and keratins.[7,8] Such defects allow for the entry of bacteria and allergens into the body, eliciting an inflammatory response which subsequently stimulates the adaptive immune system, causing increased expression of T helper type 2 (Th2), Th22, and Th17 cytokines, further weakening the skin barrier.[9] Inhibition of a targeted cytokine molecule—such as IL-4, IL-13, IL-31, or IL-23—involved in the inciting disease pathway can be of potential therapeutic benefit in children with AD. Innate immune system dysfunctions can result in modification of toll-like receptors on keratinocytes, allowing for alteration of the skin’s natural microbiome.[10,11]

1.3 Existing Treatments for Pediatric AD
AD can affect different regions of the body, varying by age (Table 1).[12] The appearance of AD is distressing and can be socially isolating, resulting in a negative psychological impact.[13] The chronic relapsing-remitting pattern of AD contributes to the frustration and anxiety common among patients and their family members.[14] One challenging aspect in the treatment of pediatric AD is finding an effective long-term therapeutic plan given the chronicity of the disease. For years, therapeutic tactics have centered around the use of gentle skincare practices, avoidance of triggers, and the use of anti-inflammatory, antipruritic, and antibacterial strategies (Table 2).[12,15,16] Mild-to-moderate AD is treated with emollients, topical corticosteroids, and topical calcineurin inhibitors which often require repeated daily applications to large body surface areas. The required strength and vehicle of topical medications may vary for different parts of the body, adding complexity to the treatment regimen and potentially compromising patient adherence.[16] Moderate-to-severe AD is treated with phototherapy, off-label systemic immunosuppressants, or biologics.[17] There is a lack of safe and approved treatments for moderate-to-severe AD in children. Medications used for treatment of severe disease can be problematic due to health coverage and toxicities. This article will discuss the mechanism of action, safety profiles, and efficacy of currently approved (dupilumab) and emerging biologic therapies (lebrikizumab, tralokinumab, nemolizumab, risankizumab) undergoing investigation in clinical trials for their use in the treatment of pediatric AD.

2 Approved Biologic Therapy

2.1 Interleukin-4 Antagonists

Interleukin (IL)-4 and IL-13 are proinflammatory cytokines that increase immunoglobulin-E (IgE) production and Th2 polarization. Th2 cytokines, IL-4 in particular, can augment the interaction between IL-31 with its receptor, IL-31Rα, leading to an enhanced pruritic reaction in
Th2-prone immune conditions such as AD.[18,19] IL-4 and IL-13 compromise the integrity of the skin barrier by downregulating the expression of filaggrin, loricrin, and involucrin, structural proteins involved in the regulation of keratinocyte differentiation and maintenance of an adequate skin barrier.[20-23] Additionally, IL-4 and IL-13 enhance the production of chemokines such as chemokine (C-C motif) ligand 26 (CCL26), augmenting the migration of eosinophils to the epidermis in the Th2 immune response.[24,25] IL-4 and IL-13 also affect colonization of the skin with *Staphylococcus aureus* by inhibiting the formation of antimicrobial peptides, allowing for enhanced entry of this bacteria while concomitantly allowing for keratinocyte cell death.[26,27]

### 2.1.1 Dupilumab (REGN668, SAR231893)

Dupilumab is an IL-4 receptor-alpha (IL-4Rα) antagonist developed by Regeneron Pharmaceuticals. It inhibits IL-4 and IL-13 signaling by binding to the shared IL-4Rα subunit. Dupilumab blocks IL-4 signaling via inhibition of the type I and type II receptors; IL-13 signaling is blocked via inhibition of the type II receptor (Figure 1).[28] In March 2019, dupilumab was the first biologic therapy to receive United States Food and Drug Administration (FDA) approval for the treatment of moderate-to-severe AD not controlled with topical prescription therapies in patients 12 years and older. As of May 2020, dupilumab received additional approval for the treatment of AD in children ages 6 to 11 years old who are poorly controlled with topical prescription medications.[28] Dupilumab is administered via subcutaneous injection: initial dose of either two 200 mg injections (weight < 60 kg) followed by 200 mg every other week (Q2W) or two 300 mg injections (≥ 60 kg) followed by 300 mg Q2W.[28]
2.1.1.1 Efficacy

Dupilumab performed favorably in phase III trials in pediatric patients (Table 3). A phase III randomized, double-blind, placebo-controlled study (LIBERTY AD ADOL [NCT03054428]) involving 251 subjects investigated the efficacy and safety of dupilumab monotherapy in patients ages 12 to 17 years old with moderate-to-severe AD and an inadequate response to topical medications.[29] Patients were randomized 1:1:1 to receive either a weight-based regimen of 200 mg dupilumab (baseline weight < 60 kg) following a 400 mg loading dose or 300 mg dupilumab (baseline weight ≥ 60 kg) following a 600 mg loading dose every two weeks (q2w), 300 mg dupilumab following a 600 mg loading dose every four weeks (q4w), or placebo q2w. Therapeutic response was measured by attaining the primary outcome of an Investigator’s Global Assessment (IGA) score of 0 or 1 (0 = clear; 1 = almost clear) with a reduction from baseline IGA of two or more points, and an Eczema Area and Severity Index (EASI)-75 (≥ 75% improvement from baseline) measurement at week 16. Achievement of an IGA score of 0 or 1 was greater in both dupilumab groups (24.4%, dupilumab q2w [p < 0.001]; 17.9%, dupilumab q4w [p = 0.0007]) compared to the placebo group (2.4%, placebo q2w) at week 16. A higher percentage of patients in the dupilumab q2w (41.5%) and q4w (38.1%) groups achieved EASI-75 at week 16 compared to placebo (8.2%; p < 0.0001).[29]

