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REVIEW ARTICLE

The Use of TNFα Inhibitors in Treating Pediatric Skin Disorders

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Abstract
Tumor necrosis factor alpha (TNF) inhibitors have had a significant impact in medicine since the approval of the first drug of its class by the US FDA in 1998. New clinical data and indications have emerged for TNF inhibitors in recent years. Currently, four TNF inhibitors have been approved by the US FDA for dermatology, two of which include US FDA-approved pediatric use. In particular, growing evidence supports the use of etanercept and adalimumab as attractive therapies for pediatric psoriasis. Data for use of etanercept in treating toxic epidermal necrolysis and either etanercept or infliximab for Kawasaki disease is expanding. In addition, there have been clinical reports on the use of TNF inhibitors to treat a variety of other pediatric dermatologic conditions. To help clinicians keep pace with the new data provided by many pediatric dermatology studies involving TNF inhibitors, this review provides an overview of the use of TNF inhibitors in the treatment of pediatric plaque psoriasis, hidradenitis suppurativa, atopic dermatitis, pyoderma gangrenosum, toxic epidermal necrolysis, and Kawasaki disease. For TNF inhibitors with little data in the pediatric population, data on adult use is discussed. Furthermore, the review summarizes available clinical data on efficacy, safety, and tolerability of agents currently available.

Key Points

TNF inhibitors are a class of drugs used to treat a variety of inflammatory diseases, including several pediatric dermatological conditions.

To date, etanercept is approved for treatment of pediatric plaque psoriasis and adalimumab is approved for hidradenitis suppurativa in adolescent patients in the US and EU, while adalimumab is approved for pediatric plaque psoriasis in the EU.

Growing evidence supports use of etanercept to treat toxic epidermal necrolysis, and for etanercept or infliximab to treat Kawasaki disease.

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1 Introduction

Discovered during the 1960s, tumor necrosis factor alpha (TNF) is a cytokine produced primarily by activated macrophages to help initiate and regulate inflammation [1, 2]. TNF can also be secreted by other cells such as neutrophils, CD4 + lymphocytes, and NK cells. The naming of TNF was based on its ability to kill mouse fibrosarcoma cells [3]. TNF was initially overlooked by immunologists as a mediator of autoimmune disease as the cytokine was an important host defense molecule [4]. The first clinical trial for TNF inhibitors was performed in the 1990s, when infliximab was investigated for rheumatoid arthritis [5]. The results from this clinical trial helped promote interest from experts in other chronic inflammatory diseases such as Crohn's disease and psoriasis.

Currently, four TNF inhibitors have been approved by the US Food and Drug Administration (FDA) for dermatology, two of which include US FDA-approved pediatric use (Table 1). Infliximab is a chimeric monoclonal antibody administered intravenously that is approved for use in adult psoriasis (2006). Etanercept is a human fusion protein of TNF receptor II bound to the Fc component of human IgG1 administered subcutaneously that is approved for use in adult psoriasis (2004) and pediatric psoriasis (ages ≥ 4 years) (2016). Adalimumab is a recombinant human monoclonal

Table 1 Summary of FDA-approved dermatologic indications for TNF inhibitors in pediatric patients

TNF inhibitor	Dermatologic indication for pediatric patients	Dermatologic indication for adults	Non-dermatologic indications
Adalimumab	Plaque psoriasis (US: not yet approved, phase III trial data available; EU: ages 4 + years) Hidradenitis suppurativa (US: ages 12 + years; EU: 12 + years, weighing at least 30 kg)	Plaque psoriasis (US and EU) Hidradenitis suppurativa (US and EU)	Juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, ulcerative colitis, uveitis
Certolizumab pegol	None	Plaque psoriasis (US and EU)	Axial spondylarthritis, ankylosing spondylitis, psoriatic arthritis
Etanercept	Plaque psoriasis (US: ages 4 + years; EU: ages 6 + years)	Plaque psoriasis (US and EU)	Juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis
Infliximab	None	Plaque psoriasis (US and EU)	Crohn's disease, ulcerative colitis, ankylosing spondylitis, psoriatic arthritis
Golimumab	None	None	Psoriatic arthritis, ankylosing spondylitis

FDA Food and Drug Administration, *EU* European Union, *US* United States

antibody administered subcutaneously approved for use in adult psoriasis (2008) and hidradenitis suppurativa (ages ≥ 12 years) (2015). Adalimumab has been approved for pediatric psoriasis in the European Union (from 4 years of age, 2015). Certolizumab pegol is a PEGylated antigen-binding antibody fragment administered subcutaneously that is approved for use in adult psoriasis (2018). Golimumab is another anti-TNFα monoclonal antibody that is not yet approved for treatment of dermatologic conditions, but is used to treat rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, and ulcerative colitis (see Table 2).

