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.

C. J. van der Laken, MD, PhD
W. F. Lems, MD, PhD
Slotervaart Hospital and Vrije Universiteit Medical Center
R. M. van Soesbergen, MD, PhD
J. J. van der Sande, MD, PhD
Slotervaart Hospital
B. A. C. Dijkmans, MD, PhD
Slotervaart Hospital and Vrije Universiteit Medical Center
Amsterdam, The Netherlands

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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

unproven. We doubt that dynamic enhanced MRI is a valid method to discriminate between 2 different treatments in RA. Future studies with an appropriate number of patients, a predefined sample size, and targeting of the most frequently involved finger joints in RA are needed to provide a definite answer to the question of the validity of using dynamic enhanced MRI to detect inflammatory changes in patients with active RA in response to treatment.

Sebastian Schnarr, MD
Jan L. Hülsemann, MD
Henning K. Zeidler, MD, PhD
Medizinische Hochschule Hannover
Hannover, Germany

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Reply

To the Editor:

Schnarr et al make a number of comments about our recent MRI study of leflunomide and methotrexate. Their comments largely relate to conventional approaches to comparing active therapies and may have misinterpreted the point of our article, which was not to demonstrate a significant difference between 2 groups, but to illustrate the power of a new imaging technology that is 100% reproducible.

Schnarr et al mention the small number of patients in each treatment arm. This aspect was central to the study, which demonstrated that by using these very precise techniques (directly imaging the site of pathology), there was an ability to precisely show differences in synovial inflammation. Although the primary outcome variable was not included in the article, it was predefined, and the sample size was calculated on that basis. Of the 2 predefined MRI measures, the IRE was significantly different for leflunomide, and a trend was observed for the maximal rate of enhancement. The results did not call for any statistical correction.

The authors also mention that there was a large overlap between the groups; this is totally expected, because the response clearly is neither exclusive nor diagnostic. Our explanation—that the reduction in synovitis was attributable to the loading dose of leflunomide—remains the most plausible and is supported by the fact that methotrexate has a very slow effect on the synovium, as demonstrated by other imaging studies (1). The fact that large studies have not shown differences between the 2 drugs over prolonged periods of time is quite a separate issue, dependent on factors such as maintenance therapy and the long-term effects of treatment on bony destruction. In particular, the lack of radiologic difference cannot be used as supporting evidence either way, because of the insensitivity of this method of assessment.

We did not suggest in our report that leflunomide is better than methotrexate. Instead, we noted that at the recommended doses, leflunomide reduced synovitis earlier, and that this reduction could be detected by the imaging methods used. We suspect that there would be a correlation between MRI and radiologic erosions, but the study period was too short for detection by the insensitive radiology method (1,2).

Whereas most of the comments by Schnarr et al remain open to debate, one of their statements is clearly no longer true; namely, that MRI is not validated. Previous data have shown a close correlation between histology and MRI findings, both globally and specifically at the site of biopsy (3). Furthermore, there are close correlations between magnetic resonance imaging for synovitis, and ultrasound. Overall, the comments by Schnarr and colleagues are appropriate to studies of conventional drugs but fail to appreciate the sophistication of the new imaging methods and the fact that the aim of this study was to assess a mode of action rather than to evaluate equivalence or superiority of one drug over the other.

Paul Emery, MD
Richard J. Reece, MD
Maarten C. Kraan, MD, PhD
P. J. O'Connor, MD
Aleksandra Radjenovic, MD
Douglas J. Veale, MD
John P. Ridgway, PhD
W. W. Gibbon, MD
Ferdinand C. Breedveld, MD, PhD
Paul P. Tak, MD, PhD
University of Leeds
Leeds, UK

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