

## PULMONARY FUNCTION IN RHEUMATOID ARTHRITIS TREATED WITH LOW-DOSE METHOTREXATE: A LONGITUDINAL STUDY

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### SUMMARY

Lung volumes and gas exchange were investigated prospectively in 96 patients with rheumatoid arthritis selected without regard to pulmonary disorders and treated with i.m. methotrexate (MTX) injections [mean weekly dose 13.0 mg (5th-95th percentile (5-95 PC) 7.6-20.8)]. Individual changes over time during MTX treatment [mean duration 2.9 yr (5-95 PC 0.4-5.3)] were assessed by regression analyses in each individual. Forced vital capacity (FVC) remained stable in the majority of patients [mean annual change +0.8% (5-95 PC -8.1 to +14.0) of calculated normal value]. In addition, transfer factor using the indicator gas CO ( $T_{L,CO}$ ) was unaltered in most patients [mean annual change -2.1% (5-95 PC -16.2 to +11.8) of predicted value]. However, there were significant decreases in the forced expiratory volume in 1 s ( $FEV_1$ ) before and after inhalation of 0.2 mg salbutamol [mean annual change -0.8% (5-95 PC -8.4 to +3.2) and -1.3% (5-95 PC -7.8 to +3.9) of the FVC measured, respectively]. In addition, there were significant increases in alveolar-arterial  $P_{O_2}$  gradients ( $P_{(A-a)O_2}$ ) at rest and after exercise [mean annual change +1.7 mmHg (5-95 PC -5.2 to +12.2) and +1.8 mmHg (5-95 PC -3.5 to 9.0), respectively]. Nevertheless, the amounts were small in view of the reliability of the methods applied and reflect, at least in part, the normal process of ageing. The annual change in  $FEV_1/FVC$  was negatively correlated with  $FEV_1/FVC$  at baseline ( $R_s = -0.46$ ,  $P < 0.001$ ). The annual change in  $T_{L,CO}$  was also negatively correlated with  $T_{L,CO}$  at baseline ( $R_s = -0.31$ ,  $P = 0.028$ ). No other risk factors for deterioration of lung volumes or gas exchange were found, including mean weekly MTX dose, age, gender, smoking, presence of rheumatoid factor and pulmonary function at baseline. We conclude that MTX has no major effect on pulmonary function in the majority of patients and that there is no evidence that patients with pre-existing pulmonary disease are at increased risk for further deterioration of lung function.

KEY WORDS: Pulmonary function, Lung, Rheumatoid arthritis, Methotrexate.

LOW-DOSE weekly methotrexate (MTX) is increasingly used in the treatment of rheumatoid arthritis (RA) [1-3]. MTX has a favourable efficacy to toxicity profile over short and intermediate periods compared with other disease-modifying anti-rheumatic drugs (DMARDs) [4]. Nevertheless, in recent years there have been a growing number of communications about MTX-related pulmonary complications [5, 6]. Among the non-infectious adverse effects, interstitial pneumonitis, lung fibrosis, accelerated pulmonary nodulosis and drug-induced asthma have been reported. Among the pulmonary infections, *Pneumocystis carinii* pneumonia has been described most frequently [7]. Lung fibrosis and nodulosis may be pulmonary manifestations of RA itself [8]. A slowly progressive restrictive pattern and a deterioration of gas exchange may develop. Therefore, it may be very difficult to relate this pathology to MTX treatment or the underlying disease, or both.

There is some controversy about the usefulness of pulmonary function testing in patients with RA treated with low-dose MTX [9-11]. In the present study, we investigated lung volumes and gas exchange prospectively in a cohort of patients with RA with the following aims: (1) to determine the incidence of pulmonary complications requiring MTX withdrawal, (2) to assess pulmonary function over time and

(3) to search for risk factors for a loss of pulmonary function.

### PATIENTS AND METHODS

#### Patients

Between September 1988 and July 1992, patients with RA were recruited from the in- and out-patient Department of Rheumatology, University Hospital, Berne. All patients fulfilled the modified ARA criteria [12] and had disease activity sufficient to warrant the introduction of low-dose MTX. Patients were excluded from the study according to the following criteria: renal failure defined by a serum creatinine >1.2 times the upper limit of the reference range; active liver disease with laboratory evidence of liver cell necrosis; patients with a significant history of alcohol consumption and unwillingness to refrain from regular alcohol consumption; active bone marrow disease defined by leucopenia <3000/mm<sup>3</sup> or thrombopenia <100 000/m<sup>3</sup>; patients testing positive for human immunodeficiency virus (HIV); pregnant women and patients of child-bearing age not practising effective contraception. Informed consent was obtained from all patients at the start of the study.

