Evolving Landscape of Systemic Therapy for Pediatric Atopic Dermatitis

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KEYWORDS

• Atopic dermatitis • Quality of life • Comorbidities • Biologic • Dupilumab • Safety

KEY POINTS

- Atopic dermatitis (AD) is a common, chronic inflammatory skin disease associated with type 2 T-helper (TH2) dysfunction.
- People with AD are at increased risk for multiple atopic morbidities, including allergic rhinitis, allergic conjunctivitis, asthma, and eosinophilic gastrointestinal disease.
- Dupilumab is the first biologic agent approved by the United States Food and Drug Administration that downregulates TH2 inflammation.
- Dupilumab is currently licensed to treat AD in adults, adolescents, and children down to age 6 years, with ongoing trials including younger children and infants to age 6 months.
- Optimal treatment of AD remains a significant unmet medical need, but multiple new drugs, targeting a range of proinflammatory molecules, hold promise for safer and more effective treatment.

INTRODUCTION

Atopic dermatitis (AD) is a chronic, relapsing inflammatory skin disease that occurs in a characteristic distribution, with associated xerosis and intense pruritus. AD affects approximately 15% of children in the United States with an annual direct and indirect economic burden of ~$5 billion.[1] Moderate-severe AD is not typically life threatening, but can be enormously life altering, with a significant impact on quality of life, restful sleep, school performance, as well as psychological and emotional well-being.

AD is primarily a disease of childhood, with onset at age less than 2 years in the most cases. The condition spontaneously improves in many children with mild-moderate AD, but can be lifelong in those with more severe disease. The pathophysiology of AD is believed to result from a complex interplay of impaired skin barrier function, environmental factors, colonizing and pathogenic microbes, and immune dysregulation, with enhanced type 2 T-helper (TH2) responses and increases in corresponding inflammatory cytokines. Onset in infancy may be developmentally related to more active type 2 immune function in infants, followed by spontaneous improvement in childhood as normal immune maturation biases toward type 1 immune expression.[13] However, for children with moderate-severe AD, the disease is more likely to persist into adulthood. The phenotypic result is erythema, induration, lichenification, and excoriation. There is also an association with subsequent development of other atopic morbidities including asthma, allergic rhinitis, food allergies, and eosinophilic gastrointestinal disease.[2] Immune and skin barrier dysfunction contribute to relative cutaneous anergy, manifest as chronic colonization with *Staphylococcus aureus* and more frequent infections with a variety of microbes, including group A *Streptococcus*, dermatophyte, molluscum, and herpes simplex.

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These infections may be occult, lacking the clinical features that characterize similar infections in nonatopic hosts.

In infants and toddlers, AD presents with pruritic, red, weeping or scaly, and crusted lesions more prominent on the extensor surfaces of limbs and on the trunk, face, and scalp, classically sparing the diaper area (**Fig. 1**). Prominent sparing of the nose ("lightbulb sign or Yamamoto sign") has also been described. In older children and adolescents, AD typically affects antecubital and popliteal fossae, with frequent involvement of the volar aspect of the wrists, ankles, and neck (**Fig. 2**). Histologically, AD demonstrates features that include epidermal spongiosis and parakeratosis, and superficial dermal perivascular infiltrate (**Fig. 3**).

Low socioeconomic status, which disproportionately impacts black children, limits access to specialty care, and this has a negative effect on management of children with AD, contributing to poor disease control. A higher percentage of skin changes are also more persistent and dramatic in children with darker skin types, especially lichenification and hyperpigmentation. Secondary tinea may also be more common in African American children who are at higher risk for tinea capitis.[3]

MANAGEMENT

Until there is a cure for AD, management focuses on relieving symptoms and preventing flares while minimizing therapeutic risks. Mounting evidence suggests that early control of inflammation may support normalized immune maturation and decrease long-term risk of extracutaneous atopy. Variables that impact optimal choice of treatment include patient preference and ability, safety and efficacy, cost and access, and comorbidities.

Treatment strategies are aimed at restoring impaired barrier function, reducing itch, minimizing inflammation, recognizing and treating infection, and promoting restful sleep.[4] Approach to therapy can be organized in a stepwise fashion, based on disease severity (see **Fig. 3**).[5] Initial therapy includes bleach baths, avoidance of complex topical allergens. Topical corticosteroids (TCS) have been used first line since their discovery in the 1950s. Widespread and long-term use has informed safety. Because children have a higher ratio of body surface area to weight, safe and effective use of TCS requires monitoring to avoid risks associated with percutaneous absorption, including adrenal suppression. Long-term use of TCS is safest when applied in the morning and no more than an average of once every other day, using a product with the lowest effective potency and in supervised quantities.[6] Maintenance therapy with a TCS-sparing agent is added for children who require daily medication. Choices include topical calcineurin inhibitors (tacrolimus and pimecrolimus) and crisaborole, an inhibitor of type 4 phosphodiesterase (PDE4); however, access to these medications is often limited by payers, often based on labeling for children aged 2 years or greater.

