Evolving Landscape of Biologic Therapy for Pediatric Psoriasis

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KEYWORDS

• Psoriasis • Pediatric psoriasis • Biologics • Biologic therapy

KEY POINTS

- Biological agents are an attractive treatment option in cases of moderate-to-severe psoriasis recalcitrant to other therapies, such as topical medications and phototherapy.
- Approved biological therapies for pediatric psoriasis include TNF-alpha inhibitors, IL-17 inhibitors, and IL-12/23 inhibitors.
- Choosing an appropriate biological medication requires consideration of patient factors (clinical manifestation, comorbidities) and drug characteristics (dosage frequency, safety and efficacy profile, frequency of laboratory monitoring, and potential contraindications).
- Ongoing clinical trials point to expanding treatment options and highlight the need for continued research in the pediatric population.

INTRODUCTION

Pediatric psoriasis is a chronic, immune-mediated, inflammatory skin condition characterized by well-demarcated, erythematous, scaly plaques. The prevalence of pediatric psoriasis is estimated at 128 cases per 100,000 individuals.[1] Approximately one-third of psoriasis cases manifest during childhood,[2–4] with a median age of onset between 7 and 10 years.[5]

The pathophysiology of pediatric psoriasis mirrors that of adult psoriasis, involving a complex interplay between genetic predisposition, immune dysregulation, and environmental triggers, with T-helper (TH1, TH17, and TH22) cell responses that increase proinflammatory cytokines and induce keratinocyte proliferation.[6,7]

Pediatric psoriasis has variable degrees of severity and manifests differently across age groups. The scalp, face, and anogenital region are frequently involved in younger children. Involvement in the diaper area may mimic other dermatoses, resulting in a delay in diagnosis.[8] In older children and adolescents, the involvement of the scalp, elbows, knees, and umbilicus is more common.[9,10] Histologically, pediatric psoriasis shares similarities with adult psoriasis, demonstrating epidermal hyperproliferation, parakeratosis, and dermal inflammatory infiltrates.[11] While some children experience spontaneous remission, the condition may persist into adulthood with a relapsing course.

Psoriasis is associated with multiple comorbidities in children and adolescents, including obesity, hyperlipidemia, hypertension, diabetes mellitus, arthritis, inflammatory bowel disease, anxiety, and depression.[9,12] Quality of life is impacted due to stigma, and patients experience impairment in social interactions, emotional well-being, and school performance.[12–14] The annual direct and indirect economical burden associated with pediatric psoriasis totals approximately 75 billion, encompassing medical costs, loss of productivity, and

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Dermatol Clin 42 (2024) 377–386
https://doi.org/10.1016/j.det.2024.02.003

lowered quality of life.[15] The multifaceted nature of this condition requires safe and effective therapeutic options to improve and optimize patient health.

MANAGEMENT

There is currently no cure for pediatric psoriasis. Management focuses on the prevention of flares and the control of associated health conditions, such as psoriatic arthritis and obesity, while minimizing therapeutic risks. Treatment options are influenced by disease severity, comorbidities, impact on quality of life, safety, efficacy, and patient/family preferences.

Mild or limited disease is commonly controlled with topical medications.[16] Moderate-to-severe disease may warrant treatment with phototherapy or systemic medications.[17] Narrowband ultraviolet B (NB-UVB) phototherapy is an effective treatment option for pediatric plaque and guttate psoriasis; however, time constraints (initial treatment generally 3 days per week) may affect access to and adherence to care - especially for pediatric patients enrolled in school.[4] However, home phototherapy is a viable option for many and can delay the need for systemic medications in some patients. While nonbiologic systemic medications (methotrexate, cyclosporine, and acitretin) have been shown to successfully manage symptoms of pediatric psoriasis for decades, many have fallen out of favor due to side effect profiles, including the risk of organ toxicity, and frequent laboratory monitoring.[18]

In recent years, biological therapy has become an appealing option for pediatric patients with moderate-to-severe psoriasis. Defined as immunomodulators that target specific cells of the immune system, biologics disrupt the inflammatory cascade process to achieve clearer skin.[19] Patients reported greater improvement in the quality of life with systemic treatment compared with topical treatment.[20] Biologics, in particular, have higher rates of adherence when compared with other systemic agents.[21]