Positive clinical experiences combined with post-marketing surveillance led dermatologists to recognize the clinical benefits of TNF inhibitors. In this review article, available clinical data on pediatric dermatological use of TNF inhibitors will be discussed for plaque psoriasis, hidradenitis suppurativa, atopic dermatitis, pyoderma gangrenosum, toxic epidermal necrolysis, and Kawasaki disease.

A literature search was performed in December 2019 in PubMed using the terms 'tumor necrosis factor alpha inhibitor,' 'TNF inhibitor,' 'pediatric,' 'plaque psoriasis,' 'hidradenitis suppurativa,' 'atopic dermatitis,' 'pyoderma gangrenosum,' 'kawasaki disease,' and 'toxic epidermal necrolysis.' Literature from pediatric research is presented, and relevant literature on adult patients is included for drugs that lack pediatric data.

Table 2 Dosing for TNF inhibitors for FDA-approved and evidence-based off label use in pediatric patients

Dermatologic condition	TNF inhibitor pediatric dosing
Plaque psoriasis	Adalimumab: weight based, 0.8 mg/kg every other week or 0.4 mg/kg every other week with maximum dose of 40 mg every other week [13] Etanercept: weight based, 0.8 mg/kg once weekly; maximum dose of 50 mg weekly with body weight > 62.5 kg [8]
Hidradenitis suppurativa	Adalimumab (12 + years and between 30 kg to < 60 kg): Initial dose of 80 mg (Day 1) and subsequent doses (starting Day 8) of 40 mg every other week Adalimumab (12 + years and ≥ 60 kg, or patients who are 12 + years and < 60 kg with inadequate response): Initial dose of 160 mg, second dose two weeks later of 80 mg (Day 15), and subsequent doses of 40 mg every week [29, 32, 33]
Atopic dermatitis	No high-level data available
Pyoderma gangrenosum	Infliximab: 5 mg/kg of body weight at 0, 2, and 6 weeks or 0, 2, and 10 weeks [45, 46]
Toxic epidermal necrolysis	Etanercept: 25 mg once daily for 2 days [70] Infliximab: 5 mg/kg, single dose [65]
Kawasaki disease	Etanercept: 0.8 mg/kg with maximum dose 50 mg [82] Infliximab: 5 mg/kg single dose [83]

FDA Food and Drug Administration

2 Plaque Psoriasis

Psoriasis is usually characterized by raised, well defined, erythematous plaques of varying size with silvery-white scale. This dermatosis is relatively common in children, accounting for approximately 4% of all dermatologic diseases seen in patients under 16 years old [6]. Furthermore, approximately 40% of adults with psoriasis have reported childhood onset [7]. Etanercept and adalimumab have been studied in both adult and pediatric populations with plaque psoriasis. Studies on use of infliximab and certolizumab for plaque psoriasis are limited to adult populations.

The use of etanercept was investigated initially in a phase III clinical trial for pediatric moderate to severe psoriasis that included a 12-week double-blind treatment period followed by a 24-week open-label treatment and a 12-week double-blind withdrawal period [8]. A total of 211 subjects were enrolled, with ages ranging from 4 to 17 years. The dosing of etanercept was weight-based, 0.8 mg/kg once weekly. Among patients who were treated with etanercept, at week 12, 57% had at least 75% improvement on the Psoriasis Area Severity Index (PASI 75), and 27% had at least 90% improvement (PASI 90) compared with 11% and 7% with placebo, respectively ($p < 0.0001$, both). The study reported good tolerability and safety. Of note, although an increase in infections was observed (47.2% for etanercept compared with 31.4% for placebo), no serious infections were reported at week 12. Results from a 5-year extension study showed stable response rates with long-term use of etanercept, demonstrating PASI 75 rates of approximately 60% and PASI 90 rates of approximately 30% [9]. Safety outcomes were also stable, with no observations of malignancies or opportunistic infections during the 5-year extension. Pharmacokinetic data for the etanercept 0.8-mg/kg once-a-week dosing regimen shows similar exposure when compared to etanercept treatment in adults with psoriasis and pediatric patients with juvenile idiopathic arthritis (JIA) [10]. No differences in etanercept trough pharmacokinetics between children aged 4–11 years and older children aged 12–17 years have been observed. In addition, efficacy is retained in pediatric patients receiving the maximum dose of 50 mg weekly with body weights > 62.5 kg. This study also reported similar serum concentrations and safety profiles for patients with and without anti-etanercept antibodies.

