Investigation of the chronic pulmonary effects of low-dose oral methotrexate in patients with rheumatoid arthritis: a prospective study incorporating HRCT scanning and pulmonary function tests

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Abstract

Objective. Methotrexate has a well-recognized side-effect of acute hypersensitivity pneumonitis. There is concern about whether chronic pulmonary toxicity can occur with methotrexate treatment. Our objective was to compare chest high-resolution computed tomography (HRCT) findings and serial pulmonary function tests in rheumatoid arthritis (RA) patients on methotrexate with findings for a control group of patients with RA who were not being treated with methotrexate.

Methods. Study patients had an initial chest radiograph, full pulmonary function tests and chest HRCT. Pulmonary function tests were then performed regularly over a 2-yr period.

Results. Fifty-five RA patients on methotrexate and 73 control patients with RA were enrolled for the study. Mean dose of methotrexate was 10.7 mg/week (s.d. 2.5 mg/week) and mean duration of treatment at entry into the study was 30 (20) months. Twenty per cent of patients with RA treated with methotrexate had pulmonary fibrosis (PF) on initial HRCT compared with 23% in the control group. When the patients with and without PF were compared, there was no statistical difference in the duration (mean difference 2 4.18 months, P = 0.237) or dose (mean difference 2 0.8 mg/week P = 0.52) of methotrexate therapy. Mean changes after 2 yr in forced expiratory volume, forced vital capacity, diffusion capacity for carbon monoxide and residual volumes were not different in the methotrexate group compared with the control group.

Conclusion. There is no evidence to suggest clinically, from HRCT assessment or serial pulmonary function tests, that low-dose methotrexate is associated with chronic interstitial lung disease.

Key words: Methotrexate, Interstitial lung disease, Rheumatoid arthritis, Pulmonary fibrosis.

Low-dose methotrexate treatment is used extensively as a second-line therapy in rheumatoid arthritis (RA). Two forms of interstitial lung disease related to low-dose methotrexate therapy have been reported. Life-threatening acute methotrexate pneumonitis is the most feared complication and is thought to occur in 0.3–11.6% of RA patients treated with methotrexate [1]. Concerns have also been raised as to whether chronic pulmonary fibrosis (PF) can be caused by low-dose methotrexate. Several case reports describe the development of PF in patients treated with methotrexate for psoriasis [2–4], and with this dermatological disorder there is no recognized association with interstitial lung disease. In studies of patients with RA treated with methotrexate whilst having regular pulmonary function testing, the number of patients investigated has been small and control groups have not been incorporated in the studies [5–7]. In these circumstances it is difficult to be certain whether methotrexate is producing significant impairment of lung function.

High-resolution computed tomography (HRCT) scanning has been shown to be a very useful non-invasive investigation in diagnosing interstitial lung disease [8] and has yet to be incorporated in a study assessing patients on methotrexate.
We aimed to determine whether chronic PF is caused by low-dose oral methotrexate in patients with RA. This was assessed clinically, physiologically and with chest HRCT over a 2-yr period. A control group of patients with RA treated with therapy other than methotrexate was also assessed for any alteration in pulmonary function over the study period.

Methods

Subjects

The study population consisted of consecutive patients with RA attending the rheumatology out-patient departments of St Helens and Knowsley Hospitals NHS Trust. They were part of an extensive, ongoing study of HRCT-diagnosed interstitial lung disease. This hospital is based in northwest England and its catchment population is from an industrialized area. The patients were diagnosed with definite RA as defined by the American Rheumatism Association 1987 criteria [9] and were enrolled irrespective of chest symptoms or signs. Patients were excluded if they were pregnant, planning a pregnancy or were known to have extrinsic allergic alveolitis, asbestosis, pneumoconiosis or Caplan syndrome.

The methotrexate group comprised 55 patients with RA who were being treated with low-dose methotrexate at the time of initial assessment. The control group consisted of 73 patients with RA who were not being treated with methotrexate. Therapy was with second-line drugs other than methotrexate, non-steroidal anti-inflammatory drugs, corticosteroids or simple analgesics.

The research ethics committee of St Helens and Knowsley Hospitals approved the study. Fully informed voluntary consent was obtained from each patient by JKD.

