EXTENDED REPORTS

# Survival and drug discontinuation analyses in a large cohort of methotrexate treated rheumatoid arthritis patients

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**Abstract**

***Objectives*—To determine the probability of drug continuation in a large cohort of methotrexate treated rheumatoid arthritis (RA) patients, the reasons for discontinuation of methotrexate, the overall survival of the members of this cohort, and the causes of death in these patients.**

***Methods*—Yearly follow up was conducted in methotrexate treated RA patients who formed a cohort between 1981 and 1986 at a tertiary care centre. The probability of drug continuation and the patients' survival were calculated using standard statistical procedures; standardised mortality ratios were calculated using death certificate data and USA general population and mortality tables.**

***Results*—The probability of methotrexate continuation at 10 years from the time the first members entered the cohort was 30%. Toxicity (and its severity) was the most frequent cause of discontinuing methotrexate. The cumulative probability of survival was 85% for women and 45% for men. A greater than expected number of deaths from infections was observed, but the number of deaths from cancer and cardiovascular diseases were within the range expected.**

***Conclusions*—Toxicity remains the most common cause for methotrexate discontinuation. Survival was comparable to that of other RA cohorts. Methotrexate may be implicated as an associated factor in the deaths from infections.**

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Methotrexate (MTX) is currently considered a standard therapeutic option for the treatment of rheumatoid arthritis (RA).[1] Although its ability to halt disease progression remains to be determined, MTX is now being used earlier in the course of this disease than in the randomised clinical trials conducted in the 1980s, and which were the basis for its approval for the treatment of RA by the USA Food and Drug Administration. Between 1981 and 1986, we assembled a cohort of RA patients in whom MTX treatment was to be started. Five years after initiation of this treatment,[2] we were favourably impressed by an approximately 50% probability of continuing MTX. Several demographic, clinical and practice features were identified in the univariate analyses as predictors of MTX discontinuation, but only the year of initiation of methotrexate treatment and the occurrence of toxicity remained explanatory in multivariate analyses. We now present our observations up to the autumn of 1991, or 10 years after the first patients entered this cohort.

## Patients and methods

### PATIENTS

Between 1981 and 1986, 152 patients with RA defined according to the 1958 American Rheumatism Association classification criteria (ARA, now the American College of Rheumatology, ACR), and followed at the University of Alabama at Birmingham Outpatient Rheumatology Clinic, started weekly oral MTX treatment. The experience of the first 72 patients of this cohort with regards to MTX toxicity, and that of the entire cohort with relation to the probability of drug discontinuation and reasons for drug discontinuation have been reported previously.[2 3]

Demographic and clinical data were ascertained by chart review, and severity of disease was graded on the four point scale (both used previously[2]): 1 = mild; 2 = moderate; 3 = severe; 4 = very severe. This score includes different permutations of three (weighted) measures: function (determined by the ARA functional class), anatomy (scoring hand/wrist radiographs), and presence (and number) of extra-articular manifestations (clinical assessment of anaemia, nodules, serositis, pulmonary involvement, vasculitis).

Data regarding MTX intake, MTX discontinuation, reasons for MTX discontinuation, and the occurrence of side effects and their severity, were obtained on a yearly basis by both chart review and a telephone interview conducted by an experienced research assistant (ICT). As before, a major toxic event was defined a priori as one that was potentially life threatening, whereas a minor side effect was defined as one which was not. For those patients in whom MTX had been permanently discontinued, the yearly record was limited to the patient's survival. Causes of death were identified using death certificates for the Alabama Department of Vital Statistics for all but one patient, who died in another state and

*Table 1 Baseline demographic and clinical features of RA patients (n = 152)**

| | |
|---|---|
| White (%) | 81 |
| African-American (%) | 19 |
| Women (%) | 70 |
| Age at entry to cohort (yr) | 61·2 (12·4) |
| Disease duration (yr) | 18·7 (15·2) |
| Seropositivity for IgM-RF (%) | 73 |
| Disease severity† | 2·8 (1·2) |

*Modified from Alarcón *et al.*[2]
Values are percentages, or mean (SD).
†Scale 0–4 (see text).
RF = Rheumatoid factor.

for whom the cause of death was ascertained from hospital records. The status of all patients was accounted for at the time of the last yearly record.

