Targeted therapies for pediatric psoriasis

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Abstract

Children who are recalcitrant to topical therapy for their moderate to severe plaque psoriasis and/or highly visible lesions may be candidates for systemic therapy. Methotrexate has been the most commonly used systemic agent in children. However, at least 25% of patients are now treated with biologics, especially tumor necrosis factor-α inhibitors, and their use is expanding as their availability, demonstrated safety and efficacy, and practitioner experience are increasing. In the United States, etanercept is Food and Drug Administration approved for ages 6 years and older and ustekinumab for 12 years of age and older. In Europe, adalimumab is also approved for pediatric psoriasis for 4 years of age and older. While biologics have the advantage of less frequent administration, greater and more rapid efficacy than methotrexate, fewer side effects, and a less rigorous need for monitoring, their cost is much higher than that of methotrexate and other systemic medications, concerns about the development of neutralizing antibodies necessitate continuous treatment, and their long-term safety profile remains to be determined.

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Approximately one-third of individuals with psoriasis have their disease onset during pediatric years, with a prevalence of only 0.13% during the first 2 years of life (often as diaper-area psoriasis) and a gradual increase in prevalence to 0.61% in 11- to 13-year-olds and 0.67% in 14- to 18-year-olds.¹ Between 1970 and 2000, the annual incidence of pediatric psoriasis in the United States doubled; it is unclear whether this increase merely represents better physician recognition or results from the increase in obesity, infections, or psychosocial stress for children during the past few decades.²

Overall, 13% to 27% of children have moderate to severe plaque psoriasis,³,⁴ with a 10% or greater body surface area, and may warrant the use of systemic therapy. Although the risks versus benefits of therapy need to be weighed, consideration should also include the visibility of lesions because children are at risk for lifelong psychosocial impairment from social withdrawal, stigma, or bullying. As such, children with nail, facial, or palmoplantar involvement that is recalcitrant to topical therapies might also be candidates for systemic therapy.⁵,⁶ There is currently no guideline for when to advance to systemic therapy and which to choose in pediatric disease, but questions to consider are suggested in Table 1.

While overweight or obesity is the most common comorbidity of pediatric psoriasis regardless of severity,⁷,⁸ the risks of obesity and central adiposity are highest for those with moderate to severe disease (37%).⁵,¹⁰ Obesity tends to precede the development of psoriasis and thus may be a risk factor.¹¹ There is evidence of an increased risk of hyperlipidemia (and more often, lipid function abnormalities), hypertension, diabetes mellitus, and polycystic ovarian syndrome as well.¹²,¹³ Psoriatic arthritis (accounting for 7% of patients with juvenile idiopathic arthritis) occurs in 1.2% to 10% of children⁴,⁹,¹⁴ and is much less common than in adults. Psychiatric comorbidities include depression,² anxiety, and bipolar disease,¹⁵ while Crohn disease, ulcerative colitis, and asthma¹⁶ occur more often in children with psoriasis as well.¹⁵ Patients with pediatric psoriasis should be screened for these comorbidities and be referred to specialists as appropriate.³,²¹ It is unclear whether

Table 1. Factors to consider when choosing a systemic medication to treat pediatric plaque psoriasis

- Does the patient have moderate to severe psoriasis based on lesional severity, extent, and location(s), and/or is there a significant impact on the child’s quality of life?
- Has topical therapy been optimized?
- Is phototherapy practical for this patient based on availability and time constraints?
- Are there comorbidities that might affect choice (eg, obesity with nonalcoholic fatty liver disease or elevated transaminases might preclude methotrexate; if associated arthritis, might choose methotrexate ± a biologic per rheumatologist regimen)?
- What about age and sex (eg, if a female teenager of childbearing potential, might not choose retinoid; in a younger child, might choose etanercept versus other biologics)?
- What is accessible based on the patient’s insurance and previously used treatments (on-label indication may affect approval)? Is cost an issue?
- Does the patient and/or family have a preference (eg, monthly laboratory testing with methotrexate versus annual tuberculosis testing with a biologic; refusal to use an injectable; rapidity of action to choose biologic versus methotrexate)?

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the “psoriatic march” towards more metabolic abnormalities and systemic inflammation can be slowed by earlier, more aggressive systemic treatment in children, as has been considered in adult disease.

