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Propensity-Adjusted Association of Methotrexate With Overall Survival in Rheumatoid Arthritis

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Objective. **While medications used to treat rheumatoid arthritis (RA) may affect survival in RA, few studies take into account the propensity for medication use, which may reflect selection bias in treatment allocation in survival models. We undertook this study to examine the relationship between methotrexate (MTX) use and mortality in RA, after controlling for individual propensity scores for MTX use.**

Methods. **We studied 5,626 RA patients prospectively for 25 years to determine the risk of death associated with MTX use, modeled in time-varying Cox regression models. We used the random forest method to generate individual propensity scores for MTX use at study entry and during followup in a time-varying manner; these scores were included in the multivariate model. We also investigated whether selective discontinuation of MTX immediately prior to death altered the risk of mortality, and we examined the association of duration of MTX use with survival.**

Results. **During followup, 666 patients (12%) died. MTX use was associated with reduced risk of death (adjusted hazard ratio 0.30 [95% confidence interval 0.09–1.03]). Selective MTX cessation immediately before death did not account for the protective association of MTX use with mortality. Only MTX use for >1 year was associated with lower risks of mortality, but associations were not stronger with longer durations of use.**

Conclusion. **MTX use was associated with a 70% reduction in mortality in RA.**

Rheumatoid arthritis (RA) is a systemic autoimmune disease associated with reduced survival, with standardized mortality ratios (SMRs) ranging from 1.3 to 3.0 (1–6). In 1 population-based cohort, survival had not improved over a 4-decade span, despite new treatment options and changes in patterns of RA medication prescribing practices (7).

Medications used to treat RA may influence survival. In 1 study, methotrexate (MTX) use was reported to reduce the risk of all-cause mortality by 60% and death from cardiovascular disease by 70% (8). Others have shown that patients who had a therapeutic response to MTX had better survival than those who did not (9). Factors such as disease severity and comorbidities influence medication selection in RA. This propensity for selecting one medication over another is especially important to consider when determining the relationship between medication use and outcomes, as patients with more severe RA but less comorbidity might have been more likely to be treated with MTX, particularly in the years shortly after its adoption. MTX use has expanded over time, and it is now prescribed across the full spectrum of disease severity and at doses higher than commonly used 20 years ago. This raises the question of whether previous results underestimate the protective association of MTX as currently used.

Protective associations with medication use are important to identify, but may be spurious, particularly for associations with serious health outcomes such as mortality, due to a commonly overlooked bias. Medication use may be altered in the setting of escalating

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comorbidities and imminent death. If medications for RA are selectively discontinued in the months prior to death, medication use will appear protective, as the number of deaths would be enriched in the subgroup of patients who have stopped the medication (10). Ongoing medication use in this situation is a surrogate for relative wellness.

We sought to determine the relationship between the use of MTX and mortality in patients with RA, with attention to 2 issues not previously emphasized: risk adjustment for the propensity for initiating and continuing MTX, and assessment of possible bias in the association due to selective discontinuation of MTX immediately prior to death. The propensity adjustment was necessitated by the vast changes in MTX use and prescribing patterns over the 25 years of this study. We also explored the relationship between cumulative duration of MTX use and mortality to determine whether long-term use was associated with survival.

PATIENTS AND METHODS

Study design and enrollment. Patients with RA from 10 North American rheumatology practices were recruited to participate in the Arthritis, Rheumatism, and Aging Medical Information System study between 1981 and January 2005. Seven university centers and 3 community practice sites participated. The purpose of this prospective observational study was to assess longitudinal changes in treatment, costs, and outcomes in patients with RA. To be eligible, patients needed to be age ≥18 years and to fulfill the 1987 revised American College of Rheumatology criteria for RA (11). The diagnosis was verified by study rheumatologists at each site or, in 6% of cases, by review of outside medical records. The study established an open cohort, with participant enrollment and dropout occurring over 25 years.

Participants were asked to complete a mailed questionnaire biannually that asked about sociodemographic characteristics, health status, including the Health Assessment Questionnaire disability index (HAQ DI) and a pain visual analog scale, comorbidities, medication use, physician visits, and other health care utilization (12,13). Participants were followed up from study entry to death, withdrawal from the study, or to July 31, 2006. Death was ascertained by communication with next of kin or by searching the National Death Index. Patients who died >1 year after returning their last questionnaire were treated as censored rather than dead, because information on their MTX use was not available through the time of death. Patients who were missing followup data for >12 months (≥3 consecutive questionnaire cycles) were censored from the time-varying analyses during the time data were not available. If data were available subsequently, the patient was then reestablished as a subject with left-truncated data. The outcome was all-cause mortality.

