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Infections During Low-Dose Methotrexate Treatment in Rheumatoid Arthritis

Agnes M. Th. Boerbooms, Pit J.S.M. Kerstens, Jos W.A. van Loenhout, Jan Mulder, and Leo B.A. van de Putte

We studied the infection rate in patients with rheumatoid arthritis (RA) treated with low-dose methotrexate (MTX) in a 6-year open prospective study and in a 12-month randomized double blind trial comparing MTX with azathioprine (AZA) that was followed by a 3-year open prospective study. The literature on infections during low dose MTX in RA was reviewed. We also did a search for therapy-related opportunistic infections in RA and in MTX-treated psoriasis and psoriatic arthropathy patients. In our studies the infection rate during MTX treatment was higher in severe RA than in moderate RA. In severe RA there were often 2 infections simultaneously. The majority of the infections occurred in the first 1.5 years of treatment. There was no difference in the infection rate of MTX and AZA in the comparative trial. In the literature the infection rate was highest in short-term double-blind studies. Opportunistic infections are increasingly reported in RA treated with MTX and rarely with AZA, cyclosporine A, and cyclophosphamide or in MTX treated psoriasis and psoriatic arthropathy. In RA it appears that the initial period of treatment with MTX is the most vulnerable phase for infections, with the exception of opportunistic infections, which are not limited to a certain treatment period. Probably there are more MTX-associated infections in severe RA than in moderate RA.

Indexed Words: Rheumatoid arthritis, psoriasis (arthropathy), infections, methotrexate.

LOW-DOSE methotrexate (MTX) has become a standard treatment for rheumatoid arthritis (RA). Its popularity is due to several factors such as a rapid onset of action and a favorable side-effect profile compared with that of other disease-modifying antirheumatic drugs (DMARDs). In addition there is extensive experience with MTX in the treatment of psoriasis and psoriatic arthropathy. The dose-schedule usually used in RA is derived from that for psoriasis. Therefore it might be assumed that the MTX side-effect profile is comparable in RA and psoriasis. However some years ago reports emerged indicating that MTX was associated with more opportunistic infections and probably more perioperative bacterial infections in patients with RA. We also had the impression that more infections occurred in our MTX-treated patients than with other DMARDs, such as hydroxychloroquin, gold, D-penicillamine and azathioprine (AZA). Because we had two ongoing prospective studies with MTX, we reviewed our data on this subject. We also reviewed the literature on infectious complications during oral low-dose MTX treatment in RA patients over the last 25 years. Moreover, a separate search was performed for opportunistic infections occurring...
during treatment with immunomodulating drugs such as low-dose MTX, AZA, or cyclosporine A in RA, and for treatment with MTX in psoriasis and psoriatic arthropathy.

In this paper we try to answer the following questions: (1) Was there a substantial increase of infections in our RA patients treated with low dose MTX compared with AZA treatment?27 (2) Can risk factors be indentified for these infectious complications. (3) What is the infection rate in MTX-treated RA patients in the literature? (4) Are there more opportunistic infections reported in patients treated with MTX compared with AZA or cyclosporine A? (5) What is the incidence of opportunistic infections in patients with psoriasis or psoriatic arthropathy treated with (oral) MTX?

PATIENTS AND METHODS

Two sets of data on RA patients were used in this study: a prospective 6-year open label study of MTX\(^ {15,16}\) and a 12-month randomized double-blind trial comparing MTX and AZA\(^ {27}\) in a 4-year prospective study. All patients met the American Rheumatism Association (ARA) criteria for RA.\(^ {55}\) The demographic characteristics at entry are given in Table 1. The patients in the open study were in a later phase of disease and generally had more severe RA those in the double-blind study. This was reflected by a longer disease duration, higher percentages of Steinbrocker functional class III, more subcutaneous nodules, and higher frequency of arthroplasty. Patients in the open study were treated more often with prednisone as they were either unresponsive to or had side effects from all standard DMARDs. At a minimum, patients in the double-blind study had received intramuscular gold. Because the risk for infection may increase in cases of immunodeficiency, we studied serum immunoglobulin (Ig) M, IgG, and IgA levels.

