**Pulmonary Function in Patients Receiving Long-term Low-dose Methotrexate**

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**Study objective:** Acute interstitial pneumonitis is the main pulmonary side effect during methotrexate (MTX) treatment for rheumatoid arthritis. The aim of the study was to determine the following: (1) the incidence of MTX-induced pneumonitis during low-dose long-term MTX treatment for chronic arthritis; (2) whether periodic pulmonary function tests were useful for detecting MTX pneumonitis before clinical symptoms; and (3) whether any subclinical abnormality of pulmonary function was present in asymptomatic patients receiving MTX treatment.

**Design:** Pulmonary function tests, including diffusing capacity for carbon monoxide (Dco) measurements, were performed in 124 patients receiving low-dose MTX for rheumatologic diseases at the time of initiating treatment, and then at 3 months, 6 months, and at 6-month intervals thereafter. Mean duration of treatment was 23 months.

**Results:** MTX treatment was interrupted in six patients for acute onset of clinical symptoms; criteria for diagnosis of MTX pneumonitis were fulfilled in four cases (incidence: 3.2%); no risk factor could be identified. No significant decrease in pulmonary function parameters could be observed before the onset of clinical symptoms of MTX pneumonitis, and this adverse effect could not be predicted by periodic function tests. A statistically significant decrease was found in FVC (−2.2%, p=0.04), FEV1 (−5.0%, p<0.001), and diffusing capacity per alveolar volume, Dco/Va (−4.8%, p=0.03), but not Dco (−1.3%, p=0.05), in the 118 other asymptomatic patients during MTX treatment.

**Conclusion:** We found minor subclinical alterations in pulmonary function in asymptomatic patients receiving low-dose long-term MTX treatment, but periodic pulmonary function tests did not allow us to detect MTX-induced pneumonitis before clinical symptoms. Therefore, we recommend that these tests should not be systematically performed while patients are receiving treatment.

Methotrexate (MTX) is a widely used antineoplastic agent.1 The value of low-dose MTX is also well established in rheumatoid diseases, especially in the treatment of refractory rheumatoid arthritis.2-4 Most patients are able to continue MTX treatment, with generally sustained efficacy, for long intervals.5

The main pulmonary side effect of MTX is an interstitial pneumonitis. Its incidence has been found to be about 7 to 8%, in studies in which MTX at antineoplastic doses was used, in combination with other cytotoxic agents.6 However, these studies did not systematically rule out a contribution of infectious processes.7 Since 1983, acute MTX-induced pneumonitis has also been reported after low-dose therapy (<20 mg/wk) for rheumatoid arthritis.8-13 Although MTX pneumonitis is not considered a dose-related phenomenon, the incidence of this adverse effect during low-dose and long-term MTX therapy needs further investigation.

Pulmonary function tests during MTX-pneumonitis may show a restrictive ventilatory defect with an impairment in the carbon monoxide diffusing capacity (Dco).14 It is known that in patients receiving other cytotoxic drugs such as bleomycin, abnormalities in pulmonary function can be detected before the patients become symptomatic.15

We report a prospective survey of patients who were beginning a low-dose MTX treatment for chronic arthritis. The aim of the study was to determine the following: (1) the incidence of MTX-induced pneumonitis during low-dose long-term MTX treatment for chronic arthritis; (2) whether periodic pulmonary function tests were useful for detecting MTX pneumonitis before clinical symptoms; and (3) whether any subclinical abnormality of pulmonary function was...
present in asymptomatic patients receiving MTX treatment.

**Materials and Methods**

**Population Studied**

We prospectively studied each patient who was beginning low-dose weekly MTX therapy, in a department of rheumatology, from 1985 to 1992. We studied 124 patients for a mean period of 23 months (range, 1 to 85 months). The patients were treated for rheumatoid arthritis (115 patients), psoriatic rheumatism (6 patients), or systemic lupus erythematosus (3 patients). MTX treatment was begun after all conventional treatments, including salazopyrine, D-penicillamine, and gold therapy, had led to intolerance or inefficacy. MTX, 7.5 to 15 mg, was administered weekly, by mouth or by IM injection. The mean age in this group of patients was 56 years (range, 22 to 85 years); 68 patients (71%) were women. A control group was not available.