ANALYSES

For the purpose of determining the probability of drug continuation or discontinuation (rather than patients' survival), the time on MTX was measured as the time since MTX was first administered to time at the last follow up visit; periods of up to three months of discontinuation of MTX were subtracted from the total duration of the intake. A patient discontinuing MTX for a greater period of time was considered as having discontinued the drug permanently.

The probabilities of MTX discontinuation for the entire cohort and for different subsets of the cohort were ascertained using the method of Merrell and Shulman.[4] The decision to continue or discontinue MTX was that of the patient's treating rheumatologist rather than by criteria defined a priori. Differences between these probability curves were examined by the method of Greenwood.[5] One sided tests were used for variables previously identified as significant predictors in the five year analyses; otherwise two sided tests were used. $p \leq 0{\cdot}05$ was considered significant. Variables identified as significant in the univariate analyses were entered into a Cox regression model in order to determine their value as independent predictors of drug continuation or discontinuation.

The Kaplan-Meier method was used to estimate the overall probability of survival for these patients;[6] these curves were compared with data available in the literature[7–12] and with USA actuarial data for a population with the same characteristics for age, gender, and race (no figures are available for the state of Alabama).[13] Standardised mortality ratios (SMRs) were calculated (observed number of deaths *v* expected number of deaths) on the basis of race, gender, age, calendar year, and cause specific mortality rates for the USA population.[14] The expected number was calculated by multiplying the USA rate by the number of person-years of follow up accrued by the cohort in each category of race, gender, age, and calendar year (five year categories). Observed and expected deaths were also cross classified by duration of treatment (one year categories) and time since onset of the disease (five year categories). SMRs and their 95% confidence intervals (CI) are reported. Hypothesis testing and interval estimation procedures pertaining to the SMR analyses are based on the assumption that the observed number of deaths followed a Poisson distribution.[15 16]

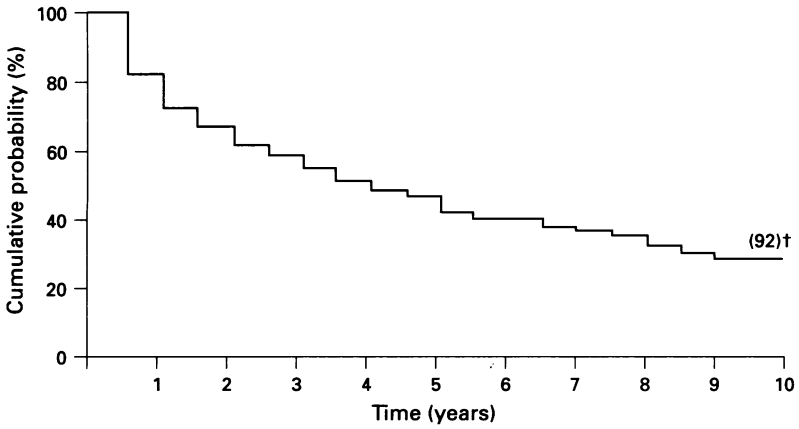


*Figure 1 Cumulative probability of continuing to take methotrexate in a cohort of 152 rheumatoid arthritis patients. †Number of patients remaining in cohort.*

## Results

MTX ADMINISTRATION

Table 1 shows the baseline demographic and clinical data of the RA patients studied. At the time of the present follow up study, the mean (SD) duration, weekly dose, and cumulative dose for those patients still taking MTX were 80·4 (20·2) months, 13·6 (7·1) mg and 4741·7 (2684·4) mg, respectively; for those no longer taking MTX, the values were 26·4 (25·1) months, 10·2 (7·5) mg, and 1358·5 (1875·9) mg, respectively. The differences between the mean weekly doses of MTX for the two groups was not statistically significant but, as expected, there were differences between the mean cumulative doses and duration of MTX administration for patients in the two groups. Ninety four patients had discontinued MTX permanently whereas 58 were still taking it, giving an overall cumulative probability of MTX continuation at 10 years of approximately 30% (fig 1). The probability was 23·4% for those who developed a toxic event and 53·2% for those who did not do so (fig 2A), 7·9% for those who experienced a major toxic event and 53·2% for those who did not experience any toxic event (fig 2B), and 23·4% for those who started MTX before 1984 compared with 48·7% for all other patients. When these variables were entered into the Cox regression model (table 2), the occurrence of toxicity and the severity of the toxic event were retained in the model.

