Methotrexate-Induced Pneumonitis in Patients with Rheumatoid Arthritis and Psoriatic Arthritis: Report of Five Cases and Review of the Literature

F. SALAFFI*, P. MANGANELLI**, M. CAROTTI***, S. SUBIACO+, G. LAMANNA*, C. CERVINI*

Summary  Pneumonitis is emerging as one of the most unpredictable and potentially serious, adverse effects of treatment with MTX. Its prevalence in rheumatoid arthritis (RA) has been estimated from several retrospective and prospective studies to range from 0.3% to 18%. On the other hand, MTX-induced pneumonitis seems to be very rare in psoriatic arthritis (PsA).

Our review of 194 RA patients and 38 PsA patients receiving MTX has identified four RA patients and one PsA patient with MTX-induced pneumonitis, giving a prevalence of 2.1% and 0.03%, respectively. Diagnosis was suggested by clinical history and radiographic findings, but the bronchoalveolar lavage plays an important role both in excluding infectious agents and in providing information for understanding the pathogenesis of lung injury. The presence of a lymphocyte alveolitis with a predominance of CD4+ T cells in 3 RA patients and CD8+ T cells with a concomitant increase in neutrophils in another case suggests that immunologically mediated reactions may be one damage mechanism in MTX-induced pneumonitis. Although risk factors for MTX-induced pulmonary toxicity are poorly understood, the presence in 3 out of 5 of our patients of pre-existing lung disease, represented by diffuse interstitial changes on chest X-ray, and mild bronchial asthma in two RA patients and by pulmonary silicosis in the patient with PsA may account for a predisposition to the development of MTX pneumonitis.

Key words  Methotrexate, Pneumonitis, Rheumatoid Arthritis, Psoriatic Arthritis, Bronchoalveolar Lavage.

INTRODUCTION

The value of low dose methotrexate (MTX) in the treatment of refractory rheumatoid arthritis (RA) (1-6) and severe and disabling psoriatic arthritis (PsA) is well established (7).

Pneumonitis is emerging as one of the most unpredictable and potentially serious adverse effects of treatment with MTX (1-5,8,9). The prevalence in RA has been estimated from several retrospective and prospective studies to range from 0.3% (20) to 18% (21). On the other hand, MTX-induced pneumonitis seems to be very rare in PsA. The clinical manifestations of this disorder have been described in detail, (8,10,11,15,22-26), but the mechanism of lung injury is unknown. Moreover, the diagnosis remains difficult to establish since no pathognomonic clinical, laboratory or radiological features which allow differentiation between infectious and non-infectious pulmonary disease (except for the isolation of a pathogenic micro-organism) have been described. Although no predisposing factors for the development of MTX pneumonitis are known, abnormalities on chest radiographs or preexisting pulmonary disease, smoking, use of acetylsalicylic acid and abnormal renal function have been suggested to increase the risk of pulmonary toxicity (11,21,24,27-29).

Our aims were to describe five additional patients with MTX pneumonitis, estimate the prevalence and identify risk factors. Further, to help clarify the pathogenesis of lung injury in this disorder, we used bronchoalveolar lavage (BAL) to study the immune response of the low-
er respiratory tract in these patients compared to a control group of RA patients receiving MTX without evidence of pulmonary toxicity (MTX controls).