Statistical methods. Because patients may begin or discontinue medications over time, the association between MTX use and mortality was estimated using Cox regression models with time-varying covariates. In these models, information on the use of individual medications was updated with each 6-month questionnaire cycle. We also used the time-varying model to adjust the association between MTX and mortality for potential confounding factors.

The following variables were included in the multivariate models as time-invariant covariates: age at study entry, sex, ethnicity, education level, duration of RA at entry, and calendar year at entry. We also included the following time-varying covariates in each model, updating the status of the variable every 6 months with new data obtained with each new questionnaire: body mass index (BMI), pain score, HAQ DI score, presence of each of 10 comorbid conditions during the preceding 6 months, a visit to a rheumatologist in the preceding 6 months, use of disease-modifying antirheumatic drugs other than MTX, use of anti–tumor necrosis factor (anti-TNF) medications, use of cyclooxygenase 2–selective nonsteroidal antiinflammatory drugs (NSAIDs), and use of nonselective NSAIDs. The 10 comorbid conditions were hypertension, coronary artery disease, congestive heart failure, stroke, lung disease, diabetes mellitus, cancer, gastrointestinal disease, liver disease, and infections. Because the associations of BMI and the HAQ DI score with death were not linear over time, we modeled BMI and the HAQ DI score using restricted cubic splines to capture the nonlinear variations in the strengths of associations of these variables with mortality (14). Models were stratified by study site and year of study entry to account for variation among patients enrolled at different centers and potential cohort effects.

Propensity scores. Because patients selected to receive a particular medication likely have different clinical and demographic characteristics from those who do not receive that medication, adjustment for selection bias in treatment allocation is also needed for proper comparison of outcomes between medication groups. The goal of this adjustment is to make the treatment groups as comparable as possible in factors associated with receipt of medication so that the comparisons approximate those of a randomized allocation of medication. A common method to do this is to compute propensity scores and use these as model covariates. A propensity score is a predictor, ranging in value from 0 to 1, that estimates the probability that an individual patient should have received a particular medication, based on how similar his or her clinical and demographic characteristics are to the characteristics of other patients in the cohort who did receive the medication.

We used random forests to compute propensity scores in this study (see Supplemental Data, available on the *Arthritis & Rheumatism* web site at http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)1529-0131) (15). Random forests are scalable and accurate for prediction problems in a wide variety of contexts. They have been recommended as a means for performing more robust, model-free propensity estimation (16). In this analysis we used all demographic and clinical characteristics as potential predictors; parsimony in variable selection does not aid prediction in random forests. Each random forest was based on 500 classification trees.

Two separate propensity scores were calculated for likelihood of treatment with MTX. Because some patients entered the study while taking MTX, a propensity score based on baseline variables was computed to capture the likelihood of entering the study while taking the medication. To capture variations in prescribing of MTX during the time of observa-

tion, a second, time-varying propensity score was computed using data on variables obtained during the followup. This was particularly important because the characteristics of the patients who were prescribed MTX, for example, in 1990 were different from those who received it in 2002, based on changing patterns of use. The time-varying propensity scores were updated every 6 months with new information from each questionnaire cycle. Models estimating MTX associations with mortality included both MTX propensity scores.

Simulation analysis. One potential explanation for an apparent protective association between MTX use and survival is that MTX is selectively discontinued as patients approach the end of life due to the development or progression of illness or serious comorbidities; thus, patients stop taking MTX immediately prior to death. An observed protective effect may then be attributed not to beneficial effects of the medication but to the fact that relatively healthier patients were more likely to continue taking the drug. We assessed this possibility directly using a simulation approach. The simulation tested the association between MTX use and mortality under the assumption that rates and patterns of discontinuation of MTX shortly before death were not different from the rates and patterns of discontinuation of MTX among those who did not die. We then compared the observed result with the distribution of results from the simulations to test how likely it would be that the observed result was plausible, given no differential dropoff in MTX use prior to death.

