

## Mortality Reduction Seen with Methotrexate for Rheumatoid Arthritis

Choi HK, Hernan MA, Seeger JD, et al. Methotrexate and mortality in patients with rheumatoid arthritis: a prospective study. *Lancet* 2002;359:1173–7.

### Study Overview

**Objective.** To compare all-cause mortality in patients with rheumatoid arthritis (RA) who had received methotrexate versus those who had not.

**Design.** Prospective cohort study.

**Setting and participants.** 1240 patients treated for RA at a single center in Kansas were included. Mean age was 57 years; 71% of patients were women.

**Main outcome measures.** Unadjusted and multiply adjusted mortality hazard ratios were calculated for patients who had used methotrexate compared with those who had never used the drug. Additional analyses compared cardiovascular and noncardiovascular mortality. Mortality also was compared among methotrexate users, users of other disease-modifying antirheumatic drugs (DMARDs), and non-DMARD users. A weighted Cox proportional hazards model was used to adjust for confounding by indication (methotrexate was often prescribed for those with worse prognostic factors).

**Main results.** The mean follow-up was 6 years. The unadjusted mortality hazard ratio (HR) of methotrexate users compared with nonusers was 0.8 (95% confidence interval [CI], 0.6–1.0) and, after adjustment, was 0.4 (95% CI, 0.2–0.8). There was substantially lower cardiovascular mortality seen among methotrexate users compared with nonusers (adjusted HR, 0.3 [95% CI, 0.2–0.7]). Adjusted all-cause mortality was lower in users of methotrexate compared with those not using DMARDs (HR, 0.2 [95% CI, 0.1–0.7]), but the mortality of patients using other DMARDs was similar to that of non-DMARD users (HR, 1.0 [95% CI, 0.6–1.6]). Lower mortality with methotrexate was similar for subgroups treated in the 1980s and 1990s.

**Conclusion.** After controlling for confounding by indication, patients with RA treated with methotrexate appeared to

have a large survival benefit. This effect was largely due to reduced cardiovascular death.

### Commentary

Increased total and cardiovascular mortality has been described in patients with RA, though these findings have not been completely consistent [1]. Choi et al's study is very provocative because it suggests that 1 drug, methotrexate, may provide a mortality advantage over other traditional DMARDs or no DMARD therapy for RA. Obtaining an appropriate estimate of this effect was difficult because the decision to use methotrexate often was based on factors associated with a worse prognosis. Despite this limitation and even before adjustment for the baseline characteristics of patients treated with methotrexate (they were sicker), there was a noteworthy 20% reduction in mortality in this group. Adjustment using weighted regression models gave a much larger estimate of risk reduction with methotrexate (HR, 0.4). While it is possible that confounding factors not accounted for by the authors may explain some of the observed effect, even the more conservative estimate of risk reduction is clinically important given that cardiovascular disease is the leading cause of death in people with RA. Recent research on inflammation's role in the development of atherosclerotic disease has elucidated plausible mechanisms through which systemic inflammatory diseases such as RA could act to increase cardiovascular death [1]. It is possible that methotrexate acts favorably to block damaging effects of inflammation, but this area will require further investigation.

### Applications for Clinical Practice

Symptomatic relief and preservation of joint function have been the chief aims of therapy for RA. This study demands that we increase the attention paid to long-term outcomes when deciding on RA treatment. Although methotrexate is now generally preferred over the older DMARDs for other reasons, it is not known whether it offers a mortality benefit compared with newer drugs or older drugs (including glucocorticoids) used in combination. Because of the inherent limitations of the cohort

