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The Widening Mortality Gap Between Rheumatoid Arthritis Patients and the General Population

Angel Gonzalez, Hilal Maradit Kremers, Cynthia S. Crowson, Paulo J. Nicola, John M. Davis, III, Terry M. Therneau, Veronique L. Roger, and Sherine E. Gabriel

Objective. **Overall mortality rates in the general US population have declined substantially over the last 4–5 decades, but it is unclear whether patients with rheumatoid arthritis (RA) have experienced the same improvements in survival. The purpose of this study was to determine the mortality trends among RA patients compared with those in the general population.**

Methods. **A population-based incidence cohort of RA patients was assembled, comprising all residents of Rochester, Minnesota ages ≥18 years in whom RA was first diagnosed (according to the American College of Rheumatology [formerly, the American Rheumatism Association] 1987 criteria) between 1955 and 1995 and all residents of Olmsted County, Minnesota in whom RA was first diagnosed between 1995 and 2000. The patients were followed up longitudinally through their complete (inpatient and outpatient) medical records until death or January 1, 2007. Expected mortality was estimated from the National Center for Health Statistics life tables on the white population in Minnesota, using person-year methods. Poisson regression was used to model the observed mortality rates, adjusting for age, sex, and disease duration.**

Results. **A cohort of 822 RA patients (72% women, mean age at RA incidence 58 years) was followed up for a median of 11.7 years, during which 445 of the RA patients died. Between 1965 and 2005, the mortality rates across the calendar years for female and male RA patients were relatively constant at 2.4 and 2.5 per 100 person-years, respectively. In contrast, the expected mortality rate in the Minnesota white population decreased substantially over the same time period in both sexes. Mortality in the female general population declined from 1.0 per 100 person-years in 1965 to 0.2 per 100 person-years in 2000. Mortality in the male general population decreased from 1.2 per 100 person-years in 1965 to 0.3 per 100 person-years in 2000. Therefore, the difference between the observed and expected mortality rates increased in more recent years, resulting in a widening of the mortality gap.**

Conclusion. **Our findings show that RA patients have not experienced improvements in survival over the past 4 decades, despite dramatic improvements in the overall rates of mortality in the general US population. Further research into the causes of the widening gap in mortality between RA patients and the general population, and the influence of current therapeutic strategies on mortality, is needed in order to develop strategies to reduce the excess mortality observed in RA patients.**

Although it is well known that rheumatoid arthritis (RA) is associated with excess mortality, less is known regarding whether survival in RA patients has improved over time. Some recent studies have demonstrated improvements in survival in recent years, and have suggested that these improvements may be related to earlier diagnosis and the use of more aggressive and newer antirheumatic treatment regimens (1–6). Yet, some of these studies are subject to survival bias; i.e., because survival was examined in prevalence cohorts rather than incidence cohorts, RA patients who died or left the population soon after their incidence date were excluded. This potential bias is particularly important in

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Angel Gonzalez, MD, Hilal Maradit Kremers, MD, MSc, Cynthia S. Crowson, MS, Paulo J. Nicola, MD, MSc, John M. Davis III, MD, Terry M. Therneau, PhD, Veronique L. Roger, MD, MPH, Sherine E. Gabriel, MD, MSc: Mayo Clinic, Rochester, Minnesota.

Address correspondence and reprint requests to Sherine E. Gabriel, MD, MSc, Professor of Medicine and Epidemiology, Chair, Department of Health Sciences Research, Mayo Foundation, 200 First Street SW, Rochester, MN 55905. E-mail: gabriel.sherine@mayo.edu.

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studies of RA, given the increased risk of cardiovascular events and mortality early in the course of RA (7).

Considering the dramatic improvements in overall mortality rates in the general population over recent decades (8), it would be reasonable to expect that the mortality trends among RA patients have followed the same general pattern. The objective of this study was to determine trends in mortality rates in a population-based inception cohort of patients in whom RA was first diagnosed between 1955 and 2000 and who were followed up until 2007, as compared with the expected mortality rates in a general population of individuals of the same age and sex.

PATIENTS AND METHODS

Study population. The study was conducted within the population of Olmsted County, Minnesota. This population is well suited for the investigation of mortality trends, because comprehensive medical records for all residents seeking medical care, by any medical care provider, for more than half a century are available. Using the resources of the Rochester Epidemiology Project, virtually all clinically recognized cases of RA can be identified from among Olmsted County residents. Complete vital status information is also available.

The study population consisted of a previously described inception cohort of all patients with RA first diagnosed between January 1, 1955 and January 1, 1995 among Rochester, Minnesota residents ≥18 years of age (9). This cohort was extended to include all Olmsted County residents in whom RA was diagnosed between January 1, 1995 and January 1, 2000. All cases fulfilled the American College of Rheumatology (ACR; formerly, the American Rheumatism Association) 1987 revised criteria for the classification of RA (10). The RA incidence date was defined as the first date of fulfillment of at least 4 of the 7 classification criteria. All patients were followed up longitudinally through their entire medical records until death or January 1, 2007.