Since infections vary from the common flu to life-threatening sepsis, and because the minor infections were less consistently reported, we arbitrarily classified them as major or minor according to clinical importance. We defined major infections as those that required antibiotic treatment. Uncomplicated lower urinary tract infections were excluded (except those with signs of systemic involvement, such as high fever), because they are relative frequent in women with RA\(^ {56}\) and because their occurrence is dependent on other factors such as impaired self hygiene and hormonal changes. In general, lower urinary infections have little clinical importance, are often treated by the general physician, and are not well documented in the

<table>
<thead>
<tr>
<th>Table 1: Characteristics of Patients With RA at Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Open Prospective Study(^ {15,16})</strong></td>
</tr>
<tr>
<td>MTX</td>
</tr>
<tr>
<td>----</td>
</tr>
<tr>
<td>No.</td>
</tr>
<tr>
<td>Age (yr, mean [range])</td>
</tr>
<tr>
<td>Disease duration (years, mean [range])</td>
</tr>
<tr>
<td>Female/male</td>
</tr>
<tr>
<td>Steinbrocker functional class II/III (N [%])</td>
</tr>
<tr>
<td>HLA-DR4 positive (%)</td>
</tr>
<tr>
<td>Rheumatoid factor positive (%)†</td>
</tr>
<tr>
<td>Previous arthroplasty (%)‡</td>
</tr>
<tr>
<td>Subcutaneous nodules (%)</td>
</tr>
<tr>
<td>Prednisone (n [%])§</td>
</tr>
</tbody>
</table>

**NOTE.** Unless indicated otherwise, values are the number of patients.

\( *P = .01, \) between MTX and AZA group in the double-blind randomized study.

†Latex fixation titer \( \geq 1/80.\)

‡Hip, knee or shoulder.

§Ten milligrams or less daily.

**Abbreviations:** MTX, methotrexate; AZA, azathioprine.
clinical record. All viral upper airway infections, fungal infections of the superficial skin and nails were also considered minor infections. Examples of major infections are pneumonia, sepsis, septic arthritis, soft tissue infections, and symptomatic urinary tract infections. For this analysis only major infections were considered. Patients experiencing major infections during leukopenic states (<3.5 x 10^9/L) at the time of diagnosis were excluded.

In both studies patients were questioned about the occurrence of infections monthly during the first 6 months and every 2 months thereafter. They were specifically asked about episodes of fever, diarrhea, skin abnormalities, cough and dysuria. Visits to the general physician and the use of antimicrobial therapy were noted. When no conclusion could be drawn from this information, verification was sought by contacting the practitioner.

The infection incident rates were expressed as percentages by dividing the number of major infections by patients years on MTX for all patients per study group and multiplying by 100.

LITERATURE

Two literature searches were made using the MEDLINE data bases from January 1966 to January 1994 and BIOS data bases from January 1970 to January 1994. The first search was directed at infectious complications of MTX therapy in general in RA. The search terms were: RA, MTX, infections (complications), open and controlled studies. Studies accepted for analysis had to contain information on the following items: the number of MTX patients at risk, duration of follow-up (per patient or group), number and types of infections, MTX dosage, concomitant immunosuppressive therapy, and other diseases or conditions, such as malignancy and leukopenia, associated with an increased susceptibility to infection. Only the data from patients who had no other identifiable reason to be prone to major infections, except the concomitant use of low dose prednisone (<20 mg daily) were used in this study. If more than one report of a particular study existed the latest update was used. When only intervals of a study were reported they were entered separately. The infection incident rate was calculated in the same way as our data (above).

