Mortality Trends in Rheumatoid Arthritis: Zooming in on Interstitial Lung Disease

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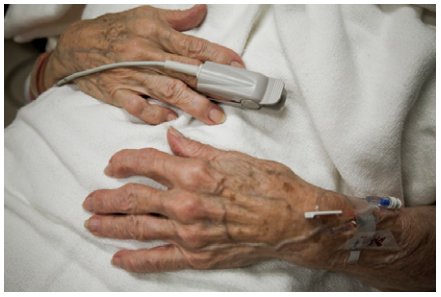

With the advent of disease-modifying agents, the field of rheumatoid arthritis (RA) has seen considerable therapeutic advances in recent decades. However, the burden of disease remains high and patients with extraarticular manifestations such as interstitial lung disease (ILD) continue to suffer from associated morbidity and mortality. Age- and sex-matched data from Denmark show a 5-year mortality of 36% and 18% in patients with RA with and without associated ILD, respectively (1). This discrepancy can only partially be explained by more frequent comorbidities (e.g., heart disease and diabetes) affecting patients with RA-ILD. Treatment recommendations for RA-ILD are still largely based on extrapolation from other connective tissue diseases and observational studies or small uncontrolled studies (2–4). To date, there are no large, randomized controlled trials available to inform therapeutic decisions. Antifibrotic medications show promise for patients with connective tissue disease–associated ILD; however, their efficacy in RA-ILD is still largely unknown (5–7).

In this issue of *AnnalsATS*, Jeganathan and colleagues (pp. 1970–1977) report an encouraging downward trend in overall RA mortality rates but a disappointing stagnation of mortality rates in RA-ILD (8). The group use cause of death data from the National Center for Health Statistics to identify all U.S. residents who had died with diagnoses of RA or RA in combination with ILD, as indicated by *International Classification of Diseases, Tenth Revision* (ICD)-10 codes on their death certificates. The investigators assess the evolution of mortality rates for men and women in different age strata and racial groups. ICD codes reflect an RA diagnosis in 0.35% of the death certificates, of which 9.9% have a diagnostic code for RA-ILD. The authors observe a decrease in the overall RA mortality rate from 2005 to 2018 by 30% in men and by 26% in women. The declining RA mortality rate, however, is not a novel finding: for example, an analysis of the World Health Organization mortality database similarly showed that age-standardized RA mortality rates declined by 3% per year from 1987 to 2011 (9). Beyond this, Jeganathan and colleagues draw out discrepancies within several subpopulations of patients with RA. Most notably, for decedents with RA-ILD disease codes, mortality rates stayed discouragingly unchanged over the 13 years studied. This is of particular concern for pulmonologists and rheumatologists because RA or ILD was the underlying cause of death in 77% of the RA-ILD population and mortality from other causes (cancer, heart, or cerebrovascular disease) was less frequent than that in the overall RA population.

The study also shows interesting mortality discrepancies between the sexes. Autoimmune diseases are more common in women than in men, with approximately three times as many women affected by RA (10). In contrast, men with RA are more likely to have associated ILD (1), with this study reporting ILD in 13% and 9% of deceased men and women with RA, respectively. In absolute numbers, however, more women are affected by RA-ILD, and a recent U.S.-based administrative claims database study found 70% of the patients with RA-ILD to be female (11). So it is unsurprising that RA and RA-ILD account for more deaths in women than in men, as shown in death certificate studies such as this one and those from other countries (12). Although male sex has been previously recognized as a mortality risk factor in RA and particularly RA-ILD (13), these previous studies use the RA population (and not the general population) as the denominator. Jeganathan and colleagues, on the other hand, use a population-based analysis to highlight the increased burden of disease in women, who had two times higher RA-related and 40% higher RA-ILD–related mortality rates compared with men. The reasons for this sex disparity remain unclear. Besides genetic and biological factors that predispose women to RA, health-related behavior, access to health care, time of diagnosis, and approach to therapy likely differ between men and women.

Moreover, the investigators report that some ethnic minorities might be at a discordantly higher risk of RA- and RA-ILD–related mortality. Native American patients with RA had almost two times and four times higher mortality rates compared with patients classified as White and Asian race, respectively. This corresponds to previous studies showing a higher impact of RA disease burden on Native American individuals compared with other racial groups (14). Remarkably, in Jeganathan's study, Hispanic patients from the studied RA population had a 25% lower mortality rate compared with White patients, but in the RA-ILD subgroup, Hispanic patients had a 26% higher mortality rate compared with

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White patients. Cigarette smoking, which is a well-established risk factor in RA and RA-ILD (13), is less common in Hispanic individuals compared with other ethnic groups (15). Ultimately, the interaction between smoking and race in the context of RA mortality remains to be determined.

Given the design of this study and limited information provided in death certificates, the authors are not able to provide causal explanations for the mortality discrepancies between different RA subpopulations. Key limitations of this study are largely inherent to population-based health administration studies and are well recognized by the authors. The study design relies on correct disease identification and documentation by healthcare practitioners, and RA or RA-ILD ICD codes are not perfect for case identification (16). Finally, the study results are only generalizable to the United States and need to be confirmed in other countries. Despite these limitations, the authors can be congratulated for their in-depth analyses differentiating mortality trajectories in RA subpopulations and for their identification of vulnerable RA subgroups that need our closer attention for future research and clinical practice.

Besides the lingering concerns when looking at mortality in patients with RA-ILD, women with RA, and certain ethnic subgroups, we need to keep in mind that decrease in mortality does not necessarily mean decrease in burden of disease. Ultimately, we are not just aiming for our patients to live longer lives but to decrease disability and improve their quality of life as well. In fact, toward the end of life, many patients wish to be able to die at home. Although this study demonstrates that this is possible for an increasing proportion of patients with RA, almost half of those suffering from ILD still die in hospitals. Earlier access to home oxygen therapy and palliative care services might prevent patients with RA-ILD from spending their last days in hospital (17).

Herewith, we propose a closer look at RA-ILD as this study leaves us cautiously optimistic—recent developments in the care of patients with RA seem to translate into improved long-term outcomes of the RA population, but the lack of specific, evidence-based treatment strategies for RA-ILD has likely contributed to the stagnant RA-ILD–related mortality rates Jeganathan and collaborators report. Consequently, the need to improve specific management strategies for patients with RA-ILD is imperative. Furthermore, we should focus our attention to particularly vulnerable RA subpopulations by ensuring adequate representation in future clinical trials and equal access to health care for all. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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