Reducing the risk of methotrexate pneumonitis in rheumatoid arthritis

V. Saravanan¹ and C. A. Kelly²

Methotrexate (MTX) is the most commonly used disease-modifying drug (DMARD) in rheumatoid arthritis (RA) [1]. It is a main anchor drug in many combination regimes with conventional DMARDs and biological agents. It has the longest drug-survival time and a good benefit/toxicity ratio [2, 3]. However, toxicity is a major reason for MTX withdrawal in RA [3]. Pneumonitis is the reason for withdrawal of MTX in 1 in 108 patient-years compared with 1 in 35 patient-years for hepatic toxicity and 1 in 58 patient-years for neutropenia [3]. There are guidelines for effective monitoring of the hepatic and haematological toxicity of MTX [4, 5]. Pneumonitis following MTX is a potentially fatal hypersensitivity reaction and is far less predictable than hepatic and haematological toxicity. Current guidelines [4, 5] advise a pretreatment chest radiograph (CXR), though there are wide variations in clinical practice in screening for lung disease prior to commencing MTX for RA. This is due to conflicting views as to whether pre-existing pulmonary disease increases the risk of MTX pneumonitis. Many studies [6–11] suggest that pre-existing lung disease in RA increases the risk of pneumonitis. Not all studies [12, 13] have supported this view. We discuss the evidence for predicting MTX pneumonitis in RA and the usefulness of screening for lung disease in patients with RA prior to treatment with MTX.

Prevalence and pathogenesis of methotrexate pneumonitis

MTX pneumonitis is most frequent within the first year of treatment [3, 14–16] and the reported incidence of this adverse reaction varies from 0.86 to 6.9% [3, 8, 10, 14]. Our earlier work [6] reports the prevalence in RA at 1 in 80 patient-years. Most reported cases have occurred in patients with RA [15, 17], though a higher frequency (14%) has been reported in primary biliary cirrhosis [18]. Pneumonitis is not unique to MTX and has been shown to occur with sulphasalazine and gold treatment for RA.

The variable incidence and usual occurrence within a year of starting MTX suggests that pneumonitis is an idiosyncratic immune reaction rather than a dose-related toxic insult to the lung. Pneumonitis has also been seen after alteration of the immune system by anti-tumour necrosis factor-α therapy with infliximab in patients already established on MTX [19]. Akoun et al. [20] showed that MTX stimulated lymphokine secretion by peripheral lymphocytes of patients with pneumonitis, suggesting cell-mediated hypersensitivity. Bronchoalveolar studies and biopsies show a lymphocytic alveolitis [21–24].

Risk factors

From a MEDLINE search, we identified six studies that looked at risk factors for MTX pneumonitis in RA. Pre-existing lung disease has been associated with an increased risk of MTX pneumonitis in these studies [6–11]. Meta-analytic methods were used to pool the odds ratio for MTX pneumonitis in the presence of pre-existing lung disease. The summarized data from these six studies are in Table 1. Although these studies varied in their design and definition of pre-existing lung disease, all suggested that it predisposed to MTX pneumonitis (pooled odds ratio of 7.5, 95% confidence interval CI 3.6–15.8). Pre-existing lung disease was seen in 48% of 69 patients who developed MTX pneumonitis. By comparison, only 7.4% of 1769 patients without pneumonitis had evidence of prior lung disease.

Kremer and Alarcon et al. [9, 14] described the single largest series of MTX pneumonitis (29 cases) in a retrospective case-control study of RA patients. Pre-existing lung disease, old age and previous use of DMARDs were identified as risk factors for pneumonitis after MTX. Ohosone [11] came to a similar conclusion. Age and previous DMARD use have not been identified as a risk in other studies [6–8, 10]. In a multicentre study [10] of 1162 patients with RA treated with MTX in north-east England, 27 probable cases of pneumonitis were identified, of which 10 met the Searles and McKendry criteria [25] for pneumonitis. Pre-existing pulmonary fibrosis was present in five of these 10 cases of pneumonitis. Our experience in a prospective study [6] of 120 patients with RA treated with MTX identified three cases of pneumonitis. Abnormal lung function tests (less than 70% of the value predicted for age and sex) were found to confer added risk of pneumonitis. A low forced expiratory volume in 1 s (FEV1) and vital capacity (VC) carried a relative risk of 3.2 and a low transfer factor for carbon monoxide (TLCO) carried a relative risk of 10, whereas an abnormal CXR carried a relative risk of 3.3. Golden et al. [7] reported a relative risk of 4 for patients with interstitial infiltrates on CXR.

Clinical features

Pneumonitis due to MTX presents either acutely or subacutely with cough, fever and dyspnoea. The criteria of Searles and McKendry [25] are widely accepted for defining MTX pneumonitis (Table 2). As it is mainly a diagnosis of exclusion, it is often difficult to distinguish from chest infection or exacerbations of pre-existing interstitial lung disease (ILD), which are not uncommon in patients with RA.