All subjects (irrespective of residency status) were tracked nationally (using the National Death Index and other sources) to ascertain vital status. In addition, death certificates were obtained from the respective states for out-of-state subjects who were deceased.

Statistical analysis. Cox regression models were used to compare survival between decades of RA incidence dates, adjusted for age and sex. The expected number of deaths was determined from the National Center for Health Statistics life tables for the Minnesota white population, according to the age and sex distribution of the RA cohort (11). Standardized mortality ratios (SMRs) were estimated by dividing the observed number of deaths by the expected number of deaths. Poisson regression was used to model the mortality rates (12) by calendar year of followup, adjusted for age, sex, and disease duration. Estimated mortality rates were directly adjusted for the age, sex, and disease duration of the RA cohort. The adjusted mortality rates were plotted against calendar year of followup for male and female subjects.

Table 1. Characteristics of the 822 patients with incident rheumatoid arthritis (RA) between 1955 and 2000 with followup until January 1, 2007

RA incidence date	Person-years of followup	Mean age at RA incidence, years	% women	Number of deaths	Median followup, years
1955–1964	2,963	57.5	76.7	132	17.0
1965–1974	2,659	56.7	73.2	109	17.1
1975–1984	2,605	59.1	73.9	104	15.4
1985–1994	2,108	57.6	69.8	60	13.1
1995–2000	1,370	57.0	65.8	40	7.5
Total	11,705	57.6	71.5	445	11.7

RESULTS

The overall study population comprised a cohort of 822 patients with incident RA (Table 1). The mean age of the entire cohort at RA incidence was 57.6 years, and 71.5% were women. The median duration of followup for the entire cohort was 11.7 years, for a total of 11,705 person-years of followup. During this followup period, 445 RA patients died, yielding an overall mortality rate of 3.80 (95% confidence interval [95% CI] 3.46–4.17) per 100 person-years. Overall mortality in this RA cohort was significantly higher than that expected from the general population, as indicated by an SMR of 1.35 (95% CI 1.23–1.49). Excess mortality was more pronounced among female RA patients than among male RA patients, with SMRs of 1.49 (95% CI 1.33–1.66) and 1.12 (95% CI 0.94–1.33), respectively.

The mortality experience of the patients with incident RA in each of the 5 time periods of RA incidence (i.e., 1955–1964, 1965–1974, 1975–1984, 1985–1994, and 1995–2000), obtained from a Cox regression model adjusting for age and sex, showed that there was no difference in mortality among the 5 time periods of RA incidence ($P = 0.41$). By 10 years following the RA incidence date, the estimated mortality rate in the 1955–1964 cohort was 24% (standard error 4%). Similarly, the estimated mortality rates were 25% in both the 1965–1974 and 1975–1984 cohorts, and 29% in both the 1985–1994 and 1995–2000 cohorts. Thus, patients in whom RA was diagnosed in more recent years had a mortality rate similar to that of their peers in whom RA was diagnosed in the 1950s and 1960s.

Figure 1 illustrates the observed mortality rates among female and male RA patients and the expected mortality rates among the general population, according to calendar years of followup. These values are estimated from a Poisson regression model that was adjusted for age, sex, and disease duration.