First, among all patients who did not die (i.e., were censored) and who reported MTX use in their penultimate questionnaire, we fitted a random forest model to predict their use of MTX at their last questionnaire, given clinical and demographic information at their penultimate questionnaire. Next, we used this fitted model to predict the probability of MTX use at the last questionnaire for the patients who subsequently died and who reported MTX use in their penultimate questionnaire. This procedure generalized the patterns of MTX use among the censored patients at the end of their observation time to the patients who died. We then used these predicted probabilities to simulate MTX use (present or absent) at the last questionnaire for each patient with MTX use at their penultimate questionnaire who subsequently died. We repeated this simulation 5,000 times. For each simulated data set, we estimated our previous multivariate Cox model, which provided 5,000 estimates of the hazard ratio (HR) of the MTX association with mortality. The simulation thus provided a sampling distribution of the HR for MTX under the condition that the pattern of MTX use at the end of observation was not biased between dead and censored patients. We then compared the distribution of these estimates to that obtained from our original data to determine the likelihood that the observed association was influenced by differential discontinuation of MTX prior to death.

Duration of MTX use and mortality. To determine whether there were survival differences based on how long patients received MTX, we examined associations between cumulative duration of MTX use and mortality. Since there were temporal gaps in observed data for some patients, we imputed MTX use for the missing intervals. We assumed that if a patient was receiving MTX both before and after a missing time interval, then the patient was receiving it during the interval as well. Otherwise, we chose the conservative approach of assuming the patient was not receiving MTX in the missing interval. Thus, for each patient we updated the cumulative duration of MTX use from study entry at each 6-month questionnaire, and used this as a time-dependent covariate in the multivariate Cox regression analysis. We categorized the cumulative exposure into 5 categories: 0 years, 0.1–1 year, 1.1–2 years, 2.1–5 years, and >5 years.

Missing data. There were no missing data on medication use at baseline, but there were missing data on some clinical and demographic variables at baseline, ranging from 1% to 6%. Since our outcome measure was overall survival, we fitted a survival random forest model to the available data and imputed missing data based on the fitted model (17). Missing data during followup were imputed using last value carried forward or taking into account time (e.g., for age) for a maximum of 12 months (2 questionnaire cycles).

RESULTS

Patient characteristics and followup. We enrolled 5,626 patients with RA for the present study. Patient characteristics at study entry are shown in Table 1. Patients were primarily middle-aged, female, and white, with a median duration of RA of 7.1 years at study entry. The median followup was 4.2 years (interquartile range [IQR] 1.7–9.6 years). During 40,722 patient-years of observation, 666 patients (12%) died.

The prevalence of MTX use increased over the study period, reaching a plateau of 45–50% in the late 1990s. Among all patients, 2,920 (52%) took MTX at some time during the study, and 28% of these patients entered the study while taking MTX. Forty-seven percent of patients who were treated with MTX were also taking prednisone at the time of initiation of MTX therapy. Among those taking MTX, the median duration of use during the study period was 2.5 years (IQR 1–5.5 years). The median year of entry for all patients, those who took MTX, and those who never took MTX was 1992, 1994, and 1989, respectively. The duration of RA at study entry was shorter for those who had ever taken MTX (median 6.7 years) than for those who had never taken MTX (median 9.0 years).

In general, those taking MTX had a greater number of indicators of ill health than those who did not. They were more likely to consult a rheumatologist during observation, had higher mean HAQ DI scores at entry, and were more frequently treated with prednisone at entry (Table 1). In addition, those taking MTX were more likely to have several comorbidities and, when comorbidities were totaled for individual patients, had on average 50% more comorbidities than those who never took MTX.

The propensity score for MTX use at baseline was highly accurate. The correlation between observed