Clinical assessment

A questionnaire was completed for each patient by JKD. This noted the duration of RA, extra-articular complications, current and previous disease-modifying drugs, corticosteroid use, early morning joint stiffness and patient assessment of disease activity. Each patient also completed the Modified Stanford Health Assessment Questionnaire to assess functional impairment. Respiratory questions covered previous chest disease, cough, dyspnoea, sputum production, chest pain, weight loss and risk factors for respiratory disease, such as smoking, medications, domestic pets and occupation. Cigarette consumption was evaluated in pack years (1 pack yr = 20 cigarettes/day for 1 yr). Current smokers were those who had smoked during the previous 6 months; non-smokers had smoked fewer than 20 packets of cigarettes during their lifetime. A detailed clinical examination was performed. All patients underwent chest radiography, HRCT and full pulmonary function testing.

Table 1 shows the patients’ clinical characteristics.

<table>
<thead>
<tr>
<th>Table 1. Patient characteristics</th>
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<tbody>
<tr>
<td>Age (yr) [mean (s.d.)]</td>
</tr>
<tr>
<td>Males, females</td>
</tr>
<tr>
<td>Duration of RA (yr) [mean (s.d.)]</td>
</tr>
<tr>
<td>No. positive for rheumatoid factor</td>
</tr>
<tr>
<td>Smoking status</td>
</tr>
<tr>
<td>Current smokers</td>
</tr>
<tr>
<td>Never smoked</td>
</tr>
<tr>
<td>On methotrexate</td>
</tr>
</tbody>
</table>

Pulmonary function testing

Lung function was measured using a standard protocol and included spirometry (water spirometer; Sensor Medics, Yorba Linda, CA, USA), lung volumes (helium dilution analyser; Sensor Medics) and transfer factor measured by single-breath diffusing capacity (autolink breath system; Sensor Medics). The highest of three reproducible measurements was used, and was expressed as the percentage of the value predicted for age, height and gender according to standardized tables [10]. The measurements were made in the cardiorespiratory department at Whiston Hospital by one senior technician. Pulmonary function tests were performed within 4 weeks of the HRCT scan.

HRCT

All members of the study population underwent chest HRCT scanning. This was performed with a Siemens Somatom hiQ scanner. Scanning time was 1.3 s. Supine and prone views were taken. Serial slices 2 mm in width were taken 10 mm apart. All images were obtained at window levels appropriate for lung parenchyma settings [window width 1300 Hounsfield Units (HU), window level −600 HU] and mediastinum (window width 350 HU, window level 40 HU). A chest radiograph was taken at the same time as the HRCT scan. The HRCT scans were interpreted and graded for pulmonary fibrosis (PF) by consultant radiologists JD and HEF, who were blind to clinical details. Each radiologist reviewed the scans independently of the other and a consensus of the opinions of JD and HEF was taken in the event of disagreement.

Interpretation of HRCT scan

In regard to PF, the criterion used for ground-glass pattern change was defined as a patchy or diffuse increase in lung density that did not obscure pulmonary vasculature. A reticular pattern was defined as the presence of intersecting lines forming anything from a fine network to frank honeycombing [11] that was thought to be typical of usual interstitial pneumonia [12]. Other lung disease found to be present on HRCT was noted systematically.

Follow-up assessments

Clinical. The patients were assessed clinically every 3 months by JKD. A standard questionnaire was completed on each occasion. Drug therapy and the development of chest disease were the focus of this
assessed. The patients were monitored over 2 yr. During this time, if any evidence of new or deteriorating lung disease was detected the patients underwent routine clinical investigation and treatment as appropriate for their condition. This was undertaken irrespective of whether they were on methotrexate.

**Pulmonary function testing.** The same senior technician undertook pulmonary function testing. Patients had full pulmonary function tests performed at intervals of 4 months. Pulmonary function testing was performed for 2 yr.

**End-points of the study**

The change in pulmonary function between the initial and 2 yr results was used in the final analysis. Patients in the methotrexate group who stopped methotrexate prior to the end of the study had their final pulmonary function test on methotrexate carried forward. Patients in the control group who changed to methotrexate from their previous medication had their final pulmonary function test before commencing methotrexate carried forward. In patients who left the study prematurely, the last observation was carried forward for data interpretation.

**Statistical analysis**

The Mann–Whitney U-test was used to compare quantitative data. The χ² test with Yates’ correction was used to compare frequencies. Student’s t-test was used to compare normally distributed quantitative data. Potentially significant parameters were tested for possible interrelationship by multiple logistic regression analysis. As described previously, analysis of the last observation was carried forward for data interpretation.

**Results**

Fifty-five patients were treated with methotrexate at the initial assessment and 73 patients were in the control group. Clinical details of the two groups at the baseline assessment are shown in Table 2. Forward conditional logistic regression analysis was performed to investigate whether treatment with methotrexate was more likely to be associated with normal pulmonary function at baseline. The standard for normal pulmonary function was defined as diffusion capacity for carbon monoxide greater than 75% of the predicted capacity. No significant association was seen (P = 0.9).

