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LETTERS

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Paraplegia in a patient receiving anti–tumor necrosis factor therapy for rheumatoid arthritis: comment on the article by Mohan et al

To the Editor:

Recent reports have indicated that anti–tumor necrosis factor (TNF) therapy may induce or increase demyelination in patients with rheumatoid arthritis (RA) and multiple sclerosis (MS), respectively (1,2). Anti-TNF therapy is currently successfully administered to an increasing number of patients with RA. Although the results of TNF blockade are encouraging, we are still learning about the side effects of this treatment. We now describe the development of transverse myelitis in a patient with RA shortly after etanercept therapy was initiated.

The patient, a 45-year-old woman with IgM rheumatoid factor–positive, erosive RA, was admitted because of pain in the lower thoracic spine, numbness in the left upper leg, paresthesias in the left lower leg, and a slight weakness in the left leg. For 1 year she had experienced painful paresthesias in both legs. Repeated neurologic evaluation revealed no abnormalities. At the time of admission, the patient was receiving prednisone (2.5 mg daily). Treatment of her RA using several disease-modifying antirheumatic drugs had failed in the past. Etanercept was started at a dosage of 25 mg twice a week, subcutaneously. Nine days thereafter, the patient developed an acute total sensory loss below the T10 level, a flaccid paraplegia, fecal incontinence, and urinary retention. She developed fever (39°C) and described a "belt" of pain around her trunk at the T10 level.

On examination, there were no signs of a focal infection. Blood test results included an erythrocyte sedimentation rate of 99 mm/hour, 8,500 white blood cells, positive antinuclear antibody (ANA) (it had previously been negative), negative lupus anticoagulant, positive anticardiolipin antibodies, and a C4 level of 91 mg/liter (normal range 150–400 mg/liter). Magnetic resonance images (MRI) demonstrated hyperdense signals at various levels of the spinal cord and diffuse cord swelling (Figure 1). Gadolinium enhancement of these densities suggested inflammatory sites. No MRI abnormalities in the brain were observed. Cerebrospinal fluid (CSF) analysis showed a low glucose level as compared with the glucose serum level (1.5 mmoles/liter and 6 mmoles/liter, respectively), an increased total protein level (2.65 gm/liter), and pleocytosis (337 cells/μl) that initially was mainly polynuclear, but 2 days later was predominantly mononuclear. The IgG index was slightly increased (0.65 [normal 0.20–0.60]), without oligoclonal band.

The clinical picture as well as the CSF and MRI results demonstrated the development of transverse myelitis. The differential diagnosis of transverse myelitis included infection, RA, secondary systemic lupus erythematosus (SLE), and side effects of anti-TNF (3,4). Transverse myelitis as a manifestation of MS was unlikely, because the CSF results did not correspond with characteristics observed in MS patients, and MRI abnormalities of the brain were lacking. Infection was ruled out by extensive examination. Transverse myelitis may have been attributable to RA activity, but this has only rarely been reported in the absence of MRI abnormalities of the spine (3). More often, transverse myelitis occurs in (secondary) SLE (4). In such cases, the CSF is characterized by pleocytosis, increased protein and, decreased glucose. In addition, MRI generally shows cord swelling and increased signal intensity, corresponding to the findings in our patient. Nevertheless, no other signs or symptoms of SLE were observed. In case studies, successful treatment with intravenous high-dose methylprednisolone plus cyclophosphamide, preferably administered as early as possible, has been reported (4).

Importantly, Mohan et al (1) reported that anti-TNF therapy induced/facilitated demyelination in patients with inflammatory arthritides, followed by complete or partial resolution after discontinuation of the therapy. Furthermore, anti-TNF therapy may induce ANA and antibodies to double-