Table 1. Characteristics of the study participants by use of MTX*

	Overall (n = 5,626)	Ever used MTX (n = 2,920)†	Never used MTX (n = 2,706)‡
Age, mean ± SD years	57.1 ± 13.8	57.2 ± 13.4	59.3 ± 14.0
Sex, no. (%)			
Female	4,239 (75)	2,288 (78)	1,951 (72)
Male	1,387 (25)	632 (22)	755 (28)
Ethnicity, no. (%)			
White	5,045 (90)	2,621 (90)	2,424 (90)
Nonwhite	581 (10)	299 (10)	282 (10)
Education level, mean ± SD years	12.70 ± 2.65	12.95 ± 2.48	12.4 ± 2.8
RA duration at study entry, mean ± SD years	10.58 ± 10.26	9.43 ± 9.27	11.8 ± 11.1
Year of study entry, median (IQR)	1992 (1984, 1997)	1994 (1987, 1997)	1989 (1983, 1997)
BMI, mean ± SD kg/m^2	26.51 ± 5.25	26.73 ± 5.67	26.31 ± 4.89
Rheumatology consultations during observation, no. (%)	3,921 (70)	2,223 (76)	1,727 (64)
HAQ DI score (0–3), mean ± SD	1.136 ± 0.782	1.228 ± 0.765	1.137 ± 0.814
Pain score (0–3), mean ± SD	1.252 ± 0.785	1.278 ± 0.778	1.234 ± 0.792
Followup time, mean ± SD months	81.4 ± 71.1	93.2 ± 73.9	69.0 ± 65.6
Comorbid conditions, no. (%)			
Hypertension	1,119 (20)	770 (26)	534 (20)
Coronary artery disease	198 (4)	129 (4)	114 (4)
Lung disease	590 (10)	520 (18)	264 (10)
Gastrointestinal disease	830 (15)	647 (22)	376 (14)
Liver disease	48 (1)	26 (1)	26 (1)
Diabetes mellitus	227 (4)	152 (5)	107 (4)
Cancer	204 (4)	190 (7)	87 (3)
Congestive heart failure	44 (1)	51 (2)	21 (1)
Stroke	56 (1)	40 (1)	27 (1)
Infections	544 (10)	329 (11)	215 (8)
Comorbidities, mean ± SD	1.13 ± 1.39	1.55 ± 1.54	1.06 ± 1.41
Medications, no. (%)			
Prednisone	2,245 (40)	1,556 (53)	875 (32)
TNF inhibitors	105 (2)	92 (3)	36 (1)
COX-2 inhibitors	139 (2)	144 (5)	49 (2)
NSAIDs	3,604 (64)	1,968 (67)	1,622 (60)
Non-MTX DMARDs	2,399 (43)	1,145 (39)	1,116 (41)

* RA = rheumatoid arthritis; IQR = interquartile range; BMI = body mass index; HAQ DI = Health Assessment Questionnaire disability index; TNF = tumor necrosis factor; COX-2 = cyclooxygenase 2; NSAIDs = nonsteroidal antiinflammatory drugs; DMARDs = disease-modifying antirheumatic drugs.
† Data from first questionnaire cycle at which subjects reported taking methotrexate (MTX).
‡ Data from first questionnaire cycle for each subject who never took MTX.

MTX use and MTX use as predicted by the random forest model was 0.99 (see Supplemental Figure 1, available on the *Arthritis & Rheumatism* web site at http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)1529-0131).

Associations of MTX use with mortality. In the time-varying univariate Cox regression model, MTX use was strongly associated with a reduction in risk of death, with an HR of 0.48 (95% confidence interval [95% CI] 0.40–0.59). Given the large variation in patterns of MTX use over the study period, a time-varying multivariate Cox regression model that included propensity score adjustments was generated to enable a fair comparison of the MTX effect across the long duration of this study. In this model, MTX use was associated with a 70% reduction in mortality (HR 0.30 [95% CI 0.09–1.03]) (Table 2). Older age, male sex, greater BMI and HAQ DI score, and prednisone use were also associated with poorer survival, as were hypertension, lung disease, cancer, and congestive heart failure. Results were similar when this multivariate survival analysis was performed in the subset of patients who were not taking MTX at study entry (i.e., examination of only incident MTX users) (HR 0.42 [95% CI 0.31–0.57]).

Because some clinical factors may predict both MTX use and survival (e.g., functional limitations), we repeated the analysis using covariate values from the previous questionnaire cycle (6 months earlier), rather than contemporaneous values, for computing propensity scores, with similar results (HR 0.32 [95% CI 0.19–0.56]). In another sensitivity analysis, we used the inverse probability of treatment weight method to create treatment groups with similar background characteristics for comparison (18). In this model, MTX use remained associated with improved survival, although

Table 2. Association of MTX use with mortality, by multivariate Cox regression model with time-dependent covariates, adjusted for both baseline and time-dependent MTX propensity scores*

