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Dr. Villeneuve, *et al* reply

To the Editor:

We thank Dr. Roos and colleagues for their comments about our case report of infliximab-induced pneumonitis[1]. As they mentioned, there are indeed some differences regarding our case and the ones they have reported, but this may highlight the different types of interstitial lung disease (ILD) that can be associated with infliximab therapy.

Ostor, *et al*[2] have reported 5 cases of infliximab-induced ILD, 4 of them with usual interstitial pneumonia (UIP) confirmed by pathology or high resolution chest tomography. We agree that, unlike those patients, our patient did not develop an accelerated form of UIP. As they have highlighted, our patient had no history of lung disease and no increased number of mast cells on bronchoalveolar lavage (BAL) that could be suggestive of UIP. But those findings are also true for the 6 other cases that have been reported, where infliximab seemed to have precipitated MTX-induced pneumonitis[3,4]. Indeed, the lymphocytosis found on the BAL and the reversal of symptoms with corticosteroid treatment and the withdrawal of infliximab are more suggestive of a drug-induced acute interstitial pneumonitis than a UIP. Those different presentations could be because infliximab may induce an accelerated form of UIP with poor prognosis in RA patients with preexisting ILD, or induce a more reversible form of drug-induced pneumonitis or of bronchiolitis obliterans organizing pneumonia (BOOP), similar to the fifth case reported by Roos, *et al*.

Our case also differs in that aspergillus was isolated on the BAL. But as we stated, after discussion with the microbiologist and the pulmonologist, it was considered to be a colonizing organism because it was found in only half the samples and the aspergillus antigen detection assay was negative. In fact, the patient did not improve with caspofungin therapy and only started to improve when he was treated with high-dose corticosteroids. Itraconazole was administered as a prophylaxis with the goal of preventing aspergillus reactivation while the patient was immunosuppressed with the high-dose corticosteroids. With the growing number of infliximab-induced ILD, we are able to better appreciate this rare but severe complication of TNF-α antagonist therapy. Infliximab seems to be able to induce different types of ILD ranging from BOOP to an accelerated form of UIP. Patients with preexisting lung disease seem to have a much worse prognosis and they should be informed about the risk of ILD before they receive infliximab therapy. This could also be true for other anti-TNF-α agents, but there is insufficient evidence for this at the moment.

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Adalimumab-Associated Multiple Sclerosis

To the Editor:

Several cases of demyelinating diseases have already been reported during the course of tumor necrosis factor-α (TNF-α) antagonists. We describe a case of multiple sclerosis (MS) where onset was associated with adalimumab.

A 32-year-old woman with rheumatoid arthritis (RA), who had unsuccessfully been taking methotrexate for 16 months, started taking adalimumab in April 2003 (40 mg/2 weeks). In March 2005, she reported an acute loss of vision with pain in her left eye. A retrobulbar optic neuritis was diagnosed. Adalimumab was discontinued and a 3-day course of high-dose methylprednisolone started. Her visual acuteness improved but an afferent papillary defect remained in her left eye. Magnetic resonance imaging (MRI) demonstrated multiple lesions in the white matter with high signal intensities (T2-weighted images) and enhancement after gadolinium (T1-weighted images) in the right and left semi-oval centers. Three months later, the MRI showed new gadolinium enhancing lesions leading to the diagnosis of MS according to the revised McDonald criteria[1].

The temporal relationship between adalimumab and MS and the partial improvement of optic neuritis after its discontinuation raise the question of the role of adalimumab. So far, only 2 cases of optic neuritis had been published with adalimumab, one with isolated optic neuritis and one with numerous central nervous system (CNS) plaques of various ages and a painful retrobulbar optic neuritis[2]. Four additional cases of CNS demyelination have been identified during the adalimumab clinical development program. One patient presented with optic neuritis and the other 3 with paresthesia. One of them had a prior diagnosis of probable MS[3].