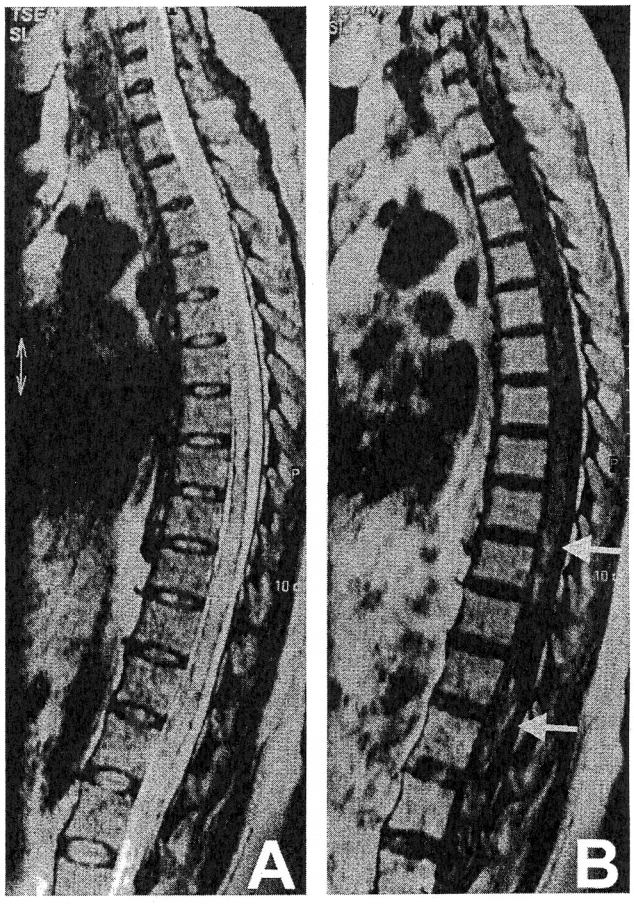

Figure 1. Sagittal magnetic resonance image (MRI) of the spinal cord, showing diffuse cord swelling and areas of increased signal intensity **A,** T2-weighted. **B,** T1-weighted. Gadolinium enhancement in several areas **(arrows)** suggests inflammatory sites.

stranded DNA (anti-dsDNA) (5). So far, the presence of these antibodies seems generally not to be related to the development of severe SLE. Interestingly, in our patient transverse myelitis was accompanied by recently developed ANA (but not anti-dsDNA), without any other SLE symptoms. Nevertheless, we think that in this particular patient, progression of neurologic symptoms during etanercept treatment is suggestive for a causative role of etanercept. It may have facilitated the development of transverse myelitis, which had already been initiated by autoimmune disease activity, and was therefore discontinued. Of course, a positive rechallenge would provide evidence for the role of etanercept in the development of transverse myelitis, but we considered that to be unethical.

Besides having etanercept discontinued, the patient was treated monthly with intravenous dexamethasone pulse therapy and intravenous cyclophosphamide. After 3 months, a slight improvement in the motor function of the legs was observed. Sensibility was virtually unchanged. CSF abnormalities completely disappeared, and MRI abnormalities improved significantly. Learning from this experience, we recommend being very careful when initiating etanercept in patients who have preexisting neurologic symptoms, and to discontinue etanercept when an otherwise unexplained neurologic deficit develops or increases during treatment.

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Unproven hypothesis that leflunomide is better than methotrexate as measured by magnetic resonance imaging: comment on the article by Reece et al

To the Editor:

In their article comparing leflunomide and methotrexate for the treatment of rheumatoid arthritis (RA), as measured by dynamic enhanced magnetic resonance imaging (MRI), Reece et al (1) conclude that in patients with RA, improvement in synovial inflammation, as measured by the initial rate of enhancement (IRE), was significantly better with leflunomide than with methotrexate over 4 months of therapy. We wonder whether this statement holds true when several methodologic and rational limitations are considered.

First, this study included a very small number of patients in each treatment arm (18 patients in the leflunomide group, 21 in the methotrexate group). The only joint investigated was the knee joint. Other joints commonly involved in RA, such as finger joints and metatarsophalangeal joints, were not investigated. Second, no primary outcome variable of the study was predefined. The sample size needed to demonstrate a statistically significant difference between leflunomide and methotrexate was not calculated. The number of patients per treatment group needed to demonstrate a difference at a defined significance level was not prespecified. In addition, improvement in clinical signs and symptoms was comparable for both active treatments, and the maximal signal intensity enhancement showed a similar reduction of inflammation with both leflunomide and methotrexate.

The only significant difference reported was the IRE 4 months after treatment. For several reasons, these data do not seem to be reliable. First, no statistical correction for multiple testing (Bonferroni correction) was performed. Therefore, the difference may be attributable to chance. Most importantly, the plot of the average change in IRE in response to 4 months of therapy with leflunomide or methotrexate (for review, see ref. 1, Figure 4) shows a very large overlap between the 2 treatment groups. Finally, the explanation given by the authors for the difference seems not to be rational. They suggested that "the early treatment effect observed in patients receiving leflunomide therapy may be accounted for by the loading-dose regimen." In fact, the loading-dose regimen is needed to reach therapeutic serum levels of leflunomide and is given over 3 days only. It is not comprehensible why these 3-day doses may affect the outcome after 4 months, when improvement in all other clinical signs and symptoms was not different between leflunomide and methotrexate. Moreover, 2 controlled trials (involving 482 and 235 patients, respectively) comparing leflunomide and methotrexate showed no difference between the 2 drugs in radiologic progression (2,3). An even larger study (with 999 subjects) also demonstrated that an equivalent degree of radiologic progression occurred during the first year of treatment with leflunomide or methotrexate, but after 2 years, progression was significantly less in patients receiving methotrexate (4).

In conclusion, because of methodologic and rational limitations, the conclusion of Reece et al (1), that improvement in synovial inflammation as measured by MRI is significantly better with leflunomide than with methotrexate, is