This review article aims to summarize approved biological therapies for pediatric psoriasis and the growing clinical evidence supporting their use. At the time of publication, 5 biologic drugs had been approved for the treatment of pediatric psoriasis by the U.S. Food & Drug Administration (FDA) or the European Medicines Agency (EMA): adalimumab, etanercept, ustekinumab, secukinumab, and ixekizumab. There are 6 drugs undergoing phase 3 clinical trials in the United States: guselkumab, risankizumab, tildrakizumab, certolizumab pegol, apremilast, and deucravacitinib. **Tables 1** and **2** summarize approved biological drugs and nonapproved biologic drugs undergoing investigation, respectively. Highlights are described later in discussion.

TUMOR NECROSIS FACTOR-α INHIBITORS

Tumor necrosis factor (TNF) is a key cytokine in the body's inflammatory response.[22] For decades, it was a pharmaceutical target to treat conditions such as rheumatoid arthritis,[23] juvenile idiopathic arthritis,[24] and ulcerative colitis.[25] Research suggests TNF-α inhibitors are safe and effective for the management of pediatric psoriasis.

Etanercept has been approved by the FDA and EMA for pediatric use, while adalimumab has only been approved by the EMA for children. For adult populations, there are 4 approved biologics for psoriasis: etanercept, adalimumab, certolizumab pegol, and infliximab.

Certolizumab pegol is under investigation in a phase 3 clinical trial for use in pediatric patients with moderate-to-severe plaque psoriasis (see **Table 2**). Infliximab is approved for Crohn's disease in pediatric patients ages 6 and older and has demonstrated successful treatment of plaque and pustular psoriasis in pediatric case reports; however, no clinical trials to explore its efficacy and safety for pediatric psoriasis existed at the time of publication.[26–28]

Etanercept (Enbrel)

Etanercept is a soluble fusion protein that binds to the TNF receptor and was the first biological medication approved to treat pediatric psoriasis in the United States.[29] In Europe, etanercept was approved by the EMA for the treatment of moderate-to-severe plaque psoriasis for children ages 8 and older in 2008 and extended to ages 6 and older in 2011.[17] Etanercept was approved by the FDA for adults with plaque psoriasis in 2004 and for children ages 4 and older in November 2016.[29] It is also approved for the treatment of rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis in adults and for juvenile idiopathic arthritis in patients 2 years and older.[29] It is also currently under investigation for nail psoriasis in adults (ClinicalTrials.gov Identifier: NCT05135312).

Numerous observational and retrospective studies have demonstrated the efficacy of etanercept for use in pediatric patients.[30–32] Its most robust clinical evidence comes from a 5-year open-label extension study of 182 patients ages 4 through 17, whereby Paller and colleagues reported 60% to 70% of patients experienced 75% improvement in Psoriasis Area and Severity Index (PASI) score as well as 30% to 40% reporting PASI

Table 1
Pediatric psoriasis approved biologics

Drug Class	Drug	FDA Approval	EMA Approval	Weight Based Dosing	Baseline Monitoring	Contraindications & Precautions
TNF- α inhibitor	Etanercept[4,12,29]	4–17 y	6–17 y	≥ 63 kg: 50 mg qw <63 kg: 0.8 mg/kg qw	Tuberculosis (TB) - repeat once a year. Hepatitis and HIV based on relevant risk factors. Continued monitoring for active infection – frequency may vary between patients.	Active TB. Severe infections (ie, sepsis, other opportunistic infections). Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF- a blockers. Demyelination disease. Avoid the use of live vaccines. Caution during pregnancy.
	Adalimumab[4,12,41]	–	4–17 y	≥ 13 kg: Initial – 0.4 mg/kg (low) or 0.8 mg/kg (high) at weeks 0 and 1 Maintenance – 0.4 mg/kg (low) or 0.8 mg/kg (high) q2w		Active TB. Severe infections (ie, sepsis, other opportunistic infections). Moderate to severe heart failure (NYHA class III/IV). Lymphoma and other malignancies, some fatal, have been reported in pediatric patients during treatment. Demyelination disease. Avoid the use of live vaccines. Caution during pregnancy
IL-17 inhibitor	Ixekizumab[4,59]	6–17 y	6–17 y	> 50 kg: Initial – 160 mg Maintenance – 80 mg q4w 25–50 kg: Initial – 80 mg Maintenance – 40 mg q4w < 25 kg: Initial – 40 mg Maintenance – 20 mg q4w		Active TB. Severe infections (ie, sepsis, other opportunistic infections). Inflammatory bowel disease – Crohn's disease and ulcerative colitis episodes and exacerbations have occurred during trials. Avoid the use of live vaccines.

