ORIGINAL ARTICLE

Etanercept in childhood psoriasis: An experience from Kuwait

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ABSTRACT

Psoriasis commonly affects children and adolescents, and the need for safe, effective therapy is a special consideration in the pediatric population. Recently, the use of biologic agents has been extensively studied for the treatment of psoriasis in adults. Of these, etanercept, a tumor necrosis factor-α antagonist, which FDA has approved for the treatment of psoriasis and psoriatic arthritis in adults, and while it is approved for use in juvenile rheumatoid arthritis, it is the closest to achieve the approval for the treatment of moderately severe plaque psoriasis in children. We present our experience of treating eighteen pediatric patients with generalized, recalcitrant stable plaque psoriasis with etanercept therapy.

INTRODUCTION

Psoriasis is a skin disease characterized by accelerated proliferation and abnormal differentiation of epidermal keratinocytes,[1] vascular dilatation and inflammatory infiltration of the affected dermis and epidermis with polymorphonuclear leucocytes, macrophages and activated T cells.[2] Previously psoriasis was thought to be primarily a disorder of aberrant keratinocyte formation with secondary inflammation. The classic antipsoriatic therapy has therefore focused on agents being antiproliferative (and anti-inflammatory), for example vitamin D3 analogues, retinoids, corticosteroids, anthralin, tar and UV therapy. But then the importance of activated T cells in the pathogenesis of psoriasis was recognized; they express high levels of CD25 [an interleukin-2 (IL-2) receptor] and major histocompatibility complex (MCH) class II molecules,[3,4] in contrast to T cells, which circulate.[5] Psoriasis is therefore now recognized as a primarily inflammatory disorder induced and sustained by skin infiltrating lymphocytes with a secondary striking proliferation of keratinocytes. The initiation and persistence of the characteristic inflammatory processes in psoriasis, such as adhesion to endothelial cells, migration towards inflammatory sites in the epidermis and dermis and their functional activities,[3] seem to be triggered by a special cytokine pattern, belonging to the Th1 type, which predominantly mediates autoimmune and antimicrobial defence mechanisms.[6] This pattern consists of signalling molecules such as interferon-γ (INF-γ), tumour necrosis factor-α (TNF-α), IL-1, -2, -3, -6, -8, granulocyte–macrophage colony-stimulating factor (GM-CSF), epidermal growth factor (EGF), Fibroblast growth factor (FGF) and transforming growth factor-α (TGF-α).[7,8] Many newer biologic agents are available now to treat psoriasis which target specific steps in the autoimmune cascade.[9-13]

No systemic therapy for psoriasis in children and adolescents is currently approved by the Food and Drug Administration; phototherapy and systemic therapies have limited use because of low toler-

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ability in children, cumulative adverse effects, and teratogenicity.[10-13] Etanercept, a soluble tumor necrosis factor (TNF) receptor fusion protein that antagonizes the effects of endogenous TNF, is widely used to treat adult patients who have moderate-to-severe plaque psoriasis and is indicated for patients as young as 4 years of age with polyarticular juvenile rheumatoid arthritis.[14] Previous 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.[15-18] The aim of the present project was to assess the efficacy and safety of etanercept in the treatment of children and adolescents with moderate to severe plaque psoriasis.

PATIENTS AND METHODS

This study was carried out at the Department of Dermatology, Farwaniya Hospital, Kuwait over a period of 3 years (August 2007 to August 2010). The institutional ethics committee of our hospital approved the protocol. Written informed consent was obtained from the parents or legal guardians of all patients.

All the patients of moderate to severe psoriasis vulgaris of ages between 4 to 17 years, attending the dermatology OPD at Farwaniya hospital were enrolled in this study. All the patients had psoriasis area-and-severity index (PASI) score of at least 12 (PASI scores range from 0 to 72), with higher scores indicating worse condition; PASI 50, PASI 75, and PASI 90 denote improvement in the PASI of 50%, 75%, and 90% over baseline, respectively). The patients had a history of psoriasis for at least 6 months; and previous or current treatment with phototherapy or systemic psoriasis therapy (e.g., methotrexate, cyclosporine, or retinoids). Patients with guttate, erythrodermic, or pustular psoriasis at the time of screening were excluded, as were those with other active skin conditions that would interfere with evaluations. Patients were permitted to use topical medications as emollients and low or moderate potency corticosteroids during the study.

Etanercept (Enbrel–Wyeth), at a dose of 0.8 mg per kilogram of body weight up to a maximum intended dose of 50 mg was dispensed to the patients in syringes for once-weekly subcutaneous injections.

All the demographic details of the patients; severity and location of the lesions; past treatments history; family history were recorded on a Performa. All base line investigations including CBC, General health profile, PPD, were done in all the patients. Baseline PASI scores and PGA scores were also recorded. The patients were then followed up every 4 weeks until 24 weeks of active treatment, and thereafter they were followed up every 12 weeks until week 48. And, on every visits the complete physical examination, and investigations were repeated. Improvement in the PASI and PGA scores, and any side effects found were also recorded.