In the second search the headings MTX, AZA, Cyclosporine A, opportunistic infections, RA, psoriasis and psoriatic arthropathy were used. Also the individual infections, i.e. pneumocystis carinii, herpes zoster, disseminated herpes simplex, cytomegalic virus, histoplasmosis, tuberculosis, aspergillosis, nocardia and cryptococcosis in combination with RA, psoriasis, psoriatic arthropathy were checked. To be acceptable for this part of the study reports had to contain information on the patient’s treatment, hematologic status, and the absence of other causes of opportunistic infections (except for use of low dose steroids).

Citations were limited to those in English. To validate the literature search, a manual search for additional citations using references in articles retrieved from the computerized search, as well as review articles, textbooks and proceedings from symposia and congresses was accomplished. Studies were reviewed by two of the authors (JvL and AB), and discrepancies between reviewers about the retrieved data were settled by consensus.

STATISTICS

In the double-blind study differences in demographic characteristics between the two treatment groups were determined using χ² tests for nominal variables; for other features, such as age and disease duration, the Student two-sample test was used. For comparison of infections in the three patient groups, probability curves (infection free survival curves) were constructed, plotting the initial episode of infection against the length of time after the start of MTX or AZA, using the Kaplan-Meier method. Differences were tested with the Wilcoxon test for censored observations.

RESULTS

Three treatment groups were studied: 16 patients were started on MTX in an open prospective study and 31 were given MTX and 33 AZA in a 48 week double blind randomized trial followed by 3 years open extension (Table 1). Major infections were observed in all three treatment groups and occurred mainly in the first 1.5 years after which they occurred sporadically (Fig 1). In the AZA group the censoring pattern was different from the other two groups.
In the AZA group 13 of 33 patients were dropped because of various side effects within the first 6 months of treatment. There were no significant differences among the 3 Kaplan-Meier infection free survival curves. In the open MTX study 4 of the 5 patients with infection had 2 infections simultaneously. In the double blind study no simultaneous infections occurred.

The incident infection rate during 4 years of follow-up was 18% in the open study, and 7% in the MTX and AZA groups in the double blind study (Table 2). Apart from 2 patients with herpes zoster in the open study and 1 in the AZA group, no opportunistic infections occurred. The infections which occurred were in order of frequency: pneumonia (4 in the MTX group and 2 in the AZA group of the double blind study); skin/soft tissue infection (3 in the MTX group of the open study and 1 in the AZA group of the double-blind study), complicated urinary tract infection (2 in the MTX group of the open study and 1 in the MTX group of the double blind study). One patient in the MTX double-blind study developed peritonitis; in the open MTX study 1 septic arthritis and 1 infected knee prosthesis were identified. There were no fatalities. In 2 cases MTX treatment was permanently abandoned after the infectious episode. In the other patients MTX was reinstituted after recovery from the infection, mostly in lower doses, and infection did not recur. At the time of infection the serum immunoglobulins (IgM, IgG, IgA) were normal, except in one patient with *Escherichia coli* urosepsis, whose IgG was 8.55 g/L (N 12.5 ± 2.1 g/L).

**Table 2: Infection Rate During the 6-Year Open Prospective MTX Therapy Study and the 48-Week Double-Blind Comparative Study With 3-Year Open Extension of MTX and AZA**

<table>
<thead>
<tr>
<th>Study Period (mo)</th>
<th>Open Study</th>
<th>Double-Blind Comparative Study With Open Extension</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MTX</td>
<td>MTX</td>
</tr>
<tr>
<td></td>
<td>No. of Patients</td>
<td>Patient Years on MTX</td>
</tr>
<tr>
<td>0-12</td>
<td>16 (12)</td>
<td>13</td>
</tr>
<tr>
<td>0-48</td>
<td>16 (6)</td>
<td>44</td>
</tr>
<tr>
<td>0-72</td>
<td>16 (6)</td>
<td>57</td>
</tr>
</tbody>
</table>

**Abbreviations:** MTX, methotrexate; AZA, azathioprine.

*Number of patients at the start of the period concerned, in parenthesis the number of patients continuing the same drug at the end of the period.

