Plaque psoriasis in children and adolescents – the role of etanercept

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Background: Childhood-onset psoriasis affects approximately one-third of the psoriatic population. Among many potential treatments of childhood psoriasis, biological agents are emerging as a valuable option in the management of this disease. In Europe, etanercept has recently been approved for children aged 6 years and over. Data from a well-designed clinical trial indicate that in children, etanercept effectively reduces psoriasis symptoms, with beneficial effects evident as early as 4 weeks after the onset of therapy. The treatment is generally well tolerated; mild injection site reactions are the most common adverse events reported in the literature. Published data of etanercept use in children show promising results, but further clinical studies are necessary to confirm its long-term efficacy and safety.

Keywords: pediatric psoriasis, anti-TNF- α , etanercept

Introduction

Psoriasis is a chronic immune-mediated inflammatory skin disease characterized by erythematous squamous lesions; the lesions can be extremely variable in distribution on body surface, severity, and extension.¹ Like all forms of autoimmunity, susceptibility is genetic, but environmental triggers are required to start disease activity.

The prevalence of psoriasis ranges between 1%–3% in the population worldwide.² It may begin at any age. In more than 33% of patients, the initial presentation of psoriasis occurs within the first two decades of life.³ It is estimated that 10% of patients develop psoriasis before the age of 10 years, and 2% before the age of 2 years.⁴

Psoriasis in children and adolescents may represent “early-onset disease,” which is associated with specific human leukocyte antigen (HLA) subtypes including HLA Cw6 and B57.⁵ Early onset psoriasis is often an indicator of a more severe disease phenotype. The psychosocial impairment, in addition to the physical affliction that can result from psoriasis, is a reminder that early recognition and management of psoriasis in children and adolescents is crucial.

Pediatric psoriasis consists of three age groups of psoriatic patients: infantile psoriasis (a self-limited disease of infancy), psoriasis with early onset, and pediatric psoriasis with psoriatic arthritis. The varied clinical presentations in childhood include plaque-type, guttate, erythrodermic, napkin, and nail-based disease. Plaque type is the most common form of disease in children; erythroderma, arthropathy, and localized and generalized pustular psoriasis are less frequently observed. Psoriasis in children is more frequently precipitated by infections and manifests as acute guttate psoriasis.⁶

Many studies have investigated the use of standard psoriasis therapies in children with psoriasis, including topical treatments, phototherapy, and systemic therapies.

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When treating children with psoriasis, it is important to educate both patients and parents about the nature of the disease. Psoriasis is a chronic skin disorder without a permanent therapy and therefore the goal of treatment is to establish disease control and extend the periods between flares. The patient's age, quality of life factors, Psoriasis Area and Severity Index (PASI) score, and therapeutic preferences should all be considered when choosing treatment.

Topical therapy remains the first-line treatment of skin-limited disease in children. Corticosteroids remain the first-line topical agents. However, very high potency steroids should be avoided in children if possible or used sparingly in combination with a regime of steroid-sparing alternatives such as coal tar, vitamin D analogues, or retinoids.

In cases of refractory, diffuse, or severe forms of psoriasis, systemic treatments are indicated. Phototherapy and systemic therapies (such as retinoids, cyclosporine, and methotrexate) have limited use because of low tolerability in children, cumulative adverse effects, and teratogenicity.⁷⁻⁹

Newer, more targeted biologic treatments, specifically tumor necrosis factor (TNF)- α inhibitors, are also gaining popularity in the management of refractory psoriasis. TNF is a cytokine that plays a central pro-inflammatory role in many chronic inflammatory diseases. The TNF- α inhibitors represent an important new group of agents which significantly improve symptoms and signs, function, and quality of life, and induce remission in patients with chronic inflammatory and rheumatic conditions. In patients with psoriasis, the immune system releases a cytokine response that enhances the inflammatory response and leads to the epidermal hyperproliferation and perpetuation of the disease. Biologic agents such as TNF- α antagonists stop the inflammatory pathways active in psoriasis.

