REVIEW

Methotrexate-related pulmonary complications in rheumatoid arthritis

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Methotrexate (MTX) was described as a drug in 1946¹ and first used in the treatment of human disease (childhood leukaemia) in 1948.² Successful MTX treatment for rheumatoid arthritis (RA) and psoriasis was reported in 1951,³ although the interest in this drug at that time was probably overshadowed by the impressive results of cortico-steroid treatment until approximately 1980. MTX was approved by the food and drug administration (FDA) for the treatment of severe and disabling psoriasis in 1971 and for RA only in 1988.⁴

MTX-related pulmonary toxicity was first observed during treatment of childhood leukaemia in 1969⁵ and later in malignancies,^{6,7} psoriasis^{6,7} and polymyositis.^{7,8} Though it was postulated that pulmonary toxicity would appear only with a weekly dose higher than 20 mg,⁷ this did not prove to be true when in 1983 pneumonitis was also reported during low-dose MTX treatment for RA.^{9,10}

Infectious and non infectious pulmonary complications

In recent years there has been an increase in the number of reports of pulmonary complications associated with low-dose methotrexate therapy for rheumatic and non-rheumatic diseases including both non infectious and infectious pathology. Among the non infectious complications observed in patients with RA, interstitial pneumonitis has been most often reported^{7,9-13} (more than 35 cases since the first reports in 1983).^{9,10} Interstitial lung fibrosis has been observed during MTX treatment for RA, malignancies and psoriasis.^{6,13} Furthermore, one case of accelerated pulmonary nodulosis¹⁴ and one of drug-induced asthma¹⁵ have so far been described during MTX treatment for RA. Lung fibrosis and nodulosis may be pulmonary manifestations of RA,¹⁶ and it is therefore difficult to ascribe this pathology only to MTX treatment. Two other complications, so far only observed during treatment with MTX in malignant diseases, are pulmonary oedema¹⁷⁻¹⁸ and isolated pleuritis.¹⁹

Among the pulmonary infections during MTX treatment of RA, the most frequently reported has been *Pneumocystis carinii* pneumonia with more than eight cases published since 1983.²⁰⁻²⁵ Less frequently observed infections include pulmonary cryptococ-

cosis,^{26,27} aspergillosis,^{28,29} disseminated histoplasmosis,²⁸ parainfluenza virus infection¹² and cytomegalovirus pneumonia.³⁰ Pulmonary candidiasis was described in one patient with polymyositis/dermatomyositis treated with MTX³¹ but, to our knowledge, not in RA. Although some of the reported infections appeared during concomitant treatment with corticosteroids, these studies suggest a potential immunosuppressive effect of low-dose MTX treatment at least in some patients. The present review will focus on MTX-pneumonitis.

Pathogenesis

The mechanism of MTX-induced lung pathology remains unclear. Lung damage due to folate deficiency has been suggested³² but seems unlikely since MTX pneumonitis may occur after a single MTX dose^{33,34} and is not prevented by folinic acid treatment.³⁵ A hypersensitivity reaction is suggested by findings in lung biopsies: interstitial pneumonitis, granuloma formation and bronchiolitis,⁷ and in bronchoalveolar lavage: lymphocytic alveolitis, increased eosinophils and reversed CD4/CD8 ratio,^{36,37} together with the clinical findings of fever, peripheral eosinophilia and response to corticosteroids. The reports of spontaneous remission during MTX treatment⁷ and rechallenge of the drug without recurrence of lung pathology¹³ argue more for an idiosyncratic reaction than for hypersensitivity. A specific cellular immune reaction to the drug has been suggested by the production of a lymphokine which inhibits leukocyte migration [leukocyte inhibitor factor (LIF)] by peripheral blood lymphocytes after incubation with MTX. LIF production was observed in patients with MTX pneumonitis but not in other patients treated with MTX or healthy controls.^{38,39} A toxic drug reaction is suggested by the accumulation of MTX in lung tissue,⁴⁰ the biopsy findings of alveolar and non-specific lung injury,⁶ and the resolution of pathology after stopping or lowering the drug.⁴¹ The fact that pulmonary pathology does not appear to be related to cumulative MTX dose argues, against this hypothesis.