2.1.1.2 Efficacy in Younger Children

The use of dupilumab in younger age groups has also been studied. A phase III randomized, double-blind, placebo-controlled trial (LIBERTY AD PEDS [NCT03345914]) involving 367 patients ages 6 to 11 years old with severe AD and a previously inadequate response to topical medications investigated the efficacy and safety of dupilumab when administered concomitantly with medium potency topical corticosteroids (TCSs).[30,31] Patients were randomized to receive
either 100 mg or 200 mg dupilumab (100 mg if baseline weight < 30 kg; 200 mg if baseline weight ≥ 30 kg) plus TCSs q2w, 300 mg dupilumab plus TCSs q4w, or placebo plus TCSs.[30,31] Both the q2w and q4w dupilumab groups reported clinically meaningful improvements in signs and symptoms of AD compared to the placebo groups.[30,31] By week 16, more patients in the dupilumab groups (29.5%, q2w plus TCSs [p = 0.0004]; 32.8%, q4w plus TCSs [p < 0.0001]) achieved the primary outcome of an IGA score of 0 or 1 compared to the placebo plus TCSs group (11.4%).[30,31]

2.1.1.3 Ongoing and Future Trials

Many dupilumab trials are ongoing with a wide scope of investigation, including the evaluation of dupilumab in patients younger than six years old as well as characterization of long-term safety and efficacy with prolonged drug use. A phase II open-label, single-ascending-dose, sequential cohort study (Liberty AD PRESCHOOL [NCT03346434]) by Regeneron Pharmaceuticals is currently underway to characterize the safety of dupilumab in patients ages six months to five years old with severe AD.[32] The second portion of this study is a phase III randomized, double-blind, parallel-group, placebo-controlled study which aims to evaluate the efficacy of dupilumab dosed multiple times across 16 weeks with TCSs in patients ages six months to six years old with moderate-to-severe AD.[32] This two-part clinical trial is expected to conclude in July 2022.[32] An ongoing phase III open-label extension study (NCT02612454) by Regeneron Pharmaceuticals assessing the long-term safety and efficacy of dupilumab in patients age 6 months to 17 years old with AD is expected to conclude in December 2026.[33] A phase IV long-term, prospective cohort study (DRS [NCT03411837]) by Northwestern University examining the efficacy and safety of dupilumab as well as its use in the prevention or mitigation of comorbid conditions in patients 12 years and older is estimated to conclude in
March 2027.[34] A similar prospective observational study (PROSE [NCT03428646]) by Regeneron Pharmaceuticals involving subjects ages 12 years and older is in progress with the aim of characterizing patients receiving dupilumab for AD, characterizing real world use patterns, assessing long-term effectiveness, and assessing comorbid conditions in patients receiving dupilumab.[35] The study is expected to conclude in December 2025.[35] A long-term prospective observational study (BioDay [NCT03549416]) by UMC Utrecht involving adult and pediatric patients receiving systemic treatments for AD aims to assess the long-term effectiveness of systemic treatments for AD, the drug survival (length of time that a patient continues to take a particular drug), and adverse effects of systemic treatments.[36] This study is estimated to conclude in December 2028.[36] Lastly, a multicenter phase III, randomized, double-blind, placebo-controlled, parallel-group study (NCT04417894) by Regeneron Pharmaceuticals began in July 2020 and will evaluate the efficacy and safety of dupilumab in adolescent patients with moderate-to-severe atopic hand and foot dermatitis. This trial is estimated to conclude in June 2022.[37]

2.1.1.4 Safety

Though no results are available, a phase II open-label trial (NCT02407756) by Regeneron Pharmaceuticals that completed in March 2016 investigated dupilumab’s safety in pediatric patients ages 12 to 17 years old with moderate-to-severe AD as well as patients ages 6 to 11 years old with severe AD.[38]