Table 3 shows the reasons for discontinuing MTX. Approximately 53% of all permanent discontinuations were because of toxicity; lack of efficacy, and surgery accounted for a relatively small percentage of discontinuations (~ 14%). No case of serious liver disease (as defined by Walker *et al*[17]) was observed, and no association was found between increased serum creatinine concentrations and the occurrence of major or a minor toxic event. A number of other reasons accounted for the remaining discontinuations (33%); they

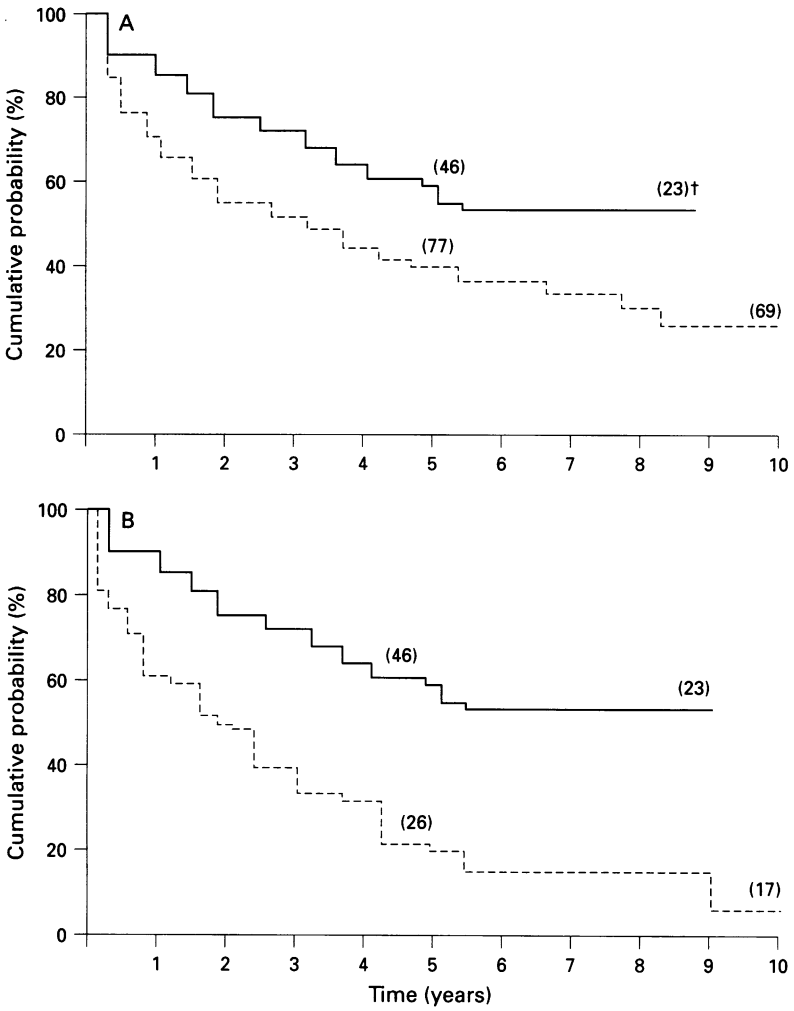


*Figure 2 Cumulative probability of continuing to take methotrexate. A: Patients who developed one or more (---) or no (—) toxic events during treatment. B: Patients who developed a major (---) or no (—) toxic events during treatment. †All values in parentheses represent numbers of patients remaining in the cohort groups at the stages indicated.*

included financial difficulties, poor compliance, and intercurrent medical events.

SURVIVAL

The overall cumulative probability of survival at 10 years from entry to the cohort was 85% for women, and 45% for men.

