Azathioprine or Methotrexate Maintenance for ANCA-Associated Vasculitis

To the Editor: In their prospective, open-label trial, Pagnoux et al. (Dec. 25 issue) compared azathioprine (at a dose of 2 mg per kilogram of body weight per day) with methotrexate (at a dose of 0.3 μg per kilogram per week, progressively increased to 25 mg per week) as maintenance therapy for antineutrophil cytoplasmic antibody (ANCA)–associated vasculitides (Wegener’s granulomatosis and microscopic polyangiitis). They provide evidence-based data about both the efficacy and the safety profile of these drugs. Like the authors, we were surprised by the tendency toward a better safety profile for azathioprine (a trend that did not support their initial hypothesis) in spite of concomitant treatment in this group with trimethoprim–sulfamethoxazole, which was associated with similar adverse events. Since methotrexate-related adverse events are increased if renal function is impaired, we wish that renal function had been evaluated more precisely in both groups by calculation of the estimated glomerular filtration rate (GFR) instead of the creatinine level, especially since there was a significant sex-ratio imbalance between the two groups. Creatinine levels were similar between the groups, but the estimated GFR may have been lower in the methotrexate group (in which 60% of the patients were women). Therefore, we cannot rule out the possibility that more impaired renal function contributed to the lack of benefit and to the absence of a decrease in toxic effects in the methotrexate group as compared with the azathioprine group.

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To the Editor: We learned from the French Vasculitis Study Group that neither methotrexate nor azathioprine maintained remission any more effectively than the other. Above and beyond this primary message, there is another important clinical message that received no comment in the published article.

In particular, a major challenge in the care of
patients with systemic vasculitis is the ability to determine when the inflammatory vascular process has been brought under control, at which time the dose of medication may be tapered and the risk of drug-associated toxicity minimized. There is substantial debate as to whether serial measurements of ANCA levels may function as a sensitive measure of vasculitis disease activity and as a predictor of remission. In the study by Pagnoux et al., nearly 91% of the patients with Wegener’s granulomatosis and microscopic polyangiitis were ANCA-positive at diagnosis by means of immunofluorescence or enzyme-linked immunosorbent assay before induction therapy. Notably, the ANCA-positive proportion of patients decreased by half, to 43%, at randomization, when either methotrexate or azathioprine treatment was assigned. Perhaps other patients in the study had diminished ANCA levels (or titers) but did not undergo seroconversion?

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THE AUTHORS REPLY: Jourde et al. ask whether patients in the methotrexate group had lower GFRs, which might explain our finding that methotrexate was not safer than azathioprine, especially because of the slight between-group sex imbalance. We reported only creatinine levels, as prespecified in the study protocol, but we also looked at the estimated GFR, which indeed takes sex into account. With the use of the equations from the Modification of Diet in Renal Disease (MDRD) study, the mean estimated GFR among patients in the methotrexate group was 57.2±36.2 ml per minute per 1.73 m² of body-surface area at diagnosis and 59.5±23.9 ml per minute per 1.73 m² at randomization (P=0.45), as compared with 61.9±31.0 and 61.8±22.4 ml per minute per 1.73 m², respectively, among patients in the azathioprine group (P=0.60). Estimation with the use of the Cockcroft–Gault formula yielded similar results (57.7±38.0 ml per minute per 1.73 m² at diagnosis and 62.9±31.7 ml per minute per 1.73 m² at randomization in the methotrexate group [P=0.78] vs. 59.4±28.8 and 64.9±27.1 ml per minute per 1.73 m², respectively, in the azathioprine group [P=0.74]). Hence, methotrexate toxicity cannot be explained by higher creatinine levels or by a lower estimated GFR. However, we think, as we state in the article, that methotrexate should be used prudently or even avoided when renal function is severely impaired.

Gelber raises the interesting but still controversial issue of whether ANCA titers parallel disease activity and thus could help in the evaluation of treatment response. Unfortunately, our study did not generate data allowing an extensive examination of this possibility. ANCA testing was not centralized, and only 75.7% of the ANCA-positive patients at diagnosis had been retested when maintenance therapy was initiated. However, 40.5% of the persistently ANCA-positive patients had a relapse during the study period, as compared with 31.5% of those who became ANCA-negative (P=0.97) and 36.4% of those who had been ANCA-negative at diagnosis (P=0.92). The results of several previous studies have indicated that neither ANCA status nor titers could be used to confidently predict the risk of relapse, at least for ANCA directed against proteinase 3, although a few studies suggested the contrary.

Thus, at present, we remain thoroughly convinced that induction must not be aimed at achieving ANCA negativity or decreasing ANCA titers and that therapy should not be adjusted on the basis of their measurement.

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