Risk factors

Age, sex, and disease duration are not associated with the development of MTX-pneumonitis. This complication has been

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observed after oral,⁴¹ intravenous,⁴² intramuscular,⁴¹ intrathecal⁴³ and even local³⁴ administration of MTX. No correlation has been found between the occurrence of lung toxicity and cumulative or weekly dose or dosage schedule.¹³ Pneumonitis has been observed after as little as 12.5 mg MTX^{33 34} and may appear even weeks after discontinuation of treatment.^{44–46} In view of the relative rarity of MTX pneumonitis in other non-malignant diseases like psoriasis⁴⁷ and bronchial asthma,⁴⁸ a propensity to pulmonary involvement in RA has been suggested³³ but so far comparative studies on the incidence of MTX-pneumonitis in RA and other diseases are lacking. A possible relationship between certain HLA haplotypes and increased risk for MTX-pneumonitis has been mentioned in two previous reports: DRw3 in one case³³ and A2,24;DR4 in two cases.⁴⁹ We also observed the HLA DR4 haplotype in four of five patients with MTX-related lung toxicity admitted to our unit during 1993, but studies in larger patient groups are needed.

Renal function impairment^{13 50} and concomitant use of non steroidal anti-inflammatory drugs¹² have been suggested to predispose to MTX-toxicity in some studies but this has not been confirmed by others.⁵¹ Specific risk factors for the development of MTX pneumonitis are not known exactly but some studies have suggested that a history of smoking,¹² pre-existing pulmonary disease^{12 52 53} and abnormal chest radiographs before MTX institution⁵³ might be predisposing factors.

Diagnosis

The diagnosis of MTX-pneumonitis is difficult since there are no pathognomonic findings and this condition may mimic other pulmonary diseases. When a patient treated with MTX develops new respiratory symptoms, the differential diagnosis includes MTX-pneumonitis, rheumatoid lung disease, and pulmonary infection or emboli. Exclusion of other pathology, particularly of infectious origin, is time consuming and therefore MTX-pneumonitis is often diagnosed retrospectively. Criteria, proposed by two different groups,^{12 13} (table 1) are helpful for diagnostic purposes, but the term ‘definite’ MTX-pneumonitis¹² should be avoided in view of the presumptive

character of the diagnosis.¹³ The incidence of abnormalities in clinical, laboratory and radiological examination in patients with MTX-pneumonitis is difficult to estimate since this complication is relatively uncommon and large patient series are lacking. Data presented in the following sections were deducted from previous studies.

Clinical features and physical examination

The most usual complaints include dyspnoea and fever.^{9–13} Non productive cough has been reported in 75% of the patients.⁵⁴ Pleuritic chest pain may also be present but is rare.^{13 19} In most patients a subacute clinical course is observed during some weeks, but acute presentations have been also described.³³ On examination, tachypnoea (in 38–52% of the patients), crepitant rales (in 31–45% of the patients) and cyanosis (in 52% of the patients) are common findings.^{7 9–13 54} Abnormalities on auscultation may be disproportionately scarce compared with the extensive radiological findings.³³

Laboratory investigations

As for the clinical findings and physical examination, no specific results of laboratory tests are diagnostic for MTX-pneumonitis. Hypoxaemia is observed in 90–95% of the cases.^{7 9–13 54} The white blood cell count may be normal⁷ or show moderate leukocytosis without left shift.^{9 13} Mild eosinophilia has been reported in 41% of the patients^{7 54} and elevated levels of lactate dehydrogenase (LDH)^{10 13} have been reported.