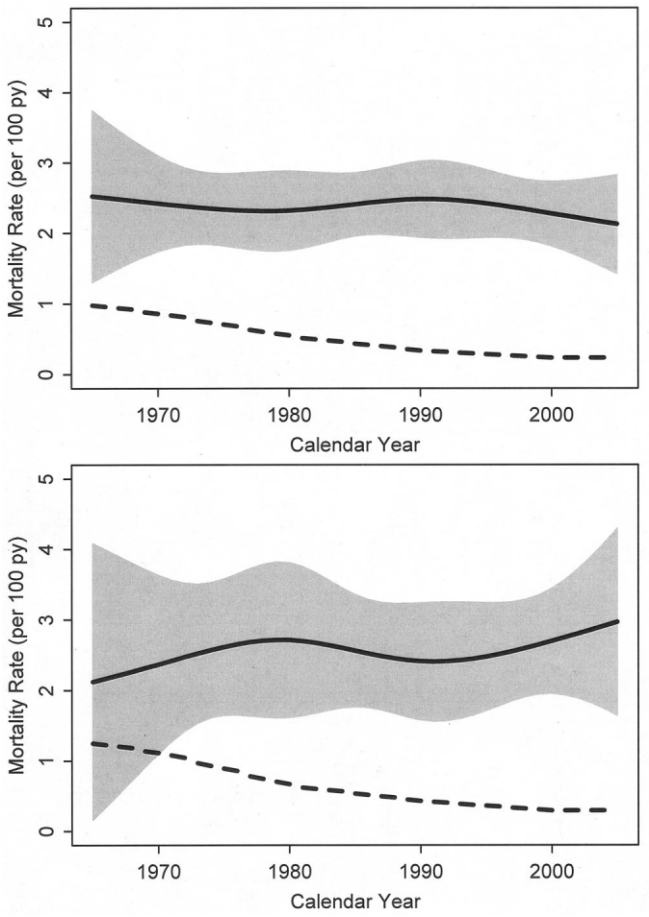

Figure 1. Observed mortality rates (solid line) in female patients with rheumatoid arthritis (RA) **(top)** and male patients with RA **(bottom)** and expected mortality rates (broken line) from the Minnesota white population, over the last 4–5 decades. Shaded areas indicate the 95% confidence limits for the observed mortality. Values are expressed per 100 person-years (py).

The mortality rate for female RA patients was relatively constant across the calendar years, at 2.4 per 100 person-years. The same was true for male patients, with a relatively constant mortality rate of 2.5 per 100 person-years. In contrast, the expected mortality rate (i.e., based on the Minnesota white population) decreased substantially for both female and male subjects from the same underlying community over the same time period. Mortality in women in the Minnesota general population declined from 1.0 per 100 person-years in 1965 to 0.2 per 100 person-years in 2000. Similarly, mortality in men decreased from 1.2 per 100 person-years in 1965 to 0.3 per 100 person-years in 2000. Consequently, the difference between the observed mortality rates in RA patients and the expected mortality rates in the general population increased over the years, resulting in a widening of the mortality gap.

DISCUSSION

In the study reported herein, we evaluated whether the mortality trends in patients with RA were similar to those in the population at large over the last 4–5 decades. Given the dramatic declines in overall mortality rates in the general population, the underlying hypothesis was that RA patients have experienced similar declines in mortality. However, our findings indicate that this is not the case. We found no evidence indicating that RA patients experienced improvements in survival over the last 4–5 decades. In fact, RA patients did not even experience the same improvements in survival as their peers without arthritis, resulting in a worsening of the relative mortality in more recent years, and a widening of the mortality gap between RA patients and the general population throughout time.

The fact that RA patients experience a higher mortality when compared with the general population has been well described throughout the years. However, trends in RA mortality over time have been specifically documented in only a few published population-based studies, 2 of which are from our group (9,13,14). The results from these studies have consistently indicated that the excess mortality associated with RA has remained unchanged. In France, Coste and Jougla (14) examined annual proportional mortality ratios for RA according to age and sex between 1970 and 1990, and found no evidence of improvement in survival over these 2 decades. These findings are very similar to those previously reported by our group (13). The findings are also consistent with those from a recent report by Sacks et al (15), in which the authors relied on national cause-of-death data, collected from death certificates, to analyze trends in deaths from arthritis and other rheumatic conditions.

The current report updates and extends our previous findings (13). We not only documented lack of improvement in mortality rates in RA patients up to 2007, but also extended previous knowledge by defining the mortality gap between the RA patients and the general population. Moreover, our present analyses included patients with incident, rather than prevalent, RA, with a followup to 2007. The remarkably similar estimates of 10-year mortality for the patients with incident RA in each of the 5 periods of RA incidence (i.e., 1955–1964, 1965–1974, 1975–1984, 1985–1994, and 1995–2000) clearly indicate that there was no change in

overall mortality in successive RA incidence cohorts. This finding is illustrated in Figure 1, in which the mortality rate in RA patients appeared relatively flat, despite the significant decline in expected mortality in a general population of individuals of the same age and sex.

Life expectancy in the US and Europe has increased substantially and continuously during the last decades (8). In 2002, the life expectancy at birth for the total population of the US reached 77.4 years, representing an increase of 9.2 years from the life expectancy in 1950 (16). These dramatic improvements in survival were driven largely by declines in mortality from cardiovascular diseases and unintentional injury. Despite these significant improvements in the population at large, mortality rates in RA patients remained relatively constant during the past 4–5 decades. This suggests that the dramatic changes in therapeutic strategies for RA in the last 4–5 decades have not had a major impact on the excess mortality. Although the reasons for the widening mortality gap are unclear, cardiovascular deaths constitute at least half of the deaths in patients with RA, and it is possible that the cardiovascular interventions that improved life expectancy in the general population may not have had the same beneficial effects in patients with RA.