Anti-TNF- α have been used for more than a decade for pediatric autoimmune diseases including rheumatoid arthritis,¹⁰ juvenile idiopathic arthritis,¹¹ and Crohn's disease.¹² Juvenile rheumatoid arthritis patients have the longest usage history with TNF inhibitors, with up to 8 years of published safety and efficacy data.

Etanercept

Etanercept is a human soluble TNF- α type 2 receptor fused to the constant portion of human immunoglobulin-G1; it antagonizes the effects of endogenous TNF.

Etanercept is widely used¹³ to treat adult patients who have moderate-to-severe plaque psoriasis. Numerous clinical trials of etanercept have shown significantly reduced disease severity, fatigue, and symptoms of depression,

and significantly improved overall health-related quality of life in adult patients with psoriasis. It is also indicated for patients as young as 2 years or older for treatment of moderately to severely active polyarticular juvenile idiopathic arthritis.¹⁴

In January 2009, etanercept was approved in Europe for the treatment of chronic, severe plaque psoriasis in children aged 8 years and older. Recently, the therapeutic application was extended to a lower age range. The actual indication is for treatment of chronic severe plaque psoriasis in children and adolescents from the age of 6 years old who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies.

The approved dosage forms of etanercept include powder and solvent to produce a solution for injection, and solution for injection in a prefilled syringe. All etanercept dosage forms are intended for subcutaneous injection. The approved dose for the treatment of chronic, severe, plaque psoriasis in children and adolescents from the age of 6 years old is 0.8 mg/kg (up to a maximum of 50 mg per dose) once weekly for up to 24 weeks. Treatment should be discontinued in patients who show no response after 12 weeks. If re-treatment is indicated, the above guidance on treatment duration should be followed. There is generally no applicable use of etanercept in children under the age of 6 years old in the indication for plaque psoriasis. Treatment should not be initiated in patients with active infections, including chronic or localized infections.

The evidence published in the last 5 years on the use of etanercept in pediatric psoriasis includes case reports, case series, and a randomized, double-blind, placebo controlled trial (Table 1). The youngest patient treated with etanercept reported in the medical literature is a 22-month-old child affected by suberythrodermic recalcitrant psoriasis.¹⁵

As the indication for pediatric plaque psoriasis is restricted to severe disease where other systemic therapies are unsuitable because of contra-indications or intolerance or have not been effective, etanercept remains a third-line option for children with plaque psoriasis.

Efficacy

In the literature there are several case reports attesting to etanercept efficacy in the treatment of various forms of pediatric psoriasis.¹⁶⁻²⁰

However, only a few studies have been conducted in pediatric populations, compared to the large amount of data regarding etanercept efficacy in adult psoriasis.

A pioneering retrospective study of etanercept treatment was made in 9 children and adolescents (aged 8-17 years) with recalcitrant generalized psoriasis who were dosed

Table I Summary table

Study	Number of patients	Intervention	Conclusion	Level of evidence
Fabrizi et al ¹⁵	1	Etanercept (0.4 mg/kg twice weekly) for 6 months	"Suberythrodermic, recalcitrant psoriasis in a 22-month-old child successfully treated with etanercept".	3
Safa et al ¹⁸	1	Etanercept (0.4 mg/kg twice weekly) for 6 months	"Etanercept therapy may be an effective treatment option for severe psoriasis in children".	3
Ruiz-Villaverde et al ¹⁹	3	Etanercept (25 mg a week) for 24 weeks	Efficacy of etanercept in the treatment of three adolescents with moderate psoriasis.	3
Papoutsaki et al ¹⁷	4	Etanercept (0.4 mg/kg twice weekly)	"Etanercept may be efficacious and well tolerated for severe forms of childhood psoriasis".	3
Hawrot et al ²¹	9	Etanercept (25 mg or 0.4 mg/kg/biweekly or 50 mg once a week)	Results ranged from equivocal/insignificant effect in two patients to marked and sustained in the remaining seven patients.	3
Paller et al ²²	211	Etanercept (0.8 mg/kg/week for 12 weeks) vs placebo followed by 24 weeks of Etanercept at the same dose (open-label). At week 36, 138 patients were randomized to placebo or etanercept for 12 weeks	Etanercept significantly reduced disease severity in children and adolescents with moderate-to-severe plaque psoriasis. Four serious adverse events occurred in the open label part of the study: an ovarian cyst removal, gastroenteritis, and gastroenteritis-related dehydration, pneumonia. Longer term data is needed to fully assess the safety profile of Etanercept.	1+

biweekly with 25 mg, or 0.4 mg/kg/dose, or 50 mg once per week; seven patients had a marked and sustained improvement of psoriasis after 3 to 6 months of treatment.²¹