No serious adverse events (AEs) were reported in dupilumab-treated subjects in the LIBERTY AD ADOL trial compared to the placebo group (1.18%, infections such as appendicitis).[29] In the LIBERTY AD PEDS trial involving children ages 6 to 11 years old, the overall incidence of
TEAEs was lower in the dupilumab plus TCSs groups (65%, q4w plus TCSs group; 67.2%, q2w plus TCSs group) compared to the placebo plus TCSs group (73.3 %).[30,31] TEAEs were defined as AEs that developed, worsened, or became serious during the treatment period from the time of the first dose of study drug through the end of the study. [30,31] Two patients receiving placebo plus TCSs and two patients receiving 300 mg dupilumab q4w plus TCSs reported serious TEAEs; none were related to the study drug. The TEAEs with the highest rate of occurrence were AD exacerbation as well as upper respiratory tract infection (both 8.2%, q2w plus TCSs group), nasopharyngitis (12.5%, q4w plus TCSs group), and AD exacerbation (14.2%, placebo plus TCSs group). Discontinuation of treatment due to AEs was uncommon (q2w plus TCSs, n=2; placebo plus TCSs, n=2). No deaths or treatment-related events of anaphylaxis or hypersensitivity occurred during the study.[30,31] As in previous dupilumab trials, conjunctivitis and injection-site reactions were more common in the dupilumab-treated groups than in the placebo group (conjunctivitis: 14.8% q2w plus TCSs and 6.7% q4w plus TCSs vs. 4.2% placebo plus TCSs; injection-site reactions: 10.7% q2w plus TCSs and 10% q4w plus TCSs vs. 5.8% placebo plus TCSs). The highest incidence of conjunctivitis (20.6%) occurred in the 100 mg q2w plus TCSs group. All but one conjunctivitis event were of mild-to-moderate severity. One patient receiving 200 mg dupilumab q2w plus TCSs discontinued treatment due to bacterial conjunctivitis of moderate severity.[30,31] Considering phase IV data and long-term safety and efficacy of dupilumab in pediatric AD patients are not yet published, a low-risk profile upon discontinuation of long-term dupilumab use cannot be assumed.

3 Emerging Biologic Therapies

3.1 Interleukin-13 Antagonists

3.1.1 Lebrikizumab (LY3650150, DRM06)
Lebrikizumab is a high-affinity anti-IL-13 monoclonal antibody that prevents formation of the IL-13Rα1/IL-4Rα heterodimer receptor signaling complex by binding to the IL-13 cytokine at an epitope overlapping with the IL-4Rα receptor binding site.[39] It is currently in phase III trials in children with AD over the age of 12 years old.[40-43] Lebrikizumab is administered via subcutaneous injection.[40-43]

3.1.1.1 Ongoing and Future Trials

Two phase III randomized, double-blind, parallel group, placebo controlled 52-week trials (ADvocate1 [NCT04146363] and ADvocate2 [NCT04178967]) by Eli Lilly and Company examining the efficacy and safety of lebrikizumab in adolescents 12 years and older with moderate-to-severe AD began enrollment in September and October of 2019, respectively.[40,41] A similarly designed phase III 52-week trial (NCT04392154) by Eli Lilly and Company is planning to enroll 900 participants with moderate-to-severe AD over the age of 11 years.[42] This trial began recruiting in June 2020 and is estimated to conclude in May 2023.[42]

A phase III randomized, double-blind, parallel group, placebo controlled trial (ADhere [NCT04250337]) by Eli Lilly and Company is investigating the safety and efficacy of lebrikizumab used in combination with TCSs for 16 weeks compared with placebo used with TCSs in subjects ages 12 years and older with moderate-to-severe AD.[44] This trial began enrollment in February 2020 and is expected to conclude in October 2021. An additional phase III, open-label, single-arm trial (ADore [NCT04250350]) by Eli Lilly and Company assessing the safety and efficacy of lebrikizumab over 16 weeks in subjects age 12 years and older with
moderate-to-severe AD also began enrollment in February 2020. This trial is expected to conclude by May 2022.[43]

3.1.2 Tralokinumab
Tralokinumab is a monoclonal IgG4 anti-IL-13 antibody that binds to the IL-13 cytokine at an epitope overlapping with the IL-13Rα receptors binding site, preventing binding to both IL-13Rα1 and IL-13Rα2.[45] It is currently in phase III trials for the treatment of pediatric AD. Tralokinumab is administered via subcutaneous injection.[45]

3.1.2.1 Ongoing and Future Trials
Use of tralokinumab is currently being studied in two phase III clinical trials. A randomized, double-blind, placebo-controlled, parallel-group, multi-center trial (ECZTRA 6 [NCT03526861]) by LEO Pharma is evaluating the efficacy of tralokinumab in adolescent subjects ages 12 to 17 years old with moderate-to-severe AD. Enrollment began in June 2018 and is estimated to conclude in February 2021.[46] A phase III open-label, single-arm, multi-center, long-term 140-week extension trial (ECZTEND [NCT03587805]) in subjects with AD ages 12 years and older began enrollment in September 2018 and is estimated to conclude in September 2021.[45]