**Design of the Study**

Physical examination was assessed before the treatment was initiated, then 3 months after the onset of treatment, and repeated every 6 months thereafter. Pulmonary function tests were performed with the same frequency, including the measurement of FVC, FEV1, total lung capacity (TLC), Dco, and diffusing capacity per alveolar volume (Dco/Va). Clinical evaluation of disease activity, including the use of Lee and Ritchie scales, radiographic analysis, and standard laboratory measures of disease activity, were assessed with the same frequency. Standard laboratory measures for hematologic, renal, and hepatic toxicity were performed at each clinical assessment. Clinical or biological evidence of inefficacy or unbearable extrapulmonary toxic reactions were considered reason for terminating the treatment.

MTX treatment was immediately interrupted if patients showed acute or subacute onset of respiratory symptoms, such as cough and/or dyspnea, without evidence of infectious process. Patients with MTX pneumonitis were identified using the criteria described by Searles and Mc Kendry:10 (1) acute onset of shortness of breath; (2) temperature greater than 38.0°C; (3) tachypnea of 25 breaths or more and a nonproductive cough; (4) radiologic evidence of pulmonary interstitial or alveolar infiltrates; (5) WBC count of 15×10^9/L or less (with or without eosinophilia); (6) negative blood and sputum cultures for pathogenic organisms (obligatory); (7) pulmonary function tests demonstrating restrictive pulmonary function with decreased diffusion capacities; (8) PaO₂ on room air of less than 55 mm Hg at time of hospital admission; and (9) biopsy specimen histopathologic findings consistent with bronchiolitis or interstitial pneumonitis with giant cells and without evidence of pathogenic microorganisms, eg, *Pneumocystis carinii*. The diagnosis of MTX pneumonitis was stated "definite" as the presence of at least six of the nine criteria, "probable" as five of nine, and "possible" as four of nine. Treatment of MTX pneumonitis included withdrawal of MTX therapy and continuation of oral prednisone therapy with no increase in dose.

**Methods**

Spirometry and maximal expiratory flow rates were measured using a rolling-seal spirometer. All spirometry measurements were made from at least three acceptable curves and two curves with FEV1 and FVC within 5%, according to the recommendations of the American Thoracic Society. Dco was determined by the single breath-holding method using computerized equipment, according to standard techniques.17 The patients were requested to avoid smoking before the lung function tests. The breath-holding time was preset to 10 s, and the washout volume was set to 750 mL. The inspired and alveolar samples were analyzed for oxygen with a paramagnetic oxygen analyzer. For the measurement of carbon monoxide and helium, gas analyses were performed with a carbon monoxide electrochemical analyzer and a thermal conductivity helium analyzer. The basic formula recommended by the American Thoracic Society17 was applied to the calculation of Dco. Dco was corrected for hemoglobin concentration, according to the equation of Cotes and coworkers,15 in which 14.6 g/dL is the standard value of hemoglobin: hemoglobin adjusted Dco=observed Dco−[(10.22+hemoglobin)/1.7×hemoglobin]). A venous blood sample was drawn before the transfer test for determination of hemoglobin concentration. Analysis was based on measurement of the transmission of light through the sample.

**Statistical Analysis**

Data are presented as the mean±SD. Normal values for pulmonary function tests were calculated according to the recommendations of the European Respiratory Society19,20 Calculations for descriptive statistics were done using statistical software (Epi info R V5.01 French).21 The paired t test was used to evaluate the significance of differences before and while receiving MTX treatment. The nonparametric Kruskall Wallis’s H test was used to compare the variables between the patients with MTX pneumonitis and the other patients. The x² test was calculated to evaluate the difference of sex ratio between these two subgroups of patients. Statistical significance was set at p<0.05.

**Results**

**Incidence of MTX Pneumonitis**

Four patients developed MTX pneumonitis according to criteria from Searles and Mc Kendry;16 three had

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**Table 1—Characteristics of the Four Patients Who Developed MTX Pneumonitis**