#### Methotrexate treatment

Weekly i.m. MTX injections, usually between 10 and 15 mg, were started. Every single dose applied was documented on a patient control sheet and the cumulative dose calculated. Regular clinical follow-ups were performed, usually every 3 months or in the case

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of deterioration. Appropriate safety investigations included full haematology, liver and renal function tests, and erythrocyte folate concentrations. Weekly MTX doses were repeatedly adjusted according to disease activity, minor side-effects, potential interactions with concomitant drug treatment and renal function. Reasons for stopping MTX were carefully documented and classified into the following categories: pulmonary and non-pulmonary adverse effects of MTX, disorders associated with an increased risk for the development of MTX adverse effects, inefficacy of MTX, remission of RA, and disorders not directly related to RA or MTX. In the case of incomplete follow-up of pulmonary function testing, special attention was paid to verification of non-compliance due to different reasons in order not to miss any adverse effects of MTX. If MTX was stopped for >1 month for any reason, results obtained after the interruption were not included in the evaluations. Non-steroidal anti-inflammatory drugs, low-dose oral corticosteroids and other drug treatments were continued as necessary. Folic acid was substituted in the case of decreased erythrocyte folate level.

#### *Pulmonary function tests*

Before the introduction of MTX, and every year thereafter, an extensive pulmonary assessment was performed. A history was taken about dyspnoea, cough, expectoration and smoking. An extensive physical examination was carried out, looking for signs of pulmonary and cardiovascular diseases. Detailed pulmonary function tests comprised forced vital capacity (FVC), forced expiratory volume in 1 s (FEV<sub>1</sub>) before and after inhalation of 0.2 mg salbutamol, FEV<sub>1</sub>/FVC, residual volume (RV), total lung capacity (TLC) and transfer factor using the indicator gas CO (T<sub>LCO</sub>). After puncture of the radial artery at rest and after exercise, if possible despite physical disability, arterial blood samples were analysed for partial pressures of oxygen (P<sub>aO<sub>2</sub></sub>) and carbon dioxide (P<sub>aCO<sub>2</sub></sub>), pH, base excess (BE) and CO haemoglobin (HbCO). All tests were performed by experienced staff using the same apparatus. Observed values were compared with those predicted for patients of similar age, sex and height as described by the official statement of the European Respiratory Society [13, 14]. Alveolar (A)-arterial (a) P<sub>O<sub>2</sub></sub> gradients, P<sub>(A-a)O<sub>2</sub></sub>, were calculated according to the alveolar gas equation  $P_{(A-a)O_2} \text{ (mmHg)} = [( \text{barometric pressure (mmHg)} - 47 ) \times 0.209] - (1.25 \times P_{aCO_2} \text{ (mmHg)}) - P_{aO_2} \text{ (mmHg)}$ . Values were considered normal if P<sub>(A-a)O<sub>2</sub></sub> (mmHg) was less than two-fifths of the age (in years) of the patient. Smokers were defined by a HbCO  $\geq$  2.0% at rest.

Chest X-rays in two projections were performed by standard techniques. Data collection was stopped in June 1994.

#### *Calculations*

The mean weekly MTX dose was estimated by dividing the cumulative dose at the time point of the

last pulmonary function testing by the duration of treatment. Change in pulmonary function over time was assessed by calculations of slopes for each parameter in each individual. In the 22 patients with two measurements only, the slope of the fitted line was calculated. In the 57 patients with three or more values, linear regression analyses were performed. Each individual graph was carefully studied for deviation from linearity (sudden change, curvature). Use of the linear model was judged appropriate for all parameters. The mean coefficients of variations calculated and the percentage of patients with coefficients of variation <0.2 as an indicator of good predictive power of the linear regressions were as follows: FVC 0.04, 100%; FEV<sub>1</sub> before inhalation 0.04, 100%; FEV<sub>1</sub> after inhalation 0.05, 98%; T<sub>LCO</sub> 0.10, 94%; P<sub>(A-a)O<sub>2</sub></sub> at rest 0.25, 46%; P<sub>(A-a)O<sub>2</sub></sub> after exercise 0.35, 28%. Therefore, the precision of the slopes estimated was good for FVC, FEV<sub>1</sub> before and after salbutamol, and T<sub>LCO</sub>, but poor for P<sub>(A-a)O<sub>2</sub></sub> at rest and after exercise.

