Treatment with methotrexate (MTX) in rheumatoid arthritis (RA) can lead to severe side-effects, especially pulmonary and haematological complications. The aim of this retrospective study was to evaluate, during a 6 yr period, the prevalence and severity of bronchopulmonary side-effects in RA patients treated with MTX. A cohort of 130 RA in-patients (106 women, 24 men) treated with MTX was studied for the occurrence of respiratory adverse events. Adverse bronchopulmonary side-effects were observed in 12 patients (two men, 10 women), with a mean disease duration of 15 yr. Only three patients had previously suffered from pulmonary disease. MTX treatment duration was between 1 month and 4.5 yr. The diagnosis was that of hypersensitivity pneumonitis (HSP) in four cases, non-HSP pneumonitis in five patients with one case of Pneumocystis carinii infection, and bronchitis in three cases. The initial respiratory symptoms were not discriminatory between the different conditions. Risk factors were not identified for the occurrence of HSP. HSP always occurred in the first 5 months of treatment. Two patients with HSP died, and another patient with opportunistic infection underwent tracheostomy. HSP represents a potentially lethal side-effect in RA patients treated with MTX. Improved education of patients and physicians should certainly lead to a reduction of both the prevalence and severity of pulmonary side-effects during MTX therapy in RA.

KEY WORDS: Methotrexate, Pneumonitis, Alveolitis, Hypersensitivity, Infection.

METHOTREXATE (MTX) is a disease-modifying drug currently used in rheumatoid arthritis (RA), with a high maintenance rate and the highest efficacy/risk ratio [1-3]. Several benign side-effects occur during MTX therapy in RA, and most of them are easily managed by a reduction of the dose or a transient discontinuation of the drug, or by the concomitant administration of folic acid. Long-term hepatotoxicity is a rare event in RA patients treated with MTX [1]. The occurrence of serious, potentially lethal side-effects, such as haematological and pulmonary complications, should be considered. The frequency of MTX-induced pneumonitis is estimated to be between 2 and 5% in RA [4-5], and the role of several risk factors, such as smoking, previous lung disease, use of non-steroidal anti-inflammatory drugs and abnormal renal function, has been suggested [4-6].

The aim of this study was to determine the prevalence and course of MTX hypersensitivity pneumonitis (HSP) and to compare it with non-HSP bronchopulmonary events in the same cohort of RA patients treated with MTX.

METHODS

Patients belonged to a cohort of 130 RA in-patients seen in our department between 1986 and 1993. Charts were reviewed for the occurrence of pulmonary complications. There were 26 men and 104 women; mean age at the beginning of MTX therapy was 60 yr and mean disease duration at MTX initiation was 13 yr. One hundred and 12 patients were treated with MTX parenterally and 18 patients orally. RA was defined according to ARA criteria [7]. The mean total dose of MTX was 1144 mg; 117 patients were treated with oral steroids (mean dose 9.2 mg/day).

The diagnosis of HSP was based on the Searles and McKendry criteria [6]: (1) acute onset of shortness of breath; (2) fever > 38.0°C; (3) tachyphoea ≥ 28/min and a non-productive cough; (4) radiological evidence of pulmonary interstitial or alveolar infiltrates; (5) white cell count ≤ 15.0 x 10^9/l; (6) negative blood and sputum cultures (obligatory); (7) pulmonary function tests demonstrating restrictive pulmonary function with decreased diffusion capacities; (8) pO_2 < 55 mmHg on room air at time of admission; (9) histopathology consistent with bronchitis or interstitial pneumonitis. The diagnosis is definite if ≥ 6 criteria are present, probable if 5/9 are present and possible if 4/9 are present.

Bronchoalveolar lavage (BAL) was carried out in seven patients to rule out infection. Cultures from BAL fluid or sputum were performed in all patients.

RESULTS

A bronchopulmonary complication was recorded in 12 patients (Tables I and II). Four patients had HSP and eight patients had non-HSP lung disease, most probably of infectious aetiology.

Patients with HSP

There were four women, with a mean age of 71 yr (60-78) and mean disease duration of 12 yr (7-17). The four patients received oral prednisone, with a daily dose ranging from 5 to 10 mg. None of the patients had previous lung disease. One patient had Sjögren's syndrome. The diagnosis of MTX pneumonitis was

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TABLE I

| Characteristics of patients at the onset of HSP |
|---|---|---|---|---|
| Gender | F | F | F | F |
| Age | 75 | 70 | 60 | 78 |
| RA duration (yr) | 12 | 13 | 17 | 7 |
| Previous lung disease | No | No | No | No |
| Extra-articular involvement | No | Sjögren | No | No |
| Rheumatoid factor | + | + | + | - |
| ANA (titre) | 1/1000 | - | - | - |
| Corticosteroid treatment duration (months) | 4 | 4 | 6 | 4 |
| Prednisone (mg/day) | 5 | 10 | 7 | 10 |

There were two men and six women, with a mean age of 67 yr (40–78) and mean disease duration of 16 yr (3–29). Seven patients received oral prednisone (5–10 mg/day). Three patients had previous respiratory tract involvement, two had chronic obstructive disease and one rheumatoid interstitial lung disease with restrictive respiratory insufficiency.