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>56</td>
<td>62</td>
<td>58</td>
<td>68</td>
</tr>
<tr>
<td>Sex</td>
<td>M</td>
<td>F</td>
<td>F</td>
<td>F</td>
</tr>
<tr>
<td>Duration of rheumatoid arthritis, yr</td>
<td>18</td>
<td>8</td>
<td>5</td>
<td>16</td>
</tr>
<tr>
<td>Preexisting lung disease</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Tobacco use</td>
<td>Never</td>
<td>Never</td>
<td>Never</td>
<td>Never</td>
</tr>
<tr>
<td>MTX dosage on hospital admission, mg-wk⁻¹</td>
<td>10</td>
<td>7.5</td>
<td>7.5</td>
<td>15</td>
</tr>
<tr>
<td>Duration of MTX treatment, mo</td>
<td>22</td>
<td>5</td>
<td>12</td>
<td>36</td>
</tr>
<tr>
<td>Route of MTX administration</td>
<td>IM</td>
<td>Oral</td>
<td>Oral</td>
<td>Oral</td>
</tr>
<tr>
<td>Concomitant treatment by oral prednisone, mg-d⁻¹</td>
<td>15</td>
<td>10</td>
<td>10</td>
<td>7.5</td>
</tr>
<tr>
<td>Serum creatinine, μmol/L⁻¹</td>
<td>101</td>
<td>111</td>
<td>95</td>
<td>91</td>
</tr>
</tbody>
</table>
a definite diagnosis, defined as the presence of at least six criteria; one had a probable diagnosis with five criteria. Two other cases were not taken into account as the criteria were insufficient: one patient with four criteria (possible diagnosis) and one patient with three criteria. This result corresponds to an incidence of 4 cases among 124 patients (3.2%). Drug-induced bronchospasm was not observed. Several cases of bacterial bronchopneumonia occurred, which regressed rapidly after antibiotic therapy, and did not require the interruption of MTX therapy.

First Manifestations of MTX Pneumonitis

In these patients, pulmonary symptoms of MTX pneumonitis appeared at months 5, 12, 22, and 36 (mean, 18.8 months) (Table 1). The main symptom was an acute dyspnea with dry cough in the four patients (Table 2). In one patient, sudden dyspnea, with subsequent fever and hypoxemia, revealed a pneumothorax complicating a bilateral infiltrative pneumonia. Fever (temperature of 38°C) was present in three patients. Virus isolation, blood cultures, and sputum cultures were negative in all cases. A complete clinical and radiologic recovery took place in all patients after 1 or 2 months.

In the four patients, results of pulmonary function tests were normal at the onset of the MTX treatment. Interestingly, they remained normal during MTX treatment in each case. No significant decrease in FEV₁, FVC, FEV₁/FVC, TLC, Dco, or Dco/Va could be observed before the onset of clinical symptoms, as shown in Figure 1. The values of FEV₁, FVC, TLC, and Dco were decreased in the four patients after the occurrence of clinical MTX-induced pneumonitis. Flow parameters rapidly returned to normal values thereafter, whereas Dco remained at a low value in one patient (Fig 1) and slowly returned to normal values in the three other patients (not shown). Relative kinetics of clinical symptoms and alterations in pulmonary function test results are illustrated in Figure 1 (patient 1).

Risk Factors for MTX Pneumonitis

None of the four patients who developed MTX pneumonitis was known to have preexisting lung disease or previous chest radiographic abnormalities (Table 1). The four patients were nonsmokers. Results of pulmonary function tests before MTX treatment were within the normal range in these four patients: FVC was, respectively, 83%, 127%, 99%, and 103% of predicted values; FEV₁ was 108%, 97%, 93%, and 97%; TLC was 104%, 106%, and 98% (not done in patient 4); Dco was 109%, 89%, 80%, and 87%; and Dco/Va was 130%, 89%, 80%, and 87%. These four patients received concomitant long-term corticosteroid therapy, without any recent change in regimen. No statistically significant difference in age, sex ratio, and duration of treatment appeared among these four patients and the 118 other patients without clinical symptoms: age (years), 59.5±7.5 vs 55.8±12.3 (p>0.05); sex ratio (male to female), 1/3 vs 34/84 (p>0.05); and duration of treatment (months), 18.8±13.5 vs 23.3±21.6 (p>0.05). None of the cases occurred during obvious worsening in articular or systemic symptoms of the rheumatologic disease.

Changes in Pulmonary Function Test Results in Patients Receiving MTX Treatment Who Did Not Develop MTX Pneumonitis

Whether MTX treatment induces changes in pulmonary function parameters was studied in the population of the 118 patients without clinical symptoms in whom MTX interruption was not required. In each patient, the pulmonary function parameters at the latest test under MTX treatment were compared with the same parameters before MTX treatment. We considered a variation to be significant when it exceeded ±20%. In 7 patients (5.9%), FVC and/or FEV₁ de-

<table>
<thead>
<tr>
<th>Table 2—Clinicoradiologic Findings in the Four Patients With MTX Pneumonitis</th>
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</thead>
<tbody>
<tr>
<td><strong>Patient No.</strong></td>
</tr>
<tr>
<td>Acute onset of dyspnea</td>
</tr>
<tr>
<td>Dry cough</td>
</tr>
<tr>
<td>Temperature ≥38°C</td>
</tr>
<tr>
<td>Interstitial infiltrates on chest radiograph</td>
</tr>
<tr>
<td>Interstitial infiltrates on CT scan of the chest</td>
</tr>
<tr>
<td>BAL</td>
</tr>
<tr>
<td>Total cell count, mL⁻¹</td>
</tr>
<tr>
<td>Lymphocytes, %</td>
</tr>
<tr>
<td>Neutrophils, %</td>
</tr>
<tr>
<td>Eosinophils, %</td>
</tr>
<tr>
<td>Macrophages, %</td>
</tr>
<tr>
<td>Cultures of BAL</td>
</tr>
</tbody>
</table>

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Liver function tests remained normal throughout treatment.