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Table 1
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Drug Class	Drug	FDA Approval	EMA Approval	Weight Based Dosing	Baseline Monitoring	Contraindications & Precautions
	Secukinumab[4,52]	6–17 y	6–17 y	≥ 50 kg: 150 mg (the EMA recommends 300 mg) 15 kg – 50 kg: 75 mg Injections given at Week 0, 1, 2, 3, 4 and then q4w		Active TB. Severe infections (ie, sepsis, other opportunistic infections). Inflammatory bowel disease – Crohn's disease and ulcerative colitis episodes have occurred during trials. Severe eczematous eruptions. Avoid the use of live vaccines.
IL-12/23 inhibitor	Ustekinumab[4,12,67]	6–17 y	6–17 y	< 60 kg: 0.75 mg/kg 60 kg – 100 kg: 45 mg >100 kg: 90 mg Injections given at Week 0, 4, and then q12w		Active TB. Severe infections (ie, sepsis, other opportunistic infections). Non-infectious pneumonia – interstitial pneumonia, eosinophilic pneumonia, cryptogenic pneumonia have been reported. Reversible posterior leukoencephalopathysyndrome Avoid the use of live vaccines. Caution during pregnancy.

Table 2
Biologics on the Horizoqn

Drug	Drug Class	ClinicalTrials.Gov Identifier	Route of Administration	Ages of Participants	Proposed Study Completion Date
Guselkumab	IL-23 inhibitor	NCT03451851	Subcutaneous	12–17 y	June 2025
Risankizumab	IL-23 inhibitor	NCT04435600	Subcutaneous	12–17 y	August 2025
Certolizumab Pegol	TNF inhibitor	NCT04123795	Subcutaneous	12–17 y	December 2026
Apremilast	PDE4 inhibitor	NCT04175613	Oral	6–17 y	February 2027
Tildraizumab	IL-23 inhibitor	NCT03997786	Subcutaneous	6–17 y	July 2031
Deucravaitinib	Tyrosine Kinase 2 inhibitor	NCT04772079	Oral	12–17 y	September 2031

90 response while on a weekly etanercept regimen of 0.8 mg/kg (maximum dose of 50 mg) through week 264.[33] These long-term efficacy results are consistent with PASI 75 responses reported in adults on stable weekly etanercept doses of 50 mg.[34] Additionally, intermittent treatment with etanercept appears safe, with 80% of pediatric study patients maintaining PASI 75 responses at the end of the 12-week withdrawal period and no reported serious adverse effects or infections.[35]

Common adverse events included injection site reactions, upper respiratory tract infections, nasopharyngitis, and headaches.[33] Use of TNF inhibitors is associated with increased rates of viral and fungal infections in both adult and pediatric populations[36]; however, no cases of opportunistic infections or malignancy were reported during Paller and colleagues's study.[33] Antidrug antibodies were detected in a small sample of participants, but no patients developed neutralizing antibodies.[33] Etanercept's clinical benefit also improved health-related quality of life in both short-term and long-term treatments.[37] When compared with methotrexate, treatment with etanercept demonstrated a decreased incidence of adverse effects, with only 4 out of 106 patients discontinuing treatment, compared with 44 out of greater than 370 patients discontinuing therapy with other systemic agents.[21]

Adalimumab (Humira)

Adalimumab (ADA) is a fully human monoclonal antibody and TNF-α blocker.[18] The EMA has approved adalimumab to treat pediatric plaque psoriasis in patients 4 years and older who failed topical therapy and phototherapy.[38,39] In the United States, though not approved for pediatric psoriasis, adalimumab is FDA-approved for juvenile idiopathic arthritis and Crohn's disease in pediatric patients.[40]