	HR (95% CI)	*P*
Age at study entry	1.06 (1.05–1.07)	<0.001
Education level	1.00 (0.97–1.03)	0.94
Sex (male vs. female)	2.57 (2.15–3.08)	<0.001
Ethnicity (nonwhite vs. white)	0.73 (0.49–1.09)	0.12
Disease duration at study entry	1.00 (0.99–1.00)	0.33
BMI†	–	<0.001
Nonlinear†	–	<0.001
HAQ DI score†	–	<0.001
Nonlinear†	–	0.003
Pain score	0.97 (0.86–1.09)	0.56
Rheumatology consultation	0.94 (0.79–1.13)	0.54
MTX	0.30 (0.09–1.03)	0.06
Time-dependent MTX propensity	2.91 (0.58–14.56)	0.19
Prednisone	1.72 (1.44–2.05)	<0.001
NSAIDs	0.91 (0.77–1.08)	0.28
Non-MTX DMARDs	0.93 (0.77–1.12)	0.45
TNF inhibitors	0.61 (0.26–1.45)	0.26
COX-2 inhibitors	1.11 (0.673–1.84)	0.68
Hypertension	1.21 (1.00–1.45)	0.05
Coronary artery disease	1.03 (0.80–1.32)	0.82
Lung disease	1.43 (1.18–1.72)	<0.001
Gastrointestinal disease	1.00 (0.83–1.20)	0.97
Liver disease	1.29 (0.67–2.48)	0.45
Diabetes mellitus	1.29 (0.98–1.71)	0.07
Cancer	1.39 (1.10–1.75)	0.005
Congestive heart failure	2.31 (1.74–3.06)	<0.001
Stroke	1.16 (0.75–1.81)	0.51
Infections	0.65 (0.53–0.80)	<0.001
MTX propensity at study entry	0.67 (0.42–1.08)	0.10

* HR = hazard ratio; 95% CI = 95% confidence interval (see Table 1 for other definitions).
† BMI and HAQ DI scores are both modeled nonlinearly as restricted cubic splines, and as such have no single HR estimate (see Supplemental Figure 3, available on the *Arthritis & Rheumatism* web site at http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)1529-0131). Their *P* values are based on a chi-square test with 4 df, and the test for nonlinearity is a chi-square test with 3 df.

the strength of the association was attenuated somewhat (HR 0.65 [95% CI 0.52–0.79], $P < 0.001$).

The prevalence of MTX use varied over the course of the study. To determine whether the association of MTX with mortality also varied over the study duration, we split the data set at the point when roughly half of the deaths had occurred (i.e., at April 1991, when 60% of deaths had occurred), producing 2 study groups based on observation periods: one from study initiation (July 1981) to April 1991, defined as the "early period," and the other from May 1991 to study conclusion (December 2006), the "late period." In multivariate propensity-adjusted analyses, MTX use had no association with mortality in the "early period" study (HR 2.099 [95% CI 0.24–18.33]). MTX use had a strongly protective association with mortality in the "late period" study (HR 0.07 [95% CI 0.009–0.569]).

Because the protective association of MTX may be due in part to the fact that MTX is discontinued in the months prior to death as comorbidities develop, we tested this possibility using a simulation study (see Patients and Methods). Using this approach, the median HR for the association of MTX with survival was 0.28 (IQR 0.19–0.44), in the simulation of no differential discontinuation in MTX use prior to death. The observed HR estimate of 0.30 was not significantly different from the simulated distribution of results under the assumption of no differential discontinuation of MTX shortly before death (1-tailed $P = 0.55$), indicating that differential discontinuation of MTX was unlikely to account for the protective association (see Supplemental Data, available on the *Arthritis & Rheumatism* web site at http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)1529-0131).

Associations of cumulative MTX use with survival. To determine the relationship between cumulative MTX use and survival, we tested associations with the duration of MTX use using time-varying multivariate Cox regression models. These analyses, shown in Figure 1, indicate that the protective association was evident only after >1 year of MTX use and did not increase with longer duration of use.