TRADITIONAL SYSTEMIC THERAPY

Until 2017, the only systemic treatments US Food and Drug Administration (FDA)-approved to treat AD were corticosteroids. Only after decades of experience were the risks of this approach recognized to outweigh the benefits. The standard-of-care alternative for patients with severe disease requiring long-term therapy was off-label treatment with immunomodulating and immune suppressive medications. Choices include methotrexate, cyclosporine, mycophenolate mofetil, and azathioprine. Each of these medications has the potential for drug-specific side effects. All require regular laboratory monitoring for associated toxicity.

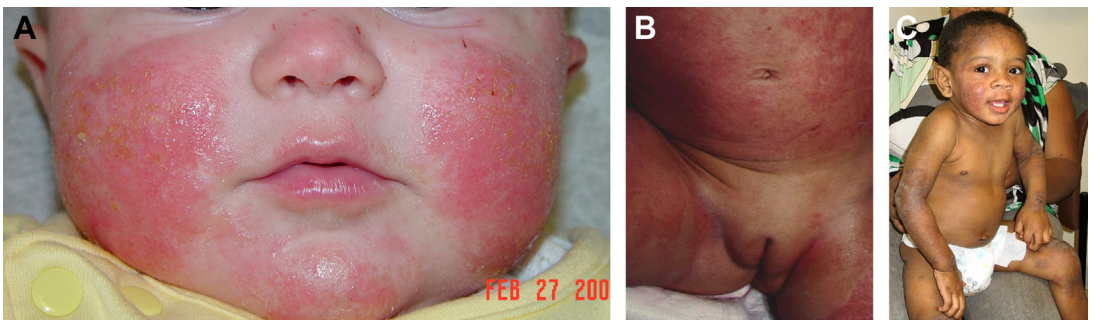

Fig. 1. (*A*) Erythema, edema, and crusting on the face of an infant. Note "Yamamoto sign" sparing of the nose. (*B*) Prominent diaper area sparing is characteristic of atopic dermatitis in infants. (*C*) This infant with atopic dermatitis has involvement of his extensor extremities and face as well as Yamamoto sign.

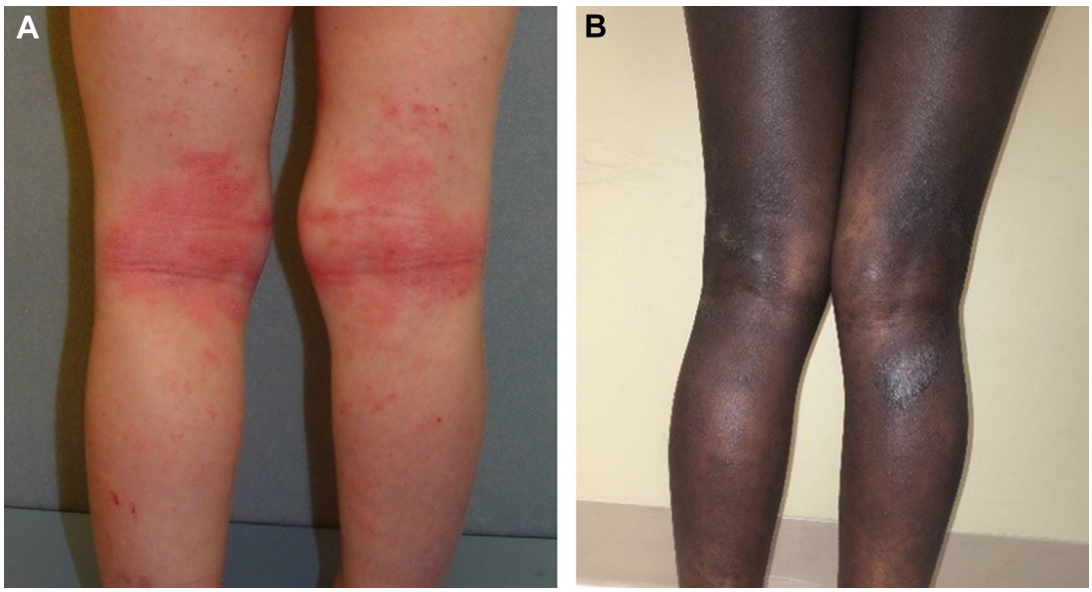

Fig. 2. (*A* and *B*) Scaly and lichenified plaques involving the popliteal fossae are characteristic of AD; associated hyperpigmentation is most prominent in skin of color.