Investigations directed to exclude infectious pathology should consist of extensive cultures of sputum, blood and bronchoalveolar lavage (BAL) fluid and serological test for common respiratory viruses, mycoplasma, rickettsia and legionella. Microscopical examination of BAL fluid is recommended to exclude *Pneumocystis carinii*, fungi and mycobacteria. BAL cell analysis usually reveals hypercellularity and lymphocytosis.^{36 37} Mild eosinophilia³⁶ or neutrophilia³⁷ and increased percentages of either CD4³⁶ or CD8 lymphocytes^{37 38} have also been reported. The diagnostic value of BAL cell analysis is limited since lymphocytosis, increases in CD4 and decreases in

Table 1 Diagnostic criteria of MTX-pneumonitis

	Searles et al 1987 ¹²	Carson et al 1987 ¹³
Clinical	1 Acute onset of dyspnoea	1 Course consistent with a hypersensitivity reaction
Laboratory	2 Fever > 38°C	2 Exclusion of infection and other pulmonary disease
	3 Tachypnoea ≥ 28/min and nonproductive cough	
	4 WBC ≤ 15,000 × 10 ⁹ /l (± eosinophilia)	
Radiological	5 PO ₂ on room air < 55 mm/Hg at admission	3 Infiltrates
	6 Negative blood and sputum cultures (obligatory)	
	7 Pulmonary interstitial or alveolar infiltrates	
Pulmonary function tests	8 Restrictive pattern, decreased diffusion	4 Consistent with drug-induced injury
Histopathology	9 Bronchiolitis/interstitial pneumonitis with giant cells without evidence of pathogenic micro-organisms	
Classification		
Definite	6 out of 9 criteria	not used
Probable	5 out of 9 criteria	≥ 3 out of 4 criteria
Possible	4 out of 9 criteria	2 out of 4 criteria

CD8 lymphocytes may be present in patients with RA (not treated with MTX) even in the absence of rheumatoid lung disease.⁵⁵ Furthermore, similar findings and increased percentage of eosinophils have been observed during hypersensitivity pneumonitis induced by other antirheumatic drugs like gold, D-penicillamine, non-steroidal anti-inflammatory drugs and more rarely azathioprine and sulphasalazine.^{16 55}

Radiological and scintigraphic examinations

A great variety of chest x ray patterns have been described but bilateral interstitial (in 50% of the patients) or mixed interstitial and alveolar infiltrates (in 41% of the patients), most prominent at the lung basis are probably the most common.^{9 13 54} Unilateral infiltrates,^{13 57} a reticulonodular pattern⁵⁸ and more rarely pleural effusions¹⁹ and transient hilar lymphadenopathy^{7 57} have also been reported. High-resolution computer tomography may show parenchymal ground-glass opacities (alveolitis), granulomas and fibrosis.⁵⁹⁻⁶¹ Gallium-67^{62 63} and Tc-99 diethylene-triamine-pentacetate (DTPA) lung scintigraphy⁶⁴ may show increased pulmonary uptake. These are sensitive but non-specific investigations in drug-induced lung disease and their value in the diagnosis and follow up of lung pathology related to MTX or other drugs has yet to be determined.

Pulmonary function tests

Apart from hypoxaemia, thorough pulmonary function evaluation during MTX-pneumonitis has not often been reported. Restrictive and obstructive patterns and low CO diffusion capacity^{7 52} have been observed. So far uncomplicated long term treatment with low dose MTX has not been associated with deterioration in pulmonary function.⁶⁵⁻⁶⁷

Lung biopsy

This procedure has been recommended not only for histopathological examination but also to exclude other diseases, especially infections. Before performing a lung biopsy, the clinician should balance the condition of the individual patient against the morbidity and mortality⁶⁸ associated with such a procedure. In some studies, patients have been managed without pathological examination of lung tissue.¹³ Transbronchial biopsy may be adequate in establishing the diagnosis,⁵⁷ but if inconclusive, open lung biopsy may be required.^{10 13 69} The pathological findings of interstitial pneumonitis with lymphocytic^{9 10 13 57} and sometimes eosinophilic^{41 57} infiltration, bronchiolitis and granuloma formation^{9 10 57} resemble other forms of hypersensitivity pneumonitis and have lead to the classification of MTX-pneumonitis as a hypersensitivity reaction. Alveolar damage with hyaline membranes and type 2 alveolar cell hyperplasia and dysplasia⁵⁷ may also be present. Interstitial fibrosis^{7 9 10 13} has been

described but this may be observed also in uncomplicated RA.^{9 13} Electron microscopy examination reveals intact basement membranes and proliferation and desquamation of lymphocytes and eosinophils.⁷

