

PDF hosted at the Radboud Repository of the Radboud University Nijmegen

The following full text is a publisher's version.

For additional information about this publication click this link.

<http://hdl.handle.net/2066/22450>

Please be advised that this information was generated on 2017-12-05 and may be subject to change.

Major Infection During Methotrexate Treatment for Rheumatoid Arthritis

Dear Sir:

We read with interest the article of Boerbooms et al in the June 1995 issue of *Seminars*, who reported the frequency of infection in rheumatoid arthritis (RA) patients being treated with methotrexate (MTX) or azathioprine (AZA).¹ In a comparative study of 31 and 33 patients treated with MTX and AZA, respectively, and in an open, prospective study of 16 MTX-treated patients, the authors found no difference in the rate of infection between the two treatment modalities, no opportunistic infections other than herpes zoster, and no association of infection with concomitant corticosteroid treatment. We feel impelled to relate their results to the data of our prospective study of the long-term tolerability of MTX in RA, which, on the basis of a much larger number of patients, strengthen some, but not all, of their conclusions.²

In our study, 185 consecutive patients with RA according to American Rheumatoid Association criteria were recruited from the inpatient pool of a single clinical department.³ This department is a referral center for rheumatic diseases, and the cohort was thus characterized by a high rate of patients with severe disease. Patients were randomized to receive 15 or 25 mg MTX/week initially. Adjustment of the MTX dose according to efficacy and tolerability resulted in mean doses of 16.8 ± 5.5 mg and 19.7 ± 6.0 mg/week, respectively, after 12 months and 17.6 ± 6.2 mg and 18.5 ± 6.9 mg/wk at month 30. For the purpose of this analysis, the two groups were pooled. This resulted in 168 patients eligible for evaluation during months 1 through 12 and 123 patients during months 13 through 30. Adverse events were registered during follow-up examinations on a regular basis by the patients' local physicians in collaboration with the clinical department. Intervals for monitoring were 2 weeks initially and 2 to 4 weeks later. All episodes of bacterial infection severe enough to require antibiotic treatment, and of herpes zoster, were catego-

rized as major infections and registered. Nonexudative pharyngitis and bronchitis are not considered to need antibiotic treatment in this country and thus were not registered.

A total of 65 episodes of major infection occurred in 56 patients during the follow-up period of 30 months (Table 1). Twenty episodes occurred during the first year and 45 during months 13 through 30. The lower respiratory tract was affected most frequently. Specifically, purulent bronchitis occurred in 16 instances and bacterial pneumonia in 9 instances. Together with 6 episodes of purulent sinusitis and exudative angina, the upper and lower respiratory tracts accounted for 31 of 65 episodes (48%) of major infection. Urinary tract infections necessitating antibiotic treatment accounted for 25% of total infections and were second in frequency only to respiratory tract infections. Purulent skin infections were less frequent, and cholecystitis, febrile enteritis, and wound infection after hip joint replacement were only observed in isolated cases. Herpes zoster developed in five patients, but no other opportunistic infections were seen.

The mean dose of MTX at the time of infection was 18.7 ± 6.9 mg/wk, which did not differ significantly from the respective figure in the entire cohort. Twenty-nine of the 65 episodes (45%) occurred during concomitant methylprednisolone treatment, the median dose being 4 mg/day. When all infections were combined, the percentage of patients on corticosteroid and the median dose of corticosteroid in the patients with infections did not differ significantly from the respective figures in the entire cohort.

Four deaths occurred during the study, with infections being implicated as causative. The age of these patients was 64, 69, 81, and 84 years; all had severe, long-standing RA (ARA class III to IV). One patient died of bacterial sepsis during apparently MTX-induced pancytopenia. Although no risk factors for MTX toxicity were apparent in this patient, there is little doubt that MTX-induced toxicity played a decisive role in this patient's death. In the remaining three patients, leukocytes were within the nor-

Table 1: Number of Bacterial Infections Necessitating Antibiotic Treatment, and of Herpes Zoster Infections, During Methotrexate Treatment

	Months 1-12	Months 13-30
	(total no./no. with corticosteroids)	
Purulent bronchitis	5/1	11/3
Bacterial pneumonia	4/4	5/3
Purulent sinusitis or pharyngitis	3/0	3/1
Urinary tract infection	4/0	12/6
Purulent skin infection	2/2	6/3
Cholecystitis	0	2/1
Febrile enteritis	2/1	0
Surgical wound infection	0	1/1
Herpes zoster	0	5/3

mal range at the time of demise. Two patients died of bronchopneumonia together with congestive heart failure resulting from mitral incompetence in one and coronary heart disease in the other. The fourth patient became bedridden because of Parkinson's disease and developed recurrent and eventually lethal sepsis caused by decubital ulcers. Thus the last three patients had a condition that by itself would provide a plausible explanation for the lethal outcome, although a contributory role for MTX cannot be excluded.

These data support three main findings of the study of Boerbooms et al.¹ First, the respiratory tract was the organ system most frequently affected. This calls for heightened vigilance for infection at this site in RA patients receiving MTX and causes us to seek alternative second-line treatment in patients at increased risk for respiratory tract infection, eg, severe chronic bronchitis, bronchiectasis, or chronic left heart failure. Second, the percentage of patients receiving concomitant corticosteroid medication and the median corticosteroid dose were no higher in patients with infection than in patients without. This tends to support the conclusion of Boerbooms et al that less than 10 mg prednisolone equivalent does not have a major effect on susceptibility to infection, although the number of patients in the two studies may be too small

to detect a minor effect. Third, no opportunistic infections other than herpes zoster were observed in these patients. This confirms the notion that conventional pathogens are the main problem during MTX treatment, although available studies may be too small to detect a minor effect.