Further statistical analyses included calculations of mean, standard deviation (s.d.), 5th and 95th percentiles (5-95 PC), one-group *t*-test and Spearman's rank correlation *R<sub>s</sub>*. The significance level was set at *P* = 0.05.

## RESULTS

The 96 patients with RA included in the study had a mean disease duration of 9.3 yr (s.d. 10.0) and 72 (75%) patients were rheumatoid factor positive. Mean age was 61 yr (s.d. 13.6), 66 were women, 30 were men; mean weight was 64 kg (s.d. 11.3), mean height 162 cm (s.d. 9.2) and mean serum creatinine at entry to the study 82  $\mu$ mol/l (s.d. 17.3) (reference range 44-115). Serum creatinine was 95% of the baseline value (s.d. 13.5) at the end of the study. Thirty-one (32%) patients were smokers.

Lung volumes and gas exchange before treatment with low-dose MTX are summarized in Table I.

Until the end of the study in July 1994, the mean duration of MTX treatment was 2.9 yr (5-95 PC 0.4-5.3) and mean weekly MTX dose was 13.0 mg (5-95 PC 7.6-20.8). The time course of the number of patients with pulmonary function tests and MTX withdrawal is shown in Fig. 1. Follow-up was incomplete in 18 patients (18.8%) due to different MTX-unrelated causes and MTX was stopped in a total of 35 patients (36.5%). The reason was remission of RA in nine patients (9.4%), concomitant disorders not related to RA or MTX in seven patients (7.3%), inefficacy of MTX in four patients (4.2%), toxicity of MTX in 15 patients (15.6%) with adverse effects of MTX in 10 patients (10.4%) or concomitant disorders necessitating interruption of MTX treatment in order to prevent MTX adverse effects in five patients (5.2%): gastrointestinal intolerance (*n* = 3), stomatitis (*n* = 2), 4-fold increase of aminotransferases (*n* = 1), cutaneous vasculitis (*n* = 1), accelerated nodulosis (*n* = 1), post-injection pruritus (*n* = 1), extended infections (*n* = 3), infection of a hip prosthesis (*n* = 1) and development of

TABLE I

Lung volumes and gas exchange in 96 patients with rheumatoid arthritis before and during treatment with low-dose methotrexate. For abbreviations and calculation of predicted values, see Patients and methods. The significance levels of the mean annual changes during treatment with MTX were calculated by the one-group *t*-test

Parameter	Unit	Mean values at baseline (5th-95th percentile)	Mean annual change during treatment with MTX (per year) (5th-95th percentile)	<i>P</i>
FVC	ml	3427 (1930-5240)	-21 (-290 to +316)	n.s.
	% predicted	117 (89-162)	+0.8 (-8.1 to +14.0)	n.s.
FEV <sub>1</sub> /FVC before inhalation	%	70 (47-87)	-0.8 (-8.4 to +3.2)	< 0.05
FEV <sub>1</sub> /FVC after inhalation	%	73 (50-88)	-1.3 (-7.8 to +3.9)	< 0.001
T <sub>LCO</sub>	ml/min/mmHg	21.4 (12.9-32.0)	-0.6 (-4.0 to +1.9)	< 0.01
	% predicted	88 (61-115)	-2.1 (-16.2 to +11.8)	< 0.05
P <sub>(A-a),O<sub>2</sub></sub> at rest	mmHg	19.9 (0.6-34.5)	+1.7 (-5.2 to +12.2)	< 0.001
P <sub>(A-a),O<sub>2</sub></sub> after exercise	mmHg	9.7 (-3.4 to 29.6)	+1.8 (-3.5 to +9.0)	< 0.01

respiratory symptoms ( $n = 2$ ). A 70-yr-old man developed a probable MTX pneumonitis according to Searles' or Carson's criteria [15, 16] within a few days after 6 months of low-dose MTX treatment with a cumulative dose of 405 mg. A 77-yr-old man showed progression of a pre-existing rheumatoid lung disease with progressing restrictive ventilatory defect and deteriorating gas exchange after 16 months of MTX treatment with a cumulative dose of 1305 mg. The relation to MTX treatment is arguable. Therefore, MTX was stopped in two patients because of respiratory complaints, resulting in an incidence of 0.72 withdrawals per 100 patient-years due to pulmonary complications.