Methotrexate and cyclosporine are the most widely used agents, cyclosporine for its rapid onset and methotrexate for ease of administration and relatively better safety profile. Although the well-established mechanism of action for high-dose methotrexate as cancer chemotherapy is to inhibit dihydrofolate reductase, impairing DNA synthesis, the pharmacologic basis of low-dose methotrexate in controlling inflammation is unclear. Weekly administered, low-dose methotrexate is generally well-tolerated. The most common adverse effects, nausea and abdominal

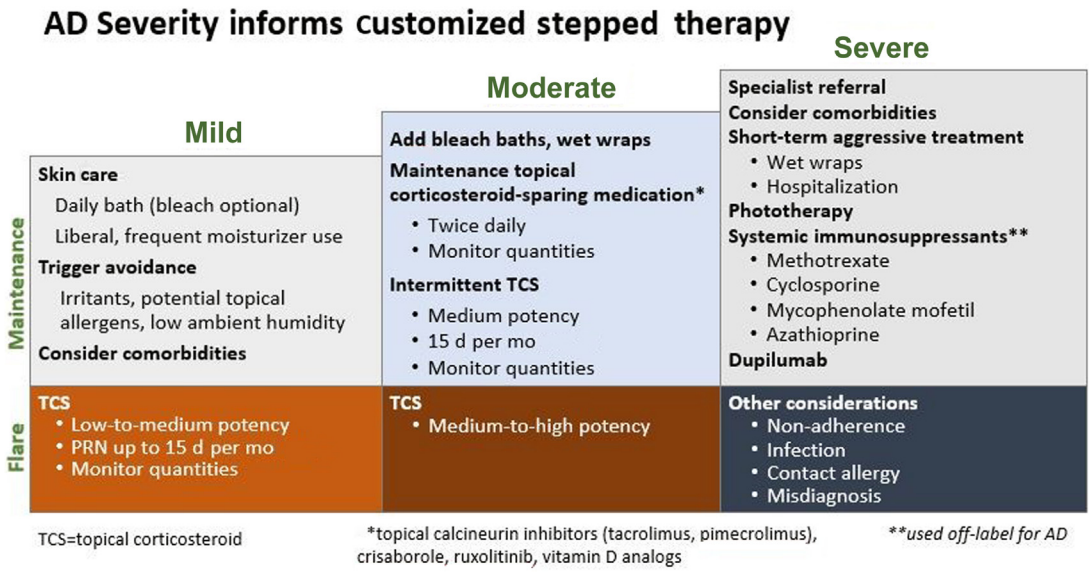

Fig. 3. Stepwise treatment approach for AD. Patients with moderate-severe AD whose skin disease cannot be adequately controlled using adjunctive skin care and optimal amounts of TCS and topical calcineurin inhibitors are candidates for systemic treatment or phototherapy. PRN, as needed; TCS, topical corticosteroids. (*Adapted from* Boguniewicz M, Fonacier L, Guttman-Yassky E, et al. Atopic dermatitis yardstick: practical recommendations for an evolving therapeutic landscape. Ann Allergy Asthma Immunol 2018;120(1):10–22.e2.)

pain, can be mitigated by folic acid, using doses of 1 to 5 mg per day. Standard monitoring for patients on methotrexate is with baseline and follow-up blood tests for hepatic and renal function, and hematologic parameters for associated macrocytosis and leukopenias. Methotrexate is an abortifacient and teratogen, so relatively contraindicated in females of childbearing age.[7]

DUPILUMAB

Development of the first biologic medication to specifically target type 2 immune dysfunction addressed a significant unmet medical need for patients with moderate-severe AD. Dupilumab is a fully human monoclonal antibody that binds the interleukin (IL)-4 receptor alpha subunit, blocking signaling via IL-4 and IL-13, key cytokines that trigger TH2 inflammation. Dupilumab was FDA approved for adults in March 2017, for adolescents in March 2019, and in children down to age 6 years in May 2020. Ongoing clinical trials include children with moderate-severe AD as young as 6 months. Dupilumab is also approved for treatment of asthma in patients down to age 12 years, and for allergic sinusitis with rhinopolyposis in adults.[8]

Dupilumab is administered subcutaneously, with a loading dose, to accelerate onset of response, followed by maintenance dosing every other week or once per month, depending on weight. Data from long-term clinical trials in adults support the safety of dosing as often as once a week, or as infrequently as once a month. It is available in 200- and 300-mg prefilled syringe and 300-mg autoinjector. Labeled dosing for pediatric patients is weight-group based.