A retrospective review of pediatric patients with moderate to severe psoriasis being treated with systemic medications or phototherapy in 20 centers in North America and Europe showed that TNF inhibitors resulted in less medication-related adverse events compared with methotrexate. Injection-site reactions occurred in 20 of 106 patients in this study. Of six reported serious treatment-related adverse events (SAEs), one (appendicitis) was observed in a patient taking adalimumab, whereas three SAEs were reported with methotrexate, and two with fumaric acid esters [11]. Etanercept was found to be effective and well tolerated in a multicenter retrospective study of 23 patients with severe plaque psoriasis in Italy as well, with 56.5% of patients achieving PASI 75 and 86.9% achieving PASI 50 after 12 weeks of treatment [12].

The use of adalimumab for pediatric psoriasis has also been studied in a phase III clinical trial, which involved an initial 16-week treatment period, followed by a 16-week withdrawal period and a 1-year open-label treatment [13]. A total of 114 subjects were enrolled, ranging from 4 to 17 years of age. Dosing of adalimumab was also weight-based, 0.8 mg/kg every other week or 0.4 mg/kg every other week with maximum dose of 40 mg every other week. The control arm received methotrexate (0.1–0.4 mg/kg weekly). After completing the initial 16-week treatment period, 58% of subjects in the higher-dosed adalimumab group (0.8 mg/kg every other week) achieved PASI 75 compared with 32.5% of the subjects in the methotrexate control group ($p = 0.027$). Adalimumab was tolerated well, with only one serious infection reported. For patients who had worsening of their psoriasis after discontinuing the study drug after the initial 16-week treatment period, PASI 75 recapture after 16 weeks of retreatment were 54.5% and 78.9% for the adalimumab 0.4-mg/kg group and adalimumab 0.8-mg/kg group, respectively.

Infliximab and certolizumab pegol are approved by the FDA for adults with plaque psoriasis. Data on use of infliximab in pediatric plaque psoriasis are lacking. However, one case report showed improvement in pustular psoriasis with use of infliximab as a first-line medication in a 9-year-old female patient [14]. In the phase III randomized trial on certolizumab pegol in adult patients, patient responses to certolizumab pegol 400 mg were superior and responses to certolizumab pegol 200 mg were noninferior at week 12 when compared with etanercept [15]. There are currently no known clinical trials on certolizumab pegol for pediatric dermatological conditions. Finally, data on use of golimumab for dermatologic conditions is sparse; however, one adult case in which golimumab was used to treat erythrodermic psoriasis has been reported [16].

While there is strong evidence for use of anti-TNFs to treat pediatric patients with plaque psoriasis, there have been cases of paradoxical psoriasis reported that should be accounted for when considering use of anti-TNF agents. For example, a retrospective chart review on children under the age of 19 years with inflammatory bowel disease (IBD) showed 14 cases of new-onset or recurrent psoriasiform skin lesions. Anti-TNF agents used in this study were infliximab, adalimumab, and certolizumab pegol, all of which resulted in lesions consistent with psoriasis. The majority of cases

were plaque psoriasis and two cases were palmoplantar pustular psoriasis [17]. Another retrospective cohort study of IBD adult patients treated with anti-TNF medications reported 42 incident cases of psoriasis of 839 participants (incidence rate of five per 100 person-years). Smoking or history of smoking was a risk factor for developing psoriasis in this patient cohort, whereas patients on concomitant immunosuppressive therapies were less likely to develop psoriasis. Finally a case has been reported in which an adult female patient being treated with infliximab (5 mg/kg every 8 weeks) for rheumatoid arthritis developed psoriasis on the trunk, back, and limbs after 10 months [18]. Lesions increased and worsened when the authors attempted to switch to adalimumab and ultimately the medication class was changed. Overall, strong evidence supports the use of etanercept and adalimumab in treating pediatric patients with plaque psoriasis.