Individual annual changes in lung volumes and gas exchange during MTX treatment are summarized in

Table I. FVC remained stable over time. In contrast, mean FEV<sub>1</sub>/FVC decreased little but statistically significantly before and after inhalation ( $t = 2.04$ ,  $P < 0.05$  and  $t = 3.35$ ,  $P < 0.001$ , respectively). In addition, gas exchange deteriorated with a significant decrease of mean T<sub>LCO</sub> ( $t = 2.58$ ,  $P < 0.01$  for observed values and  $t = 1.88$ ,  $P < 0.05$  for measured values related to predicted values) and with significant increases in mean P<sub>(A-a),O<sub>2</sub></sub> at rest and after exercise ( $t = 3.22$ ,  $P < 0.001$  and  $t = 2.68$ ,  $P < 0.01$ , respectively).

Risk factors for a loss of pulmonary function during MTX treatment were sought. No effect of gender, smoking and the presence of rheumatoid factor became evident. In addition, no correlations were found

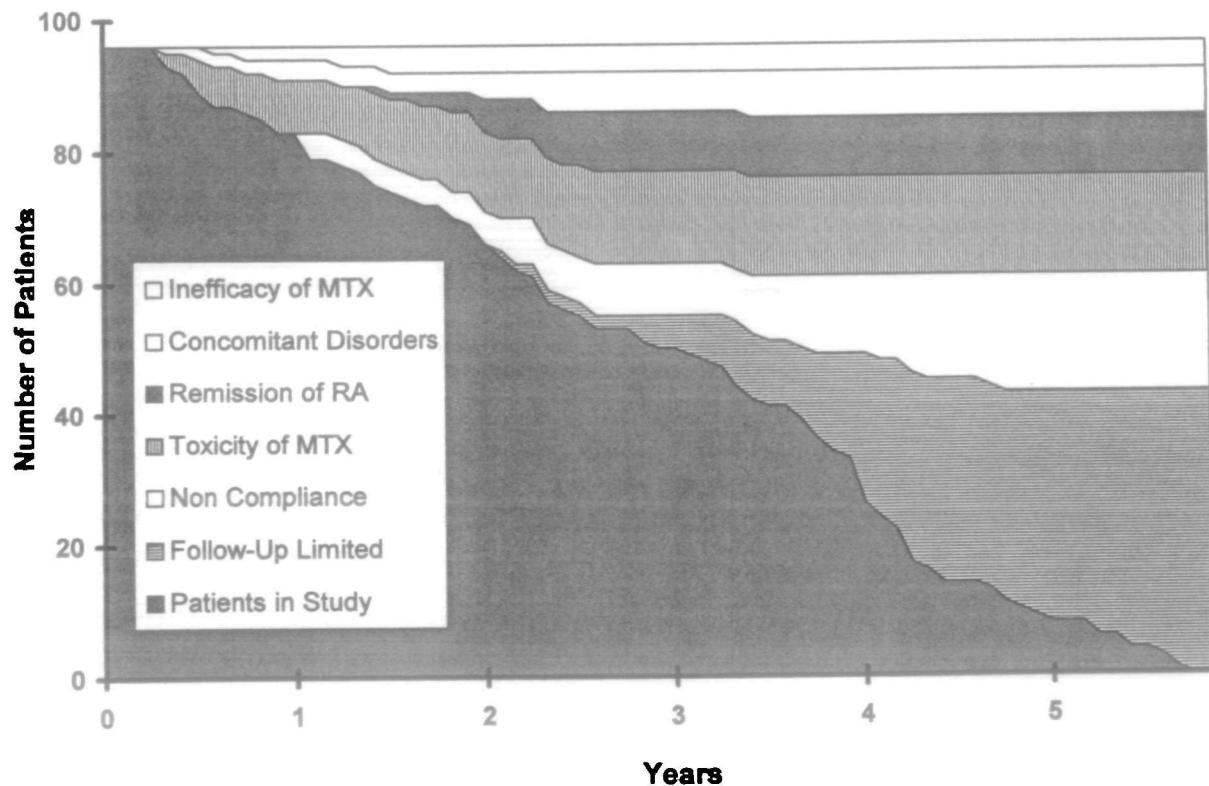


FIG. 1.—Life table graph with the number of patients with pulmonary function tests and withdrawal of MTX due to different reasons over time.

