
Mortality in rheumatoid arthritis and ankylosing spondylitis

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ABSTRACT

The rheumatic diseases not only bring pain, disability and poorer quality of life, but also a premature mortality which is often overlooked. Alongside mortality due to the direct complications of disease comes an increase in deaths related to specific therapies and indirect causes such as cancer and cardiovascular mortality. By comparing mortality and its causes in two of the most common inflammatory arthritides, rheumatoid arthritis and ankylosing spondylitis, common threads emerge which give us insight into the impact of chronic inflammatory disease and new directions for patient management.

Introduction

The main aims of therapy in the rheumatic diseases are to reduce pain, maintain physical functioning and to prevent joint damage. Inflammatory joint disease is however also associated with a significant premature mortality, which needs to be considered in any management plan. The topic of mortality has been extensively reviewed in a special supplement to this journal in 2008 (1), looking at mortality over the wide spectrum of rheumatic diseases encountered in daily practice. The purpose of this review is not to represent that data, but to compare some of the key points regarding premature mortality in two of the most common inflammatory arthritic diseases, rheumatoid arthritis (RA) and ankylosing spondylitis (AS), to gain some insight into the mechanisms of inflammatory disease and its impact on our patients, and to better focus our treatments to include mortality considerations.

Overall mortality rates

The standardized mortality rates (SMR) associated with both rheumatoid arthritis and ankylosing spondylitis are approximately 50% higher than in the general population (2, 3). There has been extensive data published on mortality

in RA with generally consistent results. Non-inception cohorts report SMRs between 1.5 and 1.6 (mean SMR 1.54), which have been stable over the past 65 years. Inception cohorts as might be expected show slightly lower rates of 1.2 to 1.3 (mean 1.29), as the study populations include patients with self-limiting disease, non-progressive RA and non-RA which dilute the effect of established RA on mortality. There are fewer published studies in AS, and many of these are concerned with the effect of radiotherapy on long-term mortality in AS patients and thus not generalizable. The 4 non-inception cohort studies published to date quote SMRs of 1.33 (4, 5), 1.5 (6) and 1.8 (7), consistent with those seen in RA. It is not clear if there is any change in mortality over time in AS, although limited data suggests that survival rates decline steadily with time over 25 years (5, 6, 8).

A differential effect of inflammatory joint disease on mortality in males compared to females has not been specifically described in either RA or AS, and gender does not emerge as an independent predictor of mortality in these groups. It has been estimated that patients with RA have a shortened lifespan of 4–10 years relative to expected mortality according to age and gender (9, 10).

Direct disease-related mortality

Although population studies show us patients with RA and AS are likely to die at a younger age than individuals without inflammatory joint disease, the attributable causes of this premature mortality are not dissimilar from causes of death seen in the general population (Table I). Rheumatological diseases are not commonly listed on death certificates as a primary cause of death, with the possible exception of SLE or scleroderma whose lethality are better recognized by the general medical community. RA appears on the death certificate in approximately 25% of deaths in patients with RA (2). The links between rheumatic

“Pale Death with impartial tread beats at the poor man’s cottage door and at the palaces of kings”.

Horace, Odes

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Table I. Acute causes of death (% of total deaths) in rheumatoid arthritis (RA) and ankylosing spondylitis (AS) studies.

	Rheumatoid arthritis (2)	Ankylosing spondylitis (3)	US normal population*
Circulatory	43.5%	37-45%	38%
Coronary artery disease/myocardial infarction	–	25-30%	30%
Cerebrovascular	–	12-18%	7%
Cancer	16.3%	9-15%	23%
Haematologic malignancy	–	0-5%	–
Pulmonary	7.8%	6-12%	5%
Renal	4.3%	0-3%	1.5%
Gastrointestinal	5.8%	0-6%	–
Peptic ulcer disease	–	0-5%	–
Infection	5.8%	1-9%	4%*
Musculoskeletal	9.2%	5-18%	–
Amyloidosis (secondary)		0-13%	–
Accidents and Violence	5.2%	5-11%	5%

*Numbers estimated for 1999 in the United States from http://www.disastercenter.com/cdc/Table_9_2006.html

disease, chronic inflammation and life expectancy are complicated; one way of thinking about it is to consider the direct effects of rheumatic disease on mortality and then the contributory or indirect effects on life expectancy. A direct causative link is easy to see in an individual with ischaemic heart disease who succumbs to acute myocardial infarction; joint disease alone is less likely to be lethal in its own right, and this is likely to underpin the low rate of reporting RA and AS as causing death. Erosive rheumatoid disease at the atlanto-axial joint, traumatic fracture of the ankylosed cervical spine causing cervical cord compromise, amyloidosis or vasculitis resulting in renal failure, pulmonary fibrosis or Felty's syndrome with pancytopenia are all easily recognizable as being directly related to underlying inflammatory joint disease; combined, however, these direct influences on mortality do not feature highly when we break down the causes of death in RA and AS populations.

