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Methotrexate and mortality in patients with rheumatoid arthritis: A prospective study

Abstrak (Abstract): Our study has strengths and limitations. Our cohort is one of the largest and longest prospective rheumatoid arthritis cohorts and it includes longitudinal health assessment questionnaire disability index scores, physical exam and laboratory data, which are rarely available in long-term rheumatoid arthritis cohorts. That these variables were available for adjustment in our analysis was important, since most of them are predictors of mortality among individuals with rheumatoid arthritis.[15,16] The mortality rate among our participants was about the same as that of the entire Wichita Arthritis Center database,[3] and similar to that of other rheumatoid arthritis cohorts, especially those in similar settings.[28] In a non-randomised efficacy study such as ours, identification and appropriate adjustment for confounding due to imbalances in predictors of treatment and outcome is essential. Potentially, any factor that enters into the decision to initiate methotrexate therapy can constitute such a confounder. Because all the patients in our cohort were treated by one rheumatologist (FW), we were able to specify all of the characteristics that went into the decision to initiate methotrexate therapy. We then adjusted for these factors with a statistical method specifically developed to adjust for time-dependent confounding due to intermediate variables such as rheumatoid arthritis activity.[11,12] Furthermore, we used an intent-to-treat definition of methotrexate exposure irrespective of adherence to therapy. Although this is a conservative assumption in the sense that the true causal effect of treatment is possibly underestimated as in randomised trials, this assumption protects against bias caused by selective, differential adherence to treatment due to reasons such as adverse drug effects or lack of efficacy.

Abstrak: Methotrexate is the most frequent choice of disease-modifying antirheumatic therapy for rheumatoid arthritis. Although results of studies have shown the efficacy of such drugs, including methotrexate, on rheumatoid arthritis morbidity measures, their effect on mortality in patients with the disease remains unknown. Our aim was to prospectively assess the effect on mortality of methotrexate in a cohort of patients with rheumatoid arthritis.
Our cohort included 1240 patients with rheumatoid arthritis seen at the Wichita Arthritis Center, an outpatient rheumatology facility. Patients' details were entered into a computerised database at the time of their first clinic visit. We also obtained and recorded demographic, clinical, laboratory, and self-reported data at each follow-up visit (average interval 3.5 months). We estimated the mortality hazard ratio of methotrexate with a marginal structural Cox proportional hazards model.
191 individuals died during follow-up. Patients who began treatment with methotrexate (n=588) had worse prognostic factors for mortality. After adjustment for this confounding by indication, the mortality hazard ratio for methotrexate use compared with no methotrexate use was 0.4 (95% CI 0.2-0.8). Other conventional disease-modifying antirheumatic drugs did not have a significant effect on mortality. The hazard ratio of methotrexate use for cardiovascular death was 0.3 (0.2-0.7), whereas that for non-cardiovascular deaths was 0.6 (0.2-1.2). Our data indicate that methotrexate may provide a substantial survival benefit, largely by reducing cardiovascular mortality. This survival benefit of methotrexate would set a standard against which new disease-modifying antirheumatic drugs could be compared.

Teks lengkap: Headnote

Articles

Headnote

Summary

Headnote

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Methods Our cohort included 1240 patients with rheumatoid arthritis seen at the Wichita Arthritis Center, an outpatient rheumatology facility. Patients' details were entered into a computerised database at the time of their first clinic visit. We also obtained and recorded demographic, clinical, laboratory, and self-reported data at each follow-up visit (average interval 3.5 months). We estimated the mortality hazard ratio of methotrexate with a marginal structural Cox proportional hazards model.

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Findings 191 individuals died during follow-up. Patients who began treatment with methotrexate (n=588) had worse prognostic factors for mortality. After adjustment for this confounding by indication, the mortality hazard ratio for methotrexate use compared with no methotrexate use was 0.4 (95% CI 0.2-0.8). Other conventional disease-modifying antirheumatic drugs did not have a significant effect on mortality. The hazard ratio of methotrexate use for cardiovascular death was 0.3 (0.2-0.7), whereas that for non-- cardiovascular deaths was 0.6 (0.2-1.2).

