Adverse drug reaction of the month

Methotrexate pneumonitis in a patient with rheumatoid arthritis

R Clearkin, PA Corris, SHL Thomas

Methotrexate has been used for rheumatoid arthritis for many years¹ and is now used extensively as a second-line therapy in doses of 7.5 to 20 mg per week.² The drug has several well-recognised serious adverse effects which include myelosuppression, hepatotoxicity, enteritis, nephrotoxicity and embryotoxicity. Pulmonary complications associated with methotrexate are uncommon,³ and include infections secondary to myelosuppression and methotrexate pneumonitis. These must be differentiated from the pulmonary complications of the underlying disease.

Although formal criteria have been proposed for the diagnosis of methotrexate pneumonitis, confirmation of the diagnosis is difficult and often made retrospectively by exclusion when all microbiological results have returned.⁴ While potentially fatal when unrecognised, full recovery usually occurs within two months when methotrexate is withdrawn.^{3,5}

Case summary

A 59-year-old man with a six-year history of sero-positive rheumatoid arthritis commenced methotrexate therapy at a dose of 10 mg per week. He also received folic acid 5 mg per week and diclofenac 75 mg twice daily. He received a total of 40 mg methotrexate before presenting with a one-week history of severe dyspnoea.

On examination there were stigmata of rheumatoid arthritis. He was afebrile, tachypnoeic and centrally cyanosed with coarse bibasal inspiratory crackles. He was not clubbed. Arterial blood gases (breathing air) were: pH 7.49, PaCO₂ 3.9 kPa, PaO₂ 5.1 kPa, and standard bicarbonate 25 mmol/l. On 40% oxygen his PaO₂ was 14.2 kPa. The white cell count was 11.6×10^9 with a polymorphonuclear leucocytosis but no eosinophilia. The erythrocyte sedimentation rate was 16 mm/h. Rheumatoid factor and IgM and IgG anti-cardiolipin antibodies were present. Antinuclear antibodies and viral serology were negative. The chest X-ray initially showed patchy

lung shadowing which progressed over the next two weeks to involve the mid and lower zones of both lungs. A chest X-ray performed before starting methotrexate had revealed only some fibrotic changes at the left base. Echocardiography was normal. Pulmonary function tests performed after admission are shown in the table.

Methotrexate was withdrawn immediately and the patient started on oxygen therapy. Fibre-optic bronchoscopy and right lower lobe broncho-alveolar lavage (BAL) revealed no evidence of infection, in particular no *Pneumocystis carinii*; a cell count was not performed. Histology of transbronchial biopsies revealed mild interstitial fibrosis with thrombosed vessels consistent with either rheumatoid disease or methotrexate pneumonitis.

The patient was treated with intravenous methylprednisolone, 500 mg daily for three days, then prednisolone, 60 mg orally for one month. This was reduced to zero over the next two months. Supplementary oxygen was also required while he was in hospital and for a few weeks after discharge. Twelve weeks after initial presentation he was considerably improved, mobilising without oxygen, and his arterial oxygen saturation was 94%.

Discussion

The aetiology of methotrexate pneumonitis is unclear.⁴ It usually occurs in the first months of therapy, as in this case, but the onset may be delayed for years. Risk factors, although not identified in all studies, are thought to include pre-existing lung disease,^{5,7} diabetes mellitus, and use of nonsteroidal anti-inflammatory drugs.¹

The condition has no pathognomonic clinical, laboratory, or radiological features. The diagnosis should be considered in a patient receiving methotrexate who develops an acute respiratory illness. It is essential to exclude infections as a cause and investigations should include viral serology. BAL is also important as *Pneumonitis carinii* pneumonia can occur in

Department of
Respiratory
Medicine, Freeman
Hospital,
Newcastle NE7 7DN,
UK

R Clearkin
PA Corris

Wolfson Unit of
Clinical
Pharmacology,
University of
Newcastle upon
Tyne, Newcastle
NE2 4HH, UK
R Clearkin
SHL Thomas

Correspondence to Dr
SHL Thomas

Accepted 20 March 1997

Table Pulmonary function tests after presentation with dyspnoea

	Predicted values	Interval following presentation		
		1 day	16 days	12 weeks
FEV ₁ (l)	3.1 ± 0.51	2.35	2.20	2.90
FVC (l)	4.2 ± 0.56	3.15	2.60	3.60
TLCO (mmol.min ⁻¹ .kPa ⁻¹)	8.5 ± 1.87	2.30	2.25	not done