Therapy-related mortality

As chronic musculoskeletal diseases, both RA and AS have a lifelong impact on patients' lives. In order to preserve physical functioning, prevent joint damage and disability and maintain quality of life, long term medication with potentially toxic therapies is often required.

Most series examining mortality in RA and AS do not address the role of therapeutic misadventure, with the exception of radiotherapy used for the treatment of AS pre-1960. Effective for treating pain and stiffness in AS (11), spinal irradiation was shown in large series to be associated with an increased mortality due to hematological malignancy (12, 13) and is no longer in use.

Non-steroidal anti-inflammatory drugs (NSAIDs) are commonly used in both RA and AS for symptomatic relief. Well known for potential gastrointestinal, renal and now cardiovascular toxicities, Finnish researchers have shown 18 of the 1666 RA patient deaths in 1989 were due to gastrointestinal bleed (peptic ulceration or lower intestinal complications) attributable to NSAID use (14). In the same study, 11 deaths were attributable to glucocorticoid therapy. Small numbers of bone marrow suppression (2 due to methotrexate, 2 due to sulfasalazine) and one case of lymphoma due to azathioprine were also described. At the time of this study, methotrexate was a relatively new therapy for RA (in terms of measuring mortality) and therefore numbers may be underestimated. The best current evidence regarding mortality with methotrexate therapy is presented in a recent systematic review on methotrexate safety in RA (15), concluding that methotrexate therapy does

not increase mortality in RA patients. In the largest prospective study, over 1200 RA patients were followed over a mean of 6 years in Kansas, USA (16), recording sufficient deaths to allow comparison of RA mortality with and without methotrexate therapy. The estimated mortality incidence rate in methotrexate-treated patients (mean dose 13mg/week) was 23 per 1000 patient years, not significantly different to 26.7 per 1000 patient years seen in methotrexate-naïve patients. Nevertheless, patients with severe disease seem to have a survival benefit from methotrexate therapy (17). Mortality hazards ratios adjusted for demographics and disease severity for methotrexate use compared with no methotrexate use were estimated at 0.4 (95% confidence interval 0.2–0.8) for all-cause mortality, 0.3 (0.2–0.7) for cardiovascular mortality and 0.6 (0.2–1.2) for non-cardiovascular mortality, showing methotrexate therapy does not increase mortality in RA patients.

There have been no specific signals suggesting an increased mortality due to NSAIDs in AS, although the literature base for mortality in AS is far smaller than for RA as previously mentioned, and this will undoubtedly be addressed in coming years as large patient databases come of age. Corticosteroids, methotrexate and other DMARDs are generally not widely used in AS unless there is significant peripheral joint involvement (18), although it may be reasonable to infer that potential treatment-related mortality (independent of disease-related mortality) might be similar between the two inflammatory joint diseases. The newer biologic therapies have been available in clinical practice for approximately 5 years, and as such their impact on mortality is yet to be defined. Tumor necrosis factor blockade is associated with a small increase in the incidence of serious infections, which might translate to an increase in mortality, although careful patient selection and early recognition may well limit this effect.

Of particular interest is the positive effect of these therapies on mortality. It is known that both RA and AS are associated with an increased premature mortality compared to the normal popu-

lation; does effective therapy aimed at disease remission also alleviate the risk of an earlier demise? Although there is no data in AS, methotrexate use in RA decreases overall mortality rates in RA patients independent of disease severity (14), supporting the theory that successful management of RA has a positive effect on mortality outcomes. More controversial is the role of corticosteroids in RA; although low dose steroid will suppress inflammation and aid in symptom control, it is also associated with an increased risk of infection (19, 20) and infection-related mortality (21, 22) not seen with other DMARDs. The recent large multi-national cross-sectional QUEST-RA project reporting cardiovascular risk (morbidity) in 4363 individuals with RA (23) shows prolonged therapy with many of the DMARDs may be protective against cardiovascular events, including methotrexate (hazards ratio 0.85), leflunomide (HR 0.59), sulfasalazine (HR 0.92), biologics (HR 0.42) and corticosteroids (HR 0.95). How well this translates into reduced cardiovascular mortality is not clear, although rates are consistent with the improved cardiovascular mortality described with methotrexate. Increasing numbers of national biologics registries are actively collecting data on the safety of biologic therapies, which should address the question of potentially improved mortality with biologics in RA and AS.