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Interpretation Our data indicate that methotrexate may provide a substantial survival benefit, largely by reducing cardiovascular mortality. This survival benefit of methotrexate would set a standard against which new disease-modifying antirheumatic drugs could be compared.

Introduction

Rheumatoid arthritis is a chronic progressive disease associated with systemic inflammation. The disease directly affects physical function and mobility and results in substantial short-term and long-term morbidity. Furthermore, individuals with rheumatoid arthritis have a substantially shorter life expectancy than does the general population.[1-3] Deaths from cardiovascular disease, infection, and cancer are increased among individuals with rheumatoid arthritis.[1-4]

A number of disease-modifying antirheumatic drugs exist, and low-dose methotrexate is the main choice.[5] Although results of many clinical trials and their follow-up studies suggest that these drugs, including methotrexate, are effective in reducing morbidity measures (rheumatoid arthritis specific outcomes and relevant quality of life measures), their effect on mortality in patients with rheumatoid arthritis remains unknown. Our aim was to assess the potential survival benefit conferred by methotrexate given to individuals with rheumatoid arthritis.

Methods

Study data

Since 1974, we have enrolled more than 2000 consecutive individuals with rheumatoid arthritis seen at the Wichita Arthritis Center, an outpatient rheumatology facility. We entered details of participants into a computerised database at the time of their first clinic visit, and obtained and added demographic (education level, smoking history, total income, and marital status), clinical (tender joint count, grip strength, morning stiffness, health assessment questionnaire disability index score,[6] arthritis impact measurement scales, including depression scales,[7] visual analogue scale for pain, visual analogue scale for patient's global assessment of disease status, and bodymass index), laboratory (erythrocyte sedimentation rate, white blood cell counts, and concentrations of haemoglobin and rheumatoid factor), medication use, and self-reported data at each follow-up visit. Systematic longitudinal comorbidity data collection was started in 1990.

Participants

We included in our analyses individuals who were older than age 18 years and who attended the Wichita

Arthritis Center at least twice between Jan 1, 1981 (when weekly low-dose methotrexate therapy and health assessment questionnaire scores became available) and Dec 31, 1999; had rheumatoid arthritis fulfilling the 1958-- 1987 American College of Rheumatology (formerly the American Rheumatism Association) criteria for rheumatoid arthritis;8 and had not received methotrexate before their first visit to the centre. As in randomised trials assessing methotrexate,9,10 we excluded patients (irrespective of methotrexate exposure status) with any of the following contraindications for methotrexate use: pregnancy, expectation of pregnancy, heavy alcohol use, recent malignant disease, renal insufficiency, chronic liver disease, leukopenia, thrombocytopenia, and known non-- compliance.