The only reliable and accurate study regarding etanercept treatment for pediatric populations is that of Paller.²² In this study, etanercept was administered to children and adolescents (aged 4–17 years) affected by severe plaque psoriasis at a dose of 0.8 mg/kg once weekly (up to a maximum of 50 mg). 57% of patients receiving etanercept achieved PASI 75 compared to 11% of those receiving placebo ($P < 0.001$) after 12 weeks of treatment. The percentages of patients who achieved PASI 50 (75% vs 23%, $P < 0.001$) and PASI 90 (27% vs 7%, $P < 0.001$) were also significantly greater in the etanercept group than in the placebo group at week 12. Efficacy during the open-label phase was sustained through Week 36.

A sub-analysis of the previous study, assessing the efficacy and safety of etanercept only in children aged 8–17 years showed similar results.²³

PASI 50, 75, and 90 were maintained throughout week 96 of the extension of the original study, with scores at week 96 of 89%, 61%, and 30%, respectively.²⁴

Health-related quality of life was evaluated throughout the Children's Dermatology Life Quality Index (CDLQI) and Pediatric Quality of Life Inventory. Patients treated with etanercept demonstrated significantly higher mean percentage improvement in total CDLQI scores from baseline to week 12 compared with those treated with placebo (52.3% etanercept vs 17.5% placebo, $P = 0.0001$). Moreover, at week 12, patients who achieved 75% improvement in their

PASI score had higher percentage improvements from baseline in total CDLQI scores than those who did not have 75% improvement in PASI score.²⁵

Safety

The most commonly reported adverse event was upper respiratory tract infections, occurring in 24.9% patients treated with etanercept, followed by nasopharyngitis in 17.1%, streptococcal pharyngitis in 12.7%, headache in 11.6%, and sinusitis in 10.5%. Mild to moderate and generally transient injection site reactions were reported in 5.5% of patients.^{16,22}

1.7% of patients treated with etanercept developed a total of five serious adverse events: anxiety, serious episodes of gastroenteritis and gastroenteritis-associated dehydration, benign ovarian mass, pneumonia, and postoperative intestinal obstruction. None of these serious adverse events were considered to be related to the study drug and all events resolved without sequel.^{16,22}

No opportunistic infections, malignancies, deaths, tuberculosis, or demyelination events were reported through 96 weeks of the study extension.¹⁶

Conclusion

Psoriasis is a lifelong disease that often begins during childhood. Despite the fact that psoriasis in children is a common dermatologic condition, properly designed studies regarding its treatment are lacking. Commonly used medications lack scientific evidence showing their efficacy,

and newer treatments do not have long-term, post-market surveillance data of their safety.

Recent advances in therapeutics for psoriasis have been applied to the pediatric psoriasis population with good results in disease reduction and consequent improvements in quality of life.

To date, etanercept is the only biologic agent approved for plaque psoriasis treatment in children. The treatment is generally well tolerated; mild injection site reactions are the most common adverse events reported in the literature. The theoretical increased risk of tuberculosis and other severe infections occurring during etanercept treatment, although present, is very low both in clinical studies and in post-market use. Regarding the potential onset of malignancy, this has not been seen clinically, but the duration of the follow-up is still not sufficient to determine long-term risk.

The results from the long-term trial to date demonstrate that extended treatment with etanercept at 0.8 mg/kg once weekly (up to a maximum intended dose of 50 mg) was generally well tolerated in this group of pediatric patients with moderate to severe plaque psoriasis in the time period studied.¹⁶

Published data of etanercept use in children show promising results; but further clinical studies are mandatory to confirm its long-term efficacy and safety.

Disclosure

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