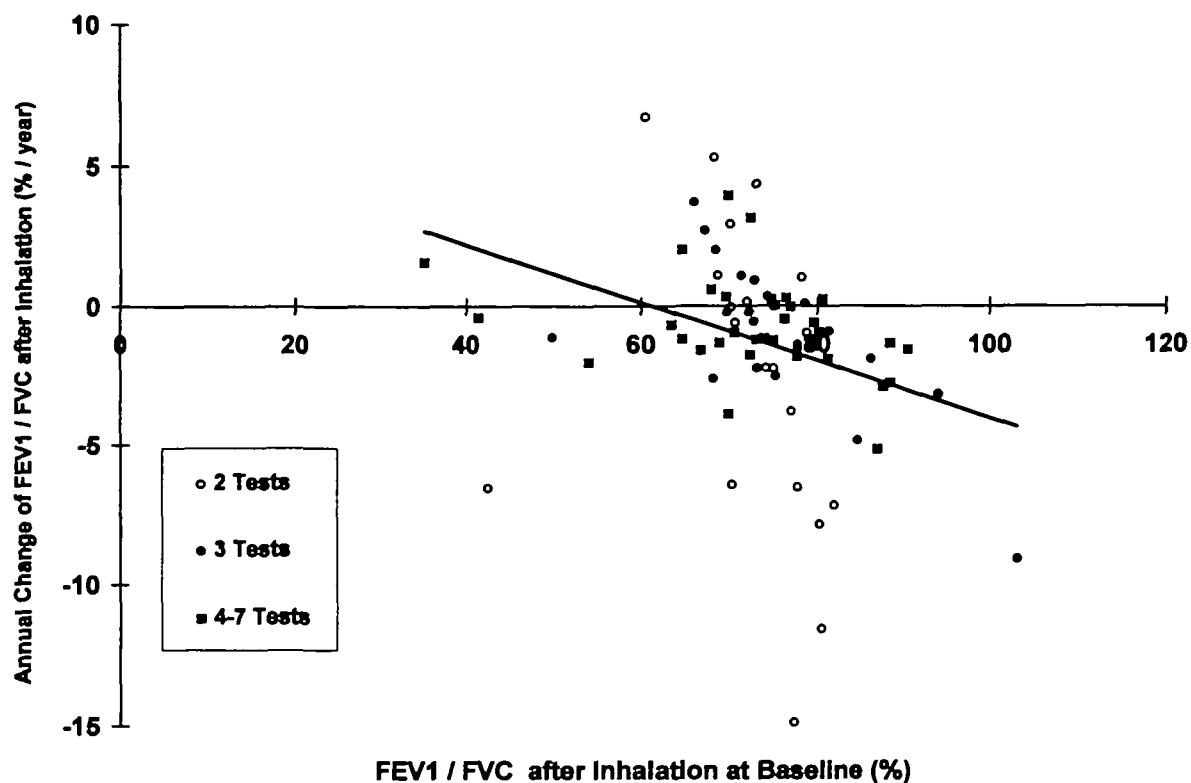


FIG. 2.—Plot of the annual change in  $FEV_1/FVC$  versus  $FEV_1/FVC$  at baseline after inhalation. Patients with a small number of tests showed a higher variability of the slopes calculated than patients with 4–7 tests.

between individual annual change in lung volumes or gas exchange and age, mean weekly MTX dose or FVC at baseline. In contrast, significant negative correlations were revealed between individual annual change in  $FEV_1/FVC$  and  $FEV_1/FVC$  at baseline before and after inhalation (both  $R_s = -0.46$ ,  $P < 0.001$ ) (Fig. 2).

