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REVIEW

Methotrexate-related pulmonary complications in rheumatoid arthritis

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Methotrexate (MTX) was described as a drug in 1946[1] 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 1969[5] 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 nodulosis[14] and one of drug-induced asthma[15] 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 oedema[17–18] 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 cryptococcosis,[26 27] aspergillosis,[28 29] disseminated histoplasmosis,[28] parainfluenza virus infection[12] and cytomegalovirus pneumonia.[30] Pulmonary candidiasis was described in one patient with polymyositis/dermatomyositis treated with MTX[31] 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 suggested[32] 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 brochoalveolar 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 treatment[7] and rechallenge of the drug without recurrence of lung pathology[13] 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] intrathecal[43] and even local[34] 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 psoriasis[47] and bronchial asthma,[48] a propensity to pulmonary involvement in RA has been suggested[33] 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 case[33] 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 drugs[12] 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 institution[53] 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-pneumonitis[12] 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 normal[7] 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 eosinophilia[36] or neutrophilia[37] and increased percentages of either CD4[36] 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
	2 Fever > 38°C	
	3 Tachypnoea ≥ 28/min and nonproductive cough	
Laboratory	4 WBC ≤ 15,000 × 10^9/l (± eosinophilia)	2 Exclusion of infection and other pulmonary disease
	5 PO_2 on room air < 55 mm/Hg at admission	
	6 Negative blood and sputum cultures (obligatory)	
Radiological	7 Pulmonary interstitial or alveolar infiltrates	3 Infiltrates
Pulmonary function tests	8 Restrictive pattern, decreased diffusion	
Histopathology	9 Bronchiolitis/interstitial pneumonitis with giant cells without evidence of pathogenic micro-organisms	4 Consistent with drug-induced injury
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 pattern[58] and more rarely pleural effusions[19] 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 scintigraphy[64] 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 diffussion 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 mortality[68] 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 dysplasia[57] 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 reported[72] 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 apondylitis (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
Haranhan	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 patient[71]) and four pulmonary infections. The latter encompassed two cases of viral pneumonitis (one of them during leukopenia[87]), one case of pulmonary aspergillosis[29] 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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1 Angier R B, Boothe J W, Hutchings B L. The structure and synthesis of the liver L. Casei factor. *Science* 1946; **103:** 667–9.
2 Farber S, Diamond L K, Mercer R D, Sylvester R F Jr, Solff J A. Temporary remission in acutet leukemia in children produced by folic antagonist 4-aminopteroyl-glutamic acid (aminopterin). *N Engl J Med* 1948; **238:** 787–93.
3 Gubner R, August S, Ginsberg V. Therapeutic suppression of tissue reactivity II. Effect of aminopterin in rheumatoid arthritis and psoriasis. *Am J Med Sci* 1951; **221:** 176–82.
4 Tugwell P, Bennett K, Bell M, Gent M. Methotrexate in rheumatoid arthritis. Feedback on American College of Physicians Guidelines. *Ann Int Med* 1989; **110:** 581–3.
5 Acute Leukemia Group B. Acute lymphocytic leukemia in children. Maintenance therapy with methotrexate administered intermittently. *J Am Med Assoc* 1969; **207:** 923–8.

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 MTX versus MTX + SASP	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	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.

6 Bedrossian C W M, Miller W C, Luna M A. Methotrexate-induced diffuse interstitial pulmonary fibrosis. *Southern Med J* 1979; **72:** 313–8.
7 Sostman H D, Matthay R A, Putman C E, Walker-Smith G J. Methotrexate-induced pneumonitis. *Medicine* 1976; **55:** 371–88.
8 Dickley B F, Myers A R. Pulmonary disease in polymyositis-dermatomyositis. *Sem Arthritis Rheum* 1984; **14:** 60–76.
9 Cannon G W, Ward J R, Clegg D O, Samuelson C O, Abbott T M. Acute lung disease associated with low-dose pulse metho-trexate therapy in patients with rheumatoid arthritis. *Arthritis Rheum* 1983; **26:** 1269–74.
10 Engelbrecht J A, Calhoon S L, Scherrer J J. Methotrexate pneumonitis after low-dose therapy for rheumatoid arthritis. *Arthritis Rheum* 1983; **26:** 1275–8.