Labeled dosing for dupilumab in AD

- 60 kg or more: 600 mg loading dose and 300 mg every other week
- 30 to less than 60 kg: 400 mg loading dose and 200 mg every other week
- Less than 30 kg: 600 mg loading dose and 300 mg every 4 weeks

Other dosing regimens, including a 200 mg load followed by 100 mg every other week for children weighing less than 30 kg and 600 mg load followed by 300 mg once per month for children weighing greater than 30 kg, were studied, but found to be less effective. Individual pharmacokinetics vary, but suggest that younger children may require higher weight-based doses.[14] Higher doses have not been associated with increased adverse effects. Optimal dosing for younger children is under investigation, but weight-based loading doses as high as 15 mg/kg and maintenance doses up to 10 mg/kg every other week have been used. The drug is supplied in 2-syringe units. Refrigerated storage is required to maintain stability. Each box of syringes is marked with a temperature-sensitive label to detect warming.

On-label initial dosing is recommended. With time, some children whose skin has cleared on bimonthly injections may be maintained with less-frequent, monthly injections.

In contrast to the other systemic agents, treatment with dupilumab does not require routine laboratory monitoring. Limited data suggest that dupilumab has no impact on humoral response to immunization. The standard class-labeled recommendation is to avoid live vaccines. Anaphylaxis has been rarely reported, so as a precaution, the first injection is usually performed in the office along with injection training. Subsequent injections are most often done by a caregiver in the home, but some families prefer the assistance of in-office administration. Itch and associated excoriation generally improve within 2 weeks of starting treatment, followed by the signs of eczema: induration, erythema, and scale.

Common adverse effects recognized during clinical trials include injection site reactions and ocular surface disease (most often conjunctivitis, but also keratitis). Eye inflammation may be more common, and more symptomatic in patients with preexisting ocular inflammation, and in adults. Worsening skin inflammation, especially on the face, has been more well-recognized postmarketing. The cause of facial inflammation is not well understood, and been attributed to a variety of triggers, including *Malassezia* colonization, psoriasis, and allergic contact dermatitis. Needle phobia is a common concern for children, but this typically improves with time.

Antidrug antibodies were detected in a small number of study subjects at baseline, and an increasing number over time. However, the clinical significance of these antibodies remains a subject of investigation, including recognition of antibodies considered neutralizing and nonneutralizing.

Ongoing long-term trials in children with AD suggest a mitigating impact of early treatment with dupilumab on the natural history of the disease. Dupilumab is also under investigation for a variety of other atopic conditions, including eosinophilic esophagitis and to enhance the efficacy of oral peanut immunotherapy; this offers hope that a safe and effective drug will one day be available to target the systemic inflammation underlying atopy and fill a significant unmet need for a single medication that can treat, or possibly prevent, the

Table 1
Biologic agents in development

	≥2 y	
Agent	**Administration route**	**Trial Phase for AD**
JAK1 inhibitor		
Abrocitinib	Oral	3 (≥12 y)
Aryl hydrocarbon receptor agonist		
Tapinarof	Topical	2 (≥12 y)
PDE4 inhibitors		
Lotamast	Topical	2a (≥2 y)

constellation of atopic comorbidities that begin in childhood.[2]

Insight into the duration of therapy will require additional information from ongoing long-term trials. However, in the author's experience a small proportion of patients have been able to discontinue dupilumab without relapse for as long as 2 years. Meanwhile, our approach is to begin by tapering treatment (dose amount or dosing interval up to 1 month) only after complete clearing for a minimum of 3 months. Discontinuation should be considered if clearing is maintained after a minimum 3-month taper.

Although the impressive efficacy and safety has been proved in large clinical trials, insurance coverage for dupilumab remains a significant barrier to access. Health care providers prescribing dupilumab are frequently challenged by need for prior authorization and subsequent denial. Before formal FDA approval for children, a retrospective analysis of patterns of insurance denials for pediatric patients found that lack of pediatric-specific labeling was the most common reason for denial. In some cases, step-edit requirements ironically demanded off-label use of immunosuppressant drugs.[9] Completion of phase 3 trials and labeling for use in children has had a positive impact on access.