**PF group**

Twenty-eight patients, from the 128 patients with RA, were found to have PF-pattern interstitial lung disease (ILD) on HRCT. Eleven of these patients were being treated with methotrexate. No statistically significant difference was noted between the numbers of patients on methotrexate with PF on HRCT and those without (P = 0.8). There was no difference in dose or duration of methotrexate therapy in these patients with RA compared with the patients with RA who were treated with methotrexate and who did not have evidence of PF on HRCT (Table 3). Average cigarette pack year exposure was 26 yr (s.d. 22 yr) in the methotrexate group compared with 21 (15) yr in those not treated with methotrexate. This was not a statistically significant difference (P = 0.94). Of the 11 patients with PF who had characteristic changes on HRCT, only two were diagnosed previously with this pulmonary complication of RA. Nine of the 11 patients had subpleural changes of a predominantly reticular pattern and two had a mixed ground-glass and reticular-pattern PF.

**Follow-up: clinical events**

No patient developed clinical features suggestive of methotrexate pneumonitis. One patient not treated with methotrexate was found to have developed PF on subsequent HRCT scans.

Within the study period, three patients died in the methotrexate group and nine patients died in the control group. Four patients defaulted from completing the study investigations; two of these were in the methotrexate group.

Eight patients in the control group switched over to methotrexate therapy and seven patients stopped

<table>
<thead>
<tr>
<th>Variable</th>
<th>Methotrexate (n = 55)</th>
<th>Control (n = 73)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean or no. s.d.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>57.6 9.9 59.6 9.8</td>
<td>0.264ab</td>
</tr>
<tr>
<td>Disease duration (yr)</td>
<td>12.5 7.7 13.6 8.7</td>
<td>0.473</td>
</tr>
<tr>
<td>Cigarette (pack yr)</td>
<td>20.2 20.8 18.2 18</td>
<td>0.633</td>
</tr>
<tr>
<td>HAQ score</td>
<td>1.66 0.64 1.88 0.67</td>
<td>0.046</td>
</tr>
<tr>
<td>C reactive protein (mg/l)</td>
<td>28.6 32 31.7 28.4</td>
<td>0.175</td>
</tr>
<tr>
<td>FEV1 (litres)</td>
<td>2.27 0.86 2.06 0.64</td>
<td>0.22</td>
</tr>
<tr>
<td>FVC (litres)</td>
<td>3.04 0.97 2.9 0.76</td>
<td>0.251</td>
</tr>
<tr>
<td>DLCO</td>
<td>71.5 19.3 67.7 20</td>
<td>0.269</td>
</tr>
</tbody>
</table>

**Table 2. Clinical features of the methotrexate and control groups**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Dose (mg)</th>
<th>Duration (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>Range</td>
<td>s.d.</td>
</tr>
<tr>
<td>All patients on methotrexate</td>
<td>10.7 5–17.5 2.5</td>
<td>30 1–84 20</td>
</tr>
<tr>
<td>No PFa (n = 44)</td>
<td>10.6 5–20 2.5</td>
<td>29 1–84 19</td>
</tr>
<tr>
<td>PFa (n = 11)</td>
<td>11.4 10–17.5 2.6</td>
<td>33 1–60 22.6</td>
</tr>
<tr>
<td>P = 0.237</td>
<td></td>
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</tr>
</tbody>
</table>

**Table 3. Details of methotrexate therapy**

*pDiagnosed by chest HRCT.

bComparison of methotrexate therapy between patients with and without PF using Mann–Whitney U-test.
methotrexate. Four patients ceased methotrexate treatment during the study period because of inefficacy. One patient had methotrexate stopped because aplastic anaemia developed. Two patients with PF stopped methotrexate. In one patient this was because the diagnosis of PF was made by being part of this study. This patient was kept under assessment; their PF became more progressive after the methotrexate was stopped. One patient, who also had asthma, stopped methotrexate because they developed a non-progressive dry cough; no evidence of methotrexate pneumonitis was seen clinically or on HRCT, and the cough was thought to be due to isolated airway irritation from methotrexate [13].

**Follow-up: pulmonary function testing (Table 4)**

Seven patients in the methotrexate group and three patients in the control group failed to have more than one set of pulmonary function tests. Change in pulmonary function tests from initial assessment to the end of the study was not shown to be clinically or statistically different between the methotrexate group and the control group.

**PF patients**

A subgroup analysis was carried out on the PF patients. One patient in the methotrexate group failed to have a second set of pulmonary function tests on initial medication. The change in pulmonary function tests is shown in Table 5. There was no clinical or pulmonary function evidence that methotrexate was detrimental to patients compared with the control group of patients, in whom PF was treated with alternative therapies.