11 Hargreaves M R, Mowat A G, Benson M K. Acute pneumonitis associated with low dose methotrexate treatment for rheumatoid arthritis: report of five cases and review of published reports. *Thorax* 1992; **47:** 628–33.
12 Searles G, McKendry R J R. Methotrexate pneumonitis in rheumatoid arthritis: potential risk factors. Four case reports and a review of the literature. *J Rheumatol* 1987; **14:** 1164–71.
13 Carson C W, Cannon G W, Egger M J, Ward J R, Clegg D O. Pulmonary disease during treatment of rheumatoid arthritis with low dose pulse methotrexate. *Semin Arthritis Rheum* 1987; **16:** 186–95.
14 Alarcon G S, Koopman W J, McCarty M J. Nonperipheral accelerated nodulosis in a methotrexate-treated rheumatoid arthritis patient. *Arthritis Rheum* 1993; **36:** 132–3.
15 Jones G, Mierins E, Karsh J. Methotrexate-induced asthma. *Am Rev Respir Dis* 1991; **143:** 179–81.
16 Cannon G W. Pulmonary complications of antirheumatic drug therapy. *Semin Arthritis Rheum* 1990; **19:** 353–64.
17 Bernstein M L, Sobel D B, Wimmer R S. Noncardiogenic pulmonary edema following injection of methotrexate into the cerebrospinal fluid. *Cancer* 1982; **50:** 866–8.
18 Lascari A D, Strano A J, Johnson W W, Collins J G P. Methotrexate-induced sudden fatal pulmonary reaction. *Cancer* 1977; **40:** 1393–7.
19 Walden P A M, Mitchell-Heggs P F, Coppin C, Dent J, Bagshawe J D. Pleurisy and methotrexate treatment. *BMJ* 1977; **2:** 867.
20 Perruquet J L, Harrington T M, Davis D E. Pneumocystis carinii pneumonia following methotrexate therapy for rheumatoid arthritis (letter). *Arthritis Rheum* 1983; **26:** 1291–2.
21 Wollner A, Mohle-Boetani J, Lambert R E, Perruquet J L, Raffin T A, McGuire J L. Pneumocystis carinii pneumonia complicating low dose methotrexate treatment for rheumatoid arthritis. *Thorax* 1991; **46:** 205–7.
22 Flood D A, Chan C K, Pruzanski W. Pneumocystis carinii pneumonia associated with methotrexate therapy in rheumatoid arthritis. *J Rheumatol* 1991; **18:** 1254–6.
23 Leff R L, Case J P, McKenzie R. Rheumatoid arthritis, methotrexate therapy and pneumocystis carinii pneumonia (letter). *Ann Int Med* 1990; **112:** 716.
24 Lang B, Riegel W, Peters T, Peter H H. Low dose methotrexate therapy for rheumatoid arthritis complicated by pancytopenia and Pneumocystis carinii pneumonia. *J Rheumatol* 1991; **18:** 1257–9.
25 Shiroky J B, Frost A, Skelton J D, Haegert D G, Newkirk M M, Neville C. Complications of immunosuppression associated with weekly low dose methotrexate. *J Rheumatol* 1991; **18:** 1172–5.
26 Altz Smith M, Kendall L G Jr, Stamm A M. Cryptococcosis associated with low-dose methotrexate for arthritis. *Am J Med* 1984; **83:** 179–81.
27 Law K F, Aranda C P, Smith R L, Berkowitz K A, Ittman M M, Lewis M. Pulmonary cyptococcosis mimicking methotrexate pneumonitis. *J Rheumatol* 1993; **20:** 872–3.
28 Erikson N, Furst D E. Significant methotrexate (MTX) toxicity in RA patients: Results of an ongoing longterm prospective trial. *Arthritis Rheum* 1987; **30:** S59.
29 Van den Hoogen F H J, Boerbooms A M Th, van de Putte L B A, Rasker J J, van Venrooij W J. Low dose methotrexate treatment in systemic sclerosis (letter). *J Rheumatol* 1991; **18:** 1763–4.
30 Clerc D, Brousse C, Mariette X, Bennet P, Bisson M. Cytomegalovirus pneumonia in a patient with rheumatoid arthritis treated with low dose methotrexate and prednisone (letter). *Ann Rheum Dis* 1991; **50:** 67.