	Individuals on methotrexate (n=588)	Methotrexate-naive group	Hazard ratio (95% CI)*
Age (mean, SD) (years)	57 (13)	57 (14)	1·0 (1·0–1·0)
Women	72%	70%	1·1 (1·0–1·4)
Smoking (current)	28%	25%	1·6 (1·2–2·1)
Smoking (past)	25%	24%	1·1 (0·8–1·4)
Education level (mean, SD) (grade)	12 (2)	13 (3)	1·0 (0·9–1·0)
Total annual income (mean, SD) (US$)	28 400 (18 300)	26 400 (17 400)	1·0 (1·0–1·0)†
Insurance status (present)	89%	83%	0·7 (0·5–0·9)
Married	72%	72%	1·0 (0·8–1·2)
Body-mass index (mean, SD) (kg/m²)	26·7 (5·6)	25·7 (5·1)	1·0 (1·0–1·1)
Disease duration (mean, SD) (years)	9·0 (9·4)	9·8 (8·4)	1·0 (1·0–1·0)
Rheumatoid factor positive	88%	83%	1·6 (1·2–2·0)
Rheumatoid arthritis activity measures			
Health assessment questionnaire (mean, SD) (0–3)	1·6 (0·7)	1·1 (0·8)	2·4 (2·2–2·7)
Number of tender joints (mean, SD) (0–18)‡	7·6 (3·7)	4·6 (3·6)	1·8 (1·7–1·9)§
Pain (visual analogue scale) (mean, SD) (0–10)	6·0 (2·4)	4·0 (2·6)	2·5 (2·3–2·7)§
Patient's global assess ment (mean, SD) (0–10)	6·0 (2·3)	4·0 (2·5)	2·9 (2·6–3·2)§
Erythrocyte sedimentation rate (mean, SD) (mm/h)	47 (28)	34 (25)	1·7 (1·6–1·8)¶
Haematocrit (mean, SD) (%)	37% (4)	38% (4)	0·9 (0·8–0·9)‖
Antirheumatic treatment			
Number of disease modifying antirheumatic drugs taken (mean, SD)	2·1 (1·0)	1·0 (0·9)	2·8 (2·6–3·0)
Prednisone use	37%	22%	2·1 (1·7–2·5)
Other characteristics			
Hypertension	13%	15%	0·8 (0·6–1·0)
Blood pressure (mean, SD) (mm Hg)	131 (19)/76 (11)	130 (19)/76 (10)	
Diabetes	4%	4%	1·1 (0·7–1·6)
Comorbidity score ever/current (mean, SD) (0–11)**	2·2/0·7 (1·7/0·8)	2·0/0·7 (1·6/1·0)	0·9 (0·8–1·1)
Cardiovascular drug use ever/current††	34%/25%	31%/19%	1·2 (1·0–1·4)
Non-diuretic cardiovascular drug use ever/current‡‡	19%/13%	16%/12%	1·2 (0·9–1·4)
Diuretic use ever/current	22%/14%	21%/10%	1·0 (0·8–1·3)
Statins use ever/current¶	3%/3%	2%/1%	2·2 (1·2–3·9)
NSAID use (aspirin use only)	89% (22%)	85% (30%)	1·4 (1·1–1·8)

Data in the first column are means or proportions; data in the second column are means of the means or proportions across all methotrexate initiation times. NSAID=non-steroidal anti-inflammatory drugs. *Hazard ratios of starting methotrexate therapy (for the presence of dichotomous variables or per one unit change in continuous variables unless otherwise specified) were estimated from standard univariate Cox models (unweighted) with time to methotrexate initiation as the outcome. These models compare the characteristics of patients who started methotrexate (individuals on methotrexate) at the time of starting the drug with those of patients who had not started the drug at that time (methotrexate-naive group); †per $1000 increase; ‡Hart-modified Ritchie index joint count;30 §per 3 units increase; ¶per erythrocyte sedimentation rate 30 mm/h increase; ‖per haematocrit 3% increase; **limited to the 1990s when statin therapy was used in our cohort; ††limited to the 1990s when the comorbidity scores were systematically collected; ‡‡antianginal drugs, heart failure drugs, antihypertensive drugs, and lipid lowering drugs.

Table 1: **Hazard ratio for methotrexate initiation according to patients' characteristics**

The study was approved by the ethics committee of the Via Christi-St Francis Regional Medical Center. Oral informed consent was obtained from all participants until 1998, written informed consent was obtained from that date onwards.

Procedures

We did a cohort study using the Wichita Arthritis Center database. We began follow-up of participants as soon as they entered the cohort or on Jan 1, 1981, and ended follow-up when individuals left the cohort, died, or on Dec 31, 1999, whichever came first. To reduce misclassification of methotrexate exposure and covariates, we censored patients 2 years after their most recent clinic visit.

Our primary outcome measure was all-cause mortality. Death was confirmed by review of medical records, death certificates, and the National Death Index (National Center for Health Statistics, US Department of Health and Human Services, Hyattsville, MD, USA). We obtained all available hospital records and all official death certificates from states in which there were decedents from our cohort, and coded specific cause of death according to the International Classification of Diseases, 9th edition (ICD-9). Our secondary outcome measures were cardiovascular death (ICD-9 codes 390-449) and non-cardiovascular death (ICD-9 codes <390 or >449). Methotrexate use and dose was recorded in the computer database at each clinic visit. We classified methotrexate exposure status as ever-treated or never-treated-ie, once a patient starts methotrexate therapy, he or she was considered on therapy for the rest of the follow-up. This approach provides a conservative estimate of methotrexate efficacy just as intent-to-treat analysis does in randomised clinical trials.