**Use of phototherapy and systemic therapy**

Narrow-band ultraviolet B phototherapy is considered the safest “systemic” therapy and results in 50% to 92% clearance. However, the onset of improvement often takes more than a month, and office-based phototherapy can be time-consuming, costly, and logistically impossible for families. Based on a retrospective analysis of use in almost 400 children from 1990 to 2014, the most commonly used systemic therapy for pediatric psoriasis in both North America and Europe is methotrexate (69% of patients on systemic therapy). Methotrexate is inexpensive and very effective, but its peak efficacy in children is at 6 months after initiation, which is much slower than other agents. In a recent multicenter evaluation of 289 pediatric patients that compared methotrexate with acitretin and cyclosporine, the 3 medications were found to be similar in efficacy. Methotrexate was tolerated the best, with no adverse events in 91% of patients; gastrointestinal side effects are the major issue and are mitigated by daily or 6-day-per-week administration of folic acid. Acitretin, a systemic retinoid, was used by 15% of the children, with cyclosporine initiated in only 8% and—given its limited availability—fumaric acid in 4.9%. In general, nontargeted therapy for psoriasis has either had greater toxicity (cyclosporine and fumaric acid), or it has been less efficacious and/or had a slower onset of action than the biologic therapies (Table 1).

**Use of targeted biologic therapies in pediatric psoriasis**

Biologic agents are immunomodulators that target specific immune pathways. The first biologic tested in pediatric psoriasis was etanercept (Enbrel; Amgen, Thousand Oaks, California), which became available on-label in Europe in 2009 (approved by the European Medicines Agency for ≥6 years of age) but was not Food and Drug Administration (FDA) approved until 2016 (approved for ages 4-17; Table 2). Adalimumab (Humira; AbbVie, North Chicago, Illinois) and ustekinumab (Stelara; Janssen, Titusville, New Jersey) were approved in Europe in 2015 for ≥4 and ≥12 years old, respectively; ustekinumab was approved for ≥12 years old in the United States (in 2016; Table 2). These biologics have different mechanisms of action, and failure to respond to one does not preclude response to an alternative biologic. The few studies have focused on pediatric plaque psoriasis; only small case series and anecdotal reports suggest the value of biologics for chronic guttate psoriasis, inverse disease, nail or palmoplantar disease, or pustular or erythrodermic psoriasis.

All biologics are injectable (all except infliximab are given subcutaneously), and as in adults, injection site pain and reaction is the most common side effect. Upper respiratory tract infections are cutaneous), and as in adults, injection site pain and reaction is the most common side effect. While there is a theoretical risk of lymphoma, no children with psoriasis who use biologics have developed a malignancy thought to be related to the use of the medication. Live vaccines should be avoided during therapy, as with any of the systemic agents for psoriasis that alter the immune system. There are no consensus guidelines for laboratory monitoring while taking biologics, but annual testing for tuberculosis is imperative; many pediatric practitioners perform no other laboratory testing. While biologics have the advantage of less frequent administration, greater and more rapid efficacy than methotrexate, fewer side effects, and a less rigorous need for monitoring, their cost is much higher than that of methotrexate and other systemic medications, concerns about the development of neutraliz-
Inhibitors of tumor necrosis factor-\( \alpha \)

Three tumor necrosis factor (TNF) inhibitors are currently available commercially: etanercept, adalimumab, and infliximab. The first 2 are used primarily for plaque psoriasis; infliximab (Remicade; Janssen, Titusville, New Jersey) is an intravenously administered biologic, which has largely been used for pustular and erythrodermic psoriasis (as well as other immune-mediated disorders) when a rapid response is needed. Infliximab has been used at a dose of 5 mg/kg, given at 0, 2, 6, and then every 8 weeks; only case reports of its use are available.\(^6,27\) Rare side effects related to TNF inhibitors, such as anaphylaxis, development of antinuclear antibodies, lupus-like syndrome, and pancytopenia, have not been described in children with pediatric psoriasis.

In a retrospective review of 390 children who had used systemic medication between 2000 and 2014, 27% had used biologics, with etanercept most common (76%) followed by adalimumab, suggesting considerable off-label use.\(^6,27\) Rheumatologists and gastroenterologists often use methotrexate concomitantly with the biologic in the hope of prolonging drug survival through reducing the risk of antidrug antibody formation; however, there is no evidence to date that the rationale for this combination is warranted in pediatric psoriasis.