31 Dickey B F, Myers A R. Pulmonary disease in polymyositis/dermatomyositis. *Sem Arthritis Rheum* 1984; **14:** 60–76.
32 Drug and poison-induced pulmonary disease. In: Fraser R G, Paré J A P, Paré P D, Fraser R S, eds. *Diagnosis of disease of the chest.* Philadelphia: W B Saunders, 1991: **4:** 2433–4.
33 Ridley M G, Wolfe C S, Mathews J A. Life threatening acute pneumonitis during low dose methotrexate treatment for rheumatoid arthritis: a case report and review of the literature. *Ann Rheum Dis* 1988; **47:** 784–8.
34 Schoenfeld A, Mashiach R, Vardy M, Ovadia J. Methotrexate pneumonitis in nonsurgical treatment of ectopic pregnancy. *Obstetrics Gynaecology* 1992; **80:** 520–1.
35 Batist G, Andrews Jr J L. Pulmonary toxicity of antineoplastic drugs. *J Am Med Assoc* 1981; **246:** 1149–53.
36 White D A, Rankin J A, Stover D E, Gellene R A, Gupta S. Methotrexate pneumonitis. Bronchoalveolar lavage findings suggest an immunologic disorder. *Am Rev Respir Dis* 1989; **139:** 18–21.
37 Akoun G M, Maynaud C M, Touboul J L, Denis M F, Milleron B J, Perrot J Y. Use of bronchoalveolar lavage in the evaluation of methotrexate lung disease. *Thorax* 1987; **42:** 652–5.
38 Akoun G M, Gauthier-Rahman S, Maynaud C M, Touboul J L, Denis M F. Leukocyte migration inhibition in methotrexate-induced pneumonitis. Evidence for an immunologic cell-mediated mechanism. *Chest* 1987; **91:** 96–9.
39 Suzuki K, Rahman S G, Akoun G M. Leukocyte migration inhibition test in drug-induced pneumonitis. *Nippon-Kyobu-Shikkan-Gakai-Zasshi* 1992; **30:** 76–81.
40 Anderson L L, Collins G J, Ojima Y. A study of the distribution of me-thotrexate in human tissues and tumors. *Cancer Res* 1970; **30:** 1344–8.
41 Clarysse A M, Cathey W J, Cartwright G E, Wintrobe M M. Pulmonary disease complicating intermittent therapy with methotrexate. *J Am Med Assoc* 1969; **209:** 1861–4.
42 Arnett F C, Whelton J C, Zizic T M, Stevens M B. Methotrexate therapy in polymyositis. *Ann Rheum Dis* 1973; **32:** 536–46.
43 Gutin P H, Green M R, Bleyer W A, Bauer V L, Wiernik P H, Walker M D. Methotrexate pneumonitis induced by intrathecal methotrexate therapy. *Cancer* 1976; **38:** 1529–34.
44 Elsasser S, Dalquen P, Soler M, Perruchoud A P. Methotrexate-induced penumonitis: appearance four weeks after discontinuation of treatment. *Am Rev Respir Dis* 1989; **140:** 1089–92.
45 Pourel J, Guillemin F, Fener P, Webanck L, Bene M C, Delorme N. Delayed methotrexate pneumonitis in rheumatoid arthritis (letter). *J Rheumatol* 1991; **18:** 303–4.
46 De Bandt M, Rat A C, Palazzo E, Kahn M F. Delayed methotrexate pneumonitis (letter). *J Rheumatol* 1991; **18:** 1943.
47 Hughes G R V. Methotrexate in rheumatoid arthritis. *Ann Rheum Dis* 1990; **49:** 275.
48 Tsai J J, Shin J F, Chen C H, Wang S R. Methotrexate pneumonitis in bronchial asthma. *Int Arch Allergy Immunol* 1993; **100:** 287–90.
49 Kremer J M, Phelps C. Long-term prospective study of the use of methotrexate in the treatment of rheumatoid arthritis. Update after a mean of 90 months. *Arthritis Rheum* 1992; **35:** 138–45.
50 McKendry R J R, Cyr M. Toxicity to methotrexate compared with azathio-prine in the treatment of rheumatoid arthritis. A case-control study of 131 patients. *Arch Int Med* 1989; **149:** 685–9.
51 Rooney T W, Furst D E. Comparison of toxicity in methotrexate treated rheumatoid arthritis patients also taking aspirin or other NSAID. *Arthritis Rheum* 1986; **29:** S76.