Six of the patients in the control group with PF, but no patient with PF who was treated with methotrexate, died. The cause of death in four of these patients with PF was reported as respiratory failure or infection. The difference in mortality between PF groups did not, however, reach statistical significance.

**Discussion**

We found PF diagnosed by means of chest HRCT in 28 patients on initial scanning, in keeping with previously published studies [14, 15]. This was found in equal proportions between the methotrexate (20%) and control (23%) groups. The PF patients did not differ significantly, clinically or statistically, from the other patients with RA treated with methotrexate in the dose and duration of methotrexate used. Thus there is no evidence to suggest, from initial HRCT scan results, that methotrexate caused the PF-pattern ILD. This was investigated further with pulmonary function testing over 2 yr; there was no significant change in pulmonary function tests in patients maintained on methotrexate when compared with a control RA group. We also found that, in the subgroup of PF patients who remained on methotrexate, there was no accelerated deterioration in pulmonary function compared with PF patients in the control group.

A concern with the study is that the patient groups were not allocated randomly to each treatment type: the physicians chose methotrexate or alternatives after consideration of drug efficacy, previous drug toxicity and according to coincidental medical conditions. This could have led to the methotrexate group having less lung disease. Consequently, we analysed the initial pulmonary function tests and radiological tests; no statistically significant difference was found in parameters of pulmonary function testing or conditions found on chest HRCT. Forward conditional logistic regression based on the most sensitive parameter of pulmonary function testing was also unable to detect any significant bias.

When no statistical difference is found between two groups then it is always a worry that the study groups are too small. We calculated that there was more than 90% power at the 0.05 level of statistical significance to detect a 15% change in diffusion capacity for carbon monoxide with 50 patients in each group. No significant difference in pulmonary function was seen when the two PF groups were compared, but the subgroup analysis was based on small numbers and these results should be interpreted cautiously as a type-II statistical error is possible.

The aim of this study was to investigate whether chronic or subacute pulmonary side-effects occur with low-dose methotrexate. The study was not designed
to investigate the incidence of acute pneumonitis. However, it is interesting to note that no cases of definite acute pneumonitis occurred. One reason for this may be that, during the 2 yr study time, only 18 patients commenced taking methotrexate or had been taking it for less than 6 months. Most reports of methotrexate pneumonitis occur during the first 6 months of therapy with methotrexate [16, 17], and with a reported prevalence of between 0.3 and 11% [1] it is perhaps not surprising that no cases were reported. In the study of Beyeler et al. [6], only one case of methotrexate pneumonitis occurred in 100 patients studied. In the prospective study by Dayton et al. [7] of 31 patients with RA starting on methotrexate, none developed methotrexate pneumonitis during 5 yr of follow-up. Our findings are in keeping with both these studies.

In three studies that serially monitored pulmonary function tests in patients with RA on methotrexate, the authors concluded that, although there was a deterioration in parameters of pulmonary function, this did not reflect a clinically significant deterioration in patients with RA treated with methotrexate [5–7]. As we found no significant difference in change in pulmonary function between the methotrexate and the control RA group, it would seem likely that the changes described previously were related to the ageing process and lung disease associated with RA rather than to methotrexate therapy.

The reports of chronic PF due to methotrexate have arisen in patients who have psoriasis. In one report the patient’s differential diagnosis was sarcoidosis, in view of the adenopathy and granuloma formation [3]. The other reports could represent the coincidental occurrence of PF and psoriasis [2, 4]. Several low-powered studies have also not demonstrated a deterioration of pulmonary function in psoriasis patients treated with methotrexate when compared with controls [18, 19].

No published controlled trials of the treatment of patients with RA-associated PF exist. Methotrexate has been reported as successfully controlling RA-associated PF in four patients [20, 21]. We found no detrimental effects of methotrexate in patients with RA-associated PF. However, this study was not sufficiently powered to investigate whether methotrexate can control PF.

In conclusion, in this controlled prospective study of patients with RA treated with low-dose methotrexate we found no evidence, either clinically or by pulmonary function testing, that methotrexate produces chronic fibrotic lung disease.

Acknowledgements

We thank the staff at Whiston Hospital Cardiorespiratory Department, in particular Karen Eyres. At the time the study was devised, John Kenny was integral to the undertaking of the study as well as the initial interpretation of chest radiographs and HRCT scans. We greatly regret that he had to retire due to ill-health. All his work is greatly appreciated. This work was supported by a grant from the British Lung Foundation.

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