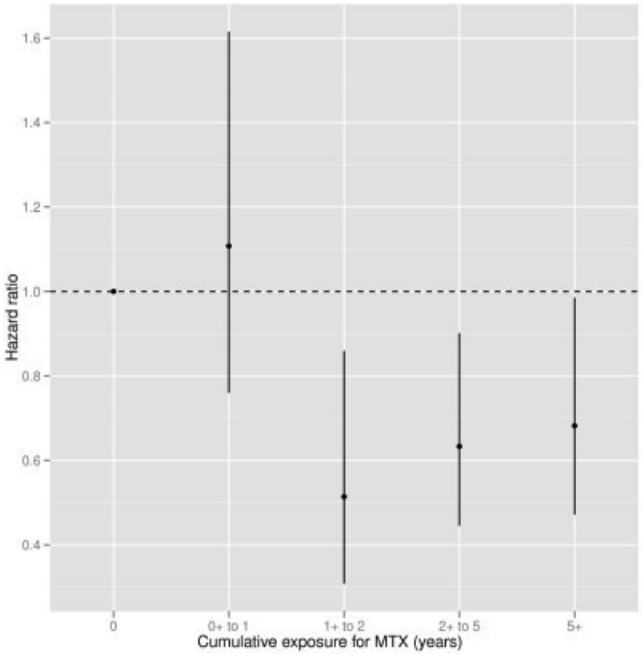

Figure 1. Hazard ratios and 95% confidence intervals for the association of duration of methotrexate (MTX) use (as a time-dependent covariate) with survival, based on a multivariate Cox model. All covariates in the base model (shown in Table 2) were included except time-varying propensity for MTX use.

DISCUSSION

Here we report the association between MTX and mortality, with propensity scores for medication use taken into consideration in addition to the traditionally recognized factors that influence survival. Our hypothesis was that, after taking into account the propensity for prescribing MTX and other important covariates, MTX use would be associated with improved survival in patients with RA. Ideally, the propensity for prescribing medications can be considered when studying the association between drug use and outcomes of interest, as prescribing patterns by practitioners influence the likelihood of selecting one treatment option over another. Inclusion of propensity scores helps to minimize the problem of confounding by indication, allowing for adjustment of these nuances that are difficult to fully account for by adjusting for sociodemographic, general, and RA-related characteristics in regression modeling. In our cohort, several characteristics differed between those taking and those not taking MTX, underscoring the value of propensity scores in determining the relationship between MTX use and survival.

The protective relationship between MTX use and mortality previously has been described in patients with RA (8). Analyzing data from a cohort of >1,000 RA patients, Choi et al used a weighted pooled Cox logistic regression model to adjust for confounding by indication and found a reduction in risk of cardiovascular and all-cause death associated with MTX use (HR 0.4), although only the lower risk of cardiovascular death was statistically significant (8). Krause and colleagues described a reduction in mortality in patients with severe RA who had >50% improvement in disease activity over a year of MTX therapy (SMR 1.47), whereas those with only a 20–50% improvement fared less well (SMR 1.85) (9). RA patients discontinuing MTX in the first year of treatment had the highest mortality (SMR 5.56), further underscoring the protective relationship between MTX use and mortality. Our results are consistent with these earlier findings. However, Landewé et al (19) reported an increased risk of all-cause mortality in RA patients who were taking MTX; in contrast to our cohort, that study included only those RA patients with prevalent cardiovascular disease and/or hypertension, and observation extended only through 1995.

In our analyses, MTX use was associated with improved overall survival in RA. This reduction in risk of death persisted in our analyses after adjustment for propensity for MTX use and factors reflecting RA activity, namely, the pain score and HAQ DI score. Thus, these findings indicate that MTX has a favorable association with survival, independent of the influence of the drug on RA activity. Interestingly, when we examined the relationship between MTX and mortality in the "early" and "late" periods of observation, we found that MTX use was associated with reduced risk of death only in the "late period." Although reasons for this difference are unclear, it may be related to a difference in the dose of MTX used, which was likely to be higher later in the study period. In the multivariate regression model adjusted for disability and other covariates, infection was strongly associated with reduced mortality (HR 0.65). However, further analyses (data not shown) indicated a strong interaction between infection and HAQ DI scores. There was no association between infection and mortality within strata of disability, suggesting that the protective association was an artifact generated by the strong association between the disability score and infection in this study population ("Simpson's paradox").

Of note, our results for MTX did not change when regression models included number of rheumatology visits among the variables controlled for in analysis. Our adjustment indicates that improved survival associated with MTX use is not a surrogate for access to or visits to a rheumatologist, as our model takes into account comorbidities and rheumatology consultations.