Criteria for methotrexate pneumonitis

- acute onset dyspnoea
- fever over 38°C
- tachypnoea ≥ 28 breaths/min
- radiological evidence of pulmonary interstitial or alveolar infiltrates
- white cell count $\leq 15 \times 10^9/l$
- negative blood and sputum cultures
- pulmonary function tests demonstrating a restrictive defect and reduced diffusion capacity
- admission $\text{PaO}_2 < 7.5$ kPa on air
- biopsy evidence of bronchiolitis or interstitial pneumonitis with giant cells, without evidence of infection

Definite diagnosis: ≥ 6 criteria met

Probable diagnosis: 5 criteria met

Possible diagnosis: 4 criteria met

Box 1

rheumatoid patients treated with methotrexate.^{4,6} If the patient's clinical condition permits, histological evidence of interstitial pneumonitis may be sought by lung biopsy. Other possible causes of interstitial lung disease are rheumatoid disease itself and treatment with nonsteroidal anti-inflammatory drugs.⁸

Suggested criteria⁵ for diagnosis of methotrexate pneumonitis are given in box 1. The reported case fulfilled at least seven criteria. The presence of possible risk factors and his improvement over a few weeks after withdrawal of methotrexate, while diclofenac was continued, also support the diagnosis of methotrexate pneumonitis.

Management of suspected methotrexate pneumonitis includes withdrawing the drug and, most importantly, exclusion of infection. Oxygen is usually required. The value of corticosteroids is uncertain, but they are

Learning points

- it may be difficult to differentiate between complications of the underlying disease and adverse reactions from drugs used in its treatment
- there is often no diagnostic test that proves that a complication is caused by an adverse drug reaction; diagnosis is by exclusion
- prescribers must be aware of the adverse effects of drugs they use, however rare, and be vigilant for them. Early recognition and withdrawal of the offending agent may be vital

Box 2

usually given. In some cases empirical treatment for *P. carinii* pneumonia is appropriate until the results of BAL are available.

The CSM/MCA database, compiled from 'yellow card' reports, contains 29 reports of pneumonitis in patients receiving methotrexate. Other reported respiratory complications include pulmonary fibrosis (11), alveolitis (7), and dyspnoea (5). There are 10 reports of lower respiratory tract infections, including two of *P. carinii* and one of varicella zoster.

The prescribing and monitoring of methotrexate therapy is increasingly being transferred to general practitioners, once patients have been stabilised on therapy by hospital doctors. It is important that doctors who prescribe and monitor methotrexate therapy should be aware of its possible adverse effects. The early recognition of these is important for the complete recovery of the patient. For potentially hazardous drugs such as methotrexate, written and agreed shared care guidelines are an important way of ensuring that they are safely monitored in primary care.

Keywords: methotrexate pneumonitis, adverse drug reaction

1 Tariq S, Tariq SM. Methotrexate in rheumatoid arthritis: can current knowledge and experience justify its use as a first line disease modifying agent? *Postgrad Med J* 1993; **69**: 775–80.

2 Weinblatt HE. Methotrexate in rheumatoid arthritis: toxicity issues. *Br J Rheumatol* 1996; **35**: 403–6.

3 Cottin V, Tebib J, Massonnet B, Souquet P-J, Bernard J-P. Pulmonary function in patients receiving long-term low-dose methotrexate. *Chest* 1996; **109**: 933–8.

4 Barrera P, Laan RFJM, van Riel PLCM, Dekhuijzen PNR, Boerbooms AMT, van de Putte LBA. Methotrexate-related pulmonary complications in rheumatoid arthritis. *Ann Rheum Dis* 1994; **53**: 434–9.

5 Searles G, McKendry RJR. Methotrexate pneumonitis in rheumatoid arthritis: potential risk factors, four case reports and a review of the literature. *J Rheumatol* 1987; **14**: 1164–71.

6 Hilliquin P, Renoux M, Perrot S, Puéchal X, Menkès CJ. Occurrence of pulmonary complications during methotrexate therapy in rheumatoid arthritis. *Br J Rheumatol* 1996; **35**: 441–5.

7 Alarcón GS, Kremer JM, Macaluso M, et al. MTX–lung toxicity: a multi-centre, case-control study (abstract) *Arthritis Rheum* 1995; **38**: S205.

8 Weber JCP, Essingman WK. Pulmonary alveolitis and NSAIDs – fact or fiction? *Br J Rheumatol* 1986; **25**: 5–6.