3.2 Interleukin-31 Antagonists
IL-31 is a cytokine secreted by various sources including basophils, macrophages, mast cells, dendritic cells, eosinophils, epidermal keratinocytes, CD8+ T cells, monocytes/macrophages, germinal center B cells, dermal fibroblasts, and Th2 cells.[47-50] It is involved in the mediation of pruritus in Th2-driven inflammation. When IL-31 binds to its IL-31Rα receptor on immune cells, nerve fibers, or keratinocytes, the Janus kinase (JAK)-signal transducer and activator of transcription (STAT) pathway is activated, enhancing pruritus.[51-55] Beyond its role in
pruritus, binding of IL-31 to IL-31Rα on keratinocytes results in cell cycle arrest, diminished filaggrin expression, and reduced epidermal thickness.[56] The stimulation of IL-31Rα on keratinocytes and eosinophils indicates that IL-31 is involved in a broader proinflammatory response.[48,57]

3.2.1 Nemolizumab (CD14152)

Nemolizumab is an anti-IL-31Rα antibody that blocks signaling mediated by IL-31.[58] Currently, there are two ongoing phase II and three ongoing phase III trials investigating its use in moderate-to-severe adolescent AD. Nemolizumab is administered via subcutaneous injection.[58]

3.2.1.1 Ongoing and Future Trials

A phase II multicenter, open-label, single-group clinical trial (NCT03921411) by Galderma R&D is investigating the pharmacokinetics and safety of nemolizumab in adolescent subjects ages 12 to 17 years old with moderate-to-severe AD.[59] Enrollment began in April 2019 and the trial is estimated to conclude in September 2020.[59] A randomized, double-blind, placebo-controlled, multi-center, parallel-group phase II trial (NCT04365387) by Galderma R&D in adult and adolescent subjects ages 12 to 54 years old with moderate-to-severe AD began enrollment in March 2020 and will conclude in January 2022.[60] This trial aims to assess the effect of nemolizumab on humoral immune responses to tetanus and meningococcal vaccination in adult and adolescent participants with moderate-to-severe AD.[60]

Three phase III nemolizumab trials by Galderma R&D assessing the efficacy and safety of nemolizumab in children over the age of 12 years old with moderate-to-severe AD are currently
underway.[61-63]. Two phase III randomized, double-blind, placebo-controlled studies (NCT03989349 and NCT03985943) are estimated to enroll 750 subjects. Enrollment for both of these trials began in June 2019 and these trials are expected to conclude in December 2021.[61,62]. A phase III prospective, multicenter, long-term 112-week study (NCT03989206) began in December 2019 and is planning to enroll a total of 1,300 subjects.[63] It is estimated to conclude in September 2023.[63]

3.3 Interleukin-23 Antagonists

In AD, greater upregulation of Th17/IL-23 may be seen in pediatric versus adult AD patients.[64] Although it is increasingly evident that many Th1 diseases have a strong IL-17 signal, the importance of Th17 T cells in Th2 diseases, such as AD, is not well understood. IL-23 is composed of two subunits, p40 and p19, and regulates the induction of IL-17 and IL-22 cytokines, which ultimately stimulates tissue inflammation and disruption of the natural skin barrier.[64]

3.3.1 Risankizumab (ABBV-066, BI 655066)

Risankizumab is an anti-IL-23 monoclonal antibody that specifically targets the p19 subunit of IL-23.[65] Risankizumab is administered via subcutaneous injection.[66]

3.3.1.1 Ongoing and Future Trials

A randomized, double-blind, placebo-controlled, multicenter, phase II clinical trial (NCT03706040) by AbbVie is investigating the safety and efficacy of risankizumab for the treatment of moderate-to-severe AD in adults and adolescent subjects 12 years and older.[66] This study began in December 2018 and is estimated to conclude in August 2021 upon
enrollment of 172 participants. While this study is currently active, it is not recruiting patients.[66]

4 Conclusion
AD is traditionally treated with gentle skincare practices, avoidance of triggers, and the use of anti-inflammatory, antipruritic, and antibacterial strategies. There is an unmet need for safe and efficacious systemic medications, such as biologics, for children with AD for whom topical medications are either inadequate or intolerable, highlighting the demand for continuous new drug development to establish long-term disease control in this population. Dupilumab, an IL-4Ra antagonist, is the only currently FDA-approved biologic for the treatment of pediatric AD. The advent of additional target-specific biologic therapies such as lebrikizumab (IL-13 antagonist), tralokinumab (IL-13 antagonist), nemolizumab (IL-31 antagonist), and risankizumab (IL-23 antagonist) that are currently in various phases of clinical trials provides potentially promising options for expanding the armamentarium of systemic treatments for pediatric AD, either as monotherapy or in combination with topicals and other systemic treatments.

Of the biologics outlined in this article, dupilumab shows the most promise for continued safety and efficacy in the treatment of pediatric AD, as there are ongoing trials further evaluating its use in hand and foot AD as well as in preventing comorbid conditions in patients with AD. Lebrikizumab, tralokinumab, and nemolizumab do not have any safety or efficacy data results, as they are currently undergoing phase III trials to evaluate their use in pediatric patients. With many of these drugs, further clinical trials and long-term prospective studies are necessary to confirm their safety and efficacy in children.
When selecting the most appropriate treatment for children with AD, physicians should take into consideration the medication’s efficacy and safety profile, the patient’s adherence patterns, and the quality of life goals of the patients as well as their caregivers. With less frequent dosing schedules, biologics may reduce the need for daily application of topical medications and may allow teenagers to feel less isolated from their peers. Considering that AD can have a substantial physical, psychological, and social impact on patients, the success of therapeutic treatment with the outlined emerging biologics could help children and adolescents feel more confident and comfortable in the appearance of their skin, while decreasing the amount of time spent managing symptoms of their disease.