Etanercept was studied in a double-blind, randomized, placebo-controlled study with 211 children (6-17 years of age).\(^8\) With subcutaneous dosing of 0.8 mg/kg weekly (maximum dose 50 mg/wk), etanercept treatment led to Psoriasis Area and Severity Index (PASI) 75 scores (75% or greater reduction in PASI) in 57% of subjects treated (versus 11% in the placebo arm) after 12 weeks (Figure 1). By 36 weeks on etanercept for those who were initially assigned to the etanercept group and 24 weeks for those who crossed over from placebo, approximately 68% achieved PASI 75.\(^8\) Adverse events in the etanercept were not greater than the control arm other than injection site reactions. Quality of life scores improved much more in the patients taking etanercept compared with placebo (52% versus 17%), with a correlation between those with at least a PASI 75 and the greatest impact on life quality.\(^6,11\) By week 96, in the long-term extension, PASI 75 and PASI 90 rates were 61% and 30%, respectively.\(^6,11\) For those 69 children who were able to stay on etanercept for 5 years while still under 18 years of age per study protocol, only 1 developed a serious infection (cellulitis), and none developed an opportunistic infection, malignancy, or died.\(^35\) Pharmacokinetic studies show the same steady-state level in children given 0.8 mg/kg/wk as adults given 50 mg weekly and children with juvenile idiopathic arthritis given 0.4 mg/kg twice weekly.\(^36\) In 208 children given etanercept for psoriasis, no neutralizing antibodies were detected.\(^36\) Case reports and a case series have further confirmed efficacy for plaque psoriasis.\(^6,27,37\) Cryptococcosis has been described in a 14-year-old with recalcitrant psoriasis administered etanercept.\(^38\)

Adalimumab was studied in a double-blind, randomized phase 3 trial in children ages 4 to 17 years in which the efficacy and safety of 2 doses of adalimumab were compared to methotrexate.\(^39\) After 16 weeks, PASI 75 was achieved in 58% of children given 0.8 mg/kg every 2 weeks (standard dosing [SD]) and in 44% of those given 0.4 mg/kg (half-standard dosing [HSD]) every 2 weeks. Clear or almost clear physician global assessment (PGA) was achieved in 61% of those on SD and in 41% of those on HSD. Infections were the most common adverse event (45% of those on SD and 56% of those on HSD), and no serious adverse events were thought related to the adalimumab.

The development of psoriasis and/or psoriasiform dermatitis is an intriguing side effect of TNF inhibitors that has been described in adults but also occurs in children with psoriasis, particularly in children with Crohn disease and, to a lesser extent, juvenile idiopathic arthritis and other disorders. Its mechanism in children has not been explored and is poorly understood in adults. In the largest series of children with inflammatory bowel disease (IBD; \(n = 409\)), 45.8% developed a psoriasis-like reaction, which was the most common skin problem. The risk was greater with infliximab than adalimumab (\(P = .05\)); in one series of 64 children with Crohn disease treated with infliximab, 47.6% developed psoriasis-like reactions, 23% of which were considered severe.\(^40\) Most patients (60%) were able to continue their IBD therapy.\(^41\) In a case series of 14 patients with IBD and the anti-TNF agent-induced psoriasis and/or psoriasiform eruptions, the median time to development was 11 months (range 0-48 months), and IBD activity was quiescent at the time of development of the skin disease. Topical corticosteroids are the initial treatment of choice, but approximately 50% of affected children have to switch their systemic biologic to control the skin disease. In this series, 50% discontinued the initial TNF inhibitor, but only 29% had to discontinue all TNF inhibitors.\(^42\) The distribution of lesions in the anti-TNF-induced psoriasis and/or psoriasiform dermatitis tends to involve the earlobes, scalp,\(^43\) face, pubic area, and palms and soles, sometimes with pustules.\(^43,44\)