Five patients had Sjögren’s syndrome, associated in two cases with secondary amyloidosis, and another patient had Felty’s syndrome.

The duration of MTX treatment prior to the pulmonary complication ranged from 1 to 52 months. The weekly MTX dose was between 5 and 15 mg, and the total dose between 60 and 2100 mg. The non-HSP complications occurred in the first 3 months of MTX treatment in four patients.

The characteristics of MTX-induced HSP and non-HSP bronchopulmonary events are presented in Tables III and IV. Cough and dyspnoea were the main clinical features, both present in eight patients. The respiratory symptoms began in an acute manner in all the patients. One patient with HSP had transient cough and dyspnoea after one MTX injection, and the next injection was followed by the development of acute respiratory distress. Seven patients with non-HSP lung disease had a purulent expectoration. Sinusitis was also present in two patients with non-HSP complication.

Chest radiograph showed an interstitial syndrome in all patients developing HSP. Chest radiograph showed a localized pneumonia in four patients with non-HSP lung disease, associated with a pleural effusion in one of them; an interstitial syndrome of the two bases was present in two patients with non-HSP complication.

Gasometry showed severe hypoxaemia in all patients.
<table>
<thead>
<tr>
<th>MTX duration (months)</th>
<th>Dose: mg/week (cumulative)</th>
<th>Clinical data</th>
<th>Blood gasometry (mmHg)</th>
<th>Chest radiograph</th>
<th>BAL Microorganism</th>
<th>Lung function tests</th>
<th>Treatment</th>
<th>Evolution</th>
</tr>
</thead>
<tbody>
<tr>
<td>48</td>
<td>10</td>
<td>Fever, cough, purulent sputum, dyspnoea, purulent sinusitis</td>
<td>pO₂: 72 pCO₂: 38</td>
<td>Pneumonia</td>
<td>416 000 c/ml M₆: 60%</td>
<td>Normal</td>
<td>Amoxycillin, clavulanic acid Roxithromycin</td>
<td>Recovery Yes</td>
</tr>
<tr>
<td>10</td>
<td>(2100)</td>
<td>Fever, cough, purulent sputum, dyspnoea, crakles, purulent sinusitis</td>
<td>pO₂: 63 pCO₂: 32</td>
<td>Normal</td>
<td>ND</td>
<td>Obstructive syndrome</td>
<td>Amoxycillin, clavulanic acid Roxithromycin</td>
<td>Recovery No</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>Fever, cough, purulent sputum, dyspnoea, diarrhoea, ronchus</td>
<td>-</td>
<td>ND</td>
<td>ND</td>
<td>Normal</td>
<td>Escherichia coli</td>
<td>Recovery Yes</td>
</tr>
<tr>
<td>32</td>
<td>3</td>
<td>Fever, cough, purulent sputum</td>
<td>pO₂: 69 pCO₂: 19</td>
<td>Normal</td>
<td>Haemophilus</td>
<td>Obstructive syndrome</td>
<td>Prednison, ampicillin, erythromycin, clavulanic acid</td>
<td>Recovery No</td>
</tr>
<tr>
<td>29</td>
<td>7.5</td>
<td>Fever, cough, purulent sputum</td>
<td>pO₂: 34 pCO₂: 30</td>
<td>Normal</td>
<td>Pneumocystis carinii</td>
<td>Obstructive syndrome</td>
<td>Amoxycillin, clavulanic acid ciprofloxacin, erythromycin, trimethoprim</td>
<td>Recovery No</td>
</tr>
<tr>
<td>15</td>
<td>5</td>
<td>Fever, cough</td>
<td>pO₂: 69 pCO₂: 32</td>
<td>Normal</td>
<td>E. coli</td>
<td>Obstructive syndrome</td>
<td>Prednison, ciprofloxacin, erythromycin, piperacillin, clavulanic acid</td>
<td>Recovery No</td>
</tr>
<tr>
<td>52</td>
<td>7.5</td>
<td>Fever, cough, purulent sputum</td>
<td>pO₂: 69 pCO₂: 32</td>
<td>Normal</td>
<td>Normal</td>
<td>Obstructive syndrome</td>
<td>Amoxycillin, clavulanic acid</td>
<td>Recovery No</td>
</tr>
<tr>
<td>3</td>
<td>10</td>
<td>Fever, cough, purulent sputum</td>
<td>-</td>
<td>Normal</td>
<td>ND</td>
<td>Obstructive syndrome</td>
<td>Amoxycillin, clavulanic acid</td>
<td>Recovery Yes</td>
</tr>
</tbody>
</table>
with HSP and in the case of *Pneumocystis carinii* infection.

