

Etanercept and demyelinating disease in a patient with psoriasis

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The tumor necrosis factor- α antagonist (TNF- α) etanercept has been approved for the treatment of rheumatoid arthritis, juvenile rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, and psoriasis. Earlier reports on the use of etanercept or infliximab in patients with rheumatoid arthritis, psoriatic arthritis, or juvenile rheumatoid arthritis suggested an increased risk of demyelinating disease. It is imperative that dermatologists have a keen awareness of this possible adverse event given the increased use of this class of drugs. We report a case of demyelinating disease occurring in a patient treated for psoriasis. The relation of TNF- α antagonist therapy to demyelinating disease/multiple sclerosis is explored. It is recommended that patients be diligently screened before starting TNF- α antagonist therapy and that vigilance for symptoms of demyelinating disease/multiple sclerosis be included in follow-up examinations during treatment with these drugs. (*J Am Acad Dermatol* 2006;54:160-4.)

B iologic agents have revolutionized the treatment of several inflammatory diseases including rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease, and psoriasis. The tumor necrosis factor- α (TNF- α) inhibitors are among the biologic agents used in psoriasis. Etanercept is approved for the treatment of chronic moderate to severe psoriasis in patients who are candidates for ultraviolet radiation or systemic therapy, as well as rheumatoid arthritis, juvenile rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis.¹ With widespread use of these agents, adverse events resulting from their use are inevitable occurrences. It is important that physicians involved in the care of patients treated with biologic agents be cognizant of such adverse events and discontinue therapy when significant events occur.

We report a case of demyelinating disease in a patient treated with etanercept for psoriasis. The patient's symptoms resolved during therapy. Subsequent neurologic work-up led to the diagnosis

of multiple sclerosis (MS). The literature on TNF- α and demyelinating disease and MS is reviewed.

CASE REPORT

An 18-year-old woman with severe psoriasis of 14 years' duration presented for follow-up of her psoriasis after relocating. Her history is significant for previous flares of psoriatic erythroderma and pustular psoriasis. She had previously been treated at various times with ultraviolet B phototherapy, methotrexate, topical steroids, topical vitamin D analogs, and systemic retinoids. She had most recently been treated at an outside institution with 25 mg of subcutaneously administered etanercept twice per week for 1 year, with excellent control of her psoriasis. At presentation she reported the gradual resolution during the week just past of left-sided tingling and numbness in the upper and lower extremities and scalp, as well as blurry vision in the left eye, lasting a total of about 4 weeks. She was still using etanercept.

Neurologic consultation was obtained. The neurologic examination revealed normal visual acuity bilaterally, no afferent papillary defect, no red desaturation; normal motor, sensory, coordination, and gait findings; however, the examination was significant for hyperreflexia throughout. A complete metabolic panel, complete blood cell count with differential count, liver chemistries, vitamin B12, antinuclear antibody, angiotensin-converting enzyme level, Lyme titer, and erythrocyte sedimentation rate values were all within normal limits. Magnetic resonance imaging (MRI) of the brain (Fig 1) showed

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numerous lesions exhibiting hyperintense fluid-attenuated inversion recovery (FLAIR) signal, including a large right frontal and a left occipital lesion. Diffusion weighted imaging indicated acute or subacute disease in the right frontal and left occipital regions. The frontal lesion showed slight mass effect and patchy enhancement on T1 post-contrast imaging, indicating an active lesion. These findings are consistent with demyelinating disease. The patient had been free of symptoms for approximately 8 weeks at the time of the MRI scan. Lumbar puncture was performed 8 weeks after presentation. Subsequent cerebrospinal fluid (CSF) studies revealed normal cell counts, chemistry, glucose and protein levels, with negative Lyme titer and cultures. CSF studies were positive for oligoclonal bands, with negative serum oligoclonal bands, further supporting the diagnosis of MS.

The patient's skin was clear of psoriatic plaques at her initial office visit. Etanercept was discontinued at presentation and alternative therapy was instituted. She has had no recurrence of her neurologic symptoms during 7 months of follow-up and has had stable findings on neurologic examination.

