

Biologics in Pediatric Psoriasis and Atopic Dermatitis: Revolutionizing the Treatment Landscape

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Psoriasis and atopic dermatitis (AD) can impact quality of life (QOL) in pediatric patients, warranting early recognition and treatment.¹ Topical agents often are inadequate to treat moderate to severe disease, but the potential toxicity of systemic agents, which largely include immunosuppressives, limit their use in this population despite their effectiveness. Our expanding knowledge of the pathogenesis of psoriasis (tumor necrosis factor [TNF] α and IL-23/T_H17 pathways) and AD has led to targeted interventions, particularly monoclonal antibody biologics, which have revolutionized treatment for affected adults and more recently children. Several agents are approved by the US Food and Drug Administration (FDA) for pediatric psoriasis, and dupilumab is approved for pediatric AD. Herein, we discuss the latest developments in the treatment landscape for pediatric psoriasis and AD.

Pediatric Psoriasis

Methotrexate (MTX) and cyclosporine have been FDA approved for psoriasis in adults since 1972 and 1997, respectively.² Before biologics, MTX was the primary systemic agent used to treat pediatric psoriasis, given its lower toxicity vs cyclosporine. The TNF- α inhibitor etanercept became the first FDA-approved biologic for pediatric psoriasis in 2016. Adalimumab has been available in Europe for children since 2015 but is not FDA

approved. Certolizumab, a pegylated TNF- α inhibitor that distinctly fails to cross the placental barrier currently is in clinical trials (ClinicalTrials.gov identifier NCT04123795). Tumor necrosis factor α inhibitors have shown more rapid onset and greater efficacy during the first 16 weeks of use than MTX, including a head-to-head trial comparing MTX to adalimumab.³ A recent real-world study showed that pediatric patients receiving biologics, primarily TNF- α inhibitors, were more likely to achieve psoriasis area and severity index (PASI) 75 or clear/almost clear status (similar to PASI 90) than MTX and had higher drug survival rates.⁴

Ustekinumab targets both IL-12 and IL-23, which share the IL-23 receptor p40 subunit. It was the first biologic to target IL-23, which promotes the proliferation and survival of helper T cells (T_H17). Ustekinumab has led to greater reductions in PASI scores than TNF- α inhibitors.^{5,6} Pediatric trials of guselkumab, risankizumab, and tildrakizumab, all targeting the IL-23 receptor-specific p19 subunit, are completed or currently recruiting (NCT03451851, NCT03997786, NCT04435600). Ixekizumab is the first IL-17A-targeting biologic approved for children.⁷ Secukinumab and the IL-17 receptor inhibitor brodalumab are in pediatric trials (NCT03668613, NCT04305327, NCT03240809). One potential issue with T_H17 pathway inhibitors is their association with

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The eTable is available in the Appendix online at www.mdedge.com/dermatology.

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inflammatory bowel disease, a contraindication when considering if a patient is a potential candidate for treatment.

Skin disease can profoundly affect QOL during childhood and adolescence, a critical time for psychosocial development. In psoriasis, improvement in QOL is proportional to clearance and is greater when PASI 90 is achieved vs PASI 75.⁸ The high efficacy of IL-23 and IL-17A pathway inhibitors now makes achieving at least PASI 90 the new standard, which can be reached in most patients.

Pediatric AD

For AD in the pediatric population, systemic treatments primarily include corticosteroids, mycophenolate mofetil, azathioprine, cyclosporine, and MTX. Although cyclosporine was the favored systemic agent among pediatric dermatologists in one study,⁹ claims data analyses show that systemic corticosteroids are used much more often overall, prescribed in 24.4% (116,635 total cases) of children with AD vs nonsteroidal immunosuppressants in less than 0.5%.¹⁰ Systemic steroids are impractical given their side effects and risk for disease rebound; however, no immunosuppressants are safe for long-term use, and all require frequent laboratory monitoring. The development of biologics for AD largely involves targeting T_H2-driven inflammation.¹¹ Dupilumab is the only FDA-approved biologic for moderate to severe pediatric AD, including in patients as young as 6 years of age. Dupilumab inhibits activation of the IL-4R α subunit, thereby blocking responses to its ligands, IL-4 and IL-13. Phase 3 trials are now underway in children aged 6 months to 5 years (NCT02612454, NCT03346434). The concomitant ameliorative effects of dupilumab on asthma and other allergic disorders, occurring in approximately 90% of children with moderate to severe AD, is an added benefit.¹² Although dupilumab does not appear to modify the disease course in children with AD, the possibility that early introduction could reduce the risk for later developing allergic disease is intriguing.

