

Development of alopecia universalis during treatment of generalized plaque psoriasis with TNF- α antagonist (Etanercept)

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ABSTRACT

The introduction of biological therapy, including the tumor necrosis factor-alpha (TNF- α) antagonists represents a major step forward in the treatment of psoriasis and other autoimmune inflammatory diseases.

The efficacy and safety of etanercept has been documented in patient with psoriasis as well as in other immune-mediated diseases. However, a number of adverse events have been reported and the most frequently were injection site reactions. As with other TNF- α antagonist, the potential increased risk of infection and malignancy are of significant concerns.

We want here to report on a rapidly progressive alopecia areata (AA) into universalis subtype during treatment of a severe case of chronic plaque psoriasis with etanercept monotherapy.

INTRODUCTION

The introduction of biological therapy, including the tumor necrosis factor-alpha (TNF- α) antagonists represents a major step forward in the treatment of psoriasis and other autoimmune inflammatory diseases. Biologic agents can be tailored to target specific molecular steps important in the pathogenesis of psoriasis and therefore their safety profile is generally considered to be more favorable than that of the classical systemic immunosuppressive agents. As the use of these new agents such as etanercept, infliximab, and adalimumab expands, the potential for related side effects may also be on the increase. Etanercept is a fully human soluble TNF receptor fusion protein composed of the extracellular portion of two TNF type II (p75) receptors joined to the Fc portion of IgG1. It was the first TNF- α antagonist approved for the treatment of psoriasis and psoriatic arthritis. The efficacy and safety of etanercept has been

documented in patient with psoriasis as well as in other immune-mediated diseases. However, a number of adverse events have been reported and the most frequently were injection site reactions. As with other TNF- α antagonist, the potential increased risk of infection and malignancy are of significant concerns.

We want here to report on a rapidly progressive alopecia areata (AA) into universalis subtype during treatment of a severe case of chronic plaque psoriasis with etanercept monotherapy.

CASE REPORT

A 29 year-old woman with severe generalized plaque psoriasis (PASI 28.5), since the age of 17, had been treated with topical corticosteroids, PUVA for many years. On March 2005, she started her first course of etanercept monotherapy (50 mg BIW subcutaneously for 12 weeks, followed by 50 mg/week for another 12 week) with an ex-

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Fig. 1 A, B. Total hair loss on scalp and eye-brows in psoriatic patient who developed AA universalis following etanercept therapy. **B.** Notice the use of black-liner on lost eyebrows.

cellent control (PASI 0). On relapses, repeated courses of etanercept were given in different dosing regimens maintaining the same good clinical response. She had a 10 years personal history of recurrent small patches of AA affecting mainly her frontal site of the scalp. She was treated for with topical potent steroids and showed excellent hair regrowth in affected sites. The patient was apparently clinically free from AA before etanercept treatment was implemented. After more than two years of etanercept therapy, while she was receiving her 4th etanercept course, Six month ago, she suddenly developed a rapidly progressive and extensive hair loss resulting within two months in a typical form of AA universalis (Fig. 1 A, B). All body hair was eventually affected except her

eyelashes. No other triggering factors such as infections, stress or trauma were detected. There was no familial history of AA or atopy. Generally, there were no complaints, and the clinical examination and laboratory investigations including complete blood picture, serum chemistry profile, antinuclear antibodies (ANA), thyroid function tests and thyroglobulins were all within normal levels. Etanercept therapy was discontinued waiting for the prognosis.

DISCUSSION

Psoriasis is a common, chronic, relapsing inflammatory disease with considerable physical and psychological impacts.^{1,2} Accumulated data from research on the pathophysiology of psoriasis over

the past two decades has emphasized the central role of the immune system in initiating and maintaining the disease. Furthermore, the fundamental involvement of T-cells and cytokines and their crucial contribution in the process has also been characterized.³⁻⁷ A parallel advancement in pharmaceutical and biotechnology industries facilitated the utilization of the available insight knowledge to developed more specific, immunologically directed interventions. Accordingly, biological agents which targeted specific steps in the pathogenesis of psoriasis have been developed and can be divided into two main groups: (I) agents targeting the cytokine tumor necrosis factor alpha (TNF- α) (e.g. etanercept, infliximab, adalimumab) and (II) agents targeting T cells or antigen-presenting cells (e.g. efalizumab, alefacept).

Etanercept, an inhibitor of TNF- α , is a fully human soluble recombinant p75 TNF receptor which blocks the binding of TNF to cell surface receptors and consequently neutralizing its biological activity. Etanercept has been extensively used in rheumatology to treat patient with rheumatoid arthritis,⁸ ankylosing spondylitis⁹ and also in patient with psoriatic arthritis who showed simultaneous improvement of their psoriatic cutaneous lesions.¹⁰ The efficacy and safety of etanercept have been demonstrated in randomized placebo-controlled clinical trials in patients with moderate to severe psoriasis.^{11,12,13} However, a number of adverse events including skin reactions have been reported with the use of etanercept. The commonest side effect of etanercept is injection site reactions.^{14,15} Infections including common and opportunistic, lymphoproliferative malignancies and aggravation of congestive heart failure are considered potentially serious risks that can oc-

cur with use of etanercept.^{16,17} A variety of adverse cutaneous effects associated with etanercept therapy has been reported and included the following: cutaneous vasculitis,¹⁸ lupus erythmatosus,¹⁹ lichen planus,²⁰ lichen planopilaris,²¹ pemphigus vulgaris,²² urticaria,²³ psoriasis²⁴ and alopecia areata.²⁵