SMR ANALYSES

A total of 27 deaths was observed, compared with 14 expected (SMR = 195, 95% CI = 128 to 283). Table 4 lists the different causes of death. Excess mortality was observed for infectious diseases and musculoskeletal conditions, but the observed mortality from cancer and cardiovascular diseases was close to that expected. Although the small numbers limit analysis of subgroups, it is of interest to note that white men fared worse than African-American men and women of either race (statistically significant: $\chi^2 = 4{\cdot}8$, $p = 0{\cdot}03$). Age and duration of treatment did not have an impact on SMRs. Finally, the SMR for patients followed up for fewer than 10 years after onset of their disease (SMR = 349, 95% CI = 174 to 624) was considerably greater than that among subjects followed up later in the course of their disease (SMR = 149, 95% CI = 85 to 242, $\chi^2 = 5{\cdot}0$, $p = 0{\cdot}03$). Of the 27 deaths, only three were attributable to MTX toxicity (pneumonitis, one patient; cytopenias and superimposed sepsis, two patients).

*Table 2 Cox regression analysis for the variables affecting probability of methotrexate (MTX) discontinuation among MTX treated rheumatoid arthritis patients (n = 152)*

| Variable | $\chi^2$ | p |
|---|---|---|
| Toxic event* | 12·8 | 0·00015 |
| Severity of toxic event† | 8·8 | 0·0015 |
| Year MTX begun | 2·4 | 0·06 |

*Present *v* absent; †major *v* none.

*Table 3 Permanent methotrexate (MTX) discontinuation (n = 94) among RA patients studied*

| Reason | No | % |
|---|---|---|
| Toxic events* | 50 | 53·2 |
| Surgery | 7 | 7·4 |
| Lack of efficacy | 6 | 6·4 |
| Other† | 31 | 33·0 |

*In three subjects the toxic event led to death; other deaths occurred either in subjects who had already discontinued MTX, or from causes not clearly attributable to MTX intake. †Includes financial difficulties, poor compliance, and intercurrent medical events.

## Discussion

Methotrexate has become the disease modifying antirheumatic drug (DMARD) used most commonly in RA patients, and is becoming the DMARD of choice in patients with early RA with potentially aggressive and destructive disease[18] in the Americas. Our previous analyses demonstrated an overall approximately 50% probability of continuation of MTX at five and six years; at 10 years this probability was approximately 30%, which greatly exceeds that for other DMARDs at five years.[19] Greater values have been reported by other investigators studying their patients under more rigorous protocols; however, our findings may be more applicable to practising rheumatologists, as the conditions of our study more closely resemble their practices.[20 21]

As in other published series,[22–25] the main reason for MTX discontinuation in our patients was the occurrence of a toxic event, including those leading to death. Toxic events, major or minor, were not related to impairment in renal function, as suggested by other investigators.[26] We did not observe new cases of serious toxic events such as pulmonary toxicity or significant cytopenia during the last few years of follow up of the members of our cohort, compared with our previous observations of the group.[2] It may be argued that one reason for better tolerance of MTX relates to the concomitant use of folic acid;[27] however, this supplementation occurred only over the last two years of follow up of the members of this cohort and is thus an unlikely explanation for the occurrence of fewer or less serious side effects. Despite the fact that the mean cumulative dose of MTX for those who continued to take it approached 5 g, no case of serious liver disease was found in our cohort; however, given the probable incidence of clinically significant liver disease, as defined relatively recently by Walker *et al*[17] our cohort was not

*Table 4 Observed and expected number of deaths*, standardised mortality ratio (SMR), and 95% confidence interval (CI) of the SMR for selected causes of death among 152 rheumatoid arthritis patients studied (862 person-years of observation)*

| *Cause of death†* | *Observed* | *Expected* | *SMR* | *95% CI* |
|---|---|---|---|---|
| All causes of death | 27 | 13·8 | 195 | 128 to 283 |
| Infectious diseases | 2 | 0·18 | 1131 | 137 to 4087 |
| Musculoskeletal diseases | 3 | 0·05 | 5693 | 1174 to 16637 |
| Cerebrovascular diseases | 3 | 1·02 | 294 | 61 to 859 |
| Non-malignant respiratory diseases | 2 | 0·93 | 216 | 26 to 780 |
| Cancer | 4 | 3·88 | 103 | 28 to 263 |
| Cardiovascular diseases | 9 | 6·56 | 137 | 63 to 261 |

*Computed on the basis of official USA race, gender, and age specific mortality rates.[14]
†From death certificates in all but one patient.

large enough for such an event to have occurred or been detected.

