Etanercept Combined with Methotrexate for the Treatment of a Pediatric Case with Erythrodermic Psoriasis and Nail Involvement; and Review of the Literature

Eritrodermik ve Tırnak Tutulumu Olan Psoriazisli Çocuk Olgunun Etanersept ve Metotreksat Kombinasyonu ile Tedavisi ve Literatürün Gözden Geçirilmesi

Hayriye SARICAOĞLU,[a]
Kenan AYDOĞAN,[a]
Sevil OVALI TOKA,[a]
Osman DÖNMEZ[b]

Departments of
[a]Dermatology,
[b]Pediatric Nephrology,
Uludağ University Faculty of Medicine, Bursa

Geliş Tarihi/*Received:* 08.02.2012
Kabul Tarihi/*Accepted:* 15.10.2012

Yazışma Adresi/*Correspondence:*
Sevil OVALI TOKA
Uludağ University Faculty of Medicine, Department of Dermatology, Bursa, TÜRKİYE/TURKEY
sevilovali@hotmail.com

ABSTRACT Psoriasis is a chronic, inflammatory skin disease. The incidence is not known in pediatric age. About one-third of psoriasis vulgaris patients have been estimated to be pediatric cases. Erytrodermic psoriasis is rare in this group. We present here a pediatric case with erythrodermic psoriasis and nail involvement recalcitrant to conventional therapies, improved by etanercept therapy. Our case is a 17-year old female patient and was first diagnosed with psoriasis at 6 years old. She has been erythrodermic since 9 years old. She had used only topical corticosteroids. Considering the ineffectivity of conventional treatments, etanercept therapy was initiated and has been continued with methotrexate for 14 months. Etanercept is a TNF-alpha inhibitor that has become popular as a specific target therapy recently. It seems to be a well-tolerated, effective treatment option with a good safety profile for pediatric psoriasis cases who can not use conventional treatments because of their systemic side effects.

Key Words: TNFR-Fc fusion protein; psoriasis; dermatitis, exfoliative; methotrexate; pediatrics

ÖZET Psoriazis kronik, inflamatuar bir deri hastalığıdır. Pediatrik yaş grubunda insidansı bilinmemektedir. Psoriazisli hastaların üçte birinin çocukluk yaş grubunda olduğu tahmin edilmektedir. Bu grupta eritrodermik formu nadir görülür. Biz bu makalede klasik tedavilere dirençli, etanersept ile iyi yanıt alınmış, eritrodermik ve tırnak tutulumu olan psoriazisli bir çocuk olguyu sunmaktayız. Olgumuz 17 yaşında kız olup 6 yaşında psoriazis tanısı almıştır. Dokuz yaşından beri eritrodermik olan hasta uzun süre kontrolsüz topikal steroid kullanmıştır. Hastaya klasik tedavilerle yanıt alınamaması nedeni ile etanersept başlanmıştır ve 14 aydır metotreksat ile kombine olarak devam edilmektedir. Etanersept son zamanlarda gündeme gelmiş, hedefe yönelik bir tedavi olan TNF-alfa blokeridir. Sistemik yan etkileri nedeni ile klasik tedavilerin kullanılamadığı pediatrik psoriazis olgularında güvenlik profili iyi olan, etkili bir tedavi seçeneği gibi görünmektedir.

Anahtar Kelimeler: TNFR-Fc füzyon proteini; psoriazis; dermatit, eksfoliyatif; metotreksat; pediatri

Turkiye Klinikleri J Dermatol 2012;22(2):107-12

Psoriasis is a chronic, inflammatory skin disease characterized by hyperproliferation of keratinoyctes. Although the exact pathogenesis is still not completely clear, it is thought to be a T-cell mediated autoimmune or autoinflammatory disease in which genetic, environmental and immunological factors play an important role.[1-4] About one-third of psoriasis vulgaris patients have been estimated to be pediatric cases.[2] In one study the prevalence of psoriasis was found to be 5% in schoolchildren.[3] The most common variant of psoriasis in pediatric cases is plaque-type (68.6%) similar to adults followed by guttate psoriasis (6.44%) which is more

frequent in pediatric patients. Erythrodermic (1.4%) and pustular psoriasis are rare in childhood.[1] 25-50% of pediatric cases have nail involvement.