Adolescent trials have been started for lebrikizumab (NCT04392154) and have been completed for tralokinumab (NCT03160885). Both agents selectively target IL-13 to block T_H2 pathway inflammation. The only reported adverse effects of IL-4R α and IL-13 inhibitors have been injection-site pain/reactions and increased conjunctivitis.¹³

The only other biologic for AD currently in clinical trials for adolescents is nemolizumab, targeting the receptor for IL-31, a predominantly T_H2 cytokine that causes pruritus (NCT03989349). In adults, nemolizumab has shown rapid and potent suppression of itch (but not inflammation) without adding topical corticosteroids.¹⁴

Advantages of Biologics and Laboratory Monitoring

By targeting specific cytokines, biologics have greater and more rapid efficacy, fewer side effects, fewer drug

interactions, less frequent dosing, and less immunosuppression compared to other systemic agents.^{3,4,15,16}

Recent pediatric-specific guidelines for psoriasis recommend baseline monitoring for tuberculosis for all biologics but yearly tuberculosis testing only for TNF- α inhibitors unless the individual patient is at increased risk.² No tuberculosis testing is needed for dupilumab, and no other laboratory monitoring is recommended for any biologic in children unless warranted by risk. This difference in recommended monitoring suggests the safety of biologics and is advantageous in managing pediatric therapy.

Unanswered Questions: Vaccines and Antidrug Antibodies

Although administration of killed vaccines is considered safe with all approved biologics, questions remain about the safety of administering live vaccines while on biologics, a particularly pertinent issue in younger children treated with dupilumab and other biologics for AD. Another unanswered question is the potential reduction in clinical response and drug durability with intermittent use of biologics due to the potential development of neutralizing antidrug antibodies (ADAs). The ability to discontinue medication intermittently is desirable, both to determine the natural course of the underlying disease and give a holiday as tolerated. Newer biologics are thought to have lower immunogenicity and less frequent ADA development.¹⁷⁻¹⁹ Even with TNF- α inhibitors, the presence of anti-ADAs is not temporally related to response in children with psoriasis.²⁰ Long-term outcomes of the use of biologics in adults have been reassuring, and safety profiles of biologics studied thus far appear to be similar in children.^{21,22} However, understanding the potential long-term effects from the use of newly approved and emerging biologics in the pediatric population will require decades of study to ensure safety, including nonrandomized studies and postmarketing reports from regulatory agencies.

Cost Considerations

Biologics are disease and QOL altering for children with moderate to severe psoriasis or AD; however, access to biologics often is an obstacle for patients and practitioners. Biologics cost \$30,000 to \$60,000 annually, while conventional systemic treatments such as MTX, cyclosporine, and acitretin cost \$100 to \$3000 annually, raising the question of cost effectiveness. In 2016, the Institute for Clinical and Economic Review concluded that biologics for psoriasis had reasonably good value based on improved QOL and concluded in 2017 that dupilumab had a benefit that outweighed its cost.^{23,24} Prior authorizations and multiple appeals have been necessary to obtain approval, especially in the pediatric population.²⁵ This difficulty highlights the need for programs to cover the cost of biologics for all children, as well as registries to further assess effectiveness and

long-term safety, especially compared to traditional systemic agents.

On the Horizon

Clinical trials for other therapies for children and adolescents are ongoing. Details on recommended dosing, approval status, and efficacy in trials are provided in the eTable. Given their high efficacy in adults with psoriasis, IL-23-specific and T_H17 pathway biologics likely are similarly efficacious and raise the bar for the expectation of achieving PASI 90 and PASI 100 responses. The long-term safety, durability of responses, and ability to modify disease, particularly when started early in life (eg, preadolescence) and early in the disease course, remains to be determined.