5 Expert Opinion

Treating pediatric patients for AD is complicated given the variety of disease severity, relationships between patients and caregivers, the psychosocial impact of AD and its treatment on school-aged patients, and the relative lack of approved medications for more severe disease. The increase in studies examining new biologics for use in pediatric AD is exciting, as it represents a shift in our current treatment paradigm away from older immunosuppressive medications towards novel therapies that target specific components of the pathways involved in the AD pathophysiology. However, we must proceed with caution, as pediatric patients are not “little adults,” but rather, are human beings undergoing significant physiologic developments in their immunity and skin. While several medications exist for the treatment of AD in children, there is still a large gap in the need for safe and efficacious systemic medications beyond drugs such as methotrexate and cyclosporin for severe AD. Dupilumab, the first biologic approved for AD, has filled much of this gap, as it was first approved for use in adults with AD and is now being approved for use in progressively younger children. Although dupilumab is a valuable
addition to the plethora of treatments available for pediatric AD, additional agents are necessary. Given the amount of existing safety data on dupilumab, it is likely that newer biologic agents will be second-line behind it for the foreseeable future. We do not yet know or understand the long-term impact of these novel biologic agents on an immature immune system. We also do not yet have a solid working knowledge of other risks and toxicities from these medications. We anticipate that the current mainstays of treatment, such as emollient therapies and topical medications, will remain first-line for the treatment of AD in pediatric patients. However, utilization of the emerging biologic therapies outlined in this review article may be of benefit and should be considered for individuals with varying degrees of recalcitrant disease or with contraindications to any of the fundamental therapeutic regimens.

There are additional considerations worth pointing out in this population related to medication adherence. Medications delivered via injection may be far less tolerable to younger patients and may preclude use in some instances over injection site pain or fear of needles. Oral medications may face adherence issues depending on whether they come in an easy to swallow small capsule versus large tablet or bitter-tasting liquid solution. Adolescent patients may be more likely to endure injections for significant improvement in their disease, but anxiety, depression, or other psychosocial issues may still impact medication adherence in this age group. Consideration should also be given to the therapeutic limitations such as cost and ease of access to targeted biologic medications, as patients may be unable to afford the estimated yearly price tag of $30,000 or more.[67]
None of the issues raised in this article are intended to dissuade physicians from pursuing these novel treatments, but rather, they are intended to serve as practical reminders that medication use in the clinical environment can be challenging and complicated. We should proceed optimistically, yet cautiously, with the study of biologic medications in some of our most vulnerable patients.

Funding
This paper is not funded.

Declaration of Interests
S Feldman has received research, speaking and/or consulting support from a variety of companies including Galderma, GSK/Stiefel, Almirall, Leo Pharma, Boehringer Ingelheim, Mylan, Celgene, Pfizer, Valeant, Abbvie, Samsung, Janssen, Lilly, Menlo, Merck, Novartis, Regeneron, Sanofi, Novan, Qurient, National Biological Corporation, Caremark, Advance Medical, Sun Pharma, Suncare Research, Informa, UpToDate and National Psoriasis Foundation. He is founder and majority owner of www.DrScore.com and founder and part owner of Causa Research, a company dedicated to enhancing patients’ adherence to treatment. Dr. Lindsay Strowd has received consulting fees or research funding from Galderma, Lilly, Pfizer, Sanofi, and Actelion. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Reviewer Disclosures
Peer reviewers on this manuscript have no relevant financial relationships or otherwise to disclose.
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>AD</td>
<td>Atopic dermatitis</td>
</tr>
<tr>
<td>AE</td>
<td>Adverse event</td>
</tr>
<tr>
<td>CCL26</td>
<td>Chemokine (C-C motif) ligand 26</td>
</tr>
<tr>
<td>EASI</td>
<td>Eczema Area and Severity Index</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
</tr>
<tr>
<td>JAK-STAT</td>
<td>Janus kinase-signal transducer and activator of transcription</td>
</tr>
<tr>
<td>IGA</td>
<td>Investigator’s Global Assessment</td>
</tr>
<tr>
<td>IgE</td>
<td>Immunoglobulin-E</td>
</tr>
<tr>
<td>IL</td>
<td>Interleukin</td>
</tr>
<tr>
<td>IL-4Rα</td>
<td>IL-4 receptor-alpha</td>
</tr>
<tr>
<td>Q2w</td>
<td>Every 2 weeks</td>
</tr>
<tr>
<td>Q4w</td>
<td>Every 4 weeks</td>
</tr>
<tr>
<td>SCORAD</td>
<td>SCORing Atopic Dermatitis</td>
</tr>
<tr>
<td>TCS</td>
<td>Topical corticosteroid</td>
</tr>
<tr>
<td>Th2</td>
<td>T helper type 2 cell</td>
</tr>
</tbody>
</table>
References


29. Efficacy and Safety of Dupilumab in Participants ≥12 to <18 Years of Age, With Moderate-to-severe Atopic Dermatitis. https://ClinicalTrials.gov/show/NCT03054428.


