LETTERS

Methotrexate-induced lung injury in patients with rheumatoid arthritis occurs with peripheral blood lymphocyte count decrease

S Inokuma, H Kono, Y Kohno, K Hiramatsu, K Ito, K Shiratori, J Yamazaki, H Nakayama, H Shoda, Y Tanaka

Ann Rheum Dis 2006;**65**:1113–1114. doi: 10.1136/ard.2005.045211

Pulsed methotrexate (MTX) treatment, of which the standard dose for Japanese patients with rheumatoid arthritis (RA) approved by the National Health Insurance System is 2–8 mg/week, is still the standard regimen. However, life threatening adverse reactions to this treatment, including lung injury, remain to be elucidated in detail.

We treated 11 patients with RA who developed lung injury during MTX treatment. Their clinical and laboratory features were examined retrospectively, focusing mainly on the changes in peripheral blood lymphocyte count.

The 11 patients (three men, eight women) had a mean (SD) age of 69.8 (7.8) years. All the patients had taken non-steroidal anti-inflammatory drugs, and nine had received steroids with a mean (SD) prednisolone dose of 6.6 (2.9) mg/day.

All of them responded well to MTX, when evaluated by American College of Rheumatology 20 core set.¹ The dose of MTX had been increased from 2.8 (1.4) to 7.1 (3.4) mg/week during 15.4 (17.8) months. At the onset of respiratory distress with a fever, plain chest radiography and/or computed tomography showed ground-glass opacities, mainly from the middle to upper central lung fields; the findings differed from those of rheumatoid pneumonitis which usually involves the periphery and results in structural derangement. The bronchoalveolar lavage fluid of five patients contained CD4+ T cells (70.7 (15.1)% of the total cells). No micro-organism was detected either in lavage fluid or sputum in any of the patients. Hypoxaemia was severe, with a mean (SD) Pao₂ of 47.1 (15.2) mm Hg. Serum C reactive protein (CRP) level was as high as 233 (136) mg/l, and serum β_2 -microglobulin level was 4.94 (1.83) mg/l (normal range 0.8–1.7). Three patients underwent mechanical ventilation, and six received pulsed steroid treatment; a patient who received both of these treatments died 1 month later. After recovery in 10 patients, the opacities in chest radiography/computed tomography completely disappeared, and Pao₂ and serum CRP and β_2 -microglobulin levels returned to normal.

The peripheral blood lymphocyte count was followed throughout from the start of MTX treatment to after the recovery from lung injury, and the counts at the start of MTX treatment, at arthritis remission, at the onset of lung injury, and after the recovery from lung injury were compared with each other (fig 1). The count did not change from the start of MTX treatment ($1.91 (0.83) \times 10^9/l$) to arthritis remission ($1.77 (0.69) \times 10^9/l$, $p = 0.293$), then decreased in all of the patients at the lung injury onset ($0.56 (0.45) \times 10^9/l$, $p < 0.0001$ v arthritis remission; $p < 0.0001$ v MTX treatment start), and re-increased to preinjury level in 10 patients who recovered ($1.96 (1.06) \times 10^9/l$, $p = 0.0002$ v lung injury onset; $p = 0.738$ v arthritis remission; $p = 0.880$ v MTX treatment start). In the patient who did not recover, the lymphocyte count did not re-increase after MTX administration was stopped. Other blood cell count changes did not correlate with the event.

The new finding in this study was the significant decrease in peripheral blood lymphocyte count concurrent with the lung injury. This observation was in agreement with our previous study that the lymphocyte count did not change during RA remission, but decreased only when various adverse reactions to MTX occurred.² Along with this, the increase in lymphocyte count in bronchoalveolar lavage fluid, particularly in the count of CD4+ T cells, in this study and in previous reports,^{3,4} suggests that lymphocytes may participate in the injury. A high serum level of β_2 -microglobulin at injury onset might be relevant to the changes of lymphocytes.

We conclude that a peripheral blood lymphocyte count decrease in a responder, concurrent with respiratory distress and fever after receiving MTX dose, strongly suggests MTX-induced lung injury, and an increase again to the preinjury level predicts recovery from the injury.

We are indebted to Dr Shinzo Tamada, Dr Natsuko Yamamoto, Dr Yuji Miyakuni, Dr Yutaka Kubo, and Ms Keiko Miyahara for assistance. This study was supported in part by a grant from the Research Committee on Complications and Treatments of Inflammatory Connective Tissue Diseases from the Ministry of Health, Labour, and Welfare, Japan.

Figure 1 Peripheral blood lymphocyte count ($10^9/l$) at the start of methotrexate treatment, at arthritis remission, at lung injury onset, and after recovery from lung injury. The numbers refer to the individual patients. Patient 2 eventually died.

Authors' affiliations

S Inokuma, H Kono, K Hiramatsu, K Ito, K Shiratori, J Yamazaki, H Nakayama, H Shoda, Y Tanaka, Department of Allergy and Immunological Diseases, Tokyo Metropolitan Komagome Hospital, Japan

Y Kohno, Department of Internal Medicine, The Second Hospital, Tokyo Women's Medical School, Japan

Correspondence to: Dr S Inokuma, Tokyo Metropolitan Komagome Hospital, 3-18-22 Honkomagome, Bunkyo-ku, Tokyo 113-8677, Japan; inokuma@cick.jp

Accepted 27 November 2005

REFERENCES

- 1 **Felson DT**, Anderson JJ, Boers M, Bombardier C, Furst D, Goldsmith C, *et al*. American College of Rheumatology. Preliminary definition of improvement in rheumatoid arthritis. *Arthritis Rheum* 1995;**38**:727–35.
- 2 **Inokuma S**, Kono H, Nakayama H, Yamazaki J. Immunoglobulin and lymphocyte decrease concurrent with adverse reactions induced by methotrexate for rheumatoid arthritis. *Ann Rheum Dis* 2000;**59**:495–6.
- 3 **Schnabel A**, Richter C, Bauerfeind S, Gross WL. Bronchoalveolar lavage cell profile in methotrexate induced pneumonitis. *Thorax* 1997;**52**:377–9.
- 4 **Fuhrman C**, Parrot A, Wislez M, Prigent H, Boussaud V, Bernaudin JF, *et al*. Spectrum of CD4 to CD8 T-cell ratios in lymphocytic alveolitis associated with methotrexate-induced pneumonitis. *Am J Respir Crit Care Med* 2001;**164**:1186–91.

Successful treatment of rheumatoid meningitis with cyclophosphamide but not infliximab

R C Chou, J W Henson, D Tian, E T Hedley-Whyte, A M Reginato

Ann Rheum Dis 2006;**65**:1114–1116. doi: 10.1136/ard.2005.042093

Rheumatoid meningitis is a rare but lethal disorder that occurs in an elderly population with longstanding rheumatoid arthritis (RA).¹ Although the majority of

patients experience neurological symptoms, up to 26% of the patients were asymptomatic in a case series study as identified by necropsy.¹ There is poor correlation between

Figure 1 Magnetic resonance images demonstrated abnormal gadolinium enhancement of the dura and leptomeninges, and hyperintense signal in the subarachnoid spaces before intravenous cyclophosphamide treatment (A, C). After 6 months of treatment with monthly intravenous cyclophosphamide and daily oral prednisone, almost complete resolution of these abnormal findings occurred (B, D). Coronal T₁ weighted images after administration of intravenous gadolinium contrast (A, B), and axial FLAIR images (C, D). (R, right; L, left).