Other reasons for discontinuing MTX, such as lack of efficacy of intervening surgery, occurred with frequencies comparable to those of the analyses at five years. Because of our initial negative experience with the use of MTX through surgery, most surgeons at our institution required that MTX be withheld before and after surgery;[28] in some of these patients, MTX was never restarted, as the disease appeared not to flare.

In order to be able to compare the 10 year data with our previously published five year data, we chose the year 1984 as a reference against which to examine the impact of year (early *v* late) at which MTX had been initiated. This parameter, which was an independent predictor of MTX discontinuation in the five year analyses, failed to reach significance at 10 years, which suggests that, for both patients and physicians, the learning curve for use of MTX had been completed. Favouring this assertion also is the fact that there were only a few MTX discontinuations because of minor side effects at 10 years, in contrast to our experience at five years (data not shown). Finally, the proportion of patients who permanently discontinued the drug because of its lack of efficacy remained relatively small, but a variety of medical and non-medical events accounted for a number of discontinuations. As changes in MTX regimens were instituted by each patient's primary rheumatologist, we have not attempted to measure the efficacy of the drug over time; as noted, our data cannot be directly compared with those obtained in long term prospective cohort studies in which efficacy was assessed using structured protocols.[29–34]

Our patients (both men and women) experienced a decreased probability of survival compared with that of the general population, but one comparable to that of other RA cohorts.[7–12 35] There are certain limitations that must be considered when survival curves are compared, in particular whether the cohorts being compared exhibit similar demographic features; in this regard, our cohort was comparable to others from the USA in terms of age, gender, and race, and comparable to others in age and gender. Published survival figures represent the cumulative experience of different RA cohorts, assembled before the widespread use of MTX in the late 1980s; if anything, MTX per se did not appear to be an added risk factor for overall decreased survival in RA patients treated with this compound. The decreased survival was also evident in the SMR analyses for this cohort of patients. As noted, causes of death included infections, cancer, stroke, heart disease, lung disease, and probably RA itself (musculoskeletal involvement, as recorded on the death certificate). Of interest, there were no excess deaths attributed to either cancer or cardiovascular disease. MTX is a known co-carcinogenic and, in the 1980s in particular, concern was expressed by patients and physicians alike regarding a possible increase in the occurrence of malignancies among RA patients treated with MTX. Although our data failed to validate this concern, the issue remains far from being settled. Tishler *et al* reported five malignancies in 126 MTX treated RA patients, but considered this number not to differ from the number expected.[25] In contrast, Kendry *et al* found the overall mortality in their MTX treated RA patients to comprise four deaths from lung cancer; although all four were smokers, the number was greater than expected for a population having demographic characteristics similar to those of the one we have studied.[36] The occurrence of Epstein-Barr virus associated lymphomas has been reported in three patients; interestingly, the tumours regressed after discontinuation of MTX.[37] With regard to heart disease, in theory MTX could contribute to atherogenesis (and possibly to increased occurrence of coronary artery disease, and deaths attributable to cardiovascular disease) if plasma homocysteine concentrations increase; however, no excess deaths from heart disease were observed in our patients. The excess in the number of deaths attributable to infections and RA per se are not unduly surprising, and are comparable to data recently published by Wolfe *et al.*[12] RA patients treated with MTX are known to be susceptible to infection by opportunistic agents, and cytopenias per se may contribute to the occurrence of serious infections caused by common organisms.

We do not have a good explanation for the excess in the number of deaths in white men (compared with African-American men and women of both races)—a finding which seems to conflict with the survival experience of the general population[13 14] in addition to that of RA patients in the USA.[8 12] It may be speculated that our white patients, and particularly white men, had more severe disease or added comorbidities, but this was not readily evident at the baseline examination. The observation that patients followed up for less than 10 years experienced greater mortality than those followed longer suggests that a subset of the entire cohort consisted of patients who were sicker.

In summary, analysis of this cohort at 10 years has further demonstrated an adequate continuation of MTX treatment or survival rate and, by inference, its efficacy and tolerability when the drug is used for the treatment of RA. It has also highlighted the importance of minimising the side effects of this drug. Methotrexate does not appear to contribute

further to the decreased life expectancy seen in RA patients. Until better therapeutic agents become available for the treatment of RA, MTX will remain an important element in our therapeutic armamentarium.

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