Biological Agents in Pediatric Dermatology

27

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Introduction

Biological agents ("biologics") include a broad group of often complex products, such as antibodies, blood components, vaccines, gene therapy, and recombinant proteins. They may be isolated from natural sources, whether microorganism, animal, or human, or produced using biotechnology methods. They can be designed to specifically target disease pathogenesis.

Structurally, biologics used for psoriasis fall into two classes: antibodies and fusion proteins. Functionally, biologics modulate the immune system by interfering with cytokine production, inhibiting T-cell activation, or depleting B-cells. While used widely in adult dermatology and for many years in pediatric patients with rheumatologic and gastrointestinal disorders, biologics have only recently been approved for pediatric psoriasis in Europe and the United States. To date, three biologics have been tested in double-blinded, randomized controlled trials for pediatric psoriasis: etanercept, adalimumab, and ustekinumab (1, 2, 3; Table 27.1). All of these are anti-cytokine agents, with etanercept and adalimumab targeting tumor necrosis factor alpha (TNF-α), and ustekinumab targeting the shared p40 component of interleukin (IL) -12 and 23. Etanercept and ustekinumab are now approved by the Food and Drug Administration (FDA) for treatment of moderate-to-severe chronic plaque psoriasis in children, for ages 4–17 years and 12–17 years respectively. Adalimumab is approved in Europe for the treatment of severe plaque psoriasis in children starting at age 4 etanercept at age 6, and ustekinumab is approved for the treatment of moderate-to-severe plaque psoriasis starting at age 12. Although infliximab has occasionally been used in severe cases that require rapid-acting intravenous administration, it is not approved and rarely considered for plaque psoriasis in children.

Approximately one-third of individuals with psoriasis experience disease onset prior to 16 years of age, with the prevalence increasing linearly throughout childhood [1, 2]. The most common predisposing genetic risk factor is the human leukocyte antigen (HLA) type Cw6 (*PSOR1*). Having a pathogenic mutation in *CARD14* (caspase recruitment domain family 14; *PSOR2*) causes a rare familial form, which may manifest as pityriasis rubra pilaris or psoriasis [3, 4]. Triggering environmental factors are skin trauma (Koebner phenomenon), infections (most notably streptococcal, but also staphylococcal and varicella), Kawasaki disease, certain medications, as well as psychological and physical stress [5–10].

The role of the immune system in the pathophysiology of psoriasis accounts for the responsiveness of this disease to the targeted immunomodulatory effects of biologics. Although our understanding of psoriasis is based strictly on studies in adults, it is thought that TNF-α and IL-17A synergistically upregulate the production of other cytokines, chemokines, and antimicrobial peptides from keratinocytes and regional immune cells, initiating and perpetuating the immune activation of psoriasis [11]. Most pediatric psoriasis can be managed topically; however, approximately 10% are either recalcitrant to topical therapy, associated with juvenile psoriatic arthritis, or significantly severe and diffuse enough to require systemic medications or phototherapy, most often narrow-band ultraviolet light. Methotrexate is the most commonly prescribed systemic medication (69% of pediatric patients prescribed a systemic medication), but cyclosporine, retinoids, and fumaric acid are non-biologic alternatives [12]. Recent studies suggest that the more targeted biologics have superior efficacy and side-effect profiles compared to these more nonspecific systemic therapies [12, 13].

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Table 27.1 Biologics for pediatric psoriasis

Biologic	Target	Type	Dosing	Frequency
Etanercept	TNF-α	Fusion protein	0.8 mg/kg (maximum 50 mg)	Administered subcutaneously every week
Adalimumab	TNF-α	Human monoclonal antibody	0.8 mg/kg (maximum 40 mg) A loading dose of twice the calculated dose can be given the initial week	Administered subcutaneously every other week
Ustekinumab	Common p40 subunit of IL-12 and IL-23	Human monoclonal antibody	<60 kg: 0.75 mg/kg 60–100 kg: 45 mg >100 kg: 90 mg	Administered subcutaneously every 12 weeks, with an additional loading dose given 4 weeks after the initial injection.

Tumor Necrosis Factor Inhibitors

Among the biologics, TNF inhibitors are most often used. In an international study of 390 children using systemic medications for pediatric psoriasis, 27% were treated with a TNF inhibitor, second only to methotrexate in frequency; the majority of these children were treated with etanercept [12].

All TNF inhibitors carry a boxed warning about serious infections and malignancies, although to-date an increased risk of malignancy has not been documented in children treated with TNF inhibitors for psoriasis. In the end, these risks must be balanced with the risks of conventional therapies for these diseases, as well as the inherent risks of immune-mediated disease (i.e., the known increased risk of lymphoma in individuals with severe psoriasis itself) [14]. The decision to treat with a TNF blocker must weigh the potential benefits of treatment with the specific risk profile of individual patients in order to maximize the therapeutic effect of these medications.