Several potential limitations should be considered when interpreting our results. RA patients who did not seek medical attention could have been missed, but this is unlikely in a chronic disease such as RA, for which it is anticipated that all patients will eventually seek medical care. Because all cases were ascertained using the same methods and the diagnosis was confirmed to be in accordance with the ACR 1987 classification criteria, changes in physicians' approaches to RA diagnosis over time should not have influenced the results.

Our findings may not be generalizable to nonwhite individuals, because the Olmsted County population during the calendar years under investigation was predominantly white. With the exception of a higher proportion of the working population employed in the health care industry, and correspondingly higher education levels, the local population is socioeconomically similar to American whites, and the incidence of RA in local residents resembles that in other white populations. Nevertheless, the generalizability of the study findings to populations with sociodemographic characteristics different from those in Olmsted County is unknown. Although the followup of RA patients extended to 2007, the cohort of patients with incident RA was limited to those in whom RA was diagnosed prior to 2000. Therefore, we cannot extrapolate our findings to patients in whom RA was diagnosed after 2000, who may have been treated earlier, more aggressively, or with newer medications.

Our population-based design, inclusion of successive incidence cohorts, and standardized approach for case ascertainment are strengths of the present study. In addition, our long and complete followup of all subjects and ready access to general population mortality rates throughout the entire study period are advantages that made the current study feasible.

In conclusion, our findings indicate that RA patients have not experienced the same improvements in survival as the general population, and therefore the mortality gap between RA patients and individuals without RA has widened. There is an urgent need to fully understand the determinants and implications of this phenomenon so that appropriate intervention strategies can be undertaken to reduce the widening mortality gap that increasingly separates RA patients from the rest of the general population.

REFERENCES

1. Lindqvist E, Eberhardt K. Mortality in rheumatoid arthritis patients with disease onset in the 1980s. Ann Rheum Dis 1999;58:11–4.
2. Kroot EJ, van Leeuwen MA, van Rijswijk MH, Prevoo ML, van 't Hof MA, van de Putte LB, et al. No increased mortality in patients with rheumatoid arthritis: up to 10 years of follow up from disease onset. Ann Rheum Dis 2000;59:954–8.
3. Bjornadal L, Baecklund E, Yin L, Granath F, Klareskog L, Ekbom A. Decreasing mortality in patients with rheumatoid arthritis: results from a large population based cohort in Sweden, 1964-95. J Rheumatol 2002;29:906–12.
4. Peltomaa R, Paimela L, Kautiainen H, Leirisalo-Repo M. Mortality in patients with rheumatoid arthritis treated actively from the time of diagnosis. Ann Rheum Dis 2002;61:889–94.
5. Carmona L, Descalzo MA, Perez-Pampin E, Ruiz-Montesinos D, Erra A, Cobo T, et al. All-cause and cause-specific mortality in rheumatoid arthritis are not greater than expected when treated with tumor necrosis factor antagonists. Ann Rheum Dis 2007;66:880–5.
6. Sokka T, Mottonen T, Hannonen P. Mortality in early "sawtooth" treated rheumatoid arthritis patients during the first 8-14 years. Scand J Rheumatol 1999;28:282–7.
7. Maradit-Kremers H, Crowson CS, Nicola PJ, Ballman KV, Roger VL, Jacobsen SJ, et al. Increased unrecognized coronary heart disease and sudden death in rheumatoid arthritis: a population-based cohort study. Arthritis Rheum 2005;52:402–11.
8. Jemal A, Ward E, Hao Y, Thun M. Trends in the leading causes of death in the United States, 1970-2002. JAMA 2005;294:1255–9.
9. Gabriel SE, Crowson CS, Maradit Kremers H, Doran MF, Turesson C, O'Fallon WM, et al. Survival in rheumatoid arthritis: a population-based analysis of trends over 40 years. Arthritis Rheum 2003;48:54–8.

10. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988;31:315–24.
11. Therneau TM, Offord J. Expected survival based on hazard rates (updated). Technical Report Series No. 63. Rochester (MN): Mayo Clinic Department of Health Sciences Research; 1999.
12. McCullagh P, Nelder JA. Generalized linear models. Vol 1. New York: Chapman & Hall; 1983.
13. Gabriel SE, Crowson CS, O'Fallon WM. Mortality in rheumatoid arthritis: have we made an impact in 4 decades? J Rheumatol 1999;26:2529–33.
14. Coste J, Jougla E. Mortality from rheumatoid arthritis in France, 1970-1990. Int J Epidemiol 1994;23:545–52.
15. Sacks JJ, Helmick CG, Langmaid G. Deaths from arthritis and other rheumatic conditions, United States, 1979-1998. J Rheumatol 2004;31:1823–8.
16. Chartbook on trends in the health of Americans, 2004. Hyattsville, Maryland: National Center For Health Statistics; 2004. US Department of Health and Human Services (DHHS) publication no. 2004-1232. p. 10.