3 Hidradenitis Suppurativa

Hidradenitis suppurativa (HS) is a chronic inflammatory dermatologic disease of the hair follicle and apocrine glands resulting in recurrent painful inflammatory abscesses and draining sinuses affecting body areas with apocrine glands [19–21]. This condition affects approximately 1% of the population [22, 23] and is associated with other comorbid conditions such as depression and metabolic syndrome [23–26]. HS is less common in the pediatric population; children and adolescents age 0–17 years account for 2.2% of HS cases in the US [27]. Risk factors associated with HS are smoking and obesity (OR 12.55 and 4.42, respectively). Diagnosis of HS is based on clinical judgement with three criteria: typical lesions (deep-seated nodules, abscess, and/or fibrosis), typical anatomic region, and relapses.

Patients with HS were found to have elevated TNFα in the skin [28]. Accordingly, TNF inhibitors were investigated for HS, resulting in adalimumab being the first FDA-approved medication for this chronic and unrelenting skin disorder. This TNF inhibitor was investigated in two phase III clinical trials, PIONEER I and II, which enrolled subjects aged 18 years or older with moderate to severe HS to be randomized to adalimumab (160 mg at week 0, 80 mg at week 2, and 40 mg weekly as maintenance) or placebo [29]. After 12 weeks of treatment, clinical response rates were significantly higher for the subjects receiving adalimumab compared with the subjects receiving placebo (PIONEER I: 41.8% vs 26.0%, $p = 0.003$; and PIONEER 2: 58.9% vs 27.6%, $p < 0.001$). Furthermore, the observed clinical improvements were sustained for 3 years with weekly dosing, with low incidence of serious side effects similar to the placebo arm [30, 31].

While adalimumab has not been studied specifically in clinical trials involving pediatric patients with HS, the FDA and European Union (EU) approved its use in patients aged 12 years and older. Dosing in adolescents is based on population pharmacokinetic modelling and simulation [32]. The dosing schedule for adolescents with HS is 40 mg every other week or 40 mg every week for adolescents with higher body weight and inadequate response. In one case series on use of adalimumab for HS that included two pediatric patients, adalimumab was dosed at 40 mg every other week, increased to 40 mg/week if HS was inadequately controlled, and decreased to 40 mg every 3 weeks if persistent clinical remission was observed [33]. All six patients had a significant reduction in the number of affected regions and improved daily life quality index (DLQI) scores.

Less clinical data has been reported on infliximab or etanercept for children and adolescents with HS. Subjective improvement with etanercept was noted in one pediatric patient, 16 years of age, included in a case series [34]. Infliximab has been shown to improve pain intensity, disease severity, and quality of life in adult patients with HS in a phase II, randomized, prospective clinical trial. Overall, 60% of patients assigned to infliximab (5 mg/kg) reported a 25% to < 50% decrease from baseline hidradenitis suppurativa severity index (HSSI) score compared with 89% of patients in the placebo group reporting a < 25% decrease in HSSI from baseline [35]. The study included two adolescent patients, one in the infliximab group (aged 16 years) and one in the placebo group (aged 17 years).

4 Atopic Dermatitis

Atopic dermatitis (AD) is a common inflammatory skin condition characterized by intense pruritus and chronic or chronically relapsing disease course. This condition has a typical onset during early childhood and is associated with other atopic disorders such as asthma and food allergies. The estimated prevalence of atopic dermatitis among US children is 10.7% [36]. The majority of data suggest TNF inhibitors have a minimal role in the management of atopic dermatitis, if any. There are few publications where the use of etanercept and/or infliximab have demonstrated efficacy in the treatment of AD [37]. Two pediatric cases have been reported in which a trial of etanercept for treatment of atopic dermatitis resulted in increased pruritus and no improvement in eczema area and severity index (EASI) score [38].

In addition, a significant number of cases of TNF inhibitor-induced AD have been reported [39–41]. One case in which a TNF inhibitor worsened atopic dermatitis occurred in a 10-year-old female patient being treated with etanercept for juvenile idiopathic arthritis. Treatment with etanercept resulted in rapid arthritis improvement, but dramatic

worsening of her previously existing atopic dermatitis. The cutaneous symptoms cleared immediately upon cessation of etanercept 6 months later [40]. Other biologic agents, such as dupilumab, are more appropriate treatment choices for management of refractory atopic dermatitis [42, 43].