**Figure 1.** The relation between time and pulmonary function tests in patient 1 who developed MTX pneumonitis. MP=onset of clinical symptoms of MTX pneumonitis.

Discussion

Most of the studies estimating the frequency of MTX pneumonitis concern the antineoplastic use of high-dose MTX and are retrospective studies. It has been considered that a low-dose MTX regimen may reduce the incidence of such problems. Varying incidences are reported in studies on the use of MTX in the treatment of rheumatoid arthritis: from 0.3% to 11.6% in retrospective studies, and from 0.7% to 7.7% in prospective studies (review in reference 14). We personally observed four cases of MTX pneumonitis among 124 patients during a mean period of 23 months. This 3.2% incidence is lower than the estimate given for anticancer therapy. Infectious pulmonary disease was ruled out in all cases by normal findings from viral and bacterial investigations.

Although underlying rheumatoid lung disease cannot be categorically ruled out, the diagnosis of drug-induced pneumonitis seems more probable, since clinical symptoms appeared in all four patients while rheumatoid arthritis was improved or stabilized, and since all clinical and functional manifestations disap-
Table 3—Variations in Results of Pulmonary Function Tests During MTX Treatment in the 118 Patients Without Clinical Symptoms in Whom MTX Therapy Interruption Was Not Required*

<table>
<thead>
<tr>
<th>MTX Therapy</th>
<th>Before</th>
<th>During</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC, L</td>
<td>3.12 (0.88)</td>
<td>3.05 (0.85)</td>
<td>0.04</td>
</tr>
<tr>
<td>FEV&lt;sub&gt;1&lt;/sub&gt;, L</td>
<td>2.40 (0.72)</td>
<td>2.28 (0.71)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dco, mmol·min&lt;sup&gt;-1&lt;/sup&gt;·kPa&lt;sup&gt;-1&lt;/sup&gt;</td>
<td>7.20 (1.53)</td>
<td>7.10 (1.56)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Dco/V&lt;sub&gt;A&lt;/sub&gt;, mmol·min&lt;sup&gt;-1&lt;/sup&gt;·kPa&lt;sup&gt;-1&lt;/sup&gt;·L&lt;sup&gt;-1&lt;/sup&gt;</td>
<td>1.80 (0.39)</td>
<td>1.83 (0.41)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

*Data are means (SD).

appeared a few weeks after MTX therapy was interrupted. No predisposing factor for MTX pneumonitis was found in this study. Abnormalities of chest radiographs previous to MTX treatment were not present in the four patients who further developed MTX pneumonitis. Age, sex, smoking, duration of therapy, and underlying pulmonary disease have not been found to affect the occurrence of MTX pneumonitis, which is consistent with a previous report. A relationship to corticosteroid dose tapering has not been observed either. Neither MTX induced asthma nor P carinii pneumonia has been observed during this study.

Only a few studies concerning pulmonary function tests during MTX therapy have been published. Wall et al<sup>27</sup> reported no dose-related decrease in pulmonary function in 38 adolescents receiving high-dose MTX for bone malignancy, but only 12 patients were studied prospectively before beginning MTX therapy and this, only after 3 to 8 months of therapy. In a retrospective study, Phillips et al<sup>25</sup> found no statistically significant differences in FVC, FEV<sub>1</sub>, TLC, transfer factor, transfer coefficient, and PaO<sub>2</sub> in ten psoriatic patients who had received long-term, low-dose MTX, compared with ten psoriatic patients, matched for age, sex, and smoking history who had never received any systemic therapy. Pelucchi et al<sup>29</sup> reported no difference in lung function and diffusing capacity in MTX-treated and untreated patients with juvenile chronic arthritis. Jeurissen et al<sup>30</sup> performed chest radiographs and pulmonary function tests in 52 rheumatoid arthritic patients who entered a double-blind randomized study of azathioprine and MTX. After 24 weeks and 2 years, results of chest radiographs and pulmonary function tests showed no changes either within each group or between both groups. No pulmonary MTX-induced toxic reaction was observed. A similar result was reported by Crook et al.<sup>31</sup>