Statistical analysis

We used a weighted Cox proportional hazards model to estimate the mortality hazard ratio of methotrexate use

compared with no methotrexate use. Patients who did not receive methotrexate might have received other disease-- modifying antirheumatic drugs or prednisone. Thus, our main analysis compared methotrexate use with use of other disease-modifying drugs or no disease-modifying drugs.

Since treatment with methotrexate was initiated more often among patients with a worse prognosis (confounding by indication), adjustment for this confounding was necessary. However, since many of the prognostic factors are part of the postulated causal pathway between methotrexate therapy and mortality, or are affected by methotrexate therapy, adjusting for these factors by simply adding them as time-dependent variables in a Cox model would not appropriately adjust for the confounding.[11,12] For example, methotrexate therapy can improve health assessment questionnaire disability index,[9,10,13] and a lower disability index is associated with increased survival.[3,14,15] Thus, adding the time-dependent disability index score to the Cox model for the mortality effect of methotrexate as a time-- dependent covariate would lead to an underestimate of the magnitude of the methotrexate effect, since this modelling approach effectively holds the disability index score constant.

To overcome this problem, we used a weighted Cox proportional hazards model that estimates the mortality hazard ratio (and its robust 95% CI).[11,12] Weighting adjusts for confounding by use of prognostic factors to estimate weights (the inverse of the patients' probability of having the treatment history that they actually had) rather than including them in the mortality model. This approach solves the problem of adjusting for factors on the postulated causal pathway between methotrexate therapy and mortality (or affected by methotrexate), and yields a result that more closely approximates that of a randomised trial than do other adjustment techniques.[11,12] We estimated the parameters of this weighted Cox model by fitting a weighted pooled logistic model (to overcome the limitations of standard software) that included only baseline covariates and a time-dependent methotrexate treatment variable. Formally, our weighted model estimates the variables of a marginal structural model.[11,12]

To estimate the weights, we used the predicted values from a pooled logistic model for the probability of receiving methotrexate at a given time (t) with the following time-- dependent variables (measured at baseline, t, and t-12 months, if applicable) as covariates: age, education, sex, smoking, rheumatoid arthritis duration, calendar year, tender joint count, patient's global assessment of disease status, erythrocyte sedimentation rate, health assessment questionnaire score, other disease-modifying antirheumatic drugs, and prednisone use. (Co-morbidity score was additionally adjusted for in the model restricted to the period after 1990 when this variable was collected systematically.) Most of these variables were chosen as potential confounders primarily because the rheumatologist (FW) who treated all the patients used them in making the decision to initiate methotrexate, and because they predict mortality among rheumatoid arthritis patients.[15,16] Furthermore, these variables are part of standard rheumatoid arthritis assessment methods.[17] The rest of the variables were included because they predict mortality in the general population. Our estimates did not materially change when we further adjusted for annual income, insurance status, marital status, body-mass index, diabetes, hypertension, cardiovascular drug use (antianginal, heart failure drugs, antihypertensive medications, and lipid-- lowering medications, including statins), aspirin use, non-- steroidal anti-inflammatory drug use, other prednisone exposure definitions (cumulative duration of prednisone use, cumulative dose, low-dose use [</=10 mg] vs higher dose), grip strength, pain scale, depression, white blood cell counts, and presence of rheumatoid nodules. Similar weights were computed for censoring to adjust for potential selection bias due to loss to follow-up.[11,12] The product of the treatment and censoring weights was then stabilised and used to fit the weighted Cox (pooled logistic) model.[11,12] Analyses were done with SAS (version 8.2).

Role of the funding source

There was no funding source.