Treatment of psoriasis is not always easy in the pediatric group. Since successful treatment needs compliance, parents and patients should be educated initially. Topical treatment is preferred in mild and moderate types. In generalised and severe psoriasis, systemic treatment and phototherapy should be considered. In erythrodermic psoriasis first line therapies are conventional agents such as acitretin, methotrexate (MTX) and cyclosporine (CsA), second line therapies are biologic agents.[5] Conventional agents have also been used in pediatric patients, in also erythrodermic forms.[2] However clinical trials of these drugs are deficient in the pediatric group. Recently, novel drugs, such as biologic agents, have gained importance. We here present a pediatric case with erythrodermic psoriasis and nail involvement improved by etanercept therapy.

CASE REPORT

A 17-year old female patient was referred to our department with erythrodermic psoriasis. She was first diagnosed with localized psoriasis at 6 years old and her disease progressed to generalised psoriasis. She has been erythrodermic since 9 years old. She had used only topical corticosteroids. She had erythematous, thick-silvery white scaly plaques at nearly all over her body and scalp with nail involvement. PASI (Psoriasis area and severity index) score was 37.4 (Figures 1a-d). Hemogram, serum biochemistry, erythrocyte sedimentation rate and urine analyses were normal. Histopathologic examination revealed as psoriasis vulgaris. She had growth retardation and primer amenorrhea. She was 23 kilograms and 137 centimeters height. Her bone age was 11. Growth retardation was related to chronic disease and long-term uncontrolled use of topical corticosteroids as the result of pediatric endocrinology department consultation. Pelvic ultrasound, hypophysis magnetic resonance, blood and urine aminoacida, growth hormone were normal. 1 mg/kg/day prednisolone and MTX 7,5 mg/week were initiated. Her lesions improved significantly after a few days. Three weeks later during the tapering of corticosteroids, her lesions aggravated. MTX dosage was increased to 10 mg/week and combined with 4 mg/kg/day CsA (100 mg/day) while prednisolone was decreased slowly. After 1.5 months she had another relapse. Prednisolone was increased to 1 mg/kg/day and MTX and CsA were observed to be ineffective. Considering the ineffectivity of MTX and CsA and the possible side effects, etanercept therapy was planned. Prior to treatment with etanercept, the patient was screened to exclude active or latent tuberculosis. Subcutaneous etanercept, 0,8 mg/kg/week (25 mg/week) was initiated. A 75% improvement of PASI score (8.4) was achieved at week 4 and her finger and toe nails improved significantly (Figures 2a-d). Prednisolone was tapered slowly in 6 months and CsA was discontinued after 1 month. The patient is under etanercept and MTX 10 mg/week therapy for 14 months and still in remission. No adverse events have been observed during the treatment.

DISCUSSION

T-cell infiltration and keratinocyte proliferation due to the release of various cytokins play an important role in the pathogenesis of psoriasis. TNF-α is presumably one of the most significant cytokines in the pathogenesis. It induces keratinocyte proliferation while inhibiting apoptosis. Recent developments in pathogenesis have made TNF- α inhibitors more popular as a specific target therapy.[6] Etanercept is a soluble fusion protein composed of ligand binding protein of human TNF-α receptor 2 (p75) and human IgG1 Fc.[7] It has been approved for juvenile rheumatoid arthritis by FDA but not for pediatric psoriasis yet. Etanercept has been reported to be effective in pediatric cases.[8-17] 277 pediatric cases (132 female, 134 male, 11 not-stated) with ages ranging from 22 months to 18 years were treated with etanercept in literature (Table 1). Most of them were treated with subcutaneous etanercept 0.4 mg/kg twice weekly or 0.8 mg/kg once a week. Durations of the treatment had ranged from 3 to 31 months. Paller et al. reported that of the 140 cases, 30% had PASI 90, 61%