5 Pyoderma Gangrenosum

Pyoderma gangrenosum (PG) is a rare inflammatory dermatosis of unknown etiology characterized by sterile neutrophilic infiltration of the skin, which commonly presents as a deep ulcer with a violaceous border. PG occurs more commonly in the third through fifth decades of life and currently, the clinical, epidemiological, and therapeutic data on pediatric PG is relatively sparse. The Mayo Clinic estimated pediatric prevalence of PG and reported only eight (4%) of 180 PG cases diagnosed between 1930 and 1982 occurred among children younger than 15 years [44]. PG is associated with several conditions including IBD, polyarthritis, and hematologic disorders. In patients with IBD who have ostomies, PG may occur as a deep ulcer around the stoma site. Data on use of TNF inhibitors in pediatric patients with PG is sparse. Two pediatric cases have been reported on use of infliximab (5 mg/kg per dose at weeks 0, 2, 10, or 0, 2, 6) in patients with Crohn's disease, both of whom experienced resolution of PG after treatment [45, 46].

More data on use of TNF inhibitors for PG in adults has been published. Infliximab is the only TNF inhibitor that has been studied in a randomized, double-blind, placebo-controlled trial [47]. Patients were randomized to infliximab (5 mg/kg) or placebo at week 0; those who did not show a clinical response at week 2 received a further dose of infliximab. At week 2, 6/13 infliximab patients had improved compared with 1/17 for placebo. Overall, 29 patients received infliximab and 69% of these patients experienced improvement, including six patients who experienced complete resolution [47]. Clinical reports including adult patients have shown a beneficial effect of infliximab in patients with PG associated with IBD, with an overall response rate of 80–90% [48–53]. A multi-database literature review on the use of TNF inhibitors for the treatment of PG reported that TNF inhibitors, alone or in combination with systemic steroids, were used in 13.4% of cases [54]. For these cases, infliximab 5 mg/kg was the most common (63.4%), followed by 40 mg of adalimumab every other week (33.3%). Clinical improvement (which was defined as significant healing of lesions) reported in the primary articles was found to be 90.14% for all identified cases. Based on the literature review's findings, adalimumab had the highest cure rate (60%), but this was not statistically different from that of infliximab (57.9%, $p = 0.91$).

Success with adalimumab for PG has been reported in several adult case reports as well, dosed either at 40 mg per week, 40 mg twice per month with prednisone [55, 56]. Finally, off-label use of etanercept has shown improvement in several adult PG cases, most commonly dosed at 50 mg weekly or divided into two doses of 25 mg each [57–61]. More studies on use of TNF inhibitors for PG in children are warranted to establish efficacy and safety.

6 Toxic Epidermal Necrolysis

Toxic epidermal necrolysis (TEN) is a rare, acute, and life-threatening mucocutaneous disease. Pediatric prevalence of TEN is estimated at 0.4 cases per million children per year in the US [62]. Several cases of successful treatment of TEN with infliximab or etanercept monotherapy have been reported in both adult and pediatric patients [63]. A randomized, open-label study including patients 4 years of age and older compared prednisolone with 25 mg or 50 mg etanercept subcutaneously twice a week, and showed that patients receiving etanercept had a shorter skin healing time (14 days) compared with those on prednisolone (19 days) [64]. TNFα inhibitors have been reported to successfully treat TEN as combination therapy as well [65]. Three pediatric patients have been reported to have used TNF inhibitors following failure of other systemic agents in TEN [65–68]. The three patients were initially managed with corticosteroids and/or intravenous immunoglobulin (IVIG), and all were initiated on infliximab when the previous treatment failed to halt the progression of TEN. The three case reports described a rapid and favorable response to TNF inhibitor treatment, and all patients recovered [65]. In another case report of a 7-year-old boy with TEN, a single dose of infliximab 5 mg/kg resulted in complete resolution in 1 week [69]. Etanercept, when added to methylprednisone and cyclosporine, resulted in successful treatment of Stevens-Johnson syndrome/TEN in an 11-year-old female patient [70].