Results

1240 individuals with rheumatoid arthritis met our inclusion criteria. The mean length of follow-up until death or

censoring was 6 years (SD 5; 91 007 total person-- months). By the end of follow-up, 588 patients had received methotrexate (mean dose 13 mg per week; maximum dose 25 mg per week) and 191 had died. Of these 191 participants, 72 had been treated with methotrexate (37 594 exposed person-months). The mean number of months between clinic visits was 3.3 (2.3) in methotrexate users and 3.6 (2.7) in non-users.

	ICD-9 code	Deaths	Hazard ratio (95% CI)*
All-cause mortality	All	191	0·4 (0·2–0·8)
Cardiovascular mortality	390–449	84	0·3 (0·2–0·7)
Non-cardiovascular mortality	<390 or >449	107	0·6 (0·2–1·2)

*Estimated from weighted Cox models adjusted for age, sex, rheumatoid factor, calendar year, duration of disease, smoking, education, health assessment questionnaire score, patient global assessment, joint counts, erythrocyte sedimentation rate, prednisone status, and number of other disease-modifying antirheumatic drugs used.

Table 2: **Mortality hazard ratio for methotrexate use compared with no methotrexate use**

	Deaths/ person-months	Hazard ratio (95% CI)*
Methotrexate	46/27 122	0·2 (0·1–0·7)
Other DMARD	64/25 287	1·0 (0·6–1·6)
Sulfasalazine	17/4253	0·9 (0·2–4·2)
Penicillamine	27/9348	0·8 (0·3–2·5)
Hydroxychloroquine	61/23 577	0·7 (0·3–2·2)
Intramuscular gold	50/24 451	1·9 (0·7–5·2)
No DMARD	19/14 771	Reference

*Adjusted for age, sex, rheumatoid factor, calendar year, duration of disease, smoking, education, health assessment questionnaire score, patient global assessment, joint counts, erythrocyte sedimentation rate, and prednisone status. Additionally, the hazard ratio for methotrexate use was adjusted for other DMARD use, whereas the hazard ratios for non-methotrexate DMARD use were adjusted for methotrexate use. The hazard ratios for individual non-methotrexate DMARDs were adjusted for use of the other DMARDs (other than the respective DMARD).

Table 3: **Mortality hazard ratios for use of disease modifying antirheumatic drugs (DMARD) compared with no drug use**

Patients who started treatment with methotrexate had significantly worse rheumatoid arthritis activity measures (rheumatoid factor, health assessment questionnaire, joint counts, pain scale, patient's global assessment of disease status, erythrocyte sedimentation rate, and haematocrit), more disease-modifying antirheumatic drug use, and a higher prevalence of current prednisone use than those who did not take the drug (table 1). For example, a one unit increase (worsening) in the health assessment questionnaire disability index score (0-3) was associated with a 2.4-fold increase in the risk of initiating methotrexate. (A one unit increase in this score was associated with a 3.1-fold [95% CI 2.6-3.8] increase in mortality in this cohort.) Age, disease duration, sex, comorbidity score (limited to the 1990s), and use of most drugs were not associated with the decision to initiate methotrexate. Statin users were more likely to start methotrexate, but the proportion of statin users was only 2% (n=27) and use was limited to the 1990s. Other potential predictors for mortality were similar between the two groups (table 1).

The unadjusted mortality hazard ratio of methotrexate compared with no methotrexate use was 0.8 (95% CI 0.6-

1.0). The adjusted mortality hazard ratio of methotrexate use was 0-4 (table 2). A conventional timedependent Cox model showed an attenuated adjusted hazard ratio, 0.6 (0.4-0.8).

Of the 191 total deaths in our cohort, 84 (44%) were cardiovascular deaths. The hazard ratio of methotrexate use for the cardiovascular deaths was 0.3, whereas that for non-cardiovascular deaths (n=107) was 0.6 (table 2).