Inhibitors of interleukin-23

Ustekinumab, which inhibits interleukin (IL)-12/23 because of recognition of the shared p40 subunit, has been used in several pediatric patients with psoriasis in case reports or series. The pivotal
clinical trial of ustekinumab has been in adolescents, leading to its approval for 12 years of age and older. In this trial, 110 children received either SD (0.75 mg/kg if ≤60 kg; 45 mg if >60 kg and ≤100 kg; and 90 mg if >100 kg) or HSD of ustekinumab at weeks 0, 4, and every 12 weeks, while the placebo group crossed over to ustekinumab after 12 weeks. At 12 weeks, PGA of clear or almost clear (0/1) was achieved in 69.4% and 67.6% of those on SD and HSD, respectively, but only in 5.4% of those on placebo. HSD and SD also led to significantly greater achievement of PASI 75 (SD 80.6%; HSD 78.4%; placebo 10.8%) and PASI 90 (SD 61.1%; HSD 54.1%; placebo 5.4%; all \( P < .001 \)). Clinical benefit was maintained until 52 weeks. Adverse events (upper respiratory infection, headache) were not greater with ustekinumab treatment. There were no opportunistic infections and was no malignancy through week 60. Several case reports describe the use of ustekinumab for pediatric psoriasis. In a retrospective chart analysis of 80 courses of systemic therapy with methotrexate (most often with adalimumab) when monotherapy was not effective.52 PGAs showed positive treatment responses across all treatment groups at 5 to 7 months and 1 year. In general, the biologics were well tolerated, with injection site reactions, minor infections, headaches, and fatigue the most common adverse events. In another retrospective analysis of 56 treatment courses in children 5 to 17 years of age, 59% of the children were treated with etanercept, second only to methotrexate (70%).\(^\text{49}\) Clearance rates were highest for the biologics in this series, 67% for etanercept and adalimumab and 33% for ustekinumab. The only safety issues were minor infections on etanercept (25%) and adalimumab (33%). The most common reason for discontinuation was secondary failure after initial response (38% etanercept and 33% adalimumab). The most recent series included 10 children treated with etanercept (n = 9), adalimumab (n = 5), ustekinumab (n = 3), or infliximab (n = 2).\(^\text{53}\) Secondary failure was the most common reason for discontinuation (5 for etanercept and 3 for adalimumab). Adverse events were rare.

### Biologics for pustular psoriasis

Generalized pustular psoriasis often requires systemic therapy and has been successfully treated with biologics. In a review of 12 studies, etanercept, infliximab, and adalimumab were shown to have efficacy,\(^\text{54}\) with and without concomitant methotrexate.\(^\text{55}\) Since that review, the combination of etanercept and acitretin was successful in a patient with deficiency of the IL-36 receptor antagonist (DITRA).\(^\text{56}\) Etanercept has also been used to maintain clearance in a patient with pustular psoriasis cleared initially with cyclosporine.\(^\text{57}\) Adalimumab has been used for acrodermatitis continua of Hallopeau.\(^\text{58}\)

### Ongoing studies of efficacy and safety of newer biologics in pediatric psoriasis

Secukinumab has been used for generalized pustular psoriasis and DITRA in children.\(^\text{59,60}\) Ixekizumab, an IL-17A inhibitor, is currently in a double-blind, randomized clinical trial for children 6 to 17 years of age (ClinicalTrials.gov identifier: NCT03073200). There are no case reports of the experimental use of ixekizumab, secukinumab (anti-IL-17), brodalumab (anti-IL-17 receptor), or guselkumab (anti-IL-23) in pediatric psoriasis.

### Should we consider anti-IL-22 monoclonal antibody therapy in children?

Our understanding of the pathogenesis of psoriasis is largely based on studies in affected adults. Nevertheless, the interventions used for adults have shown efficacy in children, suggesting a similar mechanism. That said, a recent study of the T-cell composition in the lesional skin of children versus adults showed a predominance of cluster of differentiation (CD)4\(^+\) and CD8\(^+\) IL-22-expressing T cells in pediatric skin versus the predominance of CD4\(^+\) and CD8\(^+\) IL-17-expressing T cells in adult skin.\(^\text{61}\) While anti-IL-22 therapy (fezakinumab, ILV-094; ClinicalTrials.gov identifier: NCT00563524) was not efficacious in adult psoriasis, the greater increase in the proportion of T-cells expressing IL-22 in children (versus adults) suggests that the pediatric population may prove more responsive to anti-IL-22 therapy.

In summary, the potential therapeutic agents available for children with psoriasis has been greatly extended by the introduction of biologics. With newer biologics currently in trial or planned for pediatric testing, the future looks even more promising for children with psoriasis. Whether more aggressive early management with these agents ultimately changes the course of disease, including the potential prevention of comorbidities, remains to be tested.
References


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