The primary efficacy end point was PASI 75 at week 12. The secondary efficacy end points were PASI 50, PASI 90, Physician's Global Assessment of clear or almost clear (score of 0 or 1) at week 12.

RESULT

A total of 18 cases were enrolled in this study. Patient Demographics and Baseline Characteristic are summarized in (Table 1). The majority of patients in this study were males with male to female ratio of 12/18 (66.7 %). The age ranged between 4 to 17 years, the mean age was 13.1 years.

The mean duration of psoriasis was 2.8 years, and none of the patients had psoriatic arthritis. All the patients had previously received topical corticosteroids, and 15 patients (83.3 %) had previously received systemic therapy or phototherapy for psoriasis. The mean affected body-surface area was 26% (range: 19-46), and the mean base-line psoriasis area-and-severity index was 14.7. All the patients completed 24 weeks of active treatment, and another 24 weeks of follow up. Efficacy end point was evaluated after 12 week of therapy (Table 2). At the end of week 12, 55% (10 out of 18 patients) achieved PASI 75. Four out of these 10(25%) patients had achieved PASI 90. The remaining 8 patients achieved a PASI 50 score at 12 weeks and efficacy continued to improve with longer treatment. At week 24, all 18 patients achieved PASI 75, and 10 out of these 18 patients had PASI 90. During the follow up period at week 36 and week 48, response to treatment was lost in 8 and 12 patients respectively. No serious side effects were noted in any of our patients, 3 pa-

Table 1 Demographic profile and baseline characteristics of our patients

Patient characteristics	
Number of patients	18
M (n [%])	13 [72.2 %]
F (n [%])	5 [27.8 %]
Age (y), mean (range)	14 (range 6 -17)
Age of disease onset (mean [range]) (y)	8.3 (range 3 -14)
Disease duration (mean [range]) (y)	2.8 (range 1-5)
% BSA affected (mean [SD])	47.3 [27.42]
Any prior psoriasis therapy including systemic, phototherapy or topical) (n [%])	15 [83.3 %]
Baseline PASI (mean [range])	14.7 (range:9·2 - 27·4)
Psoriatic arthritis (n [%])	0 (0.0%)
DLQI score (mean [SD])	14.3 [6.93]
PGA (n [%])	
Almost clear	-
Mild	3 (16.7%)
Moderate	8 (44.4%)
Marked	4 (22.2%)
Severe	3 (16.7%)

SD = Standard Deviation; y = years; n = number

tients developed superficial skin infections and were treated appropriately without effecting the management of psoriasis, and all of them resolved completely without any sequel (Table 3). Three patients reported mild local reaction at injection site at some point during the 24 week treatment period.

DISCUSSION

Psoriasis can involve people of all ages. Childhood onset is not uncommon. The true incidence in the pediatric population is unknown, but it is estimated that 30% to 45% of affected patients develop signs of their disease before adolescence.[19] Within the spectrum of clinical manifestations in children,[20] the most common presentation is

Table 2 PGA, % BSA affected, and DLQI score at Week 12

PGA: mild or better and improved from baseline R (n [%]) NR (n [%])	 13 (72.2 %) 5 (27.8 %)
PGA: clear or almost clear and improved from baseline R (n [%]) NR (n [%])	 2 (11.1 %) 16 (88.9 %)
% BSA affected (mean [SD])	4 [22.2 %]
% Improvement from baseline % BSA (mean [SD])	54.69 [37.26]
DLQI score (mean [SD])	4.86 [5.21]
% Improvement from baseline DLQI score (mean [SD])	53.41 [42.53]

R = Responder; NR = Non-Responder; SD = Standard Deviation

Table 3 Adverse events

Adverse events	**n (%)**
Injection-site reaction	3 (16.6%)
Skin infections	3 (16.6%)
Headache	1 (5.6%)
Weight gain	1 (5.6%)

n = number of patients

generalized plaque psoriasis, followed by guttate psoriasis and juvenile psoriatic arthritis.[21] Many patients suffer more from the psychosocial than from the physical consequences of the disease. The primary treatment objective for psoriasis in children is to improve the physical and psychologic symptoms, thus minimizing adverse effects on future health and psychosocial development. However, the risk to benefit ratio of available treatment options is a particularly important consideration when choosing appropriate therapy for a child. Topical agents are the first line of therapy usually. However, more extensive forms of psoriasis often make topical therapy impractical.[22] In such instances, and/or recalcitrant or relapsing cases, phototherapy or systemic therapy is often deemed necessary. However, systemic therapies may be associated with long-term safety concerns. Recently, there has been growing interest in the therapeutic potential of 'biologics' for psoriasis in adults and, more recently, in children. These are selective immunomodulatory drugs that comprise biologically generated fusion proteins and chimeric, humanised and fully humanised monoclonal antibodies which target pro-inflammatory cytokines. While a number of these agents have been used in the treatment of individual paediatric patients with psoriasis on an open-label basis, etanercept was recently[23] studied in a randomized double blind fashion in 211 pediatric cases of stable moderate to severe psoriasis, and was found to be effective with no major adverse effects. Etanercept has the most significant published literature, and the fact that the drug has received FDA approval for use in children for other indications like ankylosing spondylitis and psoriatic arthropathy for children aged 2 years and older, and juvenile rheumatoid arthritis in children aged 4 years and older, substantiates recommendations for its use in the pediatric psoriasis population. It is well placed to be the first biological agent to be approved for such use.