Alopecia areata (AA) is unpredictable, usually patchy, nonscarring hair loss condition that is estimated to affect 1.7% of the population in the United States.²⁶ The disease often has a chronic and relapsing course with tremendous psychological impact.²⁷ The pathophysiology of alopecia areata is still unclear, however, genetic and autoimmune factors have been proposed.^{28,29} A large body of evidence suggests that AA is a T-cell mediated autoimmune disease directed against an assumed autoantigen of the hair follicles.³⁰ Furthermore, cytokines, including TNF- α have a significant pathogenic role in mediating inflammation and regulating cell proliferation in autoimmune diseases.³⁰ However, the precise mechanistic pathways of TNF- α in particular and other cytokines in general to induce and maintain autoimmune states are still to be elucidated. Based on the suspected role of TNF- α in the pathogenesis of AA, reports on off-label use of etanercept and other biologic agents for the treatment of alopecia areata including its subtypes can be found in the literature.^{31,32,33} However, a clear example of the contrasting roles of TNF- α in the pathogenesis of a number of immune-mediated disorders can be seen in AA. Whereas the TNF- α was thought to be an essential cytokine that has potent inhibitory effect on the hair follicle growth as demonstrated in in-vitro studies and the presence of TNF- α -producing cells in the mononuclear infiltrate surrounding the hair follicle.³⁰ In contrast, the clinical use of etan-

except, a well known TNF- α antagonist, over 8-24 weeks not only failed to show hair regrowth in 17 patients with AA, but also worsened the condition in few of them.³² Furthermore, Posten and Swan³⁴ reported recurrence of AA in a 49 year-old man treated with etanercept for rheumatoid arthritis. Similarly, our patient developed progressive alopecia universalis while on etanercept therapy for her psoriasis. AA can also occur during treatment of a number of autoimmune conditions with other anti-TNF- α agents such as infliximab,^{35,36} and adalimumab.^{37,38,39}

Moreover, a totally opposite role for TNF- α in AA was suggested. In this instance, TNF- α is allegedly protect from hair loss in view of the fact that the blockade of TNF- α mediated effects by monoclonal antibodies resulted in the induction or worsening of AA or AA universalis as reported in a number of patients treated with infliximab or adalimumab for other diseases.^{36,38,39}

In view of the conflicting data on the role of TNF- α in the pathophysiology of autoimmunity including that of AA, and the isolated clinical case reports on the development or aggravation of AA during treatment with etanercept, like our present case, and with other TNF- α antagonists, it is quite surprising that these biologic agents which meant to block TNF- α , were able to induce AA in the same patients treated for other indications. This may denote a less favorable role of TNF- α in the pathogenesis of disease.

The occurrence and progression of AA, including the subtype AA universalis, during anti-TNF- α treatment has been reported in several patients, more frequently with anti-TNF- α monoclonal antibodies (infliximab and adalimumab) than with the fully human soluble fusion protein TNF- α receptor i.e. etanercept.³⁴⁻⁴⁰ However, to our knowl-

edge, our patient is the first reported case of AA universalis that progressively developed during etanercept monotherapy for cutaneous psoriasis. Garcia Bartels et al³⁷ documented a case of AA universalis in a young woman with history of AA and rheumatoid arthritis four months following the addition of adalimumab to her treatment regimen of prednisone and leflunomide. A similar case was also reported by Pelivani et al³⁸ in a patient with a longstanding history of psoriatic arthritis and psoriasis who was treated with adalimumab monotherapy for six months.

In our patient, no obvious triggering factors such as serious psychological stress or concurrent use of other medications were detected that could explain the rapid onset of AA universalis. However, the previous history of multiple AA may be the basis for individual susceptibility that could govern such unexpected response to etanercept. The exact mechanistic reaction is still not completely elucidated.

It might worth mentioning that all TNF- α antagonists have been reported to induce or exacerbate psoriasis.^{41,42} Whether this represents a paradoxical adverse reaction or a class effect is still a matter that generates a lot of discussions. One would wonder if the paradoxical phenomenon could also be applied on the initiation or worsening of AA during TNF- α antagonist therapy.⁴³

In conclusion, the new biologic agents, including TNF- α antagonist are very useful addition to our medical therapeutic armament. Currently, etanercept is widely used to treat a broad range of immune-mediated inflammatory diseases. Despite its efficacy and safety profile, a number of adverse skin reactions are occasionally reported. We described a case of rapid onset AA universalis in a psoriatic patient treated exclusively with

etanercept, in the hopes to increase awareness on the possibility of occurrence of such condition, to adding to the already available knowledge pertaining to AA and etanercept, and to stimulate more research on mechanistic role of TNF- α in autoimmune disorders.

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