DISCUSSION

Etanercept is a fully human fusion protein constructed from the two soluble extracellular recombinant p75 TNF receptor TNF- α binding domains and the Fc portion of the human IgG1 antibody. Etanercept alone is an effective psoriasis therapy² and can be used safely in combination therapy with methotrexate.³⁻⁵ Adverse events related to TNF- α antagonists include infections (including tuberculosis); formation of autoantibodies (including antinuclear antibodies) and lupus-like reactions; exacerbations of congestive heart failure; pancytopenia; hematologic malignancies; and demyelinating disease.^{1,6}

TNF- α is an important mediator of disease in MS. TNF was demonstrated in active foci of MS in autopsy specimens⁷ and is elevated in patients with MS in both the serum and CSF.^{8,9} It is thought to be produced by inflammatory cells that infiltrate plaques in the central nervous system.⁸ CSF levels of TNF- α correlate well with degree of disability and rate of neurologic deterioration in patients with chronic progressive MS.⁸⁻¹⁰ TNF has a direct toxic effect on oligodendrocytes and a proliferative effect on astrocytes in vitro.^{11,12} Experimental autoimmune encephalomyelitis (EAE) in rodents shares many features of human MS and is considered a model for MS.¹³⁻¹⁵ TNF treatment worsens symptoms of EAE¹⁶; anti-TNF antibodies are protective

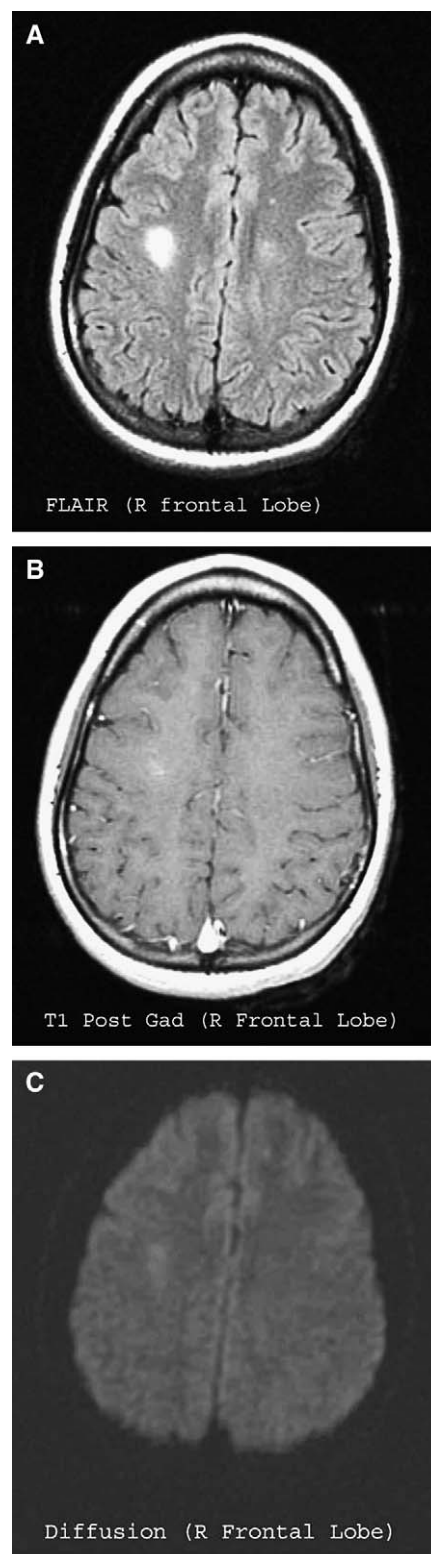


Fig 1. **A**, Axial FLAIR image shows large right frontal lobe white matter lesion. **B**, Axial T1 postgadolinium (*Post Gad*) image (same level as **A**) shows patchy enhancement of right frontal lobe lesion indicating active lesion. **C**, Axial diffusion weighted image (same level as **A**) shows slightly high signal intensity consistent with acute/subacute lesion.