Clinical trial data support adalimumab's efficacy for pediatric psoriasis. Papp and colleagues enrolled 114 patients between the ages of 4 and 18 years with severe plaque psoriasis refractory to topical therapy. Half of the patients were assigned to receive 0.4 mg/kg or 0.8 mg/kg adalimumab injections every 2 weeks, and half were assigned weekly oral methotrexate (0.1–0.4 mg/kg). At week 16, 61% (23/38) patients in the high-dose adalimumab group, and 58% (22/38) in the low-dose adalimumab group achieved PASI 75 response scores – both groups having statistically significant differences compared with their methotrexate group counterparts (41% and 32% achieving PASI 75 response, respectively).[41]

Common adverse events included nasopharyngitis, upper respiratory infections, and rhinitis, with 17 out of 38 (45%) of patients in the high-dose adalimumab group, 22 out of 39 (56%) in the low-dose adalimumab group, and 21 out of 37 (57%) in the methotrexate group reporting infections.[41] Three serious adverse events were reported from the 0.4 mg/kg adalimumab group, but all were deemed to be unrelated to the study drug.[41] An additional analysis of the safety of adalimumab with the same patient cohort revealed PASI 75 response scores improved for both high and low-dose adalimumab groups through week 52.[42] Quality of life scores, measured by CDLQI and Pediatric Quality of Life Inventory scores, improved for all groups through 52 weeks, with patients initially randomized to receive ADA 0.8 mg/kg doses experiencing the largest improvement.[42] One patient reported a serious adverse event of eye naevus considered to be possibly related to ADA.[42] Three out of 72 patients experienced severe adverse events, with one patient each reporting bronchitis and extremity pain, upper respiratory tract infection, and worsening psoriasis.[42] Only one patient (worsening psoriasis) resulted in ADA discontinuation.[42] One moderate adverse event of herpes

zoster was possibly related to adalimumab.[42] When compared with oral methotrexate, higher rates of events associated with allergic reactions (urticaria, pruritus, bronchospasm, and asthma) were seen for patients taking methotrexate versus patients randomized to ADA.[42]

Although phase 3 clinical trial data was conducted in patients with plaque psoriasis, a recent case series highlighted the use of adalimumab for the treatment of pustular psoriasis in 7 patients ages 2 to 13 years. Patients received weight-based adalimumab injections every 2 weeks. After 2 injections, 5 patients demonstrated a decreased Physician's Global Assessment (PGA) score to 0, while the other 2 patients had 90% clearance of psoriatic lesions and a PGA score of 1.[43]

INTERLEUKIN-17 INHIBITORS

Interleukin-17 plays a critical role in the pathogenesis of psoriasis and is a prime target for treatment.[7,44] The FDA has approved 3 IL-17 inhibitors for the treatment of adult psoriasis: secukinumab, brodalumab, and ixekizumab.[45] In pediatric populations, both secukinumab and ixekizumab are approved for children ages 6 and older.[46–48]

A phase 3 clinical trial was initiated in March 2020 to validate the efficacy and safety of brodalumab in adolescents between ages 12 and 17 years with moderate-to-severe plaque psoriasis; however, this study was terminated early in July 2023 due to recruitment difficulties (ClinicalTrials.Gov Identifier: NCT04305327).

Secukinumab (Cosentyx)

Secukinumab is a fully human monoclonal antibody that antagonistically binds to the IL-17A receptor.[46] The EMA approved secukinumab for adult psoriasis in 2014, and the FDA followed in 2015.[49,50] The EMA approved secukinumab for plaque psoriasis in patients ages 6 and older in 2020, and the FDA subsequently approved it in 2021 for the same indications.[49–51] The FDA has also approved secukinumab for the management of psoriatic arthritis in patients ages 2 and older.[50]

Data on secukinumab for children with psoriasis largely comes from two phase 3 clinical trials. The first study by Bodemer and colleagues focused on patients ages 6 to 18 with severe psoriasis who were administered low-dose (75 mg or 150 mg) or high dose (150 mg or 300 mg) based on their weight categories of 25 to less than 50 kg and $\geq$50 kg, respectively.[52] At week 12, PASI 75 reduction scores for low-dose and high-dose secukinumab were significantly higher than the placebo (80% vs 77.5% vs 14.6%), and efficacy was maintained through week 52.[52] A second study by Magnolo and colleagues followed the same dosing regimens for children with moderate-to-severe psoriasis and demonstrated similar results in both secukinumab intervention groups when compared with historical placebo rates at week 12 (78.6% and 83.3%).[53]