31. Study to Investigate the Efficacy and Safety of Dupilumab Administered With Topical Corticosteroids (TCS) in Participants ≥6 to <12 Years With Severe Atopic Dermatitis (AD). https://ClinicalTrials.gov/show/NCT03345914.

32. Safety, Pharmacokinetics and Efficacy of Dupilumab in Patients ≥6 Months to <6 Years With Moderate-to-Severe Atopic Dermatitis (Liberty AD PRESCHOOL). https://ClinicalTrials.gov/show/NCT03346434.

33. Study to Assess the Long-term Safety of Dupilumab Administered in Participants ≥6 Months to <18 Years of Age With Atopic Dermatitis (AD). https://ClinicalTrials.gov/show/NCT02612454.

34. Dupilumab Phase 4 Study. https://ClinicalTrials.gov/show/NCT03411837.

https://ClinicalTrials.gov/show/NCT03549416.

37. A Study to Evaluate the Efficacy and Safety of Dupilumab in Adult and Adolescent Patients With Moderate-to-Severe Atopic Hand and Foot Dermatitis.  
https://ClinicalTrials.gov/show/NCT04417894.

38. A Study to Determine the Safety and Tolerability of Dupilumab (REGN668/SAR231893) in Patients Aged ≥6 to <18 Years With Atopic Dermatitis (Eczema).  
https://ClinicalTrials.gov/show/NCT02407756.


41. Evaluation of the Efficacy and Safety of Lebrikizumab (LY3650150) in Moderate to Severe Atopic Dermatitis (ADvocate1). https://ClinicalTrials.gov/show/NCT04146363.


43. Study to Assess the Safety and Efficacy of Lebrikizumab (LY3650150) in Adolescent Patients With Moderate-to-Severe Atopic Dermatitis.  
https://ClinicalTrials.gov/show/NCT04250350.

44. Safety and Efficacy of Lebrikizumab (LY3650150) in Combination With Topical Corticosteroid in Moderate to Severe Atopic Dermatitis. (ADhere). Available from:  
https://clinicaltrials.gov/ct2/show/NCT04250337
45. Long-term Extension Trial in Subjects With Atopic Dermatitis Who Participated in Previous Tralokinumab Trials - ECZTEND.
   https://ClinicalTrials.gov/show/NCT03587805.

46. Tralokinumab Monotherapy for Adolescent Subjects With Moderate to Severe Atopic Dermatitis - ECZTRA 6 (ECZema TRAlokinumab Trial no. 6).
   https://ClinicalTrials.gov/show/NCT03526861.


60. A Study to Assess Immunization Responses in Adult and Adolescent Participants With Moderate-to-Severe Atopic Dermatitis Treated With Nemolizumab. https://ClinicalTrials.gov/show/NCT04365387.


# Table 1. Presentation of Atopic Dermatitis by Age

<table>
<thead>
<tr>
<th>Age</th>
<th>Location of Atopic Dermatitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants and Toddlers</td>
<td>Face, scalp, elbows, or knees</td>
</tr>
<tr>
<td>Adolescents</td>
<td>Antecubital fossae, popliteal fossae, neck, wrists, ankles, hands, or crease between the buttocks/legs</td>
</tr>
<tr>
<td>Adults</td>
<td>Antecubital fossae, popliteal fossae, hands, or nape of the neck</td>
</tr>
<tr>
<td>Bathing and Emollient Practices</td>
<td>Phototherapy</td>
</tr>
<tr>
<td>---------------------------------</td>
<td>------------------</td>
</tr>
<tr>
<td>“Soak and seal” bath</td>
<td>Narrowband UVB</td>
</tr>
<tr>
<td>Bleach bath</td>
<td>Broadband UVB</td>
</tr>
<tr>
<td>Wet wraps</td>
<td>PUVA</td>
</tr>
<tr>
<td></td>
<td>UVA1</td>
</tr>
</tbody>
</table>

