Longterm Observational Study of Methotrexate Use in a Dutch Cohort of 1022 Patients with Rheumatoid Arthritis

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ABSTRACT. ***Objective***. To study which factors are associated with longterm methotrexate (MTX) use in rheumatoid arthritis (RA).

Methods. All patients with RA who had started MTX after January 1, 1993, were selected from a regional hospital based registration system. Data on demographic and clinical features were retrieved through chart review. By means of life table analysis and Cox regression analysis, MTX survival and the relation between demographic variables, clinical features, and MTX survival were studied.

Results. A total of 1072 MTX treatment episodes in 1022 patients were analyzed. The cumulative MTX survival probability after 5 years was 64%, and after 9 years was 50%. Univariate analysis showed a significant relation between MTX survival probability and folic acid supplementation, attending rheumatologist, concurrent prednisolone use, concurrent sulfasalazine use, and the number of previous disease modifying drugs. In the multivariate analysis folic acid supplementation, attending rheumatologist, and concurrent prednisolone use remained significantly related to MTX survival. Age, disease duration, and creatinine clearance were not.

Conclusion. In this retrospective study of 1022 patients with RA the cumulative MTX survival probability was 64% after 5 years and 50% after 9 years. Folic acid supplementation and to a lesser extent prednisolone were associated with a longer MTX survival. In addition, treatment strategies of individual rheumatologists influenced MTX survival. (J Rheumatol 2003;30:2325–9)

Key Indexing Terms:
METHOTREXATE RHEUMATOID ARTHRITIS LIFE TABLE ANALYSIS

Methotrexate (MTX) has proven its efficacy in the treatment of rheumatoid arthritis (RA) in numerous randomized clinical trials[1-4]. In these trials patients were selected, carefully monitored, and treated per protocol. Apart from trials, observational studies of disease modifying antirheumatic drug (DMARD) therapy in RA are important to evaluate a drug's applicability and safety in general practice. In various retrospective and prospective studies, the longterm use, often termed "survival," of the different DMARD is described. Compared to other DMARD, MTX has the longest survival[5–8]. Adverse events are the most frequent reason for MTX withdrawal[9-11]. Cumulative survival varies, the 5-year survival probability ranging in longterm prospective studies from 45 to 64%[5,12-16]. In observational retrospective studies providing information about daily practice, the 5-year survival probability ranges from 31 to 75%[6-11,17-19]. In these studies several factors, including age, disease duration, race, co-medication, and attending rheumatologist, relating to MTX survival have been identified[7,9-11,15]. The majority of these studies consider patients treated before 1996, the maximum number of patients included being 587. In recent years changes in MTX treatment have taken place. In randomized clinical trials folate supplementation has reduced toxicity, without relevant influence on efficacy[20]. Moreover, higher doses of MTX are used, which may lead to better efficacy, but may also lead to more toxicity and withdrawal.

Inspired by the study by Buchbinder, *et al*, we were intrigued by the influence of the attending rheumatologist on MTX survival[10]. In our retrospective study, the aim was to define which factors determined MTX survival in the past 9 years.

MATERIALS AND METHODS

The setting of the study is a regional rheumatological group practice serving a population of 600,000 based in 3 hospitals in Twente, The Netherlands. Annually, about 2000 RA patients are seen, which is likely a representative cohort since no alternative rheumatological service is available in the region, and there is less than 1% referral to academic centers. A computer based diagnosis registration system of all patients seen by one of the rheumatologists made it possible to identify patients with RA who used

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or still use MTX. Patients were included in the study when MTX was started between January 1, 1993, and November 19, 2001. The study endpoint was MTX discontinuation. By means of chart review we collected data on patient's date of birth, year of onset of disease, rheumatoid factor (RF), sex, serum creatinine (µmol/l), height (m), weight (kg), attending rheumatologist, start and stop date of MTX, starting dose, maximum dose and dose at end of the study, previous and concurrent DMARD, prednisolone use, folic acid supplementation, and use of nonsteroidal antiinflammatory drugs (NSAID) at start and end of the study. Height and weight were measured routinely in one hospital. Reasons for censoring were continuation of MTX at the end of the study; patients were lost to followup, or patients died (unrelated to MTX). The major reasons for MTX termination were registered and classified as inefficacy, toxicity, remission, patient request, loss to followup, MTX related death, or other reasons. Toxic events leading to MTX withdrawal were categorized as: gastrointestinal (GI) complaints, liver-enzyme elevation, pulmonary complaints, hematological disorders, infections, or miscellaneous. All these data were available in the computer based registration system and were verified by chart review. The category "patient request" indicates discontinuation at the wish of the patient, e.g., due to anxiety about side effects or unwillingness to take medication.