We also examined whether the protective association of MTX use might have been a consequence of selective discontinuation of MTX in patients shortly before death. In the case of selective discontinuation, medication use is not associated with improved survival, but rather prospects for longer survival are associated with continued medication use. This possibility should be considered whenever protective associations are found for medication and when the outcomes of interest (e.g., serious illness leading to mortality) have the potential to cause clinicians to discontinue medications for conditions that are not directly life-threatening. Although this bias has been recognized in the epidemiology literature (10), solutions to test for it have not been proposed. We developed a simulation analysis to directly test the potential influence of selective discontinuation of MTX on its association with mortality and found that this potential bias did not seem to be an explanation for the protective relationship between MTX use and death.

In examining the association of duration of MTX use and survival, the protective association was evident only among those with >1 year of use. Shorter use was not associated with any difference in mortality risk compared to nonuse. However, there was no evidence of a graded association among patients with durations of use >1 year. This pattern is more consistent with a

threshold than with a cumulative response, which might imply that the mechanism of the association requires continued administration of the medication and is not due to tissue accumulation, deposition, or structural modification due to the medication.

The precise mechanism(s) for such a reduction in risk of mortality with MTX therapy are not clear. MTX use has been associated with a reduction in morbidity and mortality from cardiovascular disease in patients with RA (8,20–23). It is a potent antiinflammatory drug, and perhaps antiinflammatory effects on the vasculature deter atherogenesis and/or thrombosis (24). In RA patients, MTX use improves coronary flow reserve (25) and is associated with reduction in risk of congestive heart failure (26), although in 1 small study it appeared to have no effect on brachial artery flow-mediated dilatation (27). Thus, the impact of MTX on vascular function remains unclear and warrants further scrutiny, although its favorable effects on lipids, C-reactive protein, and markers of oxidative stress have been demonstrated (27).

The molecular mechanisms by which MTX reduces cardiovascular risk in RA may be mediated by its inhibition of dihydrofolate reductase and the release of adenosine. Reiss et al have described the effect of MTX on reverse cholesterol transport and inhibition of foam cell formation in human THP-1 macrophages, suggesting that it may retard the development of atherosclerotic plaque by increasing cholesterol efflux from macrophages (28). In those taking MTX, adenosine is produced, with subsequent up-regulation of ATP-binding cassette transporter A1 and cholesterol 27-hydroxylase, 2 proteins that facilitate the export of cholesterol from macrophages (29,30). These potential effects on atherogenesis presumably are transient and thus require ongoing MTX treatment for these protective effects to be maintained. Taken together, these findings have served as the rationale for the cardiovascular inflammation reduction trial, a randomized controlled trial testing whether low-dose MTX reduces the risk of myocardial infarction, stroke, or cardiovascular death (31). The strength of the protective relationship between MTX and survival, however, suggests that MTX may be associated with reductions in mortality not only from cardiovascular disease, but also from other conditions (8,9,32).

While we included adjustment for measures of disease activity, socioeconomic factors, and access to subspecialty care, other factors that were not considered but that are closely linked to MTX treatment may provide the true causal links. Furthermore, the association may not be MTX-specific; almost any medication that effectively suppresses the disease process in RA may improve survival in RA, although this is not true for prednisone (32–34); observational studies suggest that it may be true for the TNF inhibitors (35–37).

The following limitations in this study warrant mention. The database had incomplete data on smoking habits; therefore, we were not able to include this important covariable in our analyses. Furthermore, all data were ascertained by self-report without physician confirmation of medication use. Because data on MTX dose were not available, we were unable to assess the relationship between MTX dosage and mortality in this cohort. Finally, our cohort was fairly homogeneous, with the vast majority being Caucasian; thus, our results may not be generalizable to other ethnic groups. Several methods of propensity score adjustment are available. We chose covariate adjustment rather than matching or stratification, because the marked temporal trends in MTX propensity make the latter methods impractical, as these would group together patients from quite different eras. The fact that MTX propensities early in the study were very small makes the use of inverse probability of treatment weighting strategy prone to strong biases (38). Simulation studies have shown that covariate adjustment performs similarly to matching and stratification for propensity adjustment (39), and so we decided to use covariate adjustment by the propensity scores in this study. We have, however, performed a sensitivity analysis using inverse probability of treatment weighting models to see how use of this method affected the results. Although there was some attenuation in the association of MTX with overall survival, it was still protective and strongly statistically significant.