Our study shows a slight decrease in FVC, FEV<sub>1</sub>, and Dco/V<sub>A</sub> in the whole population of asymptomatic patients during MTX treatment; the minor decrease in Dco was not statistically significant. The mean annual decline in FVC, FEV<sub>1</sub>, Dco, and Dco/V<sub>A</sub> in the whole population of asymptomatic patients was, respectively, 36.5 mL·yr<sup>-1</sup>, 62.6 mL·s<sup>-1</sup>·yr<sup>-1</sup>, 0.1 mmol·min<sup>-1</sup>·kPa<sup>-1</sup>·yr<sup>-1</sup>, and 0.06 mmol·min<sup>-1</sup>·kPa<sup>-1</sup>·L<sup>-1</sup>·yr<sup>-1</sup>, whereas the mean annual decline in European general population is estimated, respectively, to be 26 mL·yr<sup>-1</sup> for FVC, 29 mL·s<sup>-1</sup>·yr<sup>-1</sup> for FEV<sub>1</sub> (25 mL·s<sup>-1</sup>·yr<sup>-1</sup> in women),<sup>19</sup> and 0.066 mmol·min<sup>-1</sup>·kPa<sup>-1</sup>·yr<sup>-1</sup> for Dco (0.049 mmol·min<sup>-1</sup>·kPa<sup>-1</sup>·yr<sup>-1</sup> in women).<sup>30</sup> A single value for the annual decline in Dco/V<sub>A</sub> is not available. It should be emphasized that the slight variations in pulmonary parameters may then be related almost partly to the population growing old during the study. The role of a toxic effect of MTX on lung, or the development of chronic rheumatoid lung disease, or more probably the effect of the chronic rheumatoid disease on thoracic compliance, may also be hypothesized. The toxic role of MTX on lung function cannot be tested without the use of a control group of rheumatoid patients who would not receive MTX; such a placebo-controlled study did not seem ethical to us, since the efficacy of low-dose weekly MTX therapy in patients with rheumatoid arthritis has been established by several randomized trials.<sup>2,4,32,33</sup>

Nevertheless, significant variations in the parameters studied occurred in a nonnegligible number of patients who did not develop clinical manifestations. The improvement in FVC and FEV<sub>1</sub> (13 patients) could be explained by a decrease in disease activity and pain, with a better movability and better thoracic dynamics. The impairment in FVC and FEV<sub>1</sub> in patients with chronic rheumatoid disease (seven patients) cannot be attributed surely to MTX treatment. Improvement in Dco and/or Dco/V<sub>A</sub> has been observed in 16 patients during MTX treatment, whereas initial values were in a normal range for most of them. The Dco variations appeared to be related both to changes in Dco/V<sub>A</sub>, which represents the properties of the alveolo-capillary membrane, and secondly to pulmonary volume changes. The variation in Dco without any change in Dco/V<sub>A</sub> (seven cases) could hence be explained almost in part by better thoracic dynamics and better conditions for pulmonary tests. The improvement in Dco/V<sub>A</sub> may possibly reflect the correction of moderated histopathologic lesions induced by the chronic connective disease, including endothelial damage, or edema in the alveoli and the interstitium. An improvement in symptoms, chest radiographs, or pulmonary function by MTX intermittent treatment has already been described in fibrosing alveolitis complicating rheumatoid arthritis, polymyositis, or scleroderma.<sup>34</sup> Finally, it should be noted that Dco and/or Dco/V<sub>A</sub> progressively decrease in 17 patients during MTX therapy, without clinical manifestations. Some asymptomatic patients may have moderate alterations in lung function, which remain unknown if
not systematically detected. The precise significance of such subclinical progressive variations remains unknown.

Although subclinical alterations in pulmonary function were detected, periodic pulmonary function tests did not allow us to detect MTX-induced pneumonitis before clinical symptoms or risk factors for this adverse effect. Dyspnea, cough, and fever preceded significant functional alterations in all cases of MTX-induced pneumonitis. This study shows that repeated pulmonary function tests do not contribute to an earlier diagnosis of MTX-induced pneumonitis. Hence, we recommend that these tests should not be systematically performed while patients are receiving MTX treatment. Patients should be instructed to report any pulmonary symptoms without delay, leading to an early diagnosis of MTX-induced pneumonitis, based on clinical, radiologic, biological, and functional findings.

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