the remaining 8 pAPS patients with increased serum NSE levels (representing 45% of the pAPS patients) showed multiple small ischemic lesions in the cerebral white substance, a sign of cerebral vasculopathy. Moreover, among the 10 (50%) pAPS patients with normal serum NSE values, only one (10%) showed signs of cerebral vasculopathy; the remainder (90%) had a completely normal MRI.

First of all, our study shows that cerebral vasculitis is particularly frequent in pAPS, as the MRI images demonstrated, even in the absence of clinical neurological manifestations. This evidence emphasises the importance of monitoring pAPS patients, including those who appear asymptomatic, for possible vascular involvement of the brain. Furthermore, our study shows that the serum NSE level could represent a useful screening parameter for identifying pAPS patients at risk of vascular brain disorders, thus possibly avoiding more invasive and expensive examinations. In conclusion, a rise in serum NSE levels seems to be an early peripheral marker of cerebral vasculopathy and could be very useful in the assessment of pAPS patients.

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Long-term efficacy and toxicity of a combination therapy in rheumatoid arthritis patients

Sir,

We read with interest the paper by Pascalis *et al.* published in a recent issue of this journal (1), in which they treated refractory rheumatoid arthritis (RA) patients with a combination therapy consisting of cyclosporine A (CsA), methotrexate (MTX) and steroids. They concluded that this treatment regimen demonstrated extremely good results in terms of efficacy, tolerability and safety after 96 months of treatment. We would like to make some comments concerning the above study.

Firstly, the concept of combination therapy usually means the use of 2 or more disease modifying antirheumatic drugs (DMARDs) at the same time together with other antirheumatic drugs. In the paper reported by Pascalis such a combination was not used for the following reasons: (a) the main drug given by the authors during the whole period of treatment was CsA, even when it was given on alternative days; (b) at the beginning MTX was administered every week for the first 1 or 2 months, then every 2 weeks, and thereafter every month, for a total period of 12-18 months, after which it was discontinued. For the remaining 6 or 7 years the patients continued to receive CsA.

Secondly, it would be somewhat difficult for a general practitioner or a rheumatologist in private practice to follow the authors' protocol because it is complicated: (a) at entry CsA was administered at a dose of 5 mg/kg/day and then was stopped for 2 or 3 days per week; (b) the MTX dose usually ranged between 0.1 - 0.3 mg/kg/week, administered per os or intramuscularly. In the present study MTX was given intravenously in relatively high doses (15 mg/week). However, this treatment schedule was followed only for a few weeks, after which MTX was administered every 2 weeks and then monthly; (c) steroids were given in a dose ranging between 80 - 130 mg/week/patient, which reflects a daily dose of 10 - 20 mg per patient.

Thirdly, the duration of treatment, which was 96 months or 8 years, should also be taken into consideration. It is amazing that the authors captured the idea of using CsA in combination therapy with MTX and steroids at the beginning of 1989, when CsA was administered as monotherapy in refractory RA patients (2). Nevertheless, their impressive results, presented in Tables II and III, which showed that almost all of the treated patients demonstrated beneficial effects after 2 or 4 years of therapy, have not been published in the meantime. To date, except for the present study, there are only a few published reports concerning the efficacy and safety of CsA alone or in combination therapy for a period of less than 4 years (3-7).

Finally, RA patients are usually treated with one DMARD until complete remission is reached. Unfortunately, complete remission occurs only in a very small number of patients. Furthermore patients are seldom treated for long periods with the same drug or with a combination therapy. The most common reasons for treatment withdrawal are insufficient suppression of disease activity (inefficacy) and/or adverse drug reactions. In the study by Pascalis, drug inefficacy, disease flare and/or severe side effects were not reported, and the combination treatment proposed by the authors has probably solved the problem of treating RA patients.

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