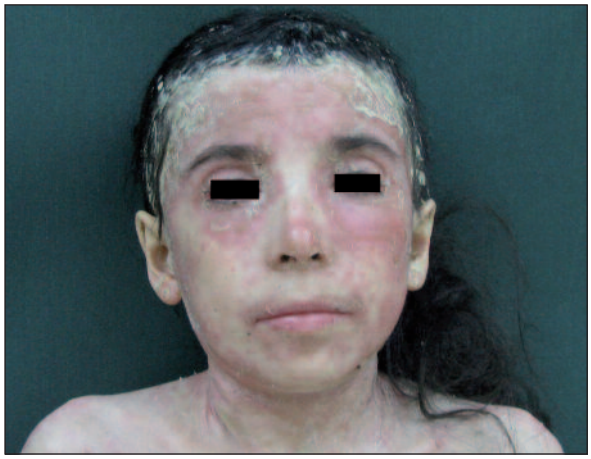

FIGURE 1a: Her face before treatment.
(See for colored form http://dermatoloji.turkiyeklinikleri.com/)

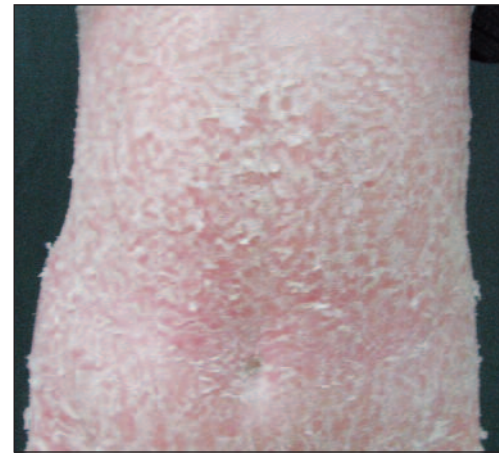

FIGURE 1b: Her body before treatment.
(See for colored form http://dermatoloji.turkiyeklinikleri.com/)

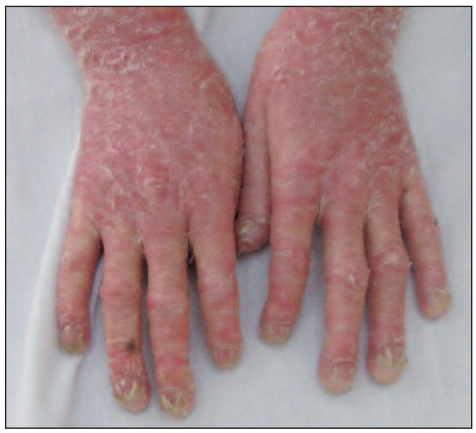

FIGURE 1c: Her finger nails before treatment.
(See for colored form http://dermatoloji.turkiyeklinikleri.com/)

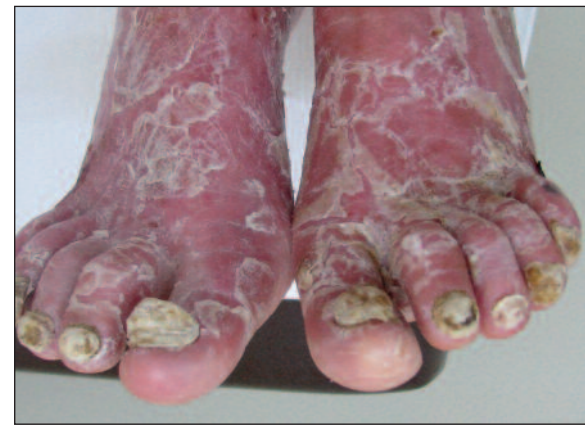

FIGURE 1d: Her toe nails before treatment.
(See for colored form http://dermatoloji.turkiyeklinikleri.com/)

had PASI 75, 89% had PASI 50 improvement at week 96.[10] In individual studies, PASI 75-100 responses were observed after 6-8 months.[8,9,12,14-16] Farnsworth et al. reported a case with no improvement after 8 months of etanercept therapy.[13] Siegfried et al. reported that intermittent etanercept therapy appeared effective and safe without any serious adverse event in their 48-week study of pediatric patients with psoriasis.[17] Our case had been erythrodermic for a long time and had used no therapy except topical steroids. She had growth retardation as a result of uncontrolled topical corticosteroid application for a long time. No sustained improvement with CsA and MTX was gained and subcutaneous etanercept 0.8 mg/kg (25 mg) once a week was initiated. A PASI 75% response was observed at week 4. The patient has been treated with concurrent use of etanercept and methotrexate for 14 months and is still in remission. Her nails also responded to therapy. Adult patients who had nail improvement with alefacept, infliximab and etanercept have been reported.[11] However, to our knowledge, no pediatric case is present in literature.

