Infirmary, London Road, Derby DE7 6GW, UK
Accepted 17 May 2005

Correspondence to: C. Deighton.
E-mail: chris.deighton@derbyhospitals.nhs.uk

E-mail: chris.deighton@derbyhospitals.nhs.uk
Accepted 17 May 2005

NYU Hospital for Joint Diseases, New York, NY, USA
Accepted 19 October 2005

Correspondence to: Yusuf.yazici@nyumc.org

Letters to the Editor

361

Rheumatology 2006;45:361
doi:10.1093/rheumatology/kei199
Advance Access publication 6 December 2005

Methotrexate induced pancytopenia is rare and concern for it should not limit its use

SIR, I read with interest the article by Lim et al. [1] and feel the need to share our experience of the safety of methotrexate (MTX) in rheumatoid arthritis (RA) patients. The authors report on 25 patients, of whom 19 had RA, who developed pancytopenia while taking MTX. They conclude that ‘MTX-induced pancytopenia is more common than expected and is probably under-reported’.

This conclusion raises some concerns. First, the reference the authors give for the prevalence of haematological toxicity of MTX is from 1985 [2]. Surely the kind of patients using MTX and the timing of MTX use have changed over the last 20 years and, along with these, the occurrence of adverse events. Secondly, they fail to give the total number of MTX-treated patients seen between 1999 and 2004 in the centre that these 25 patients came from. They give estimates of RA prevalence in their area and an assumption about other patients with other diagnoses using MTX, but the denominator is not given. It is not clear what is used as a comparator when they state that this problem is under-reported. Thirdly, in their discussion they state that 15/25 patients were over the age of 75 and that the median age was 76. I would suggest that the main reason for the cases of pancytopenia may be the increased age of their cohort and/or the multiple other medications they were on concurrently.

We have published our experience in RA patients using MTX from two university centres [3, 4]. From Nashville, among the 248 MTX-treated RA patients followed from 1990 to 2004, no patient developed pancytopenia and only seven cases of a white blood cell (WBC) count below 3.0 × 10^9/l were seen, with an incidence of 0.7 per 100 person-years. The mean age of this cohort was 59; 34/248 (14%) were older than 75. The New York cohort was reviewed from 1985 to 1999, and only three patients had WBC below 3.0 × 10^9/l, the lowest being 2.3 × 10^9/l. Their median age was 59, and 18/182 patients were older than 75 (10%).

MTX is one of the safest disease-modifying antirheumatic drugs, if not the safest. We always need to be vigilant about rare adverse events, but we must also keep in mind the benefits of this therapy and not hinder its use because of adverse events that might possibly have alternative explanations.

The author has declared no conflicts of interest.


Rheumatology 2006;45:361-362
doi:10.1093/rheumatology/kei200
Advance Access publication 6 December 2005

Methotrexate induced neutropenia associated with coprescription of penicillins: serious and under-reported?

SIR, We read Lim et al.’s concise report on methotrexate-induced pancytopenia with great interest. Among the predisposing factors they listed were old age, poor nutrition, hypoalbuminaemia, stomatitis and renal impairment [1]. No mention was made of the risks associated with penicillin usage.

Penicillin has been shown to compete with the renal tubular secretion of methotrexate and hence its clearance. This was shown by Williams et al. [2] in vivo and in vitro in rhesus and cynomolgus monkeys. It works by inhibiting the cellular uptake of methotrexate and hence stimulating its efflux. The findings were backed up in Bloom et al.’s work [3] in four patients who received high-dose methotrexate. Reduced renal excretion of methotrexate was demonstrated when penicillins were coprescribed. A total of five cases of methotrexate-induced neutropenia in association with penicillin coprescription have been reported [4, 5]. In four of the cases, who had been treated with low-dose methotrexate, renal impairment was felt to be an associated risk factor. Three of these patients were elderly. Two of the four cases reported by Mayall et al. [5] had methotrexate levels measured, which in both cases were found to be in the toxic range. The other case was in a 16-year-old patient on high-dose methotrexate.

Of the cases described by Lim et al., we note that five had renal impairment (Patients 1, 13, 19, 20 and 23). Twenty-three out of 25 of the patients reported were over the age of 65. This included Patient 23, who was also on amoxicillin. Interestingly, nine of the patients (Patients 1, 4, 6, 8, 13, 18, 19, 23 and 24) presented with sepsis. Is there any information as to whether they had been treated with penicillin antibiotics before admission to hospital or during the aplastic episode? Mayall et al. [5] felt that patients who were renally impaired were more likely to have prolonged clearance of methotrexate when a penicillin was coprescribed. This, he noted, contributed to the deaths of three of the patients reported in his series. Herrick et al. [6], on the other hand, reported no significant evidence of methotrexate toxicity in 10 patients who were coprescribed flucloxacillin. However, they did not include elderly or renally impaired patients and concentrated on measuring methotrexate levels. It seems further work on a larger scale...