52 Bell M J, Geddie W R, Gordon D A, Reynolds W J. Pre-existing lung disease in patients with rheumatoid arthritis may predispose to methotrexate lung. *Arthritis Rheum* 1986; **29:** S75.
53 Golden M R, Katz R S, Balk R A, Neu J, Golden H. The relationship of pre-existing lung disease to the occurrence of methotrexate pneumonitis in rheumatoid arthritis. *Arthritis Rheum* 1990; **33:** S40.
54 Massin F, Coudert B, Marot J P, Foucher P, Camus Ph, Jeannin L. La pneumopathie du methotrexate. *Rev Mal Resp* 1990; **7:** 5–15.
55 Kolarz G, Scherak O, Popp W, *et al.* Bronchoalveolar lavage in rheumatoid arthritis. *Br J Rheumatol* 1993; **32:** 556–61.
56 Chabot F, Aymard B, Lesur O, *et al.* Drug-induced pulmonary diseases: diagnostic, therapeutic and prognostic aspects. A propos of 10 personal case reports. *Rev Mal Respir* 1992; **9:** 593–601.
57 St Clair E W, Rice J R, Snyderman R. Pneumonitis complicating low-dose methotrexate therapy in rheumatoid arthritis. *Arch Intern Med* 1985; **145:** 2035–8.
58 Gispen J G, Alarcon G S, Johnson J J, Acton R T, Barger B O, Koopman W J. Toxicity to methotrexate in rheumatoid arthritis. *J Rheumatol* 1987; **14:** 74–9.
59 Padley S P, Adler B, Hansell D M, Muller N L. High-resolution computed tomography of drug induced disease. *Clin Radiol* 1992; **46:** 232–6.
60 Hansell D M, Kerr I H. The role of high resolution computed tomography in the diagnosis of interstitial lung disease. *Thorax* 1991; **46:** 77–84.
61 Diffuse lung disease. In: Naidich D P, Zerhouni E A, Siegelman S S, eds. *Computed tomography and magnetic resonance of the thorax.* New York: Raven Press Ltd, 1991: 341–405.
62 Bisson G, Drapeau G, Lamoureux G, Cantin A, Rola-Pleszczynski M, Bégin R. Computer based quantitative analysis of gallium-67 uptake in normal and diseased lungs. *Chest* 1983; **84:** 513–7.
63 Elstad M R. Lung biopsy, bronchoalveolar lavage and Gallium scanning. In: Cannon G W, Zimmerman G A, eds. *The lung and rheumatic diseases.* New York: Marcel Dekker, 1990: 117–42.
64 King T E. Idiopathic pulmonary fibrosis. In: King T E, Decker B C, eds. *Interstitial lung disease.* Toronto: Schwartz M I, 1988: 139–69.
65 Jeurissen M E C, Boerbooms A M Th, Festen J, van de Putte L B A, Doesburg W. Serial pulmonary function tests during a randomized, double-blind trial of azathioprine versus methotrexate in rheumatoid arthritis. *Arthritis Rheum* 1991; **34:** S90.
66 Croock A D, Furst D F, Helmers R A, *et al.* Methotrexate does not alter pulmonary function in patients with rheumatoid arthritis. *Arthritis Rheum* 1989; **32:** S60.

67 Velay B, Lamboley L, Massonnet B. Prospective study of respiratory function in rheumatoid arthritis treated with methotrexate. *Eur Respir J* 1988; **1** (supp 2): 371S.
68 Gaensler E A, Carrington C B. Open lung biopsy for chronic diffuse infiltrative lung disease: Clinical, roentgenographic and physiological correlation in 502 patients. *Ann Thorac Surg* 1980; **30:** 411–26.
69 Grubben M J A L, Kerstens P J S M, Wiersma J M, Boerbooms A M T, Festen J. Pleuro-pulmonary involvement in patients with connective tissue disease. The role of open lung biopsy. *Neth J Med* 1993; **43:** 269–76.
70 Cook N J, Carroll G J. Successful reintroduction of methotrexate after pneumonitis in two patients with rheumatoid arthritis. *Ann Rheum Dis* 1992; **51:** 272–4.
71 Kerstens P J S M, Van Loenhout J W A, Boerbooms A M Th, Van de Putte L B A. Methotrexate, pneumonitis and infection (letter). *Ann Rheum Dis* 1992; **51:** 1179.
72 Pasquinucci G, Ferrara P, Castellari R. Daunorubicine treatment of metho-trexate pneumonia. *J Am Med Assoc* 1971; **216:** 2017.