Conflicting data include a report of a proof-of-concept study involving 10 adult patients with TEN who received either a single 5-mg/kg dose of infliximab in combination with three doses of *N*-acetylcysteine, or three doses of *N*-acetylcysteine alone [71]. Patients showed no improvement of lesions, and a similar degree of increased affected skin area was observed in both groups. Of note, three patients died in this study, the majority due to septicemia [71]. In sum, of the data available on treatment of TEN in pediatric patients, etanercept has the most evidence for success among the TNF inhibitors.

7 Kawasaki Disease

Kawasaki disease is a vasculitis characterized by inflammation of small and medium-sized blood vessels, particularly the coronary arteries, that most commonly affects children under the age of 5 years [72]. Cutaneous manifestations of Kawasaki disease include maculopapular erythematous lesions, and oral signs such as red or cracked lips and strawberry tongue. Many children are treated with intravenous immunoglobulin and aspirin to reduce inflammation and prevent cardiac sequelae; however, a subgroup of children do not respond to this treatment. A Cochrane review of randomized controlled trials showed that infliximab (single dose of 5 mg/kg) and etanercept (0.8 mg/kg with a maximum of 50 mg) may be beneficial for patients with refractory Kawasaki disease when compared with no treatment or treatment with either IVIG, polyethylene glycol-treated human immunoglobulin, or placebo [73].

8 Economic Considerations of anti-TNFs

When developing a treatment plan for patients with dermatologic conditions, several factors should be considered, including patient's preference, adverse effects, mode of administration, and cost. Several studies on cost effectiveness of TNF inhibitors in treating adult conditions have been published. One group compared the cost effectiveness of several agents for treatment of psoriasis by assessing minimally important difference in Dermatology Life Quality Index (DLQI MID) and cost per patient achieving PASI 75 [74]. Etanercept, when dosed 25 mg subcutaneously once weekly, was the most cost-effective agent for achieving DLQI MID, whereas intravenous infliximab 3 mg/kg was the most cost effective in cost per patient achieving PASI 75 in this 2008 study.

Another study, published in 2016, compared relative cost of biologics for treatment of various autoimmune diseases including psoriasis using claims data from the HealthCore Integrated Research Database from 2009 to 2013. Overall, 89% of patients received etanercept, adalimumab or infliximab, and the cost per treated adult patient for 1 year was $US24,859 for etanercept, $US26,537 for adalimumab, and $US26,468 for infliximab [75]. Since market entry of the more recently developed originator TNF inhibitors, including subcutaneous and intravenous golimumab, and certolizumab pegol, the trend in annual costs of treatment significantly increased. Patient out-of-pocket spending has not fluctuated much, while Medicare spending increased [76].

For treatment of plaque psoriasis in children, the cost per quality-adjusted life-year for adalimumab, etanercept, and ustekinumab, a monoclonal antibody that targets IL-12 and IL-23, is uncertain. Studies have shown that these medications result in greater improvements in psoriasis compared with placebo or methotrexate [77]. However, incremental cost-effectiveness ratios for use of anti-TNFs in children is higher than the usual threshold reported by the National Institute for Health and Care Excellence. More randomized controlled trials are needed in order to decrease the uncertainty of the cost effectiveness of anti-TNFs.

Finally, biosimilar agents, defined as chemically similar therapeutic agents that result in comparable results and safety outcomes compared to licensed reference biologic agents, can be utilized by providers to reduce healthcare [78–81]. Currently, biosimilar versions of adalimumab, etanercept, and infliximab have been approved for use in the US and EU [79]. Safety and efficacy data on use of an anti-TNF biosimilar in treating plaque psoriasis has been reassuring [79]. Prescription of adalimumab biosimilars for HS are expected to increase as well (81).

9 Conclusion

TNF inhibitors are a class of medications that have shown promise in the treatment of inflammatory dermatoses in pediatric patients, with strong evidence for the use of etanercept and adalimumab in treating pediatric plaque psoriasis. Adalimumab also appears to be a safe and effective option for treating HS in adolescents aged 12 + years. Less data is available on use of TNF inhibitors in PG; however, case reports of success with infliximab have been published. Regarding treatment of Kawasaki disease, infliximab and etanercept are effective options. Finally, dermatologists should be aware of paradoxical atopic dermatitis and psoriasis when consulted on use of TNF inhibitors in other inflammatory conditions such as IBD and rheumatoid arthritis. Overall, TNF inhibitors have the potential to significantly advance the management of pediatric dermatologic diseases.

Compliance with ethical standards

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