* Immunosuppressants are used “off-label” in the treatment of AD

AD - atopic dermatitis; PDE-4 - phosphodiesterase 4; PUVA - psoralen and ultraviolet A; UVA1 - ultraviolet A1; UVB - ultraviolet B
<table>
<thead>
<tr>
<th>Study</th>
<th>Clinical Trial Status; Location</th>
<th>Study Design</th>
<th>Subjects (n)</th>
<th>Treatment Arms</th>
<th>Primary Outcome</th>
<th>Results</th>
<th>Patients with TEAEs (%)</th>
<th>Serious AEs (%)</th>
<th>Types of AEs</th>
</tr>
</thead>
</table>
| Simpson et al. 2018; LIBERTY AD ADOL (NCT03054428) [68] | Complete; United States, Canada                     | R, DB, PG, Phase III | 251          | Dupilumab 200 or 300mg q2w, Dupilumab 300mg q4w, Placebo | Proportion of patients with IGA 0 or 1 EASI-75 at week 16                    | Q2w: 72.0%
Q4w: 34.4%
Placebo: 2.4%
 | Q2w: 63.9%
Placebo: 69.4%
 | Q2w: 0%
Q4w: 0%
Placebo: 1.18%
 | Q2w: influenza (6.1%), URTI (12.2%), HA (11%)
Q4w: influenza (0%), URTI (8.4%), HA (4.8%)
Placebo: influenza (4.7%), URTI (17.7%), HA (10.0%)
 |  |
| Paller et al. 2020; LIBERTY AD PEDS (NCT03345914) [30] | Complete; United States, Canada, Czechia, Germany, Poland, United Kingdom | R, DB, PC, Phase III | 367          | Dupilumab 100 or 200mg + TCS q2w, Dupilumab 300mg + TCS q4w, Placebo + TCS | Proportion of patients with IGA 0 or 1 at week 16                           | Q2w: 67.2%
Q4w: 32.3%
Placebo: 11.4%
 | Q2w: 0%
Q4w: 1.7%
Placebo: 1.7%
 | Q2w: AD exacerbation (8.2%), URTI (8.2%), Nasopharyngitis (6.6%), HA (5.7%), Vomiting (4.9%)
Q4w: AD exacerbation (6.7%), URTI (10.8%), Nasopharyngitis (12.5%), HA (5%), Vomiting (5%)
Placebo: AD exacerbation (14.2%), URTI (10%), Nasopharyngitis (6.7%), HA (8.3%), Vomiting (6.7%)
 |  |
| Liberty AD PRESCHOOL (NCT03346434) [32] | Ongoing; United States, Germany, Poland, United Kingdom | Part A: I, OL, SAD; Phase II, Part B: I, R, DB, PG, PC, Phase III | 200          | Dupilumab Placebo                        | Part A Concentration of total dupilumab in serum over time and PK parameters up to week 4
Incidence of TEAEs up to week 4
Part B Proportion of participants with IGA 0 or 1 at week 16 | -                           | -                          | -                                      | -                           | -                          | -                                      | -                           | -                          | -                                      | -                           | -                          | -                                      |  |
| NCT02612454 [33] | Ongoing; United States, Canada, Czechia, Germany, Hungary, Poland, United Kingdom | I, OL, Phase III | 800          | Dupilumab q2w, Dupilumab q4w             | Rate of TEAEs per participant year up to week 272
Number of participants with  ≥ 1 TEAE per participant year up to week 272 | -                           | -                          | -                                      | -                           | -                          | -                                      | -                           | -                          | -                                      | -                           | -                          | -                                      |
<table>
<thead>
<tr>
<th>Study ID</th>
<th>Status</th>
<th>Countries</th>
<th>Design</th>
<th>Phase</th>
<th>Drug</th>
<th>Primary Outcomes</th>
<th>Key Endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>DRS</td>
<td>Ongoing; United States</td>
<td>P, O; Phase IV</td>
<td>500</td>
<td>Dupilumab</td>
<td>Quantified itch survey from 1 to 3 months, Quantified sleep survey from 1 to 3 months, Quantified quality of life survey from 1 to 3 months</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>PROSE</td>
<td>Ongoing; United States, Canada</td>
<td>P, O</td>
<td>1000</td>
<td>Dupilumab</td>
<td>Medical history characteristics at baseline, Socio-demographic characteristics at baseline</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>BioRay</td>
<td>Ongoing; Netherlands</td>
<td>P, O</td>
<td>1200</td>
<td>-</td>
<td>Assessment of effectiveness from baseline, Drug survival, Number of side effects from baseline</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>NCT04417894</td>
<td>Completed; Canada, Czechia, Germany, Hungary, Poland, United Kingdom</td>
<td>I, R, DL, PC, PG; Phase III</td>
<td>130</td>
<td>Dupilumab q2w Placebo</td>
<td>Proportion of patients with IGA (hand and foot) 0 or 1 at week 16</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>NCT02407756</td>
<td>Completed</td>
<td>I, OL; Phase II</td>
<td>78</td>
<td>Dupilumab</td>
<td>PK parameters up to week 12</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>ADvocate1 (NCT04146363) and ADvocate2 (NCT04178967)</td>
<td>Ongoing; United States, Australia, Canada, Estonia, France, Republic of Korea, Latvia, Lithuania, Poland, Spain United States, Bulgaria, Canada, Germany, Italy, Mexico, Romania, Singapore, Taiwan, Ukraine</td>
<td>I, R, DL, PC, PG; Phase III</td>
<td>400</td>
<td>Lebrikizumab q2w Lebrikizumab q4w Placebo</td>
<td>Proportion of patients with IGA 0 or 1 and a reduction ≥2 points from baseline at week 16</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>NCT04392154 [42]</td>
<td>Ongoing; United States, Australia, Bulgaria, Canada, Estonia, France, Germany, Italy, Republic of Korea, Latvia, Lithuania, Mexico, Poland, Romania, Singapore, Spain, Taiwan, Ukraine</td>
<td>I, R, DB, PC, PG; Phase III</td>
<td>900</td>
<td>Lebrikizumab q2w Lebrikizumab q4w</td>
<td>Proportion of participants discontinued from study treatment due to AEs up to week 52</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>ADore (NCT04250337) [44]</td>
<td>Ongoing; United States, Canada, Germany, Poland</td>
<td>I, R, DB, PC, PG; Phase III</td>
<td>200</td>
<td>Lebrikizumab q2w + TCS Placebo + TCS</td>
<td>Proportion of patients with IGA 0 or 1 and reduction ≥2 points from baseline at week 16</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>ADore (NCT04250350) [43]</td>
<td>Ongoing; United States, Australia, Canada, Poland</td>
<td>I, OL; Phase III</td>
<td>200</td>
<td>Lebrikizumab q2w</td>
<td>Number of AEs up to week 52 Number of subjects with AEs up to week 52</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>ET.ZTRA6 (NCT03526861) [46]</td>
<td>Ongoing; United States, Australia, Belgium, Canada, France, Germany, Japan, Netherlands, Poland, United Kingdom</td>
<td>I, R, DB, PC, PG; Phase III</td>
<td>294</td>
<td>Tralokinumab Placebo</td>
<td>IGA 0 or 1 at week 16 EASI-75 at week 16</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>ET.ZTEND (NCT03587805) [45]</td>
<td>Ongoing; United States, Belgium, Canada, Czechia, France, Germany, Italy, Japan, Poland, Spain, United Kingdom</td>
<td>I, OL; Phase III</td>
<td>1125</td>
<td>Tralokinumab</td>
<td>Number of AEs up to week 142</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>NCT03921411 [59]</td>
<td>Ongoing; United States</td>
<td>I, OL; Phase II</td>
<td>20</td>
<td>Nemolizumab</td>
<td>Nemolizumab serum concentration in adolescent subjects up to week 24 Incidence of AEs up to week 24 Number of subjects with change from baseline in physical examination (normal to abnormal) at each visit up to week 24 Number of subjects with change from baseline in vital signs at each visit up to week 24</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>NCT04365387 [60]</td>
<td>Ongoing; United States</td>
<td>I, DB, PC; Phase II</td>
<td>200</td>
<td>Nemolizumab q4w Placebo</td>
<td>Proportion of patients with positive serum IgG response to tetanus toxoid at week 16 (4 weeks post-vaccination)</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