Reports of severe etanercept adverse effects in children, such as optic neuritis, macrophage activation syndrome, atopic dermatitis, sarcoid-related uveitis, drug-induced systemic lupus erythematosus and multifocal septic arthritis have been published.[8-16] The most common adverse events that

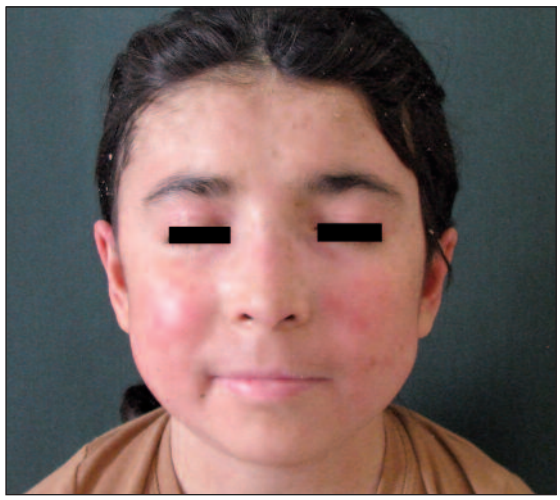

FIGURE 2a: Her face after treatment.
(See for colored form http://dermatoloji.turkiyeklinikleri.com/)

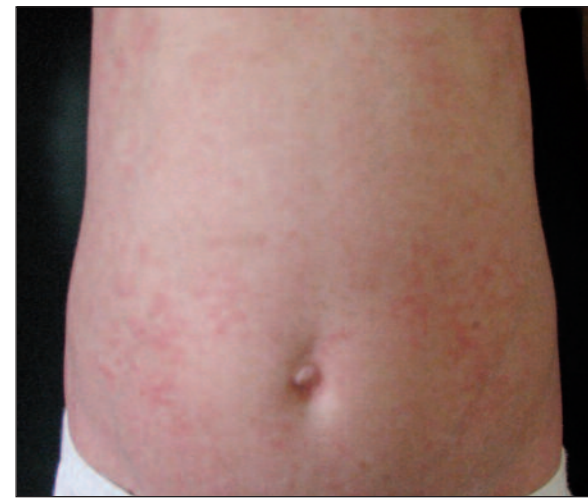

FIGURE 2b: Her body after treatment.
(See for colored form http://dermatoloji.turkiyeklinikleri.com/)

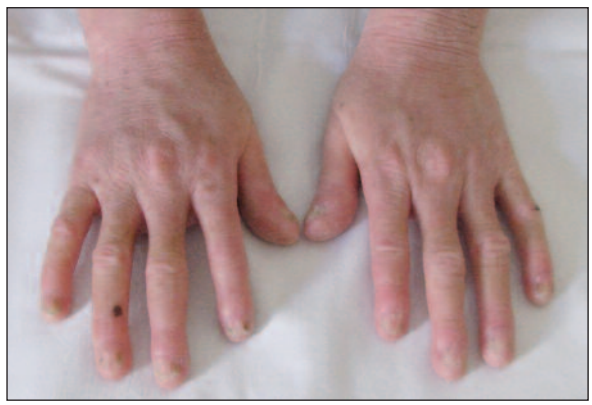

FIGURE 2c: Her finger nails after treatment.
(See for colored form http://dermatoloji.turkiyeklinikleri.com/)

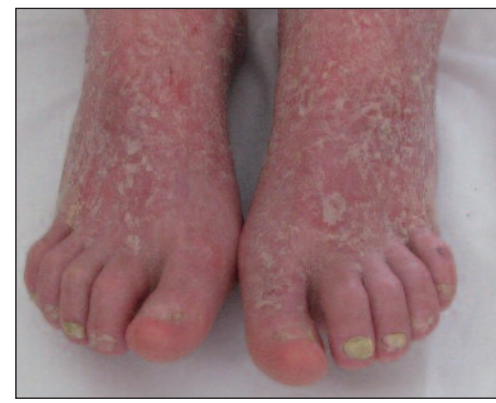

FIGURE 2d: Her toe nails after treatment.
(See for colored form http://dermatoloji.turkiyeklinikleri.com/)

were observed are listed in Table 1. One patient had mononucleosis and one patient had cryptococcus albidus infection on scalp. No adverse events occurred in four patients and also not in our case. Paller et al. performed an open-label study to evaluate the long-term safety and efficacy of etanercept in pediatric patients.[10] At week 96.80% of 145 patients reported one or more adverse events. Most common adverse events were upper respiratory tract infection. Three patients reported serious adverse events none of which were considered to be related to etanercept. In one study, 69 pediatric cases with juvenile rheumatoid arthritis was followed up for 8 years to evaluate the safety and efficacy of etanercept therapy. There was no increase in the serious adverse events with long term exposure to etanercept.[18]