73 Furst D E, Erikson N, Clute L, Koehnke R, Burmeister L F, Kohler J A. Adverse experience with methotrexate during 176 weeks of a longterm prospective trial in patients with rheumatoid arthritis. *J Rheumatol* 1990; **17:** 1628–35.
74 Weinstein A, Marlowe S, Korn J, Farouhar F. Low-dose methotrexate treatment of rheumatoid arthitis, long-term observations. *Am J Med* 1985; **79:** 331–7.
75 Cannon G W, Clegg D O, Samuelson Jr C O, Ward J R. Pulmonary toxicity during treatment of rheumatoid arthritis with methotrexate: prevalence, clinical features, treatment and follow up. *Arthritis Rheum* 1984; **27:** S26
76 Alarcon G S, Tracy I C, Blackburn W D. Methotrexate in rheumatoid arthritis. Toxic effects as the major factor in limiting long-term treatment. *Arthritis Rheum* 1989; **32:** 671–6.
77 Scully C J, Anderson C J, Cannon G W. Long-term methotrexate therapy for rheumatoid arthritis. *Semin Arthritis Rheum* 1991; **20:** 317–31.
78 Buchbinder R, Hall S, Sambrook P N, *et al.* Methotrexate therapy in rheumatoid arthritis: a life table review of 587 patients treated in community practice. *J Rheumatol* 1993; **20:** 639–44.
79 Boh L E, Schuna A A, Pitterle M E, Adams E M, Sundstrom W R. Low-dose weekly oral methotrexate therapy for inflammatory arthritis. *Clin Pharm* 1986; **5:** 503–8.
80 Andersen P A, West S G, Nordstrom D M. Toxicity of chronic therapy with pulse methotrexate in rheumatoid arthritis: potential increased risk of infection. *Arthritis Rheum* 1987; **30:** S60.
81 Hanranhan P S, Scrivens G A, Russell A S. Prospective long term follow-up of methotrexate therapy in rheumatoid arthritis: toxicity, efficacy and radiological progression. *Br J Rheum* 1989; **28:** 147–53.
82 Drosos A A, Psychos D, Andonopoulos A P, Stefani-Nikou S, Tsianos E B, Moutsopoulos H M. Methotrexate therapy in rheumatoid arthritis. A two year prospective follow up. *Clin Rheumatol* 1990; **9:** 333–41.
83 Weinblatt M E, Weissman B N, Holdsworth D E D, *et al.* Long-term prospective study of methotrexate in the treatment of rheumatoid arthritis. 84-month update. *Arthritis Rheum* 1992; **35:** 129–37.
84 Singh G, Fries J F, Williams C A, Zatarain E, Spitz, Bloch D A. Toxicity profiles of disease modifying antirheumatic drugs in rheumatoid arthritis. *J Rheumatol* 1991; **18:** 188–94.
85 Boerbooms A M Th, Jeurissen M E C, Westgeest A A A, Theunisse H, Van de Putte L B A. Methotrexate in refractory rheumatoid arthritis. *Clin Rheumatol* 1988; **7:** 249–56.
86 Kerstens P, Boerbooms A, Brummelkamp E, van de Putte L. Methotrexate in refractory rheumatoid arthritis. Results after 4 years. *Br J Rheumatol* 1993; **32** (suppl 1) 115: 60.
87 Jeurissen M E C, Boerbooms A M Th, Van de Putte L B A, *et al.* Methotrexate versus azathio-prine in the treatment of rheumatoid arthritis. A forty-eight randomized double-blind trial. *Arthritis Rheum* 1991; **34:** 761–72.
88 Haagsma C, van Riel P, van de Putte L. Combination therapy in RA: Sulphasalazine and methotrexate (abstract). *Br J Rheumatol* 1992; **31:** 32.
89 Wijnands M J H, van't Hof M A, van Leeuwen M A, van Rijswijk M H, van de Putte L B A, van Riel P L C M. Long-term second-line treatment: a prospective drug survival study. *Br J Rheumatol* 1992; **31:** 253–8.
90 Van den Hoogen F H J, Boerbooms A M Th, van Lier H J J, van de Putte L B A. Methotrexate in systemic sclerosis: preliminary 24 week results of a placebo controlled double blind trial. *Arthritis Rheum* 1993; **36:** S217.