When MTX was stopped for less than 3 months (e.g., because of surgery) this was not considered treatment discontinuation unless a new DMARD was started in this time period.

When folic acid was started, the reason was noted as prophylactic or therapeutic, i.e., for adverse events. Age and disease duration, body mass index (BMI), and creatinine clearance (Cockcroft and Gault formula[21]) at start of MTX therapy were calculated from the raw data.

All data were collected manually on standard forms by 3 observers, and entered in a database by means of a computer-reader system.

Statistical analysis was carried out using SPSS version 9.0. Life table analysis data were used to calculate cumulative drug survival probability. Univariate and multivariate analyses were carried out by means of Cox regression. In the univariate analysis the relation between demographic factors, various clinical factors, and MTX survival was studied. A p value < 0.05 was considered significant. By means of a backward conditional stepwise regression analysis the relation between the variables found to be significant in the univariate analysis and MTX survival was analyzed. Variables were excluded when the p value was > 0.10. A p value < 0.05 was considered significant.

RESULTS

Using the computer registration system we identified 3209 RA patients, of whom 1039 had started MTX within the timeframe of inclusion. The charts of 17 of these patients were not available, leaving 1022 patients for analysis. Of these 1022 patients, 48 used MTX for 2 episodes, and 1 patient for 3 episodes. The mean age at start of MTX was 60 years, 70% of the patients were female, and 83% were RF positive. The BMI could be calculated for 709 patients, and showed a mean value of 25.8. The creatinine clearance was calculated for 763 patients and showed a mean of 86 ml/min (Table 1).

Most of the patients were treated with other DMARD before starting MTX. For 230 patients MTX was the first DMARD prescribed, for 277 patients it was the second, for 285 patients the third, and for 280 patients the fourth DMARD or more. During the observation period 9 rheumatologists were following the patient population. The majority of the patients were seen by only one rheumatologist during a treatment episode. In case patients changed from one rheumatologist to another, as was the case when one of the group retired, a treatment episode was allocated to the last attending rheumatologist. The mean starting dose of MTX was 8.2 mg/week (range 2.5–20), increasing from 1993 to 2001 from 7.0 to 9.2 mg/week. The same applies to the maximum dose with a mean of 14.7 mg/week (range 2.5–40), annual averages rising from 12.0 to 15.6 mg/week.

Table 1. Demographic and clinical features of patients with RA at baseline (1072 treatment episodes, 1022 patients).

Age, yrs, mean (range)	59.7 (18–88)
Disease duration, yrs, median (range)	4.0 (0–54)
Body mass index, n = 763, mean (range)	25.8 (13.3–60)
Creatinine clearance, n = 763, mean (range)	85.6 (27–265)
Women, %	67.9
Rheumatoid factor positive, %	83.4

Concurrent medication is listed in Table 2. Folate supplementation was started in 83% of the patients, mostly for prophylactic (89.7%) in contrast to therapeutic reasons (10.3%). The folic acid treatment regimen varied from 5 to 35 mg per week. Folate supplementation was started in 60.5% of the patients that started MTX in 1993, increasing to 95.3% of the patients in 2000. Patients who received folic acid supplementation for prophylactic reasons did not differ from those who did not with regard to baseline demographic and clinical features. NSAID were used by 83% of the patients at the start of MTX. At the end of the study or end of MTX treatment this declined to 62.6%. Starting prednisolone was related to the withdrawal of NSAID.