In summary, we report the protective relationship between use of MTX and mortality in a large cohort of RA patients followed up prospectively for 25 years. These findings have implications for the use of MTX in the treatment of RA. Our results support the ongoing use of MTX as a cornerstone of RA treatment, with a survival benefit independent of its effects on pain and functional limitations. For patients in whom MTX monotherapy does not achieve complete control, add-on therapy may be more appropriate than switching to other medications, as MTX may still carry a survival benefit.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Wasko had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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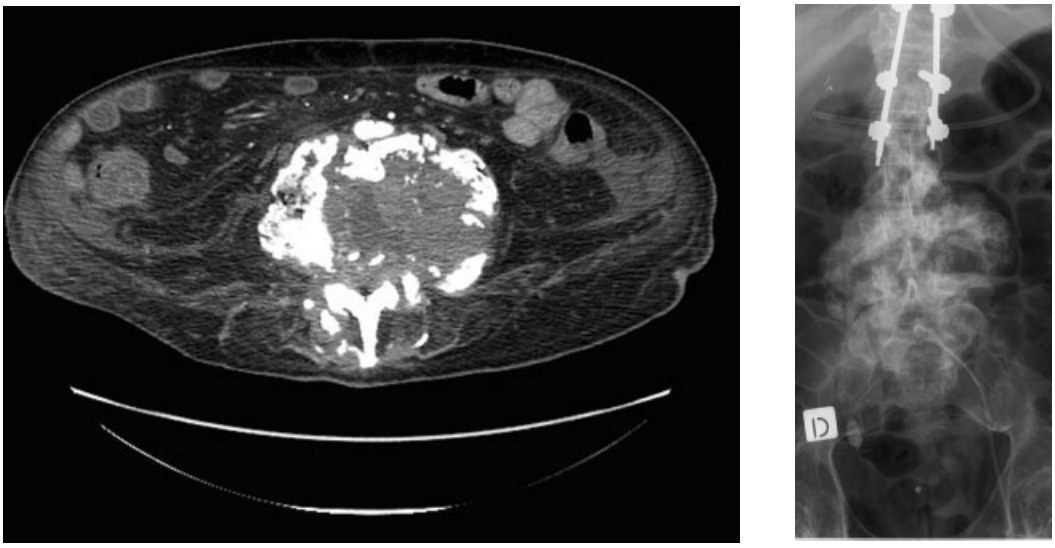
Clinical Images: Charcot's arthropathy of the spine



The patient, a 67-year-old man with a 19-year history of posttraumatic D9 sensorimotor paraplegia, was referred to our hospital for progressive fatigue. Physical examination revealed deep sacral and lumbar decubitus ulcers, but findings were otherwise normal. Blood tests revealed a modestly elevated C-reactive protein level and erythrocyte sedimentation rate. Blood cultures yielded negative results. Based on the hypothesis that the symptoms were the result of a cancerous process or chronic osteomyelitis associated with decubitus ulcers, a computed tomography scan (left) and plain radiographs (right) of the spine were obtained. A proliferative, hypertrophic L4 vertebral lesion with bone destruction and a pseudotumoral appearance was observed. Several percutaneous vertebral biopsies were performed; however, histologic and bacteriologic examination revealed nonspecific bone fibrosis. Charcot's arthropathy of the spine was diagnosed based on the findings of hypertrophic vertebral deformity with bone destruction in the absence of an infectious or neoplastic disease, in a patient with a predisposing neurologic condition. First described by Jean Charcot in patients with tertiary syphilis, Charcot's arthropathy of the spine, also known as spinal neuropathic arthropathy, is a destructive, degenerative condition affecting the intervertebral disc and the contiguous vertebral bodies, which develops secondary to a neurologic lesion. Today, it predominantly affects patients with traumatic paraplegias or congenital insensitivity to pain. Impaired proprioception and loss of pain sensation result in the lack of retraction reflexes and other protective mechanisms. The resulting unopposed, cumulative mechanical damage eventually leads to dislocation, destruction, and deformity of the affected joint (1). In imaging studies, extensive bone destruction and disorganization associated with productive hypertrophic changes, osteophytosis, peripheral bony debris, and inflammation of the paraspinal soft tissues are seen (2). The resulting pseudotumoral appearance is often misdiagnosed as infective spondylitis or as a cancerous condition. Management options comprise observation, immobilization with a body jacket, and surgery (3). This patient refused therapeutic management of the lesions.

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