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APPENDIX

eTABLE. Available and Emerging Biologics for Psoriasis and Atopic Dermatitis

Drug	Target	Recommended Pediatric Dosing	Approval Status	Efficacy in Pediatric Trials
Psoriasis				
Etanercept	TNF- α	0.8 mg/kg once weekly if weight is ≤ 63 kg; 50 mg once weekly if weight is > 63 kg	FDA approved in 2016 for patients aged 6 y to < 18 y	After 12 wk, PASI 75 and PASI 90 achieved in 57% (60/106) and 27% (29/106) of patients aged 4 y to < 18 y, respectively ²⁶
Adalimumab	TNF- α	0.8 mg/kg (maximum dose, 40 mg) at weeks 0 and 1, then every other week	Not FDA approved; EMA approved in 2015 for patients aged 4 y to < 18 y	After 16 wk, PASI 75, PASI 90, and PASI 100 achieved in 58% (22/38), 29% (11/38), and 18% (7/38) of patients aged 4 y to < 18 y, respectively ³
Certolizumab pegol	TNF- α	N/A	FDA approved in 2018 for patients aged > 18 y	Pediatric clinical trial ongoing (ClinicalTrials.gov identifier NCT04123795)
Infliximab	TNF- α	5 mg/kg at weeks 0, 2, and 6, then every 8 weeks via intravenous infusion	FDA approved in 2006 for patients aged > 18 y	No pediatric clinical trials
Ustekinumab	IL-12/IL-23	0.75 mg/kg at weeks 0 and 4, then every 12 wk if weight is < 60 kg; 45 mg at weeks 0 and 4, then every 12 wk if weight is 60–100 kg; 90 mg at weeks 0 and 4, then every 12 wk if weight is > 100 kg	FDA approved in 2016 for patients aged 12 y to < 18 y and in 2020 for those aged 6 y to < 12 y	Pediatric clinical trial ongoing (NCT03218488); after 12 wk, PASI 75 and PASI 90 achieved in 80.6% (29/36) and 61.1% (22/36) of patients aged 12 y to < 18 y, respectively ⁵ ; after 12 wk, PASI 75, PASI 90, and PASI 100 achieved in 84.1% (37/44), 63.6% (28/44), and 34.1% (15/44) of patients aged 6–11 y, respectively ⁶
Guselkumab	IL-23	N/A	FDA approved in 2017 for patients aged > 18 y	Pediatric clinical trial ongoing (NCT03451851)
Tildrakizumab	IL-23	N/A	FDA approved in 2018 for patients aged > 18 y	Pediatric clinical trial ongoing (NCT03997786)
Risankizumab	IL-23	N/A	FDA approved in 2019 for patients aged > 18 y	Pediatric clinical trial ongoing (NCT04435600)
Ixekizumab	IL-17A	40-mg loading dose, then 20 mg once every 4 wk if weight is < 25 kg; 80-mg loading dose, then 40 mg once every 4 wk if weight is 25–50 kg; 160-mg loading dose, then 80 mg once every 4 wk if weight is > 50 kg	FDA approved in 2020 for patients aged 6 y to < 18 y	After 12 wk, PASI 75, PASI 90, and PASI 100 achieved in 89% (102/115), 78% (90/115), and 50% (57/115) of patients aged 6 y to < 18 y, respectively ⁷

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Drug	Target	Recommended Pediatric Dosing	Approval Status	Efficacy in Pediatric Trials
Secukinumab	IL-17A	N/A	FDA approved in 2015 for patients aged > 18 y	Pediatric clinical trial ongoing (NCT03668613); after 12 wk, PASI 75, PASI 90, and PASI 100 achieved in 93% (39/42), 83% (35/42), and 62% (26/42) of patients aged 6 y to <18 y ²⁷
Brodalumab	IL-17RA	N/A	FDA approved in 2017 for patients aged > 18 y	Pediatric clinical trials ongoing (NCT04305327, NCT03240809)
Atopic Dermatitis				
Dupilumab	IL-4R α	600-mg loading dose, then 300 mg once every 4 wk if weight is <30 kg; 400-mg loading dose, then 200 mg once every 2 wk if weight is 30 to <60 kg; 600-mg loading dose, then 300 mg once every 2 wk if weight is \geq 60 kg	FDA approved in 2019 for patients aged 12 y to <18 y and in 2020 for those aged 6 y to <12 y	Pediatric clinical trials ongoing (NCT02612454, NCT03346434); after 16 wk, EASI 75 achieved in 38.1% (32/84) to 41.5% (34/82) of patients aged 12 y to <18 y ¹² ; after 16 wk, EASI 75 achieved in 67.2% (82/122) to 69.7% (85/122) of patients aged 6–11 y ¹³
Lebrikizumab	IL-13	N/A	Not FDA approved	Pediatric clinical trial ongoing (NCT04392154)
Tralokinumab	IL-13	N/A	Not FDA approved	After 16 wk, EASI 75 achieved in 33.2% (196/591) of patients aged 12 to <18 y (NCT03160885)
Nemolizumab	IL-31R α	N/A	Not FDA approved	Adolescent clinical trial ongoing (NCT03989349)

Abbreviations: TNF- α , tumor necrosis factor α ; FDA, US Food and Drug Administration; PASI, psoriasis area and severity index; EMA, European Medicines Agency; N/A, not applicable; EASI, eczema area and severity index.