Treatment and outcome

The therapy for MTX-pneumonitis has not been analysed in controlled trials and experience is based on case reports. Besides supportive therapy, withdrawal of MTX seems a logical approach though resolution of pulmonary pathology despite continuation of MTX treatment has been reported.^{5 41} Reinstitution of MTX treatment after MTX-related lung toxicity has been reported in five cases without event^{7 12 13 70} but recurrence of pulmonary complications may occur.^{13 71} Though improvement without corticosteroids has been reported,^{13 41 58} this therapy might hasten recovery^{9 10 13 57} and is recommended in high dose until clinical improvement is evident. No worsening of MTX-pneumonitis has yet been observed when the dose of steroids is tapered. There is no evidence that corticosteroids or folinic acid prevent MTX-related pulmonary disease.³⁵ Effective treatment with daunorubicine in three leukaemia patients with MTX-pneumonitis has been reported⁷² but, for evident reasons, this drug has not been used in non malignant diseases. In some cases (that is, when lung biopsy is not performed), additional antibiotic treatment may be warranted in view of the difficult exclusion of some pulmonary infections. Empirical treatment for *Pneumocystis carinii* should be considered in such patients. The outcome of MTX-pneumonitis is usually favourable with clinical amelioration usually preceeding radiological and functional improvement.^{7 12 57} However, fatal outcome has been described in both rheumatic^{7 57 58} and non-rheumatic^{7 18} diseases.

Prevalence in the literature and review of own experience

Data about the prevalence of MTX-pneumonitis in RA show a great variation. While in some large studies^{73 74} such pathology was not observed at all, several retrospective and prospective studies have reported prevalence rates between 0.3 and 11.6% (table 2).^{7 11-13 49 75-83} The incidence of MTX-pneumonitis is not mentioned in most studies. Carson *et al*¹³ observed 3.9 cases per 100 patient years of MTX therapy in a retrospective study including 163 patients. The prospective ARAMIS programme reported incidence rates of dyspnoea and wheezing of respectively six and two per 1000 patient years among 497 patients treated with MTX, the incidence of MTX pneumonitis was not mentioned in this study.⁸⁴ In our centre, low-dose MTX treatment for RA, systemic sclerosis (SS) and ankylosing spondylitis (AS) has been used since 1984, 1988, and 1992, respectively. Up to this year, sporadic cases of MTX-related pulmonary toxicity (see below)

Table 2 Prevalence of MTX pneumonitis in the literature

Author	Publication year	Study design	Observation years	Number cases/ Total number patients	Prevalence	Reference
Sostman	1976	retrospective	7	7/92	7.6%	7
St Clair	1985	retrospective	not mentioned	3/95	3.1%	57
Cannon	1986	retrospective	not mentioned	5/127	3.9%	75
Carson	1987	retrospective	8	9/163	5.5%	13
Gispen	1987	retrospective	3	1/72	1.4%	58
Searles	1987	retrospective	8	4/73	5.5%	12
Alarcon	1989	retrospective	5	2/152	1.3%	76
Scully	1991	retrospective	5	11/124	8.8%	77
Hargreaves	1992	retrospective	3	5/43	11.6%	11
Buchbinder	1993	retrospective	5	2/587	0.3%	78
Boh	1986	prospective	2	3/59	5.1%	79
Andersen	1987	prospective	not mentioned	1/40	2.5%	80
Harahan	1989	prospective	4	1/128	0.8%	81
Drosos	1990	prospective	2	1/137	0.7%	82
Kremer	1992	prospective	7-5	2/29	6.9%	49
Weinblatt	1992	prospective	7	2/26	7.7%	83