Other biologics such as infliximab and adalimumab can also be considered in pediatric psoriasis. Though there is not enough experience with these biologics. In literature only two pediatric psoriasis cases were reported to be successfully treated with infliximab.[19,20] No pediatric psoriasis cases were reported to be treated with adalimumab. Further evaluation of infliximab and adalimumab is needed in pediatric patients with psoriasis.

In conclusion; etanercept is as effective as conventional treatments in severe psoriasis. It tar-

TABLE 1: Summary of pediatric psoriasis cases treated with etanercept in literature.

Authors	No	Age, Sex (F/M)	Diagnosis	Previous Therapy	Dose	Duration w(week) mo(month)	Adverse Reactions	Clinical Response
Farnsworth et al. 2005[11]	1	14, M	PP	SS, TR, TS, TP, TT	25 mg biw	8 mo	No adverse reactions	No improvement
Hawrot et al. 2006[6]	9	8-18, 6/3	7 PP 1 PuP 1 GP	CsA, acitretin, UVB, TS, TT	0.4 mg/kg biw	3-14 mo	Local skin irritation, mononucleosis	2:Equivocal 4:much improved 3:cleared
Kress 2006[13]	10	8-18 NS	8PP, 1GP+PP, 1GP	TS, MTX, CsA, SS, PUVA	0.4 mg/kg<50 kg 25 mg>50 kg biw	24-31 mo	Mild injection site reaction	8: almost clear 2: clear
Papoutsaki et al. 2006[7]	4	6-15, 4M	2PP, 1PuGEP, 1PPP	TS, SS, acitretin	0.4 mg/kg biw	24-86 w	Upper respiratory tract infectious, skin injection site reaction, headache, abdominal pain , rash	PASI: 25.8-0; 21.2-0 27.4-5,9; 9.2-2.2 in 12 w, respectively
Safa et al. 2007[10]	1	7, M	EP	Acitretin, MTX, CsA, UVB	0.4 mg/kg biw	6 mo	No adverse reactions	Dramatic improvement: 100% after 6 mo
Hoang and Burress 2007[14]	1	14, M	GP	TS, TR, calcipotriene, anthralin, MTX, UVA	25 mg biw	8 mo	Localized cutaneous Cryptococcus albidus infection	Clearance of lesions except plaques on elbows and knees
Paller et al. 2010[9]	182	4-17, 90/92	PP MTX, retinoids	Phototheray, CsA,	0.8 mg/kg/w	96 w 48 w (168 cases) 96 w (140 cases)	Upper respiratory tract infectious, severe infection, skin injection site reaction	PASI 90: 30% PASI 75: 61% PASI 50: 89%
Siegfried et al. 2010[16]	138	4-17, 70/68	PP	NS	0.8 mg/kg/w	48 w	Upper respiratory tract infectious, skin injection site reaction, headache,	Etanercept; PASI 75: 80% Placebo; PASI 75: 54%
Our case 2010	1	17,F	EP	MTX, CsA, SS	0.8 mg/kg/w (25mg/w)	15 mo	No adverse reactions	PASI:37,4--8,4 (PASI 75)

NS: Not stated; M:male; F:Female; PP: Plaque psoriasis; GP: Guttat psoriasis; PuP: Pustular psoriasis; EP: Erythrodermic psoriasis; PuGE: Generalized pustular erythrodermic psoriasis; SEPP: Suberythrodermic plaque psoriasis; PPP: Palmoplantar psoriasis; MTX: Methotrexate; CsA: Cyclosporine; TS: Topical steroids; SS: Sistemic steroids; TP: Topical pimecrolimus; TT: Topical tacrolimus; TR: Topical retinoids; biw: biweekly.

gets specific molecules minimizing the adverse events associated with organ toxicity. It is appropriate for patients who can not use conventional treatments because of their nephrotoxicity and hepatotoxicity. Although more clinical trials and long-term follow-up are needed to determine the potential risks of etanercept, it seems to be a well-tolareted, effective treatment option with a good safety profile for pediatric psoriasis cases.