A link between TNF-α antagonists and a demyelinating disease is suggested by several studies. Based on the TNF-α overproduction in serum and cerebrospinal fluid of patients with MS[4] and the effect of TNF-α antagonists in animal models[5], a double-blind, placebo-controlled trial in MS with lenercept (TNF-α antagonist close to etanercept) was conducted. Unfortunately, this led to a shortening of time to flare, and a worsening of the neurological condition[6]. Similar outcomes have also been observed in an open-label trial with a monoclonal anti-TNF antibody in 2 patients with rapidly progressive MS[7].

These studies suggest that TNF-α antagonists may potentially initiate or unmask an underlying demyelinating disease. New onset, flare, or worsening of demyelinating diseases including MS have been associated with the 2 other marketed TNF-α antagonists (17 with etanercept and 2 with

infliximab)[8]. An update through August 2002 from the US Food and Drug Administration's AERS database has also reported several cases of demyelination associated with infliximab, but detailed information about these cases is not published[3]. In the French adverse event reporting system database, 4 demyelinating disorders (worsening 1, new onset 3) have been reported during treatment with infliximab over 4 years and etanercept over 5 years, respectively. However, all these data must be tempered by cases of demyelinating diseases recently reported in patients with RA who were not receiving any TNF-α antagonists[9].

Like other TNF-α antagonists, adalimumab must be stopped if a neurological event occurs and should be avoided in patients with preexisting or suspected demyelinating diseases.

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Dr. Toussirot replies

To the Editor:

Bensouda-Grimaldi, *et al* reported an additional case of demyelinating disease occurring in a patient receiving adalimumab for rheumatoid arthritis (RA). Since the beginning of the use of anti-TNF-α therapy, a limited number of neurological events have been described in patients receiving these agents for RA or other inflammatory conditions. These events included exacerbation of preexisting multiple sclerosis (MS), new onset MS, miscellaneous neurological symptoms (including optic neuritis, dysesthesia, paresthesia, motor deficits, or mental status changes)[1]. The relationship between the development of these events and anti-TNF-α therapy is still debated. The 3 available TNF-α antagonists have been associated with these neurological symptoms, most cases with etanercept. This apparent preferential association is unclear: in MS clinical studies, both infliximab, a monoclonal antibody, and lenercept, a soluble p55 TNF receptor fusion protein, have been associated with increased disease activity. TNF-α probably plays a dual role for white matter lesions in MS. Indeed, animal models of MS provided evidence that TNF-α may exacerbate or, conversely, protect the central nervous system during the development of demyelinating disease: TNF-α antagonists prevent and ameliorate experimental allergic encephalomyelitis (EAE) while in TNF-α null mice, they exacerbate EAE.

The most convincing arguments for a neurological side effect induced by anti-TNF-α treatment were the temporal relation and the resolution on discontinuation. Conversely, there are some factors arguing against a direct role for anti-TNF-α: these cases were reported with a low incidence, below the natural incidence of MS in the general population, and they may represent coincidental events. It has also been speculated that these neurological syndromes may be a clinical manifestation of another autoimmune disease occurring in a patient with a propensity to develop MS due to common genetic background, suggesting that anti-TNF-α treatment unmasks the demyelinating disease. Indeed, MS has been associated with various autoimmune diseases, including RA[2,3]. It should also be interesting to carefully examine whether patients with a disease that is not commonly associated with MS (such as psoriasis, psoriatic arthritis, or Crohn's disease) could develop MS or MS-like disease during anti-TNF-α administration. Curiously, there is no report of demyelinating disease in patients with ankylosing spondylitis receiving anti-TNF-α therapy, and this disease has been associated with MS.

Finally, the neurological potential effects of TNF-α antagonists are not limited to the central nervous system. Indeed, some cases of peripheral neuropathy with varying degrees of motor and sensory involvement were recently reported in RA patients receiving infliximab[4].

All these data highlight the need for careful clinical evaluation, including neurological examination, before starting anti-TNF-α treatment. Patients with unexplained central nervous system involvement or signs of peripheral neuropathy, with past history or familial history of demyelinating disease, should not receive this treatment before complete neurological evaluation. Finally, reporting of all new cases of demyelinating or neurological disease during the course of anti-TNF-α treatment is required to better understand the potential neurological effects of TNF-α antagonists in RA, but also in all other diseases receiving this effective class of drugs.

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