Etanercept

Etanercept is a soluble TNF-α receptor fusion protein, consisting of two p75 TNF receptors bound to the Fc portion of immunoglobulin G, which can reversibly bind two TNF-α molecules. As the longest used and best studied biologic for pediatric psoriasis, it is currently the only TNF inhibitor FDA-approved for this indication. It is also FDA-approved for adults with psoriasis, rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis, and for children with polyarticular juvenile idiopathic arthritis (JIA). It has been approved in Europe for pediatric psoriasis since 2008.

Etanercept was first investigated as a treatment for pediatric psoriasis in a phase III, double-blinded, placebo-controlled trial published by Paller et al. in 2008. Children ages 4 to 17 with moderate-to-severe plaque psoriasis, defined as a Psoriasis Area and Severity Index (PASI) score of at least 12, a static Physician's Global Assessment (PGA) of at least 3, and involvement of at least 10% of the body surface area (BSA), were enrolled. Subjects were then randomized to either placebo or etanercept 0.8 mg/kg (max 50 mg) weekly for 12 weeks. After 12 weeks, subjects entered 24 weeks of open-label treatment with etanercept. Those who achieved PASI 75 entered a 12-week blinded withdrawal-retreatment period, during which they were randomized to either placebo or weekly etanercept. Efficacy endpoints were PASI 50, PASI 75, PASI 90, and PGA 0/1 at week 12, as well as the Children's Dermatology Life Quality Index (CDLQI) score. Safety endpoints were adverse events, serious adverse events, laboratory values, serum concentrations of etanercept, and disease rebound during the withdrawal period.

The study enrolled 211 children, aged 4–17. At week 12, significantly more subjects in the etanercept group reached a PASI 75 response compared to those receiving placebo (57% vs. 11%, $p < 0.001$). Similar trends were observed for PASI 50 (75% vs. 23%, $p < 0.001$) and PASI 90 (27% vs 7%, $p < 0.001$) responses. These results were sustained throughout the 24-week open-label treatment phase. Both the original placebo group and the etanercept group experienced mean percentage improvement in their PASI scores that were greater than 70% [15]. These efficacy findings were unchanged in subgroup analysis [16]. Quality of life, as measured by the CDLQI, also improved significantly more in the etanercept group than in the placebo group (52.3% versus 17.5%, $p = 0.0001$; [17]).

During the withdrawal-retreatment phase, 42% of those assigned to placebo lost their PASI 75 response and were retreated with etanercept. These subjects were retreated with etanercept and achieved response rates similar to those seen in the initial double-blind treatment phase. Nearly half of the subjects on placebo maintained their PASI 75 response through the end of the study (week 48). No rebound of psoriasis was observed during this period [15]. In a 5-year, open-label extension of the double-blinded trial for patients who had achieved at least PASI 50 completed by 69 subjects, the percentage of patients achieving PASI 75 or PASI 90 responses remained constant [18]. Regarding safety, similar rates of infectious and noninfectious adverse events were observed between the two groups [15, 18]. In the 5-year,

open-label extension, the most common adverse events reported were upper respiratory tract infection, nasopharyngitis, and headache. No malignancies or opportunistic infections were observed [18].

Etanercept is administered subcutaneously at a dose of 0.8 mg/kg (maximum 50 mg) every week. Although the American College of Rheumatology recommends baseline complete blood counts (CBC), liver function tests, and serum creatinine and every 3–6 months thereafter for individuals with JIA who are starting a TNF-α inhibitor, this recommendation is based on consensus (level D evidence); there is no recommendation in the current dermatologic literature [19]. At a minimum, however, providers should perform a baseline history and physical examination and obtain annual TB testing. Patients administered etanercept and other TNF inhibitors should avoid live vaccines while on these medications, as infection transmission from these vaccines has not been characterized in individuals on these medications [20].

Adalimumab

Adalimumab is a recombinant, fully human monoclonal antibody to TNF-α. It binds specifically to TNF-α, preventing its interactions with the p55 and p75 cell surface receptors. In adults, it is currently FDA-approved for the treatment of psoriasis and psoriatic arthritis, rheumatoid arthritis, arthritis, ankylosis spondylitis, Crohn's disease, ulcerative colitis, hidradenitis suppurativa, and uveitis. In children, adalimumab is approved for the treatment of JIA and Crohn's disease [21]. In 2015, it was approved by the European Commission for severe plaque psoriasis in children as young as 4 years. It was studied for this indication in an international multicenter double-blinded, randomized controlled trial comparing the efficacy and safety of adalimumab to methotrexate in pediatric patients [22]. A similar study conducted in adults several years prior demonstrated the superior efficacy and comparable safety of adalimumab vs. methotrexate [23].