REFERENCES

1. Burden AD. Management of psoriasis in childhood. Clin Exp Dermatol 1999;24(5): 341-5.
2. Silverberg NB. Pediatric psoriasis: an update. Ther Clin Risk Manag 2009;5:849-56.
3. Kerkhof P, Schalkwijk J. Psoriasis. In: Bolognia JL, Jorizzo JL, Rapini RP, eds. Dermatolgy. 2nd ed. Philadelphia: Mosby Elsevier; 2008. p.115-35.
4. Benoit S, Hamm H. Childhood psoriasis. Clin Dermatol 2007;25(6):555-62.
5. Rosenbach M, Hsu S, Korman NJ, Lebwohl MG, Young M, Bebo BF Jr, et al.; National Psoriasis Foundation Medical Board. Treatment of erythrodermic psoriasis: from the medical board of the National Psoriasis Foundation. J Am Acad Dermatol 2010;62(4):655-62.
6. Atakan N, Hapa A. [The use of anti-TNF agents in psoriasis and other dermatological disorders]. Turkiye Klinikleri J Immunol Rheumatol-Special Topics 2010;3(2):32-9.
7. Jacob SE, Sergay A, Kerdel FA. Etanercept and psoriasis, from clinical studies to real life. Int J Dermatol 2005;44(8):688-91.
8. Hawrot AC, Metry DW, Theos AJ, Levy ML. Etanercept for psoriasis in the pediatric population: experience in nine patients. Pediatr Dermatol 2006;23(1):67-71.
9. Papoutsaki M, Costanzo A, Mazzotta A, Gramiccia T, Soda R, Chimenti S. Etanercept for the treatment of severe childhood psoriasis. Br J Dermatol 2006;154(1):181-3.
10. Paller AS, Siegfried EC, Eichenfield LF, Pariser D, Langley RG, Creamer K, et al. Long-term etanercept in pediatric patients with plaque psoriasis. J Am Acad Dermatol 2010;63(5):762-8.
11. de Berker D. Management of psoriatic nail disease. Semin Cutan Med Surg 2009;28(1):39-43.
12. Safa G, Loppin M, Bousser AM, Barbarot S. Etanercept in a 7-year-old boy with severe and recalcitrant psoriasis. J Am Acad Dermatol 2007;56(2 Suppl):S19-20.
13. Farnsworth NN, George SJ, Hsu S. Successful use of infliximab following a failed course of etanercept in a pediatric patient. Dermatol Online J 2005;11(3):11.
14. Fabrizi G, Guerriero C, Pagliarello C. Etanercept in infants: suberythrodermic, recalcitrant psoriasis in a 22 month-old child successfully treated with etanercept. Eur J Dermatol 2007;17(3):245.
15. Kress DW. Etanercept therapy improves symptoms and allows tapering of other medications in children and adolescents with moderate to severe psoriasis. J Am Acad Dermatol 2006;54(3 Suppl 2):S126-8.
16. Hoang JK, Burruss J. Localized cutaneous Cryptococcus albidus infection in a 14-year-old boy on etanercept therapy. Pediatr Dermatol 2007;24(3):285-8.
17. Siegfried EC, Eichenfield LF, Paller AS, Pariser D, Creamer K, Kricorian G. Intermittent etanercept therapy in pediatric patients with psoriasis. J Am Acad Dermatol 2010;63(5):769-74.
18. Lovell DJ, Reiff A, Ilowite NT, Wallace CA, Chon Y, Lin SL, et al. Safety and efficacy of up to eight years of continuous etanercept therapy in patients with juvenile rheumatoid arthritis. Arthritis Rheum 2008;58(5):1496-504.
19. Menter MA, Cush JM. Successful treatment of pediatric psoriasis with infliximab. Pediatr Dermatol 2004;21(1):87-8.
20. Farnsworth NN, George SJ, Hsu S. Successful use of infliximab following a failed course of etanercept in a pediatric patient. Dermatol Online J 2005;11(3):11.