Indirectly attributable causes of mortality

The most common causes of death in RA and AS patients are shown in Table I. Cardiovascular disease is the leading cause of death in patients with inflammatory joint disease, just as it is in the general community. Although the proportion of deaths attributable to circulatory disease is similar between patients with RA, with AS and the normal population, individuals with these inflammatory rheumatic diseases show an accelerated or premature cardiovascular mortality. The relationship between persistent inflammation in RA and cardiovascular disease is well recognized (24), higher disease activity in RA is associated with more major cardiovascular events (25, 26) and disease control using DMARDs

improves cardiovascular mortality outcomes (23). Ankylosing spondylitis is also associated with an increased cardiovascular morbidity (27, 28), thought in part to be related to chronic inflammation and its effects on the microvasculature (29), although more studies are needed to assess the relative contributions of traditional and non-traditional cardiovascular risk factors in AS patients.

Malignancy is the second most common cause of death in the contemporary normal population, as well as in these two inflammatory joint diseases. In the absence of previous spinal irradiation, AS is not associated with increased malignancy or malignancy-associated death. Rheumatoid arthritis is associated with an increased incidence of lymphoma compared to the general population (relative risk 2.7) which is not significantly altered by methotrexate or anti-tumor necrosis factor therapy (30). Other forms of malignancy are however in line with incidence rates in the general population. Lymphoma, particularly diffuse B-cell disease, is more often seen in patients with severe disease and has been related to chronic inflammation in RA patients (31), however the absence of similar findings in AS suggests there may be more to the story than simply high levels of inflammation.

Accidental and violent deaths (6, 7), including suicide and alcohol-related deaths (32), have been shown to be increased in men with AS compared to the normal population (standardized mortality ratio 1.8), but not in the RA population (33). There are many possible explanations for this discrepancy, including differential coping mechanisms and rates of alcohol use between the two diseases, one predominantly a male disease, the other predominantly female. Gender-specific rates have not been directly compared between the two diseases with regard to violent or alcohol-related death.

Predicting mortality in RA and AS

Can we predict those individuals with RA or AS who are at a higher risk of premature death due to their disease? Whatever the specific cause of death, premature mortality has been shown

to be related to more severe disease in both RA (2) and AS (6). Mortality in RA has been shown to be higher in patients whose joint disease also brings poorer physical function and poorer quality of life. The best predictive markers for early mortality in RA remain patient-based questionnaires which measure disease activity, disease severity and physical functioning. Fewer studies have examined predictors of mortality in AS, but consistent with RA studies, higher ESR and higher number of inflamed peripheral joints (indicating more severe disease) have been associated with poorer outcome in AS patients (6).

Rheumatoid factor is predictive for mortality in RA (34), and interestingly, a recent study has shown that rheumatoid factor positivity also increases all cause mortality (HR 1.31, 95% CI 1.06–1.61), cardiovascular mortality (HR 1.45, 95% CI 1.07–1.98) and non-cardiovascular mortality (HR 1.40, 95% CI 1.06–1.85) (35) in the general population. The association between rheumatoid factor and mortality was stronger in rheumatoid factor-positive individuals with co-existent joint symptoms (HR 1.56, 95% CI 1.00–2.43, adjusted for age, gender and ESR) than in those without joint symptoms (HR 1.33, 95% CI 1.01–1.74). The magnitude of the rheumatoid factor was not specifically examined in relation to mortality in this setting.

Conclusions

There are fewer differences in mortality between RA and AS than one might imagine on first glance, suggesting that it is inflammation and chronic disease that play the major role in premature death in these rheumatic diseases, rather than the individual characteristics of RA and AS. The unifying lesson is simply one of disease control: if we can limit inflammation and disease severity by appropriate treatments, then we should also improve disease survival rates. As therapies improve, as indeed they have in the last 10 years, we should see improvements in mortality rates – these rates lag behind the latest medical advances, as they reflect past interventions over a patient's lifetime, and so we have not yet seen the true effect of modern therapy on survival in RA and AS.

But are there other issues to be considered? Certainly assessing and treating other traditional risk factors for cardiovascular disease is particularly important in our RA and AS patients, who exhibit higher rates of premature cardiovascular mortality than might be expected in the normal population. Keeping a high level of suspicion for infection in patients on long-term steroids, using antibiotic prophylaxis in specific high-risk situations and limiting steroid use when possible to reduce toxicity must be considered. Assessing psychological state and alcohol use, particularly in AS patients, and timely referral to allied health services may help to improve coping skills.

The everyday management of our RA and AS patients needs to include consideration of the additional risks to survival, not merely the direct effects that inflammatory joint disease may have on mortality, but also indirect mortality related to cardiovascular disease, infection and psychological coping strategies.

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