The mortality hazard ratio did not change much when we restricted our analysis to methotrexate users who did not receive concomitant folic acid (n=472) (0.5, 95% CI 0.3-0.9). The hazard ratio did not change when we restricted our analysis to methotrexate users who did not receive statin therapy (0.4, 0.3-0.8). To assess the effect of calendar time, we did subgroup analyses limited to the 1980s and 1990s, which yielded similar hazard ratios (0.3, 0.1-0.9, and 0.4, 0.2-0.7, respectively). The latter hazard ratio did not change when we additionally adjusted for comorbidity score and statin use (0.4, 0.2-0.7).

To address potential dose effect (within the methotrexate dose range used on our cohort: </=25 mg per week), we censored patients when the methotrexate dose reached 15 mg and 20 mg per week. The resulting hazard ratios (0.4, 0.3-0.8, and 0.4, 0.2-0.8, respectively) were the same as that of all doses together, thereby not supporting a dose-- dependent effect within this therapeutic range.

We also estimated the adjusted mortality hazard ratio for use of each of the conventional disease-modifying antirheumatic drugs (methotrexate, sulfasalazine, penicillamine, hydroxychloroquine, and intramuscular gold) alone or in combination compared with never use of any conventional disease-modifying antirheumatic drug (table 3). To estimate the probability of initiating these disease-modifying drugs, our analysis was restricted to those who did not receive any of these drugs before their first visit (n=902, 67 180 person-months). The mortality hazard ratio for methotrexate use was 0.2, whereas that for any non-methotrexate, conventional disease-modifying drugs was 1.0 (table 3). None of the individual, non-- methotrexate, conventional disease-modifying drugs was significantly associated with mortality risk (table 3). The hazard ratio for cardiovascular death among users of any non-methotrexate, conventional disease-modifying drugs was 1.3 (95% CI 0.7-2.5), whereas that for non-- cardiovascular death was 0.9 (0.4-1.9).

Discussion

Our results indicate that methotrexate was initiated more often in individuals who had severe rheumatoid arthritis. After adjustment for this confounding factor, we noted a 60% reduction in risk of mortality in patients treated with methotrexate. By contrast, we did not observe a comparable reduction in mortality associated with other conventional disease-modifying antirheumatic drugs, suggesting that there might be a differential survival benefit with methotrexate.

Cardiovascular deaths were reduced by 70% among individuals treated with methotrexate. These results are important in long-term rheumatoid arthritis care, since cardiovascular death is common in this population and a prominent contributor to the excess deaths in patients with rheumatoid arthritis compared with the general population.1,18,19 Increased methotrexate use could result in a substantial reduction in cardiovascular mortality and, therefore, a considerable reduction in all-cause mortality. Speculated causes for excess cardiovascular deaths in individuals with rheumatoid arthritis include side-effects of antirheumatic medications, decreased mobility and exercise, and inflammation. Results of double-blind, randomised studies9,10 have indicated that methotrexate improves the mobility of patients (eg, improving health assessment questionnaire scores and those of other quality of life measures), and decreases systemic inflammation (eg, erythrocyte sedimentation rate, concentrations of C-- reactive protein, or signs of clinical inflammation). These effects of methotrexate therapy were also evident in observational studies,20 including our own.13 Thus, methotrexate could reduce cardiovascular mortality through these mechanisms.

Several similarities have emerged between the inflammation paradigm in the pathogenesis of atherosclerosis (and unstable angina) and the wellestablished inflammation mechanism in the pathogenesis of rheumatoid arthritis.21,22 The shared features include involvement of cytokines (eg, tumour necrosis factor-alpha and

interleukin 6);22 raised concentrations of C-reactive protein, fibrinogen, and amyloid-A,22 local expression of adhesion molecules and endothelin;21,23 neoangiogenesis;24 activated T cells (eg, increased T-helper 1/T-helper 2 cell ratio and CD4+CD28^sup null^ cells);22,25 and collagen degradation via activation of macrophages and mast cells.26 The last seems to play a major part in the destabilisation of plaques in atherosclerosis, although it is an essential component in the pathogenesis of rheumatoid arthritis.26 These similarities raise the possibility that inflammatory mechanisms responsible for synovial lesions in patients with rheumatoid arthritis might directly participate in production of atherosclerotic lesions, resulting in excess cardiovascular disease in patients with rheumatoid arthritis. Our data raise a further intriguing possibility that methotrexate reduces rheumatoid arthritis activity and cardiovascular mortality by suppressing some of these shared mechanisms. Future research in this area could lead to improvements in the understanding and management of cardiovascular complications associated with rheumatoid arthritis and other chronic inflammatory diseases,27 as well as to potential new anti-inflammatory strategies for general atherosclerosis care.