†Infection rate = (number of infections/patient years at risk) x 100.
RA and MTX Literature Search

The literature search of MTX and infections resulted in 45 entries. The main reasons for discarding studies from final analysis were: parenteral use of MTX (n = 4), stating side effects by organ system only (n = 3), inability to calculate the time at risk and/or uncertainty about the MTX dose (n = 2) and the use of dosages over 15/mg per week (n = 2); 7 entries from ongoing studies were eliminated because the data were included in studies on long-term treatment with MTX and already included in the analysis. For the final analysis 27 studies remained, including 21 prospective (13 open, 7 double blind, and 1 double blind at the start with an open extension) and 6 retrospective studies. It was assumed that all infections occurred in the presence of normal leukocyte counts if not otherwise stated. There appeared to be a slight increase in the infection rate since 1985 (Table 3). In the 6 retrospective studies the mean infection rate was 1.8%, in the 13 open prospective studies it was 4.6% and in the 8 double-blind studies it was 11.6% (Table 4). The mean disease duration in the three types of studies did not differ substantially: 13.8, 12.9 and 10.7 years, respectively. Mean patient years during MTX treatment was 336 years (range 22.5-780) in the retrospective studies, 103 years (range 13-480) in the open studies and 31 years (range 7.4-103) in the double-blind studies (Table 3).

Opportunistic Infections in RA Patients Treated With MTX, AZA or Cyclosporine

The search for opportunistic infections in patients with RA treated with MTX produced 19 reports. Four of these could not be used, 2