HORIZON

The pipeline is robust for new drugs to treat AD, as well as other atopic conditions. Although AD is primarily a disease of children, pediatric clinical trials always follow trials in adults, and always include fewer subjects. Long-term, open-label extension studies and data from use for other pediatric indications will help inform the relative risks and benefits for each product and pathway.

Several monoclonal antibodies are in development that largely target the TH2 pathway. Tralokinumab and lebrikizumab bind circulating IL-13, and ASLAN004 binds the IL-13 subunit receptor

Table 2
Biologic agents in development

	≥18 y	
Agent	**Administration route**	**Trial phase for AD**
Monoclonal antibodies (target)		
Tezepelumab (TSLP)	SQ	2a completed
Afuco (IL-31)	SQ	Ib completed
Nemolizumab (IL-31)	SQ	2 completed
GBR 830 (O × 40)	IV	2
Fezakinumab (IL-22)	IV	2 Published
Lebrikizumab (IL-13)	SQ	3
Tralokinumab (IL-13)	SQ	3
MOR106 (IL-17C)	IV	2 failed
Pitrakinra (IL-4)	SQ	2a completed
Ligelizumab (IgE)	SQ	2 completed
JAK inhibitors		
Gusacitinib (JAK-SYK)	Oral	2b
Baricitinib (JAK 1/2)	Oral	2b completed
Upadacitinib (JAK 1)	Oral	2
Ruxolitinib (JAK 1/2)	Topical	2 completed
PDE 4 inhibitors		
Roflumilast (ARQ-151)	Topical	2a

with downstream effects that are similar, but not identical to, dupilumab IL-4 receptor subunit blockade.[9] Nemolizumab binds IL-31 receptor A, known to play an important role in the pathogenesis of itch.[10] A phase 2 trial in adults with AD yielded improved itch, but less clinical improvement in the signs of eczema, arguing against the historic description of AD as "the itch that rashes."

Another less specific target for the treatment of AD is Janus kinases (JAK). This family of cytoplasmic protein tyrosine kinases is critical for nuclear signal transduction. JAK inhibitors (sometimes referred to as "jakinibs") are small molecules that offer the advantage of oral as well as topical administration, and likely more rapid response than the current biologics under investigation. A disadvantage is a likely greater impact on immune function, with a theoretically higher risk of infection or carcinogenicity with long-term use. Increased risk of venous thromboembolism is another concern.[11] Together, these risks prompted a new class black box warning for all JAK inhibitors, topical and systemic. The different products vary with regard to selectivity for the 4 recognized JAK targets, JAKs 1, 2, and 3, and TYK2.[12] Three JAK inhibitors have been FDA approved to treat a variety of inflammatory disorders, beginning with tofacitinib (Xeljanz), for adults with rheumatoid arthritis (RA), psoriatic arthritis, and ulcerative colitis, as well as children with juvenile idiopathic arthritis weighing as little as 10 kg. Upadacitinib (Rinvoq) and baricitinib (Olumiant) are labeled to treat RA in adults, but are under investigation for treating AD. Abrocitinib is a selective JAK1 inhibitor in clinical trials for moderate-to-severe AD in adults and adolescents. Clinical trials in adults and adolescents with mild-to-moderate AD are ongoing for ruxolitinib, a topical JAK1/2 inhibitor.

Other agents in development include biologics targeting TSLP (thymic stromal lymphopoietin), IL-4, IL-22, IL-17 C, IgE, PDE4, and aryl hydrocarbon receptor (see tables). Most clinical trials for moderate-severe AD have not included children younger than 12 years to date. However, the pipeline is robust, so the treatment paradigm for AD is sure to evolve (**Tables 1** and **2**).

CLINICS CARE POINTS

- AD is a chronic disease with significant impact on quality of life.
- Treatment of mild and moderate AD begins with skin care and topical medication.
- A proactive approach is more effective than reactive treatment.
- Proactive treatment is stepwise and based on disease severity and associated morbidities.
- Off-label use of oral immunosuppressant and immunomodulating medications (most often methotrexate or cyclosporine) have been the only options until recently. The following factors support the need for dupilumab therapy in pediatric patients:
  - Moderate-severe AD
  - Extracutaneous atopic morbidities (asthma, rhinitis, eosinophilic gastrointestinal disease, food allergy)
  - High total IgE
  - Strong family history of atopy

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Dr E.C. Siegfried:

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Incyte: consulting fees

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UCB: DSMB, consulting fees

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Verrica: consulting fees, honoraria; fees to SSM/SLU related to sponsoring a clinical trial.

Leo: consulting fees, DSMB.

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