against EAE induction.¹⁷⁻¹⁹ Lenercept, an early TNF- α receptor-IgG1 fusion protein was shown to be protective against the induction of clinical EAE.²⁰

These findings prompted early trials of lenercept in patients with MS.²¹ In a 1999 landmark phase II randomized double-blind placebo-controlled clinical trial, lenercept was evaluated for its efficacy in reducing new lesions visualized on MRI.²¹ This study failed to show differences in new or changing lesions, but clinical exacerbations were much increased in all treatment groups, and time to a first exacerbation was decreased in a dose-dependent manner. A previous phase I study of infliximab in two patients with rapidly progressive MS also showed increased disease activity as measured by MRI-visualized lesions, CSF leukocyte counts, and IgG indices, although clinical disease was unchanged.²² Lenercept and all TNF- α antagonists were abandoned as candidate drugs for the treatment of MS.¹³

Understanding the paradoxical failure of TNF- α antagonist therapy in MS may lie with the complexity of the TNF- α signaling pathway. Preferential overexpression of TNF- α in neurons, oligodendrocytes, and astrocytes has been achieved in transgenic murine models.²³⁻²⁵ Most of these animals show a spontaneous demyelinating phenotype of varied severity, whereas a few lack spontaneous disease but demonstrate more severe disease with induced EAE.¹⁴ The only exception was in lines in which nonsoluble transmembrane TNF- α was expressed in neurons alone.²⁴ Signaling of the TNF- α overexpression phenotype was shown to be dependent on the p55 TNF receptor I.^{26,27} Strains deficient in this receptor showed delay in onset of EAE.²⁸ When mice globally deficient in TNF- α were studied, the phenotype was a delay in onset of induced EAE and non-CNS accumulation of leukocytes.^{28,29} These studies suggest that overexpression of TNF- α promotes a predisposition to demyelinating disease as is seen in MS.¹⁴

In contrast, TNF- α -deficient animals develop severe neurological impairment with extensive inflammation, demyelination, and high mortality rates after treatment with myelin oligodendrocyte glycoprotein, a regimen that is thought to induce autoimmune demyelination similar to MS.³⁰ The disease severity is improved dramatically by treatment of the animals with TNF- α .³⁰ Mice deficient in the p75 TNF receptor II have a more severe induced EAE phenotype,²⁸ whereas animals overexpressing the receptor demonstrate a unique inflammatory disease, which was independent of TNF- α , TNF- β , or the p55 TNF receptor I.³¹

The TNF- α /TNF receptor system likely acts in a complex network to modulate disease. An additional level of complexity is realized when the effects of the soluble versus bound forms of TNF receptor on the active concentration of free TNF- α is considered. Soluble receptor forms in high concentrations are inhibitory to the function of TNF- α by competing with its binding to TNF- α cell surface receptors.³² At lower concentrations the receptor might prolong the activity of TNF- α by acting as a carrier protein, protecting it from degradation, and effectively prolonging its biological half-life.^{13,32} Indeed, higher levels of circulating p55 TNF receptor I are found in patients with MS.³³ This interplay of soluble and bound receptors with ligand creates a scenario where too much or too little TNF- α may both be detrimental states.