These findings were upheld for the proportional annual changes of  $FEV_1/FVC$  in relation to  $FEV_1/FVC$  at baseline ( $R_s = -0.39$ ,  $P < 0.0004$  and  $R_s = -0.27$ ,  $P = 0.017$ , respectively). In addition, a negative correlation was found between individual annual change in  $T_{LCO}$  and  $T_{LCO}$  at baseline ( $R_s = -0.31$ ,

TABLE II  
Reasons for deterioration of FVC in 10 patients with RA treated with low-dose MTX

Number	Age	Sex	Individual change in FVC (%) predicted per year	Individual change in $FEV_1/FVC$ after inhalation (% per year)	Individual change in $T_{LCO}$ (%) predicted per year	Individual change in $P_{(A-a)O_2}$ after exercise (mmHg per year)	Reasons for deterioration	MTX related
1	77	m	-25.5 (2)	1.0 (2)	-24.7 (2)	NA	Progression of interstitial pneumopathy	(-)
2	71	f	-11.8 (2)	5.3 (2)	NA	NA	Cardiac failure	-
3	63	f	-8.1 (7)	1.6 (7)	NA	-0.1 (2)	Progression of COPD, pulmonary embolism	-
4	80	m	-8.1 (2)	-11.6 (2)	-3.4 (2)	NA	Progression of pleural effusions	-
5	79	f	-7.7 (2)	1.1 (2)	4.5 (2)	9.7 (2)	Deterioration within normal range	-
6	76	f	-7.5 (3)	3.7 (3)	-0.2 (3)	NA	Deterioration within normal range	-
7	79	f	-7.3 (3)	-1.1 (3)	11.8 (2)	NA	Deterioration of asthma bronchiale	-
8	63	m	-6.4 (3)	-0.2 (3)	-13.5 (3)	1.9 (2)	Progression of Caplan's syndrome, recurrent pleural effusions	(-)
9	71	m	-6.2 (4)	-2.0 (4)	-2.7 (4)	NA	Progression of COPD	-
10	55	m	-6.1 (4)	-3.9 (4)	-11.9 (4)	NA	Thoracic surgery, deterioration of asthma bronchiale	-

NA = not available (number of pulmonary function tests).

$P = 0.028$ ), which became insignificant after analysing the proportional annual change in  $T_{LCO}$  in relation to  $T_{LCO}$  at baseline ( $R_s = -0.22$ , n.s.). Finally, a negative correlation was found between the individual annual change in FVC and  $P_{(A \rightarrow)O_2}$  after exercise at baseline ( $R_s = -0.35$ ,  $P = 0.029$ ).

Table II summarizes information about 10 patients with a pronounced loss of FVC, defined by negative annual changes of FVC below the 16th percentile of the whole cohort. All clinical, functional and radiological findings were reviewed and reasons for deterioration postulated. In addition, 10 patients had a deterioration of gas exchange with either a decrease in  $T_{LCO}$  below the 16th percentile ( $n = 7$ ) or an increase in  $P_{(A \rightarrow)O_2}$  after exercise above the 84th percentile ( $n = 3$ ). Reasons were postulated to be deterioration of asthma bronchiale ( $n = 1$ ), progression of chronic obstructive pulmonary disease (COPD) ( $n = 1$ ) or not evident ( $n = 8$ ).

### DISCUSSION

The present study assessed pulmonary function prospectively in a cohort of 96 patients with RA selected without regard to pulmonary disorders. The withdrawal rate due to pulmonary complications was low. The prevalence of MTX pneumonitis was 1% after a mean treatment period of 2.9 yr. This rate was at the lower part of the range between 0.3 and 11.6% reported by several retrospective and prospective studies [5]. The incidence of acute MTX pneumonitis was one case per 276 patient-years which was considerably lower than the rates of one case per 26 and 50 patient-years, respectively, observed by retrospective studies [16, 17]. None of the patients developed an opportunistic pulmonary infection. Microscopic examinations and extensive cultures of sputum and bronchoalveolar lavage fluid, and serological tests for common respiratory viruses, *Mycoplasma*, rickettsia and *Legionella*, were all negative in the patients experiencing respiratory symptoms. Two patients showed a worsening of pre-existing interstitial pulmonary disease. In addition, deterioration of asthma bronchiale, progression of COPD, pulmonary embolism, pleural effusions, thoracic surgery and cardiac failure were regarded as being responsible for declines in pulmonary function in some patients. There are little pathognomonic clinical, laboratory or radiological features which allow differentiation between MTX-related pulmonary pathology and underlying diseases. Chronic interstitial pneumonitis with lymphocytic and plasma cell infiltrates as well as fibrosis unrelated to drug therapy can be found in lung biopsies of patients with RA [18]. Exacerbation of this lingering process by MTX is possible. Nevertheless, prevalence and incidence rates of chronic MTX-related interstitial pneumonitis will remain arbitrary and are deliberately not calculated in the present study.

