

Rheumatology 2003;42:802–803
doi:10.1093/rheumatology/keg188

Chronic pulmonary toxicity of methotrexate and rheumatoid arthritis

SIR, Methotrexate (MTX) is the most frequently used second-line therapy in rheumatoid arthritis (RA) and is used widely in many other autoimmune disorders. Pulmonary toxicity has been reported in 2–7% of patients receiving low-dose MTX [1], and acute hypersensitivity pneumonitis is the most feared complication [2]. It has also been suggested that chronic pulmonary fibrosis can be caused by MTX, but specific risk factors for the development of pulmonary toxicity in patients treated with low-dose MTX have never been identified. Age, sex, smoking, duration of treatment, and underlying pulmonary disease are not associated with an increased risk of MTX pulmonary toxicity [3, 4].

Dawson *et al.* [5] have reported in this journal an interesting study concerning the chronic pulmonary effects of MTX in patients with RA. In their prospective study, which incorporated high-resolution computed tomography (HRCT) assessment and serial pulmonary function tests (PFTs), there was no evidence of association of MTX with chronic pulmonary fibrosis. Interestingly, even in the subgroup of RA patients with evidence of pulmonary fibrosis at the beginning of the study, MTX did not cause any deterioration in pulmonary function over a 2-yr period.

We have recently investigated the presence of pulmonary disease in 30 consecutive patients with RA without respiratory symptoms and with normal chest X-ray. In all these patients we performed a chest HRCT scan and complete PFTs. Our patients were predominantly women (83.3%) and had a mean age of 54 yr (range 26–72 yr), and 50% of them had a disease duration of less than 2 yr. Rheumatoid factor was present in 70% of them. Only 26.6% of the patients were current smokers and 46.7% had never smoked.

We found a rather high prevalence of functional alterations: the diffusion capacity for carbon monoxide (TLCO) was <75% in 53.3% of the patients; two patients had obstructive PFT, one patient restrictive PFT and one patient a mixed pattern. Pulmonary alterations were detected in 20% of the patients on the HRCT scan, but only one patient had a pattern

suggestive of chronic pulmonary fibrosis. In all the other patients the alterations observed were mild and non-specific (septal and non-septal lines, micronodules, bronchiectasis, pleural abnormalities).

Eighteen (60%) of our patients had received low-dose MTX: the mean duration of therapy was 23.7 months (range 3–96 months) and the mean dose 10.8 mg/week (range 5–15 mg/week). We did not find any correlation between MTX therapy and any of the pulmonary alterations reported above. In particular, TLCO <75% was detected in 50% of the MTX group compared with 58.3% of the other group, and the only patient with a HRCT pattern suggestive of chronic pulmonary fibrosis had never received MTX.

These data seem to confirm the absence of risk of chronic pulmonary toxicity with low-dose therapy with MTX.

The recent availability of new diagnostic techniques, such as HRCT scanning, has increased interest in the evaluation of pulmonary involvement in patients with RA [6] and other connective tissue diseases [7] and will probably allow a better diagnostic and therapeutic approach to this serious complication.

Until now the fear of pulmonary toxicity has discouraged the use of MTX for interstitial lung disorders [8]. However, the safety and efficacy of MTX has been proven in some autoimmune diseases with predominant lung involvement, such as sarcoidosis [9] and Wegener's granulomatosis [10]. The accumulating evidence suggests that RA patients presenting pulmonary involvement should not be denied MTX therapy. Moreover, prospective studies evaluating the potential therapeutic effect of MTX on progressive interstitial pneumonitis associated with RA and other connective tissue diseases would be of great interest.

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Accepted 4 November 2002

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