Investigations

Negative microbial cultures of sputum and blood are needed before a definitive diagnosis of pneumonitis can be made. CXR may show interstitial shadows, but this is not a sensitive test. A decline in VC and TLCO is suggestive but not specific for
Table 1. A summary of studies on the risk of MTX pneumonitis with pre-existing radiological lung disease

<table>
<thead>
<tr>
<th>Reference</th>
<th>N</th>
<th>Prior Lung Disease</th>
<th>No Prior Lung Disease</th>
<th>Odds Ratio (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Pneumonitis</td>
<td>No Pneumonitis</td>
<td></td>
</tr>
<tr>
<td>Alarcon [9]</td>
<td>111</td>
<td>9</td>
<td>6</td>
<td>5.7 (1.6 - 21.5)</td>
</tr>
<tr>
<td>Bartram [10]</td>
<td>1162</td>
<td>5</td>
<td>58</td>
<td>18.9 (4.2 - 83.8)</td>
</tr>
<tr>
<td>Golden [7]</td>
<td>125</td>
<td>5</td>
<td>24</td>
<td>4.8 (0.9 - 25.7)</td>
</tr>
<tr>
<td>Carroll [8]</td>
<td>36</td>
<td>7</td>
<td>8</td>
<td>2.8 (0.5 - 14.9)</td>
</tr>
<tr>
<td>Howes [6]</td>
<td>120</td>
<td>1</td>
<td>11</td>
<td>4.8 (0.1 - 97.5)</td>
</tr>
<tr>
<td>Obosone [11]</td>
<td>284</td>
<td>5</td>
<td>29</td>
<td>42.9 (4.5 - 2038)</td>
</tr>
</tbody>
</table>

Pooled Odds Ratio (Random-effects)

The studies of Alarcon et al. [9] and Carroll et al. [8] are case-control studies; the others are cohort studies.
Reducing the risk of methotrexate pneumonitis in RA

Table 2. Criteria of Searles and McKendry [25] for diagnosis of MTX pneumonitis

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Acute onset dyspnoea</td>
</tr>
<tr>
<td>2</td>
<td>Fever &gt; 38.0°C</td>
</tr>
<tr>
<td>3</td>
<td>Tachypnoea ≥ 28/min and dry cough</td>
</tr>
<tr>
<td>4</td>
<td>Radiological evidence of pulmonary interstitial or alveolar infiltrates</td>
</tr>
<tr>
<td>5</td>
<td>White blood cell count ≤ 15.0 × 10³ with or without eosinophilia</td>
</tr>
<tr>
<td>6</td>
<td>Negative blood and sputum cultures (mandatory)</td>
</tr>
<tr>
<td>7</td>
<td>Restrictive defect and decreased diffusion capacity on pulmonary function tests</td>
</tr>
<tr>
<td>8</td>
<td>P_O₂ &lt; 7.5 kPa on air</td>
</tr>
<tr>
<td>9</td>
<td>Histopathology consistent with bronchiolitis or interstitial pneumonitis with giant cells and without evidence of infection</td>
</tr>
</tbody>
</table>

Definite ≥ 6 criteria present
Probable 5 of 9 criteria present
Possible 4 of 9 criteria present

Pneumonitis. The negative predictive value of a stable TLC0 when suspecting MTX pneumonitis is yet to be studied. High-resolution computed tomography (HRCT) of the lungs is more sensitive than plain radiography in drug-induced lung disease and has the added ability to distinguish between different lung diseases [26]. Atypical chest infections (e.g., *Pneumocystis carinii* pneumonia) and progressive rheumatoid interstitial lung disease are the most difficult to differentiate clinically from pneumonitis due to MTX. Bronchoalveolar lavage (BAL) at bronchoscopy may be needed to rule out *P. carinii* pneumonia. The lack of fibrosis on HRCT and the cellular distribution in BAL fluid distinguish pneumonitis from RA–ILD. In pneumonitis, BAL fluid will show a high lymphocyte count and CD4/CD8 ratio [21–24] and transbronchial lung biopsy is likely to show Type II pneumocyte proliferation and inflammatory infiltrate with or without giant cells.

**Treatment**

The diagnosis is often unclear at presentation. Patients with no obvious signs of a chest infection may need to be hospitalized. Stopping MTX immediately on suspecting pneumonitis alone may be all that is necessary. Oral or intravenous pulse corticosteroid treatment is often needed [17]. Patients with significant hypoxia will require intensive care with ventilation. Cyclophosphamide has been used successfully in significant pneumonitis [27].

**Prognosis**

A review of 123 published cases of MTX-induced pneumonitis showed a mortality of 13% [15]. The long-term prognosis of MTX pneumonitis is usually favourable [17]. Most patients recover fully and do not progress to have pulmonary fibrosis as a result of the pneumonitis. Although there are instances of successful reinduction of MTX after pneumonitis [28], there is not enough evidence to support this.