Table 3: MTX Treatment and Infection Rate in RA Patients

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Patients at Risk (n)</th>
<th>Disease Duration (yr) at MTX Start, (Mean [range])</th>
<th>MTX mg/wk range</th>
<th>Patient Years on MTX</th>
<th>Infection Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wilkens, 19801</td>
<td>O</td>
<td>32</td>
<td>NM (4-45)</td>
<td>7.5-15</td>
<td>47</td>
<td>0</td>
</tr>
<tr>
<td>Steinsisson, 19823</td>
<td>O</td>
<td>21</td>
<td>9 (1.5-32)</td>
<td>7.5-25</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>Groff, 19834</td>
<td>R</td>
<td>28</td>
<td>14 (5-40)</td>
<td>2-30</td>
<td>29</td>
<td>7</td>
</tr>
<tr>
<td>Williams, 19855</td>
<td>DB</td>
<td>95</td>
<td>14 (NM)</td>
<td>7.5-15</td>
<td>21</td>
<td>0</td>
</tr>
<tr>
<td>Weinstein, 19866</td>
<td>R</td>
<td>21</td>
<td>9 (1.5-32)</td>
<td>7.5-15</td>
<td>53</td>
<td>2</td>
</tr>
<tr>
<td>Weinblatt, 19877</td>
<td>DB</td>
<td>33</td>
<td>10 (1.8-29)</td>
<td>7.5-15</td>
<td>7</td>
<td>27</td>
</tr>
<tr>
<td>Kremer, 198811</td>
<td>O</td>
<td>21</td>
<td>12 (8-33)</td>
<td>5-17.5</td>
<td>61</td>
<td>2</td>
</tr>
<tr>
<td>Hamdy, 198710</td>
<td>DB</td>
<td>21</td>
<td>9 (NM)</td>
<td>5-15</td>
<td>33</td>
<td>0</td>
</tr>
<tr>
<td>Gispen, 198712</td>
<td>O</td>
<td>72</td>
<td>14 (SD 8.1)</td>
<td>2.5-12.5</td>
<td>72</td>
<td>3</td>
</tr>
<tr>
<td>Kremer, 198813</td>
<td>O</td>
<td>25</td>
<td>11 (3.8-18)</td>
<td>Mean 14.6</td>
<td>50</td>
<td>0</td>
</tr>
<tr>
<td>Weinblatt, 198814</td>
<td>O</td>
<td>26</td>
<td>9 (1.8-27)</td>
<td>5-15</td>
<td>44</td>
<td>9</td>
</tr>
<tr>
<td>Boerbooms, 198815</td>
<td>O</td>
<td>16</td>
<td>16 (5-33)</td>
<td>5-15</td>
<td>14</td>
<td>15</td>
</tr>
<tr>
<td>Alarcon, 198918</td>
<td>O</td>
<td>152</td>
<td>19 (SD 15.2)</td>
<td>Mean 7.7</td>
<td>480</td>
<td>0</td>
</tr>
<tr>
<td>Hanrahan, 198919</td>
<td>O</td>
<td>128</td>
<td>13 (1-46)</td>
<td>5-25</td>
<td>230</td>
<td>2</td>
</tr>
<tr>
<td>McKendry, 198917</td>
<td>R</td>
<td>131</td>
<td>NM</td>
<td>Mean 8.4</td>
<td>23</td>
<td>0</td>
</tr>
<tr>
<td>Furst, 198920</td>
<td>DB</td>
<td>30</td>
<td>NM</td>
<td>7.5-35</td>
<td>13</td>
<td>23</td>
</tr>
<tr>
<td>Arnold, 199021</td>
<td>DB</td>
<td>26</td>
<td>14 (SD 8)</td>
<td>NM</td>
<td>8</td>
<td>13</td>
</tr>
<tr>
<td>Weinblatt, 199022</td>
<td>DB</td>
<td>138</td>
<td>6 (0.5-48)</td>
<td>7.5-15</td>
<td>103</td>
<td>0</td>
</tr>
<tr>
<td>Mielants, 199124</td>
<td>O</td>
<td>92</td>
<td>12 (1-41)</td>
<td>NM</td>
<td>143</td>
<td>4</td>
</tr>
<tr>
<td>Scully, 199125</td>
<td>R</td>
<td>124</td>
<td>12 (1-55)</td>
<td>Mean 9.9</td>
<td>400</td>
<td>0</td>
</tr>
<tr>
<td>Singh, 199128</td>
<td>R</td>
<td>497</td>
<td>14 (NM)</td>
<td>Low dose</td>
<td>735</td>
<td>2</td>
</tr>
<tr>
<td>Jeurissen, 199127</td>
<td>DB</td>
<td>31</td>
<td>13 (SD 10)</td>
<td>5-15</td>
<td>28</td>
<td>18</td>
</tr>
<tr>
<td>Weinblatt, 199229</td>
<td>O</td>
<td>26</td>
<td>9 (1.8-27)</td>
<td>5-15</td>
<td>56</td>
<td>7</td>
</tr>
<tr>
<td>Kremer, 199230</td>
<td>O</td>
<td>25</td>
<td>18 (12-28)</td>
<td>7.5-22.5</td>
<td>63</td>
<td>0</td>
</tr>
<tr>
<td>Wilkens, 199231</td>
<td>DB</td>
<td>67</td>
<td>10 (1-40)</td>
<td>5-15</td>
<td>35</td>
<td>0</td>
</tr>
<tr>
<td>Buchbinder, 199332</td>
<td>R</td>
<td>50</td>
<td>9 (0.3-47)</td>
<td>5-20</td>
<td>780</td>
<td>0</td>
</tr>
<tr>
<td>Kerstens, 199416</td>
<td>O</td>
<td>14</td>
<td>16 (6-33)</td>
<td>5-15</td>
<td>57</td>
<td>16</td>
</tr>
</tbody>
</table>

Abbreviations: MTX, methotrexate; O, open prospective; DB, double blind; R, retrospective; NM, not mentioned.
Table 4: Infection Rate During MTX Treatment in RA in Patients: Reports From the Literature Comparing Different Study Designs

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Patients at the Start</th>
<th>Patient Years on MTX</th>
<th>Infection Rate</th>
<th>Illustrative References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retrospective</td>
<td>1257</td>
<td>3840</td>
<td>1.8</td>
<td>4, 6, 28, 32</td>
</tr>
<tr>
<td>Open</td>
<td>650</td>
<td>1330</td>
<td>4.6</td>
<td>1, 3, 11-15, 16, 18, 19, 24, 29, 30</td>
</tr>
<tr>
<td>Double-blind</td>
<td>441</td>
<td>248.9</td>
<td>11.6</td>
<td>5, 7, 10, 20, 21, 22, 27, 31</td>
</tr>
</tbody>
</table>