In the 1072 treatment episodes the cumulative survival probability of MTX was 64% after 5 years and 50% after 9 years (Figure 1). Thirty-five episodes were censored because patients were lost to followup (Table 3). MTX was discontinued 325 times, in most cases due to toxicity (179), specified as GI complaints (46), liver enzyme elevations (47), and less frequently hematological disorders (10), pulmonary complaints (22), and infections (10). MTX pneumonitis occurred in 2 patients, both recovering after MTX withdrawal and corticosteroid treatment. Two patients died of sepsis; in one of them sepsis was preceded by pancy-

Table 2. Concurrent medication during 1072 methotrexate treatment episodes.

Treatment	Percentage
Folic acid supplementation	83
Prophylactic	89.7
Therapeutic	10.3
Prednisolone	29.6
Sulfasalazine	22.8
Hydroxychloroquine	5.7
Aurothioglucose	4.8
Penicillamine	0.5
Cyclosporine	0.8
Leflunomide	0.3
NSAID	83

NSAID: nonsteroidal antiinflammatory drugs.

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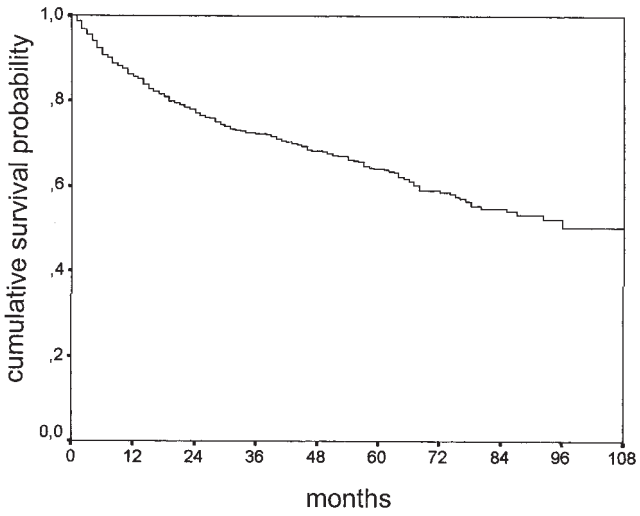

Figure 1. Life table analysis of MTX survival for the entire cohort (n = 1022, 1072 treatment episodes).

Table 3. Methotrexate withdrawal and reasons in 1072 treatment episodes (1022 patients).

	Number of Treatment Episodes	Percentage
Toxicity	179	16.7
Remission	19	1.8
Inefficacy	72	6.7
Patient's request	28	2.6
Other reason	27	2.5
Death	34	3.2
Lost to followup	35	3.3
Total	394	36.8

topenia. We considered these events related to MTX. In total, of 32 other patients who died, the cause of death was considered unlikely to be related to MTX. Univariate analysis showed a significant relation between MTX survival and folic acid supplementation ($p < 0.001$), rheumatologist ($p = 0.02$), concurrent prednisolone use ($p = 0.01$), concurrent sulfasalazine use ($p = 0.002$), and the number of previous DMARD ($p = 0.05$) (Table 4).

Figure 2 illustrates the cumulative MTX survival probability with and without folic acid supplementation, showing a significant difference in survival ($p < 0.001$). The 5-year survival probability with folic acid supplementation is 67%, and without folic acid 31%. MTX survival appears better, but not significantly so, in patients with folic acid supplementation for prophylactic reasons versus therapeutic reasons. Figure 3 shows the survival curves according to attending rheumatologist. The 5-year survival probability ranged from 47 to 94%, noting that the highest curve represented only 16 patients.

In the multivariate analysis folic acid ($p < 0.001$), attending rheumatologist ($p = 0.002$), and concurrent prednisolone use ($p = 0.005$) remained significantly related to MTX survival. Age, disease duration, BMI, and creatinine clearance were not related to MTX survival.

DISCUSSION

The cumulative 5-year MTX survival probability in our study was 64%, which is high in comparison to other retrospective studies. In only one retrospective study of 587 patients with RA was a cumulative 5-year MTX survival of 75% found[10]. However, this study was restricted to treatment terminations due to toxicity and inefficacy, MTX dosage was relatively low (5 to 20 mg per week), and folate supplementation was not common practice at that time. In an extended study of the same cohort a distinction was made between treatment termination irrespective of temporary discontinuation and discontinuation of ≥ 3 months, resembling the design of our study, leading to a 5-year cumulative survival probability of 55%[19].