In contrast to the findings of Boerbooms et al, the rate of infections did not cluster in the initial phase of MTX treatment in our study but was essentially stable over time. We cannot, therefore, support the conclusion that the first year of MTX treatment is a particularly vulnerable phase in this regard.

Taken together, the current data and previous studies provide a reasonably clear picture of the spectrum of major infection that may be encountered in RA patients receiving MTX treatment.^{1,2,4} The respiratory tract is the most common site of infection in this setting, followed by urinary tract and soft tissue infections. Because of the lack of a control group, the current study does not answer the question whether MTX increases the risk of infection in RA. The study of Boerbooms et al presents evidence against a previous, nonrandomized retrospective analysis that suggested that MTX treatment is associated with a higher rate of infection than treatment with other second-line agents.⁵ Conversely, a prospective case-control study showed a significantly higher rate of infection in MTX-treated RA patients as compared with patients receiving other second-line agents.⁴ It remains unresolved as to what extent the condition being treated contributed to the inconsistent results. Because severe RA is associated with a higher rate of infection,^{1,6} further study of this issue should be carefully controlled for disease severity and take into account the possibility that the effect of MTX on susceptibility to infection may vary with disease severity.

On the basis of the current evidence, we postulate that severe RA under treatment with MTX be considered a risk for major infection. Although the optimal management remains a matter of clinical judgment, a case can be made for prompt and vigorous anti-infectious treatment in this setting and for restricting the use of MTX in RA patients with concomitant condi-

tions that may confer an increased susceptibility to infection.

ARMIN SCHNABEL, MD
CHRISTIAN BURCHARDI, MD
WOLFGANG L. GROSS, MD
Department of Clinical Rheumatology
Medizinische Universität Lübeck
Ratzeburger Allee 160
D-23562 Lübeck, Germany
and
Rheumaklinik Bad Bramstedt
Oskar-Alexander-Strasse 26
D-24576 Bad Bramstedt, Germany

REFERENCES

1. Boerbooms AMTh, Kerstens PJSM, van Loenhout JWA, et al: Infections during low-dose methotrexate treatment in rheumatoid arthritis. *Semin Arthritis Rheum* 24:411-421, 1995
2. Schnabel A, Herlyn K, Burchardi Ch, et al: Long-term tolerability of MTX at doses exceeding 15 mg/week in rheumatoid arthritis. *Rheumatol Int* (in press)
3. Schnabel A, Reinhold-Keller E, Willmann V, et al: Tolerability of methotrexate starting with 15 or 25 mg/week for rheumatoid arthritis. *Rheumatol Int* 14:33-38, 1994
4. van der Veen MJ, van der Heide A, Kruize AA, et al: Infection rate and use of antibiotics in patients with rheumatoid arthritis treated with methotrexate. *Ann Rheum Dis* 53:224-228, 1994
5. Singh G, Fries JF, Williams CA: Toxicity profiles of disease modifying antirheumatic drugs in rheumatoid arthritis. *J Rheumatol* 18:188-194, 1991
6. van Albada-Kuipers GA, Linthorst J, Peters EAJ, et al: Frequency of infection among patients with rheumatoid arthritis versus patients with osteoarthritis or soft tissue rheumatism. *Arthritis Rheum* 31:667-671, 1988

Reply. We read with interest the comment by Schnabel et al. They describe their open prospective study on patients with rheumatoid arthritis (RA) treated with methotrexate (MTX).¹ There are two main differences between their study and ours.² First the dose of MTX in the open prospective study of Schnabel was 18.7 mg \pm 6.9 mg/week at the time of infection, which did not differ significantly from the respective figure in the entire cohort. In our studies the dose of

MTX was considerably lower, ie, 5 to 15 mg/week. Second, the follow-up period in the study of Schnabel was 13 to 30 months for 123 patients. Our follow-up for the patients in the open prospective study was 72 months, whereas the 12 months randomized double blind trial was followed by a 36-month open prospective evaluation.

In contrast to our finding, that the most vulnerable phase for developing infection during MTX treatment in RA is the first year of treatment, Schnabel found that the rate of infection did not cluster in the initial phase of MTX treatment. This may relate to the above-mentioned differences between the studies. In this context it might be of interest to mention that reviewing 24 relevant papers on the issue indicated that most infections occur in the first 1 1/2 years of MTX treatment.

Finally, Schnabel commented that we suggest that MTX treatment is not associated with a higher rate of infection than treatment with other second-line agents.^{2,3} We would like to stress that we only have reported the comparison between MTX and AZA.²

AGNES M. TH. BOERBOOMS MD, PHD
PIT J.S.M. KERSTENS MD
JOS W.A. VAN LOEPHOUT MD, PHD
LEO VAN DE PUTTE, MD, PHD
Department of Rheumatology and Department of Oncology
University Hospital Nijmegen
Nijmegen
The Netherlands

REFERENCES

1. Schnabel A, Herlyn K, Burchardi Ch, et al: Long-term tolerability of MTX at doses exceeding 15 mg/week in rheumatoid arthritis. *Rheumatol Int* (in press)
2. Boerbooms AMTh, Kerstens PJSM, van Loenhout JWA, et al: Infections during low-dose methotrexate treatment in rheumatoid arthritis. *Semin Arthritis Rheum* 24:411-421, 1995
3. Singh G, Fries JF, Williams CA: Toxicity profiles of disease modifying antirheumatic drugs in rheumatoid arthritis. *J Rheumatol* 18:188-194, 1991