The pediatric trial conducted by Papp et al. enrolled 114 children ages 5 to 18. Subjects had moderate-to-severe plaque psoriasis, defined as PGA ≥ 4, BSA involved >20%, PASI >20, or PASI >10 with psoriatic arthritis unresponsive to nonsteroidal anti-inflammatory drugs, clinically relevant facial, genital, or hand/foot involvement, or Children's Dermatology Life Quality Index >10. They were randomized to either adalimumab 0.8 mg/kg up to 40 mg every other week, adalimumab 0.4 mg/kg up to 20 mg every other week, or methotrexate 0.1–0.4 mg/kg up to 25 mg every week. After 16 weeks of double-blind treatment, treatment responders (those who had achieved at least a PASI 75 response and PGA of 0/1) proceeded to the next phase, during which treatment was withdrawn until loss of disease control. Subjects completing the second phase were then retreated with adalimumab (0.8 mg/kg for patients who previously received adalimumab 0.8 mg/kg or methotrexate, and 0.4 mg/kg for patients who previously received adalimumab 0.4 mg/kg) for 16 weeks. After this blinded retreatment stage, patients were treated and followed for 52 weeks.

After 16 weeks of treatment, significantly more subjects treated with adalimumab 0.8 mg/kg reached a PASI 75 response than those treated with adalimumab 0.4 mg/kg or methotrexate (57.9% versus 43.6 and 32.4%, respectively). Similarly, 60.5% of patients treated with standard-dose adalimumab achieved PGA 0/1 vs. 40.5% with low-dose adalimumab and 41.0% with methotrexate. PASI 100 was achieved in 18.4% of patients treated with standard-dose adalimumab vs. 10.4% with low-dose adalimumab and 2.7% with methotrexate. Adverse events were similar among the three treatment groups, and there were no serious adverse events reported in the adalimumab 0.8 mg/kg treatment group [22].

Adalimumab is administered via subcutaneous injection at a dose of 0.8 mg/kg (maximum 40 mg) every other week. A loading dose of 80 mg can be given the initial week. Prior to starting the medication, as with etanercept, TB testing should be performed and repeated annually. Immunizations should also be updated, and live vaccines withheld during treatment.

Ustekinumab

Ustekinumab is a human immunoglobulin G1 kappa monoclonal antibody targeting the common p40 subunit of IL-12 and IL-23. It prevents these cytokines from binding to the IL-12 receptor, found on the surface of immune cells. Canada approved it in 2008 for the treatment of moderate-to-severe plaque psoriasis in adults following the two global phase 3 trials (PHOENIX 1 and PHOENIX 2), which demonstrated the efficacy and safety of ustekinumab for this indication [24, 25]. FDA approval for psoriasis and psoriatic arthritis followed in 2009. It is also approved for adults with Crohn's disease [26] and, in Canada and the European Union, for adolescents 12 and older [27]. It was approved by the FDA in 2017 for treating pediatric psoriasis (12 years and older). Anecdotally, it appears to be the current treatment of choice for pediatric patients with *CARD14* mutations, with a better reported efficacy than non-biologics and TNF inhibitors.

Ustekinumab was evaluated in adolescents with moderate-to-severe plaque psoriasis in the CADMUS trial, which ultimately led to its approval in Canada and the European Union. This multicenter, double-blinded, placebo-controlled trial enrolled children ages 12 through 17 with chronic (diagnosed at least 6 months prior to screening) moderate-to-severe plaque psoriasis (PASI ≥12, PGA ≥ 3, and ≥10% BSA involved). These subjects were randomized to receive either

standard (0.75 mg/kg for ≤60 kg, 45 mg for 60 kg–100 kg, or 90 mg for >100 kg) or half-standard ustekinumab dosing (0.375 mg/kg, for ≤60 kg, 22.5 mg for 60 kg–100 kg, or 45 mg for >100 kg) or to placebo with crossover to standard to half-standard ustekinumab at week 12. Open-label treatment was continued through week 40, with adverse events collected through week 60.

Overall, 110 patients were enrolled. Ustekinumab resulted in significant clinical improvement, which was quite rapid in some cases. At week 12, 67.6% of patients on half-standard dosing and 69.4% of patients on standard dosing had a PGA of 0/1, compared to 5.4% of the placebo group ($p < 0.001$). One-third of each ustekinumab group achieved this effect by week 4. Furthermore, more than two-thirds of subjects on ustekinumab reached PASI 75 (half-standard 78.4%, standard 80.4%) and more than half attained PASI 90 (half-standard 54.1% and 61.1%) compared to placebo (10.8% and 5.4%, respectively; $p < 0.001$).