Injection site reactions were noted in some study participants, but none required treatment or withdrew from the study.[52] Commonly reported adverse events included mild-to-moderate nasopharyngitis, pharyngitis, and headache, and the overall safety profile of secukinumab treatment is consistent with phase 3 adult studies.[52] A pooled safety analysis of the 2 aforementioned studies demonstrated several cases of temporary mild neutropenia that did not result in treatment discontinuation and no detection of anti-drug antibodies in pediatric patients treated with secukinumab.[54] Furthermore, no additional safety concerns were reported with long-term secukinumab exposure with observation up to 104 weeks.[55] A combined analysis of phase 2 and phase 3 clinical trials of secukinumab in adult psoriasis patients highlighted 2 cases of exacerbations of previously diagnosed Crohn's disease and one case in a patient whose history suggested undiagnosed Crohn's disease.[56] Use of secukinumab in pediatric patients with a history of inflammatory bowel disease (IBD) is therefore cautioned. Additionally, in pediatric patients with nonspecific gastrointestinal symptoms, it may be prudent to consider further evaluation of their gastrointestinal symptoms prior to initiating therapy.

Secukinumab achieved higher rates of PASI 75 and PASI 90 when compared with weekly etanercept, as well as a lower overall incidence of adverse events.[52,54] This evidence, along with secukinumab's less frequent dosing (compared with etanercept's weekly dosing), makes it an attractive option in the pediatric population.

Ixekizumab (Taltz)

Another IL-17A blocker used for pediatric psoriasis is ixekizumab, a high-affinity humanized monoclonal antibody.[47] The FDA approved ixekizumab for adult plaque psoriasis in 2016 and extended approval for children ages 6 and older in 2020.[47] In Europe, the EMA approved ixekizumab for the same indications within similar timelines.[48] Ixekizumab is also approved for the management of psoriatic arthritis, ankylosing spondylitis, and nonradiographic axial spondylitis in adults.[57]

In the IXORA-PEDS clinical trial, ixekizumab showed significant efficacy compared with placebo for patients ages 6 and older with moderate-to-severe plaque psoriasis. Using the dosing regimen outlined in **Table 1**, 89% of patients on ixekizumab reached PASI 75, compared with 25% of placebo

patients at week 12.[58] Efficacy was sustained or improved through week 60.[58] When compared with the standard treatment of etanercept, ixekizumab performed significantly better in several metrics, including PASI 90, PASI 100, and static Physician's Global Assessment (sPGA) scores of 0 or 1.[58] Patients using ixekizumab saw significant differences in PASI 50, PASI 75, and itch numerical rating scale (Itch NRS) $\geq$ 4 as early as week one, with 36% of patients achieving PASI 50 with ixekizumab compared with only 7% on placebo.[58]

The safety profile of ixekizumab is consistent with adult studies, with common adverse effects being injection site reactions, allergic reactions/hypersensitivity, and infection.[58] Treatment-emergent infections were reported in 37 (32%) of patients receiving ixekizumab and 14 (25%) receiving placebo injections by week 12, but no serious infections were reported.[58] It is noted that, in 4 patients, Crohn's disease emerged during treatment, despite no personal history or family history of inflammatory bowel disease.[58] As a result, the same precautions, which were outlined with secukinumab above, should be taken in patients with a history of IBD or gastrointestinal symptoms concerning for possible IBD.

Ixekizumab should be considered an effective therapy for pediatric psoriasis, especially due to its efficacy and rapid onset when compared with other approved biological drugs.

INTERLEUKIN-12/23 AND INTERLEUKIN-23 INHIBITORS

Interleukin-12 and interleukin-23 are pro-inflammatory cytokines linked to the pathogenesis of psoriasis through their stimulation of epidermal hyperplasia via TNF.[59] Both IL-12 and IL-23 are heterodimers with the p40 subunit required for receptor binding[60] and are overexpressed in psoriasis plaques.[61]

For adults, the FDA has approved ustekinumab (2009), guselkumab (2017), tildrakizumab (2018), and risankizumab (2019) for the treatment of adult plaque psoriasis.[62] For children, ustekinumab is the only IL-12/23 drug approved for moderate-to-severe psoriasis in children ages 6 years and older.[63,64]

There are ongoing phase 3 clinical trials for guselkumab, tildrakizumab, and risankizumab in child and adolescent populations with psoriasis (see **Table 2**).