Fibroptic bronchoscopy showed an inflammatory aspect with purulent secretions in four patients with non-HSP lung disease. BAL was essential for the diagnosis of *P. carinii* infection and *Escherichia coli* pneumonitis. It was also contributive for the diagnosis of HSP in two patients, showing a marked lymphocytosis in one of them (Table III). Respiratory function tests revealed an obstructive syndrome in four patients with a non-HSP bronchopulmonary event. They were not performed in patients with HSP due to the severity of their respiratory symptoms.

Five patients were hospitalized in an intensive care unit (the four patients with HSP, one with a non-HSP complication). Two patients with HSP died within 1 week after admission despite life-support measures and high-dose corticosteroids. The autopsy in one of them (Tables I and III, patient 3) revealed leional oedema with hyaline membrane deposits.

All patients with a non-HSP bronchopulmonary event recovered. The infectious origin was proved in four patients; the clinical presentation and the evolution were highly suggestive of an infectious aetiology in the others. The patient with *P. carinii* infection underwent tracheostomy. MTX was restarted in four patients with non-HSP lung disease; one of them developed bronchitis 3 months after.

**DISCUSSION**

The course of low-dose MTX treatment in RA may be marked by the occurrence of pulmonary side-effects, either infectious or drug related [4, 8-10]. We report our experience of 12 MTX-treated RA patients with pulmonary complications. The severity was highly variable, ranging from bronchitis with favourable outcome to acute respiratory distress with a fatal outcome. The initial symptoms, cough, dyspnoea and fever, began in an acute manner in all patients, and were not discriminatory between HSP and an infectious process. HSP occurred in four patients and two of them died. The occurrence of HSP was unforeseeable; none of these patients had previous lung disease. However, no risk factors could be identified because of the study design.

In the same cohort of MTX-treated RA in-patients, eight patients did not meet the criteria for the diagnosis of HSP. In four of them, a microorganism was identified. However, in the four remaining patients, the clinical presentation and the outcome were highly suggestive of an infectious process; the patients were treated with antibiotics alone, all of them recovered rapidly and the fever disappeared within 2 days.

The frequency of MTX HSP has been estimated to be between 2 and 5% [4, 6]. In our experience, the prevalence of HSP during MTX therapy in a population of RA in-patients is 3% (4/130). One-third of patients (4/12) developed HSP, and the others probably developed an infectious side-effect. This frequency could be higher than that observed in the community, depending on the characteristics of our patients, referring to a hospital care unit, most of them having long-standing disease.

The diagnosis of MTX HSP is always difficult to confirm. Symptoms, radiological and gasometric alterations are not specific, and BAL must be performed to detect an opportunistic infection. In MTX HSP, BAL usually shows hypercellularity with lymphocytosis [11]. The severity of respiratory symptoms is often more pronounced in the case of HSP, and our four patients were hospitalized in an intensive care unit.

HSP occurs early in the course of MTX treatment, even with low weekly MTX doses. In our experience, HSP always occurred in the first 5 months of therapy, with a total dose of MTX ranging from 60 to 250 mg. However, some cases with late MTX HSP, occurring after >3 yr, have also been reported [12]. Thus, patients should be monitored very carefully, especially after the initiation of MTX, and should be aware of this type of complication.

Several risk factors have been suggested for MTX pneumonitis, such as pre-existing lung disease or rheumatoid lung, cigarette smoking, stomatitis and renal insufficiency [4-6, 13]. Golden et al. [14] recently reported that a pre-existing lung disease with radiographic interstitial infiltrates predisposed patients with RA to develop MTX pneumonitis. None of the four patients with HSP had one of the previously mentioned risk factors.

The reintroduction of MTX after total recovery from HSP can be performed only if absolutely necessary, and is not always accompanied by recurrence of pneumonitis. In our experience, MTX was not reintroduced to patients with HSP; it was restarted in four patients with non-HSP lung disease, a bronchitis occurring in one of them 3 months later.

Besides pyogenic infections, several opportunistic infections have been reported in RA patients treated with MTX, most of them receiving corticosteroids [15, 16]. These opportunistic infections must be recognized early, since corticosteroids are often used in combination with antibiotics to treat patients with acute respiratory symptoms.

Pulmonary complications are not a rare event during MTX therapy in RA. The occurrence of HSP is unforeseeable and the role of risk factors is not well established. These side-effects make necessary a strict education of patients and physicians, and MTX has to be stopped as soon as the early symptoms of respiratory intolerance occur.

**REFERENCES**