| NCT03989349 [61,62] and NCT0398943 [61,62] | Ongoing; United States, Belgium, Bulgaria, Estonia, France, Germany, Hungary, Italy, Republic of Korea, Poland, Romania, Singapore United States, Australia, Austria, Canada, Czechia, Germany, Republic of Korea, Latvia, Lithuania, Netherlands, New Zealand, Spain, United Kingdom | I, R, DH, PC; Phase III | 750 | Nemolizumab Placebo | Proportion of subjects with IGA 0 or 1 and ≥2 point reduction at week 16 | - | - | - |

| NCT03989206 [63] | Ongoing; United States | I, OL, P; Phase III | 1300 | Nemolizumab | Incidence and severity of TEAEs up to week 112 Incidence of serious TEAEs up to week 112 | - | - | - |

| NCT03706040 [66] | Ongoing; United States, Australia, Canada, Japan, Puerto Rico | I, R, DB, PC; Phase II | 172 | Risankizumab Placebo | Proportion of subjects with EASI-75 at week 16 | - | - | - |

AEs- adverse events; DB- double blind; EASI- 75%- ≥75% improvement in Eczema Area and Severity Index score from baseline to week 16; HA- headache; I- interventional; IGA- Investigator's Global Assessment; IgG- Immunoglobulin G; O- observational; OL- open-label; OX40L- OX40 ligand; P- prospective; PC- placebo-controlled; PG- parallel-group; PK- pharmacokinetic; Q2w- every 2 weeks; Q4w- every 4 weeks; R- randomized; SAD- single-ascending-dose; SCORad- SCORing Atopic Dermatitis; TARC- thymus and activation-regulated chemokine; TCS- topical corticosteroid; TEAEs- treatment-emergent adverse events; TSLP- thymic stromal lymphopoietin; URTI- upper respiratory tract infection
Defects in:
- Genetic factors
- Natural epithelial barrier
- Microbiome
- Innate and adaptive immune systems

Epidermis

IL-33

Dendritic cell

Th2

IL-4
IL-13
IL-5

Dupilumab
Lebrikizumab
Tralokinumab

IL-23
P19
P40

IL-31
IL-31R

Risankizumab

Th17

Nemolizumab