Ustekinumab (Stelara)

Ustekinumab is a human monoclonal antibody that inhibits the p40 subunit of both IL-12 and IL-23 cytokines.[18]

Two main clinical trials have evaluated the safety and efficacy of ustekinumab in pediatric patients. In the phase 3 CADMUS study, 110 patients ages 12 to 17 years were assigned standard weight-based dosing of ustekinumab (0.75 mg/kg [$\leq$60 kg], 45 mg [>60-$\leq$100 kg], and 90 mg [>100 kg]) or half-standard dosing (0.375 mg/kg [$\leq$60 kg], 22.5 mg [>60-$\leq$100 kg], and 45 mg [>100 kg]) at weeks 0 and 4 and every 12 weeks for a total of 60 weeks.[64] At week 12, both standard dose and half-standard dose groups achieved significantly higher rates of PASI 75 scores, with 80.6% and 78.6% of patients seeing improvement, respectively, compared with only 10.8% of patients in the placebo group.[63] Similar significant differences were demonstrated for PASI 90 scores.[63]

In the phase 3 CADMUS Jr study, patients ages 6 to 12 years with moderate-to-severe disease were started on standard weight-based dosing of adalimumab at weeks 0, 4, and every 12 weeks through week 40.[65] By week 12, 37 patients (84%) had achieved PASI 75, 28 (64%) patients had reached PASI 90, and 15 (34%) patients had achieved a PASI 100 response.[65] Clinical response to treatment and PASI scores were maintained or improved through week 52.[65] Quality of life measures using CDLQI scores improved for patients by week 12 and were maintained through week 52.[65]

Commonly reported adverse effects included nasopharyngitis, pharyngitis, and upper respiratory tract infections. Twenty-nine (66%) patients were observed to have infections, and 12 (27%) received antimicrobial treatment.[65] Three serious adverse events were reported (infectious mononucleosis, eyelid injury, and a diagnosis of attention deficit/hyperactivity disorder) through week 56 of follow-up, but none were deemed to be related to study treatment.[65]

SUMMARY

Over the past 2 decades, numerous biological agents have been approved for use in pediatric psoriasis. These agents are an attractive option in cases of moderate-to-severe psoriasis recalcitrant to first line therapies, given their dosing schedules, safety profiles, and need for less frequent laboratory monitoring. To date, no clear guidelines exist on which biological agent to choose, and as a result, the decision varies by clinical context.

In the pediatric population, fear of injections and needle phobia incidence rates are higher among infants and young children[66]; therefore, biologics with less frequent dosing (ustekinumab vs IL-17 antagonists) may be preferable.

Comorbidities may also impact biological choice. Patients with IBD should avoid IL17 inhibitors.[56,58] Additionally, biologics with approved indications for multiple diseases can be used for patients diagnosed with multiple conditions, thus decreasing the number of medications and allowing for treatment ease and adherence.

Pediatric psoriasis is strongly associated with obesity[67,68] and obesity's induction of systemic inflammation also induces an increased risk of cardiovascular disease.[48] Studies have shown TNF-α inhibitors to be cardioprotective in adult patients with psoriasis.[69] To date, no studies have explored the possibility of a similar effect in children.

Many biological drugs, including all drugs highlighted in this article, are not to be administered concurrently with live vaccines due to the risk of disseminated infections. In cases whereby live vaccines are indicated, guidelines suggest administering the vaccine 2 to 4 weeks before the initiation of biological therapy or at least 3 months after withdrawal of biological therapy.[70]

There is a paucity of clinical data that compares the safety and efficacy of different biological agents for pediatric psoriasis. Future research can also further explore transition periods between biological treatment options, sustained the management of psoriasis after biological withdrawal, and formal guidelines on combination biological therapy.

CLINICS CARE POINTS

- Pediatric psoriasis is a complex disease process that requires individualized management.
- Treatment for psoriasis is varied, with topicals, phototherapy, and systemic drugs proven to provide significant clinical benefit.
- Novel biologics, however, represent a treatment modality that can provide rapid and safe improvement for patients, and should be considered an exciting and essential resource for this patient population.

DISCLOSURE

The authors have no disclosures, conflicts of interest, or funding sources to declare.

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