CONCLUSION

Etanercept is likely to offer a further treatment option for children with moderate to severe plaque psoriasis when topical and systemic therapies have failed or are unsuitable. As is also the case with adults, vaccination schedules will need to be updated before beginning treatment and children will need to be screened before and during treatment to identify infection. Given the lack of long-term experience, regular monitoring for adverse effects will be essential.

REFERENCES

1. Weinstein GD, Krueger JG. An overview of psoriasis. In: Weinstein GD, Gottlieb AB, eds. Therapy of Moderate-to-Severe Psoriasis. Portland National Psoriasis Foundation, Portland, Oregon, 1993:1-22.
2. Christophers E, Kiene P. Guttate and plaque psoriasis. Dermatol Clin 1995; 13:751-6.
3. Christophers E. Psoriasis – epidemiology and clinical spectrum. Clin Exp Dermatol 2001; 26:314-20.
4. Strange P, Cooper KD, Hansen ER et al. T-lymphocyte clones initiated from lesional psoriatic skin release growth factors that induce keratinocyte proliferation. J Invest Dermatol 1993; 101:695-700.
5. De Rie MA, Bos JD. Immunological aspects of psoriasis. Neth J Med 1998; 53:143-4.
6. Gottlieb AB, Krueger JG. Role of T-lymphocytes (in psoriasis pathogenesis). In: Dubertret L, ed. Psoriasis. ISED, 1994:63-71.
7. Griffiths TW, Griffiths CEM, Voorhees JJ. Immunopathogenesis and immunotherapy of psoriasis. Dermatol Clin 1995; 13:739-49.
8. Baker BS, Griffiths CEM, Lambert S et al. The effects of cyclosporine A on T lymphocytes and dendritic cell sub-populations in psoriasis. Br J Dermatol 1987; 116:503-10.

9. Bos JD, Meinardi MM, van Joost T et al. Use of cyclosporine in psoriasis. Lancet 1989; 2:1500-2.
10. Lewkowicz D, Gottlieb AB. Pediatric psoriasis and psoriatic arthritis. Dermatol Ther 2004; 17:364-75.
11. Brecher AR, Orlow SJ. Oral retinoid therapy for dermatologic conditions in children and adolescents. J Am Acad Dermatol 2003; 49:171-82.
12. Lebwohl M, Ellis C, Gottlieb A, et al. Cyclosporine consensus conference: with emphasis on the treatment of psoriasis. J Am Acad Dermatol 1998; 39:464-75.
13. Stern RS, Nichols KT. Therapy with orally administered methoxsalen and ultraviolet A radiation during childhood increases the risk of basal cell carcinoma: the PUVA Follow-up Study. J Pediatr 1996; 129:915-7.
14. Enbrel (etanercept) prescribing information. Thousand Oaks, CA: Immunex (package nsert).
15. Gottlieb AB, Matheson RT, Lowe N, et al. A randomized trial of etanercept as monotherapy for psoriasis. Arch Dermatol 2003; 139:1627-32.
16. Leonardi CL, Powers JL, Matheson RT, et al. Etanercept as monotherapy in patients with psoriasis. N Engl J Med 2003; 349:2014-22.
17. Papp KA, Tyring S, Lahfa M, et al. A global phase III randomized controlled trial of etanercept in psoriasis: safety, efficacy, and effect of dose reduction. Br J Dermatol 2005; 152:1304-12.
18. Tyring S, Gottlieb A, Papp K, et al. Etanercept and clinical outcomes, fatigue, and depression in psoriasis: double-blind placebo-controlled randomised phase III trial. Lancet 2006; 367:29-35.
19. Chaudhuri SP, Gross J. A comparative study of pediatric onset psoriasis with adult onset psoriasis. Pediatric Dermatol 2000; 17:174-8.
20. Morris A, Rogers M, Fischer G et al. Childhood psoriasis: a clinical review of 1262 cases. Pediatr Dermatol 2001; 18:188-98.
21. Farber EM, Nall L. Childhood psoriasis. Cutis 1999; 64:309-14.
22. Richards HL, Fortune DG, O'Sullivan TM et al. Patients with psoriasis and their compliance with medication. J Am Acad Dermatol 1999; 41:581-3.
23. Paller AS, Siegfried EC, Langley RG et al. Etanercept treatment for children and adolescents with plaque psoriasis. N Eng J Med 2008; 358(3):241-51.