NOTE. Infection rate = (number of infections/patient years at risk) × 100.
Abbreviations: MTX, methotrexate.

due to absence of hematologic status, 1 due to higher MTX dose and 1 because of a high dose of concomitant steroids\(^4\),\(^6\),\(^12\),\(^14\),\(^23\),\(^38\)-\(^47\) (Table 5). In the remaining 15 case reports the age of the patients ranged from 42 to 83 years (mean 62 years) and the disease duration from 3 to 35 years (mean 14 years). Opportunistic infections were observed after a variable duration of MTX treatment (mean ± 20; range 0.9—> 84 months). Eleven of the 30 patients were not using prednisone when the opportunistic infection was diagnosed. No reports of opportunistic infections during AZA treatment were found. *Pneumocystis carinii* pneumonia was noted once during cyclosporine and MTX treatment in an RA patient.\(^5\),\(^8\) Gruberg et al\(^5\),\(^9\) observed a Nocardia asteroides infection complicating RA in a patient treated with a combination of AZA, hydroxychloroquine, prednisone, and MTX. No report of tuberculosis in RA patients treated with MTX, AZA, or cyclosporine was found.

*Opportunistic Infections in Patients With Psoriasis (Arthropathy) Treated With MTX, AZA or Cyclosporin A*

Only six reports were found on opportunistic infections in association with the use of MTX in the absence of leukopenia in psoriasis and psoriatic arthropathy patients (Table 6).\(^39\),\(^43\),\(^49\),\(^59\)-\(^61\) Two psoriatic patients developed tuberculosis after receiving MTX for 2 and 1½ years respectively.\(^62\) No such reports were found for AZA or cyclosporine. Wallis et al\(^63\) described a 16-year-old girl with psoriatic arthropathy who developed *P. carinii* pneumonia complicating MTX treatment. This patient developed pancytopenia during MTX, high dose nonsteroidal anti-inflammatory drug, and a low-dose prednisone treatment. Moreover herpes sim-plex hepatitis ensued in a patient with psoriatic arthritis who developed leukopenia during the use of MTX, prednisone, and a nonsteroidal anti-inflammatory drugs.\(^64\)

**DISCUSSION**

The infection-free survival curves in our open MTX study and in the MTX and AZA patients in the double-blind study were not significantly different. In RA patients the infection rates during MTX and AZA treatment were similar. This contrasts with a retrospective analysis of RA patients receiving various second-line agents showing 17 infections per 1000 person years on MTX compared with a maximum of 5 per 1000 years on AZA.\(^28\) A higher infection rate was seen in the 4 years open study, these patients having more severe RA at the start of MTX treatment. However the number of patients is too small to draw firm conclusions about the relation between infection frequency and disease severity.

Although many patients in the open study used prednisone, in contrast to the double-blind study, infections happened mostly in patients who did not use prednisone. While an association between glucocorticoid therapy and increased frequency of infection has been reported,\(^65\) a meta-analysis of controlled trials using steroids showed no enhanced infection rate in patients given less than 10 mg prednisone daily or a total dose less than 700 mg.\(^66\) Less than 10 mg of prednisone given once a day could not maintain free plasma corticosteroid levels sufficient to suppress macrophage function, and larger steroid doses are required to inhibit other host defense mechanisms such as chemotaxis or polymorphonuclear killing.\(^67\) Thus the risk of infection from low-dose corticoste-
**Table 5: Opportunistic Infections Associated With MTX Treatment in RA Patients Without Leukopenia**