Our data indicate a major influence of folate supplementation on MTX survival. Although effectiveness of folate supplementation has been demonstrated in several trials, we were surprised by the observed difference and wondered whether other factors added to it. Among 890 patients receiving folic acid supplementation, 91 (10.3%) were started for suspected MTX toxicity. This strategy was used by 3 of the 9 rheumatologists. Baseline demographic and clinical features of the patients receiving folic acid supplementation for prophylactic or for therapeutic reasons were the same, reducing the likelihood of confounding by indication. No difference was made in the analysis between folic acid started at the beginning or added during the course of MTX treatment. If this had introduced a bias, one would expect a considerably better survival of the group treated prophylactically, compared to the therapeutically treated group. This, however, was not the case. The MTX survival curve with folic acid supplementation (Figure 2) suggests that the effect of folic acid on MTX survival occurs primarily in the first 2 years. Withdrawal due to GI complaints, liver enzyme elevations, and inefficacy was less in the folic acid group. Other studies, carried out in times when folic acid supplementation was not common practice, have shown that MTX withdrawal occurs mainly in the first years[9].

Another striking result of our study is the difference in MTX survival between rheumatologists. Both toxicity and inefficacy as reason for withdrawal of MTX were significantly related to the factor "rheumatologist." By means of analysis of variance we studied which factors could explain this difference between rheumatologists. The mean age of the patient, folic acid supplementation, number of previous DMARD, starting dose, and maximum dose were significantly related to the factor "rheumatologist" (data not shown). There is a trend towards a longer MTX survival with a younger age of attending rheumatologist. The frequency of use of folates is different between the rheuma-

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Table 4. Factors related to methotrexate discontinuation—univariate and multivariate analysis (Cox regression analysis; $p \leq 0.05$).

	Univariate Analysis		Multivariate Analysis	
	p	RR (95% CI)	p	RR (95% CI)
Folate supplementation	< 0.001	0.25 (0.20–0.31)	< 0.001	0.25 (0.20–0.33)
Rheumatologist	0.02		0.002	
Prednisolone	0.01	0.72 (0.56–0.93)	0.005	0.70 (0.54–0.90)
Sulfasalazine	0.002	0.62 (0.46–0.83)	NS	
No. of previous DMARD	0.05	1.08 (1.0–1.16)	NS	
Age	NS		NS	

RR: relative risk of MTX treatment discontinuation, e.g., the risk of treatment discontinuation is one-fourth when using folate supplementation vs no folate supplementation; 95% CI: 95% confidence interval.

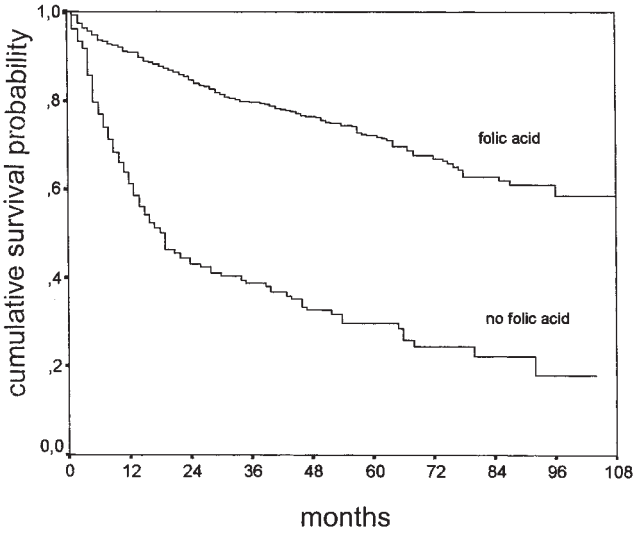

Figure 2. Life table analysis of MTX survival in groups with and without folic acid supplementation ($p < 0.001$).