**Chronic effects of MTX**

The long-term effect of MTX on the lung in RA has been of concern for many years. Longitudinal studies [12, 13, 29, 30] of lung function have been reassuring in this aspect. However, a recent Kuwaiti study [31] showed significant deterioration in lung function after 2 yr of treatment with MTX in early RA. Dawson *et al.* [29] showed no deterioration in lung function over 2 yr with MTX in patients with RA with or without pulmonary fibrosis diagnosed by HRCT. The experience was similar in two separate 1-yr longitudinal studies [13, 30] of around 100 RA patients treated with MTX. These studies, however, focused on the chronic pulmonary effects of MTX and were not designed to identify risk factors for MTX pneumonitis.

Sustained dry cough not accompanied by dyspnoea or constitutional symptoms is not uncommon with MTX. It is thought to be due to mucosal/airway irritation, and bronchoalveolar studies have shown this to be benign [32]. It often abates with symptomatic treatment or by discontinuing MTX temporarily.

**Which RA patients should be given methotrexate?**

The available evidence suggests that ILD is a risk factor for MTX pneumonitis. MTX has been reported to improve ILD due to RA [33] and is also used to treat inflammatory muscle disease with anti-synthetase antibodies, a condition associated with ILD [34]. However, the benefit of MTX in ILD has not been substantiated in a randomized trial. Patients with RA are unwilling to risk life-threatening toxicity due to DMARDs [35]. In our literature review, 48% of patients who had MTX pneumonitis had pre-existing lung disease (Table 1). We suggest avoiding MTX in patients with established ILD. Gas transfer is invariably reduced (TLC0 < 70% predicted) in such patients. If all RA patients with TLC0 < 70% are investigated for ILD by HRCT, we estimate that at least 5% of those considered for MTX may need to be treated with an alternative DMARD [36]. A more compelling reason to avoid MTX in these patients is that they may have poor lung reserve and hence are at risk of respiratory failure in the event of pneumonitis. There will be instances when the choice of DMARDs may be limited and we are compelled to use MTX for RA. The risks and benefits of using MTX in such cases should be weighed carefully. MTX has been used in the management of asthma [37] and patients with airway obstruction do not seem to be at increased risk of pneumonitis.

**What baseline tests are useful prior to methotrexate?**

Investigations done prior to MTX should serve two purposes. Identifying patients with ILD and poor lung reserve is the most important objective. The test should also serve as a reliable baseline for future comparison in the event of suspected pneumonitis.

A baseline CXR is done routinely according to current guidelines [4, 5] and is said to be a useful comparator in the event of future pneumonitis. Although it is easily available, CXR is less sensitive than TLC0 in identifying interstitial lung disease or pneumonitis [38]. However, it would seem prudent to perform a CXR if there are signs or symptoms of lung disease.

Lung function tests are quite sensitive yet very non-specific in identifying occult lung disease. Simple spirometry to measure FEV1 and VC is readily available. Spirometry alone without TLC0 is, however, less sensitive in identifying ILD [38]. In patients with an abnormal TLC0 (70%), HRCT will identify the underlying lung disease and confirm/refute ILD.

**Proposal**

We propose screening (Fig. 1) for lung disease with lung function tests prior to commencing MTX. We suggest that all patients with RA commencing MTX have baseline lung function tests, including FEV1, VC and TLC0 (corrected for haemoglobin). In patients with respiratory symptoms, MTX should be delayed until pulmonary function test (PFT) results are obtained. A mild PFT abnormality due to smoking is not a contraindication for MTX. An HRCT of the lungs should be obtained if TLC0 is less than 70% of the predicted value. If HRCT confirms interstitial lung disease (ILD) with a new-onset abnormal TLC0, MTX should probably be avoided in such patients. MTX should be continued in patients with ILD and a TLC0 > 70%.
disease, MTX should be avoided and an alternative DMARD considered. Azathioprine, steroids and cyclophosphamide have all been used successfully in the treatment of ILD associated with RA [39]. If the HRCT shows only airway disease, MTX can be used and patients with symptomatic airway disease may also be treated with inhaled steroids.

In the event of an acute respiratory illness during the course of treatment with MTX, a CXR and repeat PFT are needed. If the PFTs are stable and CXR normal, MTX can be restarted after the acute illness (Fig. 1). However a decline of 20% in TLCO from baseline within a year and/or interstitial shadows on CXR may support a diagnosis of MTX pneumonitis. These patients will need further investigation with HRCT and/or BAL. More commonly, patients on MTX complain of subjective breathlessness with no obvious cause. Without baseline PFTs with which to compare repeat tests, it would be difficult to be sure that there is no pneumonitis.

We acknowledge the implications of these recommendations for the resources needed and the costs of treatment. There may be a delay in access to PFTs in many hospitals in the UK. However, the cost of PFTs should be offset by the ability to confirm or refute MTX pneumonitis more easily in the event of an acute respiratory illness. In addition to identifying subclinical lung disease, it would be possible to avoid MTX in patients who are most at risk of respiratory failure due to pneumonitis.

Conflict of interest
The authors have declared no conflicts of interest.

References

FIG. 1. Algorithm for screening for lung disease in RA prior to MTX and managing suspected pneumonitis.
Reducing the risk of methotrexate pneumonitis in RA