<table>
<thead>
<tr>
<th>Year</th>
<th>Study</th>
<th>Pathogen</th>
<th>Gender</th>
<th>Age (yr)</th>
<th>Disease Duration (yr)</th>
<th>MTX Weekly Dose (mg)</th>
<th>MTX Duration (mo)</th>
<th>Prednisone Daily Dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1983</td>
<td>Perroquet38</td>
<td><em>Pneumocystis carinii</em></td>
<td>F</td>
<td>74</td>
<td>10</td>
<td>15</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>1983</td>
<td>Groff4</td>
<td><em>Varicella zoster</em></td>
<td>F</td>
<td>17</td>
<td>8 (max)</td>
<td>7.5</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>1983</td>
<td>Groff4</td>
<td><em>Herpes zoster</em></td>
<td>F</td>
<td>21</td>
<td>18 (max)</td>
<td>10</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>1985</td>
<td>Weinstein6</td>
<td><em>V zoster</em></td>
<td>M</td>
<td>53</td>
<td>9</td>
<td>7.5-15</td>
<td>60</td>
<td></td>
</tr>
<tr>
<td>1987</td>
<td>Altz-Smith39</td>
<td><em>Cryptococcus</em></td>
<td>M</td>
<td>53</td>
<td>9</td>
<td>10-12.5</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td>1987</td>
<td>Gispen12</td>
<td><em>Listeria monocytogenes</em></td>
<td>F</td>
<td>61</td>
<td>10</td>
<td>10-15</td>
<td>15</td>
<td>5</td>
</tr>
<tr>
<td>1988</td>
<td>Weinblatt14</td>
<td><em>H zoster</em></td>
<td>M</td>
<td>76</td>
<td>6</td>
<td>7.5-15</td>
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<td><em>H zoster</em></td>
<td>F</td>
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<td>16</td>
<td>12.5</td>
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<tr>
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<td><em>H zoster</em></td>
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<td>7.5</td>
<td>22</td>
<td>7.5</td>
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<tr>
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<td>M</td>
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<td>6</td>
<td>20</td>
<td>8</td>
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<td>F</td>
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<td>22</td>
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<td>M</td>
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<tr>
<td>1990</td>
<td>Furst23</td>
<td>Herpes virus</td>
<td>M</td>
<td>66</td>
<td>22.5 (max)</td>
<td>6</td>
<td>12</td>
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<tr>
<td>1991</td>
<td>Leff42</td>
<td><em>P carinii</em></td>
<td>M</td>
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<tr>
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<td><em>P carinii</em></td>
<td>F</td>
<td>69</td>
<td>23</td>
<td>10</td>
<td>8</td>
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<tr>
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<td>Wollner44</td>
<td><em>P carinii</em></td>
<td>F</td>
<td>83</td>
<td>23</td>
<td>10</td>
<td>&gt;84</td>
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<tr>
<td>1991</td>
<td>Flood45</td>
<td><em>P carinii</em></td>
<td>F</td>
<td>56</td>
<td>5</td>
<td>7.5</td>
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<tr>
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<td>Clerc46</td>
<td><em>Cytomegalovirus</em></td>
<td>F</td>
<td>66</td>
<td>11</td>
<td>12.5</td>
<td>3</td>
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<tr>
<td>1992</td>
<td>Porter47</td>
<td><em>P carinii</em></td>
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<td>8</td>
<td>7.5</td>
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<td>Porter47</td>
<td><em>P carinii</em></td>
<td>F</td>
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<td>18</td>
<td>7.5</td>
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</tbody>
</table>

**Abbreviations:** MTX, methotrexate.

Roids in RA appears negligible although it might be increased in combination with MTX.