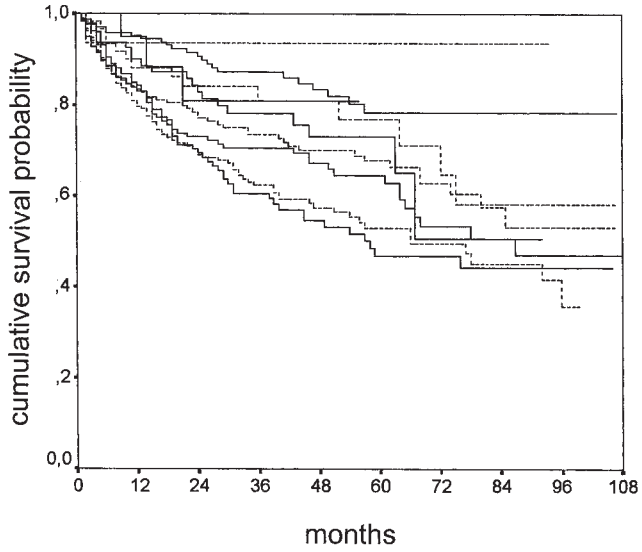

Figure 3. Life table analysis of MTX survival for 9 attending rheumatologists ($p = 0.02$).

tologists, ranging from 65 to 100% of the patients. The starting dose and maximum dose are also related to the attending rheumatologists, and with higher MTX doses there is a trend towards a longer MTX survival. None of the above mentioned variables is solely responsible for the difference in MTX survival between rheumatologists. Therefore other factors, such as physician confidence in efficacy and safety of MTX, might be responsible.

Little is known about physician behavior in clinical practice. Cabana, *et al*, in their review of reasons for non-adherence by physicians to clinical guidelines, found outcome expectancy and self-efficacy to be of importance[22]. This may also apply to dealing with treatment strategies. Another study described large variations in the judgment of disease activity by 87 rheumatologists[23]. Buchbinder observed treatment of RA patients in community-based practices by 4 rheumatologists. MTX withdrawal rates due to toxicity varied significantly between rheumatologists[10]. There seemed to be a learning curve, with reduced withdrawal of therapy in the course of time, but differences were not significant. When viewing the survival curves in our study with respect to the year of start of MTX, there is a trend towards a better survival with a later year of start. This could be due to increased experience in dealing with MTX, but an effect of the introduction of folic acid is more likely. In our study, the rate of MTX withdrawal due to inefficacy was lower with concurrent prednisolone use, resulting in a positive effect on MTX survival. Pincus, *et al* showed the same results in a DMARD survival study in 532 RA patients[7]. Kerstens, *et al* in a study of 15 patients, also found improved MTX survival with concurrent use of prednisolone[24]. Another finding in our study was a better MTX survival with concurrent sulfasalazine use. The rate of withdrawal due to inefficacy, as well as the rate of MTX withdrawal due to toxicity, was reduced. The first of these findings is not unexpected, but the latter is. Prospective studies addressing this issue gave conflicting results: in 2 studies MTX withdrawal due to toxicity was less in the combination MTX-sulfasalazine[25,26], contrary to an increased toxicity of the combination in another[27].

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With an increasing number of previous DMARD, MTX survival is slightly lower. These patients may have an increased susceptibility to any adverse events, or a decreased efficacy to DMARD due to more severe disease. Again the attending rheumatologist may have been of influence, since the way a rheumatologist deals with adverse events and efficacy in MTX may apply to other DMARD as well.

Although age is negatively, and creatinine clearance is positively, related to the maximum MTX dose, they are both not related to MTX survival. This is in agreement with most other studies. Only in the study by Buchbinder and in a retrospective study concerning 453 RA patients was treatment termination due to toxicity higher in patients aged 65 years and over[10,11]. In our data, dividing patients into groups below or above 65 years of age, there was no significant difference ($p = 0.07$), despite a trend towards a better survival in the lower age group.

In conclusion, the MTX cumulative survival probability in this retrospective study of a cohort of 1022 RA patients was 64% after 5 years, and 50% after 9 years. Folate supplementation, and to a lesser extent prednisolone use, were strongly related to MTX survival. The rheumatologist also appeared to play a decisive role in duration of MTX treatment, partly explained by patient characteristics but also by differences in individual treatment strategies.

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