Safety of low dose methotrexate in elderly patients with rheumatoid arthritis

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Abstract
Weekly low dose methotrexate is an established treatment for rheumatoid arthritis, but its use in elderly people has not been adequately examined. The aim of this study was to evaluate its safety in elderly patients with rheumatoid arthritis. A retrospective review of the clinical records of rheumatoid arthritis patients over the age of 65 attending a rheumatology unit was conducted. Eligible patients were followed for at least two years and treated with methotrexate in a dose of 7.5 mg/week while being maintained on concurrent treatment. Thirty-three patients were studied. Their mean age was 78.8 years; 32 were female and one was male. Treatment was discontinued in four patients, two because of raised serum liver enzymes and two because of gastrointestinal irritation. No serious adverse events were reported. After two years, haemoglobin levels increased from a mean (SD) of 12.4 (1.3) g/dl to 13.0 (1.1) g/dl (r = 0.226, p < 0.005). The white blood count was significantly reduced from 7.9 (1.8) × 10⁹/l to 6.8 (1.7) × 10⁹/l (r = 0.184, p < 0.05). No episodes of neutropenia or agranulocytosis were observed. There was a non-significant decrease in platelet count. The erythrocyte sedimentation rate decreased from 56.8 (30.8) to 35.2 (24.6) mm/h (r = 0.246, p < 0.01). In conclusion, low methotrexate treatment in elderly patients appears to be safe. Routine determination of serum liver enzymes and renal function may reduce individual risk.

Keywords: methotrexate; elderly; safety

The prevalence of rheumatoid arthritis among people older than 65 years is high, and 30–40% of patients treated with this disease in rheumatology centres are over 60 years of age. Methotrexate at a low weekly dose of 7.5 to 20 mg has become an accepted and widely used disease modifying antirheumatic drug for rheumatoid arthritis. While the safety profile of methotrexate under these circumstances is generally good, several studies have shown greater toxicity in elderly patients. It is assumed that reduced renal function may be in part responsible. Nevertheless, the safety of this treatment in elderly patients has not been established.

Our aim in this study was to evaluate the safety of low dose methotrexate in a cohort of elderly patients with rheumatoid arthritis.
(131) × 10^9/l to 276 (80) × 10^9/l, but this was not statistically significant. The ESR decreased over the two years from 56.8 (30.8) to 35.2 (24.6) mm/h (r = 0.246, p < 0.01).

Discussion

The prevalence of rheumatoid arthritis among elderly patients is high.1 2 3 Larger clinical studies have shown that low dose methotrexate is an effective and safe treatment for patients with rheumatoid arthritis. Major toxicity is uncommon, while gastrointestinal upset, oral ulceration, transient liver function abnormalities, and neutropenia—though encountered from time to time—are rarely sufficient reasons to discontinue the treatment.4 However, concern has been raised over the safety of this treatment in elderly patients.5 Our present study provides safety data over a two year period in a cohort of 33 elderly patients taking low dose methotrexate. Our results support the view that methotrexate is a safe and useful treatment option in the elderly.

Several large studies have shown that low dose oral pulse methotrexate is an effective and safe treatment for patients with rheumatoid arthritis. Major toxicity is uncommon, while gastrointestinal upset, oral ulceration, transient liver function abnormalities, and neutropenia—though encountered from time to time—are rarely sufficient reasons to discontinue the treatment.6 However, most data on the safety profile of methotrexate are limited to younger patients. As only a few elderly patients were included in those studies, data on the safety of methotrexate in the growing number of elderly patients are lacking.7 Felson et al, on behalf of the rheumatoid arthritis clinical trial archive group, attempted to address this issue by pooling data from 11 clinical trials. Of the 496 patients included, 90 were over the age of 65 years. The major determinant of toxicity in their analysis was renal function and not age. A possible limitation of their results is that the patients represented in the trials appeared to be a specially healthy group of elderly people.

Bologna et al assessed the influence of age on the efficacy and toxicity of methotrexate in rheumatoid arthritis.8 Four hundred and sixty nine patients were classified according to their age of onset of methotrexate treatment into those who were younger than 65 years (n = 416) and older than 65 years (n = 53). The frequency and type of side effects were similar. They concluded that age at initiation of methotrexate treatment probably did not influence its efficacy or toxicity in rheumatoid arthritis.

Our cohort represents an unselected group of elderly patients with rheumatoid arthritis treated for two years with low dose methotrexate. An increase in liver enzymes to more than twice the upper limit of normal was found in two patients (six months and one year after the start of treatment). In both of these patients, immediate interruption of treatment caused a return of liver function to normal. In two other patients, the drug was discontinued because of gastrointestinal disturbances. Both these individuals were being treated simultaneously with NSAIDs, which may have caused similar complaints. No neutropenia was reported, and there was no clinical or radiological evidence of inflammatory pneumonitis in any of the patients. Furthermore, the slight decrease in platelet count, the reduction in ESR, and the rise in haemoglobin appear to reflect an improvement in general clinical state.

The methotrexate dose in this study was 7.5 mg/week, and with this treatment, marked clinical improvement was noted in most of the patients, although the efficacy of treatment was not evaluated directly in this study. As the safety of methotrexate in elderly people has not yet been established, we employed relatively low doses of the drug in our elderly population, although a higher dose is approved for the treatment of rheumatoid arthritis.

The results of our study are limited because of its retrospective nature and the relatively small sample size. We lacked a control group, and more data on clinical efficacy would have been complementary. Unfortunately, prospective data collection was not done. The main goal of this study was to underscore the safety profile of low methotrexate treatment in elderly, as the efficacy of this treatment has already been established. Larger cohorts of elderly patients treated over a long period of time with higher doses of methotrexate are needed to finally establish the safety of this drug.

We conclude that low dose methotrexate treatment in elderly patients appears safe. Simple measures such as follow up of liver and renal function tests and full blood count may eliminate those individuals at risk of unwanted effects.