Our study has strengths and limitations. Our cohort is one of the largest and longest prospective rheumatoid arthritis cohorts and it includes longitudinal health assessment questionnaire disability index scores, physical exam and laboratory data, which are rarely available in long-term rheumatoid arthritis cohorts. That these variables were available for adjustment in our analysis was important, since most of them are predictors of mortality among individuals with rheumatoid arthritis.15,16 The mortality rate among our participants was about the same as that of the entire Wichita Arthritis Center database,3 and similar to that of other rheumatoid arthritis cohorts, especially those in similar settings.28 In a non-randomised efficacy study such as ours, identification and appropriate adjustment for confounding due to imbalances in predictors of treatment and outcome is essential. Potentially, any factor that enters into the decision to initiate methotrexate therapy can constitute such a confounder. Because all the patients in our cohort were treated by one rheumatologist (FW), we were able to specify all of the characteristics that went into the decision to initiate methotrexate therapy. We then adjusted for these factors with a statistical method specifically developed to adjust for time-dependent confounding due to intermediate variables such as rheumatoid arthritis activity.11,12 Furthermore, we used an intent-to-treat definition of methotrexate exposure irrespective of adherence to therapy. Although this is a conservative assumption in the sense that the true causal effect of treatment is possibly underestimated as in randomised trials, this assumption protects against bias caused by selective, differential adherence to treatment due to reasons such as adverse drug effects or lack of efficacy.

Although there was an expected trend toward a lower threshold for methotrexate use in the 1990s than in the 1980s in our cohort, reflecting the trend in methotrexate use in rheumatology in general, our model specification method appropriately adjusted for this trend, as evidenced by the similarity between the results from the analysis limited to the 1980s or 1990s and from the analysis combining the decades (main result). A previous research letter29 reported that methotrexate increased cardiovascular mortality among patients with rheumatoid arthritis and pre-existing cardiovascular comorbidity. Although the limited description of the study makes it difficult to rule out a chance finding, this result could also be explained by the exclusion of the main effects of methotrexate and cardiovascular disease from the model, by the absence of adjustment for cardinal predictors of mortality in patients with rheumatoid arthritis,16 and by incomplete adjustment for confounding by indication. As in any rheumatoid arthritis observational or randomised study, there were losses-to-follow-up despite our best efforts. We incorporated the possibility of differential loss-to-follow-up in our weighted analysis by adjusting for the predictors of censoring. We also did sensitivity analyses, employing different censoring schemes, which indicated that our efficacy estimates were robust (data not shown). Although we were able to adjust for low-dose prednisone use as a confounder by including various prednisone exposure definitions in our model, we were not able to adequately assess its own causal effect in the current data with the same modelling as we did with other disease-modifying antirheumatic drugs, since prednisone was started often before the first visit to the

Wichita clinic and was used more intermittently than disease-modifying antirheumatic drugs. We were able to assess the effect of methotrexate on non-cardiovascular deaths collectively, but we did not have a sufficient number of deaths due to individual non-cardiovascular diseases to provide a reliable estimate of the effect of methotrexate on each of them.

In conclusion, our data indicate that methotrexate may provide a substantial survival benefit, largely by reducing cardiovascular mortality. This gain in life expectancy could be considered in selecting a cost-effective, disease--modifying antirheumatic drug on a long-term basis. Additionally, the survival benefit of methotrexate would set a standard against which new disease-modifying antirheumatic drugs should be compared.

Contributors

H K Choi, M A Hernan, J D Seeger, J M Robins, and F Wolfe conceived and designed the study, did data management and statistical analyses, interpreted results, and wrote the report; and F Wolfe obtained the data.

Conflict of interest statement None declared.

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