The blood-brain barrier may be important in explaining the differential effects of TNF- α antagonist therapy on inflammatory diseases relative to MS and may also underlie the apparent increase in demyelinating events in patients treated for non-MS inflammatory diseases.³⁴ The blood-brain barrier restricts the entry of immunoglobulins and albumin into the CSF, making the CNS an immune-privileged and protein-restricted site, even in the setting of active MS. Peripherally administered TNF- α antagonists also are restricted from entry into the CNS, as demonstrated in a phase I study with infliximab for MS.²² Treatment, however, may increase auto-reactivity of T cells. It was shown that prolonged exposure to TNF- α antagonists enhances antigen presentation, increases T-cell receptor signaling, and decreases apoptosis of potentially autoreactive T cells,^{32,34-38} as is exemplified in the enhancement of autoimmune disease activity in nonobese diabetic and lupus mice treated on a long-term basis with TNF- α antagonist.^{32,35,37,38} The pathologic changes in the blood-brain barrier produced by MS leads to a minimal effect on protein permeability, but enhances the entry of lymphocytes and other inflammatory cells.³⁴ A population of autoimmune cells selected by TNF- α antagonist treatment could have facilitated entry into the CNS as a result of enhanced permeability, leading to worsening disease. The blood-brain barrier may also act as a semipermeable membrane between peripheral and central TNF- α reservoirs. Treatment with peripherally administered TNF- α antagonist may deplete the peripheral reservoir, leading to a gradient of TNF- α across the blood-brain barrier. The gradient so established could trigger an up-regulation of CNS TNF- α or TNF- α receptor expression (by an unknown mechanism) causing increased disease activity in the CNS.³⁴

Clinical experience with demyelinating disease and TNF- α antagonist therapy was studied in 2001.¹³ Twenty cases were examined in which 18 patients had received etanercept and 2 had received infliximab for rheumatoid arthritis, juvenile rheumatoid arthritis, or psoriatic arthritis. The most common neurologic symptoms were paresthesias, visual disturbances, confusion, gait disturbances, apraxia, facial palsy, and Guillain-Barré syndrome. Four of the 20 patients had MS or MS-like symptoms before treatment. One patient relapsed upon rechallenge with etanercept after initial improvement after cessation of the drug, which led to a permanent neurologic deficit. Of the 20 patients examined, 2 were continued on an etanercept regimen with continued symptoms, 5 had an unknown course after discontinuing the drug, and 11 had complete or partial resolution of symptoms. Two patients continued to have symptoms after discontinuing the drug, one of whom had two new MRI-visualized lesions after 2 months.

In the current case, our patient's symptoms resolved even before cessation of etanercept, but the laboratory data pointed unequivocally to MS as causing our patient's symptoms. The fact that our patient's symptoms resolved before stopping etanercept does not negate a possible relationship. Case reports of successful rechallenges with TNF- α antagonists exist.³⁹ It is impossible to rule in or rule out a cause-and-effect relationship, given the nature of MS as a waxing and waning disease as well as the abundance of data suggesting a relationship between demyelinating disease and the TNF- α pathway. A question that remains unanswered pending future studies is whether the TNF- α antagonist therapy truly increases the risk of demyelinating disease or are the reported cases the background incidence of MS in a population receiving more careful medical follow-up. Mohan et al¹³ in 2001 argued that no relationship can be significantly demonstrated in their analysis. A third intriguing possibility is that a biological link between MS and other TNF- α -mediated diseases may exist, thereby resulting in a selection bias in the reported cases of TNF- α antagonist-related demyelination. One hospital-based case-controlled study showed a significant increase in the rate of psoriasis, rheumatoid arthritis, and goiter in MS patients relative to the control group.⁴⁰ Another more recent Italian study of family members of MS patients showed a high frequency of psoriasis in family members of patients with early-onset MS.⁴¹ It is also possible that alterations in the cytokine network, in addition to perturbations of TNF- α and TNFR levels, caused by TNF- α antagonist therapy, may exacerbate MS. Of course, the lener-

cept study²¹ strongly suggests that TNF- α inhibition exacerbates MS in patients already affected. Hopefully, future studies will clarify these issues.

Regardless, it is important that physicians screen candidates for TNF- α antagonist therapy carefully to exclude those with symptoms or signs of demyelinating diseases. Follow-up examinations during the treatment courses with these medications should routinely include an evaluation of signs and symptoms of neurologic deficits. Our case demonstrates that resolution of neurologic symptoms during continual therapy with these agents does not indicate an absence of demyelinating disease. If symptoms are present, or reported in interval histories, it would be most prudent to discontinue TNF- α antagonist therapy and institute an alternative regimen for controlling the patient's psoriasis while a work-up is initiated aimed at evaluating the possibility of a demyelinating event.

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