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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 yr 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 55; 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.

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Y. YAZICI
including renally impaired elderly patients is needed in order to elucidate whether we should all avoid the coprescribing of penicillins and methotrexate.

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N. SATHI, J. ACKAH, J. DAWSON

Department of Rheumatology, St Helens Hospital, Marshalls Cross Road, St Helens, Merseyside, UK, WA9 3DA

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Correspondence to: N. Sathi. Email: Nsathi@doctors.org.uk


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Disease-modifying anti-rheumatic drugs are only one of a number of potential causes of myelosuppression: a careful drug history is necessary to elucidate the cause of an adverse event

Sir, We read with interest the article by Lim et al. [1] concerning methotrexate (MTX)-induced pancytopenia, and present here three cases of drug-induced myelosuppression that illustrate that disease-modifying antirheumatic drugs (DMARDs) are not always to blame.

Case 1 was a 76-yr-old lady who was treated with MTX for her rheumatoid arthritis (RA). A routine blood test on 1 July 2004 showed that her haemoglobin (Hb) had fallen over 1 month from 11.1 g/dl to 8.4 g/dl, the white blood count (WBC) from 5.9 x 10^9/l (neutrophils 3.1 x 10^9/l) to 2.1 x 10^9/l (neutrophils 0.5 x 10^9/l) and platelets from 581 x 10^9/l to 310 x 10^9/l. The MTX was thought to be responsible. She was admitted to hospital, her medications were stopped and she was given folinic acid rescue. Her blood parameters improved.

At clinic review a drug history revealed that she had been taking MTX, folic acid and azapropazole without problem for over 10 yr, and ferrous sulphate for the past 6 months. Two months previously she had received intravenous fluocoxacin and benzylpenicillin, and had started lansoprazole. Haematological abnormalities are well recognized in these three drugs [2], and on balance it was felt that the lansoprazole was responsible. With much reservation the patient agreed to restart MTX, and regular haematological monitoring has been unremarkable since.

The second case was a 65-yr-old lady with longstanding RA, who had previously received to MTX (nausea and headaches), sulphasalazine (diarrhoea and vomiting), gold injections (rash) and penicillinamide (flu-like illness). In March 2003 she commenced etanercept with an excellent response. Later that year she was prescribed meloxicam.

On 19 April 2004 a routine blood test showed Hb 12.9 g/dl, WBC 3.0 x 10^9/l (neutrophils 0.9 x 10^9/l) and platelets 218 x 10^9/l, having previously been normal. Etanercept and meloxicam were stopped, but repeat blood counts over the next 10 days showed no improvement. At clinic review on 4 May, a careful history revealed that she had commenced aspirin 75 mg daily on 19 February following a transient ischaemic attack.

Aspirin was stopped and she was monitored closely. She developed oesophageal candidiasis, which was successfully treated with flucanazole. A bone marrow and trephine biopsy showed maturation arrest of neutrophil production, with no evidence of dysplasia. By August 2004 her blood count had returned to normal (WBC 4.4 x 10^9/l, neutrophils 2.4 x 10^9/l). Her RA flared so she was commenced on prednisolone 10 mg daily, prior to the commencement of adalimumab.

Haematological abnormalities are well recognized with aspirin [2], but are rare with etanercept: neutropenia is listed as occurring in between 1/1000 and 1/10 000 patients. To July 2004, the Committee on Safety of Medicines (CSM) had received 16 case reports of neutropenia with etanercept. Aspirin was the likely cause in this patient as the neutropenia occurred within a few weeks of commencing therapy.

Case 3 was a 65-yr-old lady with longstanding RA who had been taking azathioprine 150 mg daily for 3 yr, along with coproxamol. A routine blood test in May 1997 showed Hb 11.1 g/dl, WBC 1.6 x 10^9/l (neutrophils 1.2 x 10^9/l) and platelets 30 x 10^9/l. She had been feeling unwell with anorexia, dry mouth, sore throat, weight loss and dysphagia, and was pyrexial. She was admitted to hospital, where repeat blood tests showed Hb 9.0 g/dl, WBC 0.4 x 10^9/l (neutrophils 0.2 x 10^9/l), platelets 9 x 10^9/l, international normalized ratio 1.8, Activated Partial Thromboplastin ratio (APTR) 2.7, bilirubin 56 µmol/l (normal range 3–20), albumin 23 g/l (37–50), aspartate transaminase 117 IU/l (12–40) and alkaline phosphatase 195 IU/l (30–95).

Examination showed established rheumatoid arthritis, but no synovitis; temperature 38°C and a purpuric rash on the legs but no other localizing signs. Azathioprine was stopped and she was given supportive treatment and repeated transfusions. Blood cultures were consistently sterile, although she developed oropharyngeal candidiasis and a coliform urinary infection. Ultrasound of the abdomen confirmed hepatosplenomegaly.

She improved over 1 month and was discharged. A drug history revealed that prior to admission she had received a week’s triple therapy with clarithromycin, metronidazole and lansoprazole for eradication of Helicobacter pylori. The lansoprazole was thought to be the cause of her pancytopenia.

Four months later her RA started to flare, and at the patient’s insistence azathioprine was restarted. Eight years later she is still taking the drug without problem.

Myelosuppression is a recognized complication of DMARD therapy, and patients should be counselled and monitored according to BSR guidelines [3]. When an adverse drug reaction (ADR) occurs it is critical to elucidate which drug is responsible, and this should be reported to the CSM. It is easy to ascribe causality to the more ‘toxic’ drug, but adverse events occur more commonly with drugs that have been recently introduced [4, 5]. The diagnostic processes underlying causality assessments have been well described, and include consideration of the time to onset of ADR, differential causes, a process of elimination, and the recurrence of the event on rechallenge [6]. In clinical practice, rechallenge after an ADR is not always possible.

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