were observed. In contrast, in 1993 such pathology appeared in five patients within a period of three months, and at least four of these cases satisfied the criteria of MTX pneumonitis.^{12 13} Apart from this cluster of five cases, we performed a review among more than 220 patients^{29 71 85-90} enrolled in prospective studies with low-dose MTX (table 3) and all hospital admissions to our unit, from 1984 to 1993, where pulmonary pathology was recorded. Eight additional cases of MTX-related pulmonary pathology were identified consisting of four episodes of MTX-pneumonitis (two in the same patient⁷¹) and four pulmonary infections. The latter encompassed two cases of viral pneumonitis (one of them during leukopenia⁸⁷), one case of pulmonary aspergillosis²⁹ and one case of pneumococcal pneumonia during leukopenia. Including the five patients observed during 1993, we have therefore observed 13 cases of MTX-related pulmonary pathology in the past nine years.

Conclusion

This review of the literature and our own experience shows that, though probably uncommon, pulmonary pathology related to low-dose MTX treatment for rheumatic diseases has been well documented.

There are no pathognomonic clinical, laboratory or radiological features which allow differentiation between infectious and non-infectious pathology except for the isolation of

a pathogenic micro-organism. To achieve this goal, transbronchial or open lung biopsy have been recommended, but the risks inherent to these procedures should be taken into account, especially in patients with a poor pulmonary condition. Our approach to a patient with suspected MTX-related lung pathology consists of: MTX discontinuation, supportive therapy, comprehensive diagnostic procedures to exclude infection (including BAL analysis), empirical antimicrobial treatment and, in some cases, intravenous corticosteroids until clinical and radiological improvement appears. This approach is warranted as excluding infection is difficult, time consuming and sometimes retrospective.

Though no predisposing factors for the development of MTX pneumonitis are known, abnormalities on chest radiographs and pulmonary pathology previous to MTX treatment have been suggested to increase the risk of pulmonary toxicity. For this reason and also to exclude underlying rheumatoid lung disease, chest radiographs should be performed before institution of MTX treatment. Uneventful MTX-treatment is not associated with deterioration in pulmonary function, therefore in our practice, pre-treatment pulmonary function tests and blood gas analysis are selectively performed in patients with a history of lung pathology.

Since MTX-related lung toxicity is potentially fatal, patients should be instructed to report any new pulmonary symptoms without delay.

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Table 3 Prospective studies with low-dose MTX treatment in our centre

Number	Patient population	Study design	Follow up time	Follow up months per patient	Number of MTX treated patients	MTX-related pulmonary pathology number of cases	Reference
1	Refractory RA	Open	1984-86	12	16	0	85
2	Follow up of number 1	Open	1986-92	72	12	0	86
3	RA	Double-blind MTX versus AZA	1986-88	12	31	1 viral pneumonitis 1 suspected viral pneumonitis	87
4	Follow up of number 3	Open	1988-92	48	25	2 MTX pneumonitis	71
5	RA	Open	1991-92	6	40	0	88
6	RA	Double blind MTX versus SASP versus MTX + SASP	1992 (ongoing)	12	90*	0	
7	RA	Open	1990-92	12	20	0	
8	Early RA	Open	1985 (ongoing)	67	67	0	89
9	Systemic sclerosis	Open	1988-89	12	8	1 Pulmonary aspergillosis	29
10	Systemic sclerosis	Double blind MTX versus Placebo	1989-92	12	28	0	90
11	Ankylosing spondylitis	Open	1992-93	9	13	0	

*: ongoing study, 90 patients enrolled, treatment code has not been broken yet.

AZA: azathioprine, SASP: sulphasalazine, ⁶⁹: 2 episodes of MTX pneumonitis presented in the same patient.

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