Values of FVC were high at baseline and remained stable throughout the observation period in the majority of our patients. These findings are in agreement with longitudinal assessments of patients

with RA treated with low-dose MTX over 24 and 42 weeks, respectively [10, 11]. Similarly, no significant loss of FVC was found in patients with RA treated with D-penicillamine and various other DMARDs for at least 6 months [19]. In contrast, follow-up studies reported a significant decrease in FVC in patients with RA treated with aurothiomalate for 2 yr and different DMARDs for 8 yr, respectively [20, 21].

Our data revealed a significant annual decrease in  $FEV_1/FVC$  both before and after inhalation, indicating some increasing airflow obstruction. Patients already with an airflow obstruction at baseline were not at an increased risk of deterioration during MTX treatment. These findings contrast with other longitudinal evaluations, which found no significant changes of  $FEV_1$  over 24 and 42 weeks of MTX treatment [10, 11]. Nevertheless, a case report gave evidence for the induction of clinical and laboratory features of asthma and an increase in airway responsiveness to methacholine chronologically related to the weekly intake of 7.5 mg MTX [22]. Another case report described a patient with a history of well-controlled asthma, whose respiratory symptoms reappeared while receiving MTX therapy [23]. However, in unselected patients with RA treated with different DMARDs, the frequency of airflow obstruction and bronchial reactivity was significantly increased compared to controls with minor degenerative joint disorders [24]. Follow-up assessments of patients treated with D-penicillamine, aurothiomalate and other DMARDs gave conflicting results, with only some of them developing obstructive ventilatory defects [19–21]. MTX has been recommended as an effective and safe glucocorticoid-sparing agent in asthma [25, 26]. However, its efficacy remains controversial [27]. The question emerged whether MTX treats or induces asthma [28]. In analogy, the question can be added whether MTX diminishes airways inflammation associated with bronchial narrowing and hyper-reactivity in RA or causes drug-induced airflow obstruction.

Our results showed a deterioration of gas exchange over time reflected by a significant annual decrease in  $T_{LCO}$  and significant annual increases in  $P_{(A \rightarrow)O_2}$  at rest and after exercise. The latter have to be interpreted with caution as values in individual patients revealed considerable variations over time, resulting in high coefficients of variation of the annual changes calculated. In addition, only half of the patients had measurements after exercise because of physical disability. Nevertheless, our findings differ from observations in smaller numbers of patients treated with MTX over shorter periods [10, 11]. On the other hand, follow-up assessments of patients treated with D-penicillamine, aurothiomalate and various other DMARDs gave conflicting outcomes with decreases [19, 20] and increases [21] of  $T_{LCO}$ . Again, our patients with a low  $T_{LCO}$  or high  $P_{(A \rightarrow)O_2}$  at baseline did not have an increased risk for a further deterioration during MTX therapy.

In summary, the present study illustrates the favourable safety of low-dose MTX treatment in RA.

Withdrawal of MTX due to pulmonary side-effects was rare and represents a justified risk in view of the improvement of the disease in the majority of patients. FVC remained stable once allowance had been made for the physiological effects of ageing. Decreases in expiratory airflow and gas exchange were measured. Although these changes were statistically significant, the amounts were moderate and clinically insignificant in view of the reliability of the methods applied [13, 14] and reflect, at least in part, the normal process of ageing. Considerable interindividual differences were observed. However, we were unable to detect risk factors such as mean weekly MTX dose, age, gender, smoking, the presence of rheumatoid factor and pulmonary function tests at baseline. In our patients, disease activity is changing all the time. Because of this no associations with disease activity were explored. This is in contrast to an attempt in a cross-sectional study in juvenile chronic arthritis [29]. Our study also demonstrates the difficulty and occasional impossibility of categorizing pulmonary abnormalities into pulmonary involvement of RA, concurrent unrelated pulmonary diseases and manifestations of adverse drug reactions. It rather emphasizes the interrelated nature of the clinical presentation of each patient who deserves individual evaluation. Our practical experience during this study showed that pulmonary function tests at baseline helped in discerning the different causes of respiratory symptoms developed during MTX treatment. However, in view of the data presented, costly routine measurements of lung volumes and gas exchange no longer seem justified in all patients. Pulmonary function tests before and during MTX treatment are recommended only in the case of a history of lung disease, the presence of respiratory symptoms, abnormal clinical signs or alterations on chest X-rays.

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