Multiple Sclerosis Onset during Etanercept Treatment

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Dear Sir,

Tumor necrosis factor-α (TNF-α) is a cytokine of known proinflammatory properties produced by cells of the monocyte-macrophage lineage and lymphocytes in certain infectious or immunological contexts [1]. There is a substantial body of evidence supporting its role as inflammatory mediator in autoimmune diseases. At present, TNF-α inhibitors constitute an effective treatment against many of these pathologies including psoriasis [2]. In multiple sclerosis (MS) patients, TNF-α levels increase in serum and in cerebrospinal fluid to an extent that depends on the phase of activity of the disease [3]. TNF-α production is higher before exacerbations [4]. Furthermore, a higher number of cells express TNF-α mRNA in active acute and chronic demyelinating lesions than in inactive or remyelinating lesions [5]. Although TNF-α antagonists have shown promising results in experimental allergic encephalomyelitis [6, 7], clinical trials with MS patients had to be suspended because of the increased number and severity of relapses [8, 9]. Some cases of demyelinating events have also been noticed in relation to their use [10–18]. In this article, we describe a patient who presented the first attack of MS during a course of etanercept treatment (a fusion protein composed of the soluble membrane of TNF-α p75 and the constant fraction of IgG1) for psoriatic arthritis.

Case Report

A 36-year-old woman with psoriatic arthritis who had received etanercept for 4 months (25 mg s.c. twice weekly) presented with a 1-week history of right eye pain and vision decline. Three weeks previously, she had developed the same symptoms in the left eye that resolved spontaneously. There was no family history of neurological disorders. Two years previously, she received (partially effective) treatment for her articular problem with methotrexate and prednisone for 12 months. A physical examination revealed deformation in both wrists, nail pitting, and 1/2 in the right and left eye respectively; fundoscopy was normal. The full blood count, erythrocyte sedimentation rate, C-reactive protein, and kidney, liver, bone and thyroid function, vitamin B-12, folate levels, antibody screen (antinuclear, anti-double-stranded DNA, antineutrophilic cytoplasmic, antiextractable nuclear antigen, antigliadin, antiphtospholipid and antithyroid antibodies) and protein electrophoresis were all within normal limits or negative. No oligoclonal bands were observed in serum. Brucella, Borrelia, human immunodeficiency virus and syphilis serologies were negative. A chest X-ray with posteroanterior and lateral views was normal. Analysis of cerebrospinal fluid showed an elevated IgG index (0.80) and oligoclonal bands detected by isoelectric focusing. Brain magnetic resonance imaging (MRI) revealed several T2 hyperintense round lesions in periventricular and juxtacortical white matter, the corpus callosum and left middle cerebellar peduncle (fig. 1). No lesion was enhanced with gadolinium. Two hypointense periventricular lesions were observed on T1-weighted spin echo sequences, corresponding to hyperintense plaques on T2 sequences. MRI of optical nerves was normal. Visual-evoked potentials demonstrated an increase in latency values of the P100 component, especially in the case of the right eye, an increase in the interocular difference of latencies and a decrease in the amplitude of the potentials in both eyes. Auditory and somatosensory-evoked potentials were normal.

Etanercept treatment was stopped and methylprednisolone hemisuccinate (1 g/day) was administered intravenously for 5 days followed by oral prednisolone. The eye pain improved after a week but the defects in the visual field persisted. Six months later, the patient showed acute left peripheral facial nerve palsy. Brain MRI at this time revealed a new non-enhancing T2 hypointense lesion in left pontine tegmentum. Pulsed intravenous methylpred-
nisolone therapy led to a recovery of the facial tone and symmetry in the following 2 weeks.

**Discussion**

The temporal association between the appearance of the symptoms of a demyelinating disease and the administration of etanercept, a drug known to alter the normal cytokine equilibrium, was striking. At the present time, the patient clearly fulfils the diagnostic criteria of relapsing-remitting MS proposed by McDonald et al. [19]. Other alternative diagnoses have been ruled out based on the clinical history of the patient and complementary examinations. Although during the course of 1 year the patient received methotrexate, a drug that has been related to demyelinating events, we do not consider there to be any relation with the present case, since such associations have only been reported after the administration of high doses accompanied by cranial radiotherapy [20]. Furthermore, this drug is the classical therapy for progressive MS. Neither celecoxib nor prednisone has been associated with an increased risk of demyelination.

To date, the Adverse Advents Reporting System of the FDA (AERS) has given notice of the following cases of demyelinating diseases related to TNF-α antagonists: 64 cases involving the use of infliximab (21 related to demyelination of the central nervous system), 17 cases involving etanercept and 3 cases related to the administration of adalimumab [14, 15]. Recently, 5 new cases have been published [12, 13, 16–18]. Although the incidence of demyelinating events with these drugs can be considered low (30 per million people per year), it is still much higher than the sporadic appearance of MS [21]. The time between the beginning of treatment and the appearance of clinical symptoms was 4 months in our case, which agrees with the reports of the Lenercept group concerning the time to the first relapses [9] and with the analysis of a series of cases extracted from the AERS database by Mohan et al. [10]. According to the same data, optical neuritis is the second most frequent manifestation after paresthesias.

It is known that TNF-α favors the induction of a peripheral inflammatory response and facilitates the initial phases of the autoimmune response, including the entrance of activated leukocytes into the central nervous system [22]. TNF-α antagonists prevent the development and lower the severity of experimental aller-
gic encephalomyelitis when applied in early stages [6, 7] but also restrict the immune response, preventing the generation of autoimmune lymphocytes and encouraging their apoptosis [23]. High levels of TNF-α accelerate the beginning of demyelinating lesions but ensure the efficient inactivation of any autoimmune-type T cell response, while low levels of TNF-α delay the onset of demyelinating lesions but favor the response of antimyelin T cells. From the above, it can be concluded that both the overproduction of TNF-α and its excessive blocking can give rise to an immune imbalance that will favor autoimmune processes, which may eventually lead to demyelination [10], as in the case we present. Nevertheless, we cannot discount any association between both autoimmune disorders, psoriasis and MS. Indeed, many studies have demonstrated the frequent coexistence of both diseases and a family connection [24, 25]. In our case, the characteristics of certain periventricular lesions in the initial MRI (like black holes) strongly suggest that etanercept encouraged the clinical expression of an already existing infraclinical disease.

In conclusion, we have reported a case of MS occurring in a patient few months after receiving treatment with etanercept. TNF-α and its soluble receptors form a complex system that controls the immune response, encouraging the initial phases of the immune-inflammatory process and at the same time regulating the magnitude of the autoimmune response. We are therefore more inclined to ascribe an exacerbating role to TNF-α inhibitors in the demyelinating disease rather than a direct causal role.

Considering the results of using TNF-α antagonists in MS patients and the number of cases of demyelinating events associated with their use, we advise caution, avoiding the use of these drugs in patients with personal history of demyelinating disease. Moreover, evaluation of neurologic symptoms and signs should be included in follow-up examinations during the treatment with these drugs. If any of these manifestations appear, it would be most prudent to discontinue until a demyelinating origin can be discarded.

References