METHODS

Between 1989 and 1995, 194 patients with RA as defined by the 1987 ARA criteria (30) and 38 with psoriatic arthritis (PsA) diagnosed according to the criteria suggested by Moll and Wright (31) began MTX therapy (5-15 mg/week). Treatment was conducted at the Department of Rheumatology, University of Ancona (108 patients with RA and 22 with PsA) and at the Rheumatic Disease Unit, University of Parma (86 patients with RA and 16 with PsA). They were monitored at regular intervals by their primary care physician and reviewed on a six month basis by a rheumatologist (FS, PM). During this period, five patients (4 with RA and 1 with PsA) were hospitalised with a syndrome consistent with MTX pneumonitis. For this study, we used the diagnostic criteria advocated by Searles and McKendry (11): 1) acute onset of shortness of breath; 2) fever > 38°C; 3) tachypnoea I> 28/min and a non-productive cough; 4) radiological evidence of pulmonary interstitial or alveolar infiltrates; 5) white cell count ≤ 15.0 × 10^9/l; 6) negative blood and sputum cultures; 7) pulmonary function tests (PFT) showing restrictive pulmonary function with decreased diffusion capacities; 8) PaO_2 < 55 mmHg on room air at time of admission; and 9) histopathology consistent with bronchiolitis or interstitial pneumonitis. The diagnosis is definite if ≥ 6/9 criteria are present, probable if 5/9 are present and possible if 4/9 are present. In all cases, BAL was performed as previously described (32). The BAL was performed also in 16 RA patients (mean age: 60 ± 6.8 years) treated with MTX, but without interstitial pneumonitis (MTX controls). All patients gave their informed consent to the BAL before entry into the study, approval for which was obtained from local ethical committees.

Statistical analysis

When applicable, data is expressed as the mean ± standard error of the mean (SEM). Statistical comparison was carried out using the nonparametric Mann-Whitney U-test for absolute values and Yates's corrected of the chi-square test for proportions. Any P values less than 0.05 were considered significant. Calculations were performed using Stat View 4.0© (Abacus Concepts Inc., 1992) for Macintosh.

CASE REPORTS

Case 1

A 66-year-old woman with a 6-year history of seropositive RA, previously treated with aurothiomalate and sulphasalazine, was maintained on diclofenac 100 mg daily and prednisone 5 mg daily. In January 1992, oral MTX was initiated at 7.5 mg weekly with significant clinical improvement. After 43 weeks, the patient was hospitalised because of increasing dyspnoea, non-productive cough, fever, headache and general malaise. Upon admission, her respiratory rate was 32/min; blood pressure, 140/90 mm Hg; pulse rate, 112/min and axillary temperature, 38.4 °C. Rare midinspiratory bilateral rales were heard. A chest X-ray demonstrated diffuse alveolar and interstitial pulmonary infiltrates, most prominent in the lower lobes (Figure 1A) and the computed tomography scan showed heterogeneous ground glass opacities and septal lines (Figure 1B). PFT were consistent with a restrictive ventilatory defect and a reduced diffusion capacity for carbon monoxide (DLCO, 58% predicted). Laboratory tests showed haemoglobin 11.1 g/dl, white blood cells (WBC) 9,200/mm^3 (neutrophils 75%, lymphocytes 15%; monocytes 6%, eosinophils 4%), erythrocyte sedimentation rate (ESR) 33 mm/h. Arterial blood analysis revealed PaO_2 of 46 mm Hg, PaCO_2 of 39 mm Hg and pH of 7.56 on room air. MTX was discontinued, and the patient was treated with prednisone 60 mg daily and supplemental oxygen with significant improvement. She was discharged after 12 days with prednisone 25 mg daily which was tapered over the following month. One month later, arterial blood gas analysis showed PaO_2 of 71 mm Hg, PaCO_2 of 29 mm Hg and pH of 7.45 on room air. The patient remained free of respiratory symptoms during a 6-month follow-up. MTX was reinstituted at a dose of 7.5 mg weekly due to a severe flare of RA. The patient did not complain of respiratory symptoms over a 14 month follow-up.

Case 2

A 57-year old woman with a 11-year history of seropositive RA unresponsive to aurothiomalate, hydroxychloroquine and sulphasalazine, began in March 1993, MTX 10 mg/week and prednisone 5 mg daily with significant clinical improvement. After approximately 8 months the patient complained of shortness of breath, non-productive cough, general malaise and fever. Upon admission, her respiratory rate was of 30/min, blood pressure of 105/70 mm Hg, heart rate of 100/min and axillary temperature of 38.7°C. Physical examination revealed inspirato-