Some retrospective studies based on questionnaire design have shown that regardless of treatment RA patients are not more susceptible to common infections than control patients with osteoarthritis or soft tissue rheumatism. Older studies often focused on hepatic side effects. More recent studies reported side effects in more detail with greater emphasis on infection. Our results are in accord with recent infection rates. (Table 3). An infection rate of greater than 13% was found in several double blind studies and in only one (our) open study that showed an infection rate of 15.7%. All of the patients in this trial had severe dis-
Table 6: Opportunistic Infections Associated With MTX Treatment in Patients With Psoriasis and Psoriatic Arthropathy in the Absence of Leukopenia

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Year</th>
<th>Author</th>
<th>Pathogen</th>
<th>Patient/Disease Characteristics</th>
<th>Treatment Characteristics</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Age (yr)</td>
<td>MTX Weekly Dose (mg)</td>
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<tr>
<td>Psoriasis</td>
<td>1971</td>
<td>Smith62</td>
<td>Microbacterium</td>
<td>M 48</td>
<td>25*/5</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>tuberculosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>M tuberculosis</td>
<td>M 37</td>
<td>25*/20</td>
</tr>
<tr>
<td></td>
<td>1975</td>
<td>King61</td>
<td>Hepatitis B</td>
<td>M 42</td>
<td>NM</td>
</tr>
<tr>
<td></td>
<td>1992</td>
<td>Witty60</td>
<td>Histoplasmosis</td>
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<td>F 36</td>
<td>7.5</td>
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<td></td>
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<td>F 28</td>
<td>10</td>
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<td>Psoriatic arthropathy</td>
<td>1987</td>
<td>Altz-Smith59</td>
<td>Cryptococcosis</td>
<td>M 45</td>
<td>12.5-15</td>
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<td></td>
<td></td>
<td></td>
<td>F 54</td>
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<td>Shiroky43</td>
<td>Herpes zoster</td>
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</table>

Abbreviations: NM, not mentioned.

*Initial dosage gradually reduced to final dosage.

ablating RA and most infections occurred in the first 1½ years of MTX treatment. The double blind studies with a high infection rate have a short term follow-up,7,20,21,27 so most infections happened in the first year of treatment. This finding suggests that MTX has the strongest immunosuppressive effect soon after initiation. Another possible explanation for a lower infection rate long term is that if MTX controls the disease, the inflammatory activity will be down regulated and defense mechanisms restored. MTX might be a double edged sword: adversely influencing macrophage and granulocyte function and subsets of T lymphocytes,74,75 while on the other hand restoring the immune response/balance by controlling the underlying disease. The mechanism of action of MTX is unknown, whether primarily anti-inflammatory or immunosuppressive, despite several known effects on immunoinflammatory processes both in experimental animals and in humans.76,77 T cells have a central role in the pathogenesis of RA. During MTX treatment serum immunoglobulin levels8,15 and rheumatoid factor27 titers decrease. Significant reductions in sIL-2R and p55 concentrations were also observed in patients treated with MTX, but not with AZA.78 A reduction of granulocyte chemotaxis has also been noted.79

Based on the literature opportunistic infections are considered a specific side effect of MTX therapy in RA patients. They were not associated with AZA (in RA) and only once with combined MTX and cyclosporine treatment.37 Opportunistic infections were reported in RA patients treated with cyclophosphamide,80-82 but we are not aware of an association with other DMARDs. Interestingly, our literature search revealed only occasional opportunistic infection in psoriasis and psoriatic arthropathy patients treated with MTX39,43,49,61-64 despite the large number of treated patients. Probably the underlying immunological disturbance in RA patients is more important in this respect, as are the modifying effects of MTX on the immunological functions.83-86 As with acquired immunodeficiency syndrome (AIDS) patients, Pneumocystis carinii is the most frequent opportunistic infection in RA treated with MTX. Interestingly, in the literature search we did not find tuberculosis in RA patients treated with MTX, AZA, or cyclosporine, in contrast with AIDS and other immunosuppressed patients.

In conclusion: The most vulnerable phase for developing infection during MTX treatment in RA is in the first year of treatment. The risk for opportunistic infections are not limited to any period of treatment. In our studies patients with severe RA had more infectious complications than patients with moderate RA, although our numbers are too small to draw firm conclusions.
REFERENCES

34. Schnabel A, Gross WL. Low-dose Methotrexate in
INFECTIONS AND MTX TREATMENT IN RA