Therapeutic response was sustained during the course of the study period, with little change in the proportions of patients who achieved PGA0/1, PASI 75, or PASI 90 from week 12 to week 52. Beyond week 12, the clinical response in the standard dosing group was sustained better than in the half-standard dosing group.

Nine subjects (8.2%) discontinued study treatment because of poor clinical response ($n = 5$), adverse events ($n = 3$), or death ($n = 1$, car accident). There was no significant difference between the groups in the number or types of adverse events, which were reported. Most were mild or moderate, with only six serious adverse events reported throughout the course of the study. The most common adverse events were infections, specifically nasopharyngitis. There were no malignancies or active TB infections reported [28].

Like other biologics, the immunogenicity of ustekinumab may decrease its effectiveness with time. In the Landells et al. study, 8.2% of subjects tested positive for antibodies to ustekinumab at week 60. Most of these patients had minimal disease at this time point, further confirming that these are not neutralizing antibodies [28]. Studies in adults suggest that the durability of ustekinumab may be superior to that of the TNF inhibitors [29].

Ustekinumab is typically administered by subcutaneous injection. Dosing is weight-based. Individuals weighing less than 60 kilograms should be given 0.75 mg/kg, 60–100 kilograms should be given 45 mg, and those weighing more than 100 kilograms given 90 mg. Injections are given every 12 weeks, with an additional loading dose given 4 weeks after the initial injection. As with the TNF inhibitors, there are currently no formal recommendations for baseline or monitoring laboratory testing. However, taking a baseline history, including of immunization history, performing a physical examination, and testing for tuberculosis are a minimal expectation to identify those at increased risk for a serious infection on an immunomodulatory drug. TB testing should be repeated on an annual basis. Furthermore, as there is no data available on the transmission of infection from live vaccines while on ustekinumab, it is currently recommended that patients on ustekinumab avoid live vaccines. Vaccines should be updated prior to starting ustekinumab, and if a live vaccine needs to be administered, ustekinumab should be discontinued for 15 weeks prior to the vaccination. It can be restarted 2 weeks after the vaccine is given [27].

Conclusions

While biologics are highly effective for treatment of psoriasis and well tolerated, access is limited by cost, lack of guidelines for pediatric use, and limited long-term safety data. The cost of 1 year of induction and maintenance treatment can exceed $50,000, with out-of-pocket costs for patients between $250 and $350 each month. Because of these high costs, obtaining insurance coverage for these medications can be difficult, particularly in children, and treatment abandonment by patients is high [30]. Furthermore, there is no published consensus on the dosing and course length, or the baseline evaluation and optimal monitoring required by these medications in pediatric psoriasis. As a result, treatment paradigms are extrapolated from experiences in adult dermatology or other pediatric disciplines. Also complicating the use of the medications is the theoretical decrease in therapeutic effect of biologics with time, which is problematic for children with a chronic disease that may require lifelong therapy. In one report in adults, the 1-year drug survival rates for ustekinumab, adalimumab, and etanercept were 85%, 74%, and 68%, respectively, with overall 79% showing good quality of life [31]. Regarding safety, in addition to concerns about increased risk for malignancies and opportunistic infections, the effect of these immunomodulatory medications on the developing immune system is unknown. As these and other biological agents will increasingly be used to treat children with psoriasis and other immune-mediated dermatologic conditions, collaborative research is important to optimize efficacy, safety, and access to these medications for children with psoriasis.

Case

KK is a 16-year-old girl with moderate plaque psoriasis whose course began at age 7 years when she developed guttate psoriasis after streptococcal pharyngitis. During the subsequent years, her guttate psoriasis evolved into plaque psoriasis. She was initially managed with topical corticosteroids and a topical vitamin D analog, but advanced to narrowband UVB therapy because of suboptimal control, with

subsequent improvement. However, due to continued flares, she initiated weekly oral methotrexate and 6 days per week of folate (skipping on the day of the methotrexate). Although showing signs of improvement within the first 2 months of use, she was unable to tolerate the nausea, leading to discontinuation. Physical examination showed psoriatic plaques on the scalp, trunk, upper and lower extremities, covering approximately 15% of the body surface area. She underwent tuberculosis testing (negative) and transitioned to adalimumab 40 mg administered subcutaneously every other week. She experienced excellent improvement within two months after initiation of the adalimumab. Other than discomfort at her injection site, she tolerates adalimumab well and continues to maintain control.

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