Patients with rheumatoid arthritis (RA) die at a younger age than their peers in most hospital series [1], while an increase in standardized mortality rate (SMR) has not been a consistent feature in recent studies of RA patients from date of diagnosis (inception cohorts) [2]. The reasons for this apparent discrepancy are likely to be the presence of more severe disease in hospital-based series and the advent of earlier and more effective treatment in recent years. However, an increased mortality from vascular disease in RA has been consistently reported in both established and inception studies [1, 3], and an increased SMR for respiratory disease and lymphoreticular cancers has also been recognized in most series.

A detailed study in this month’s issue addresses the important question of whether patients with RA treated early and actively with disease-modifying anti-rheumatic drugs (DMARDs) still have increased mortality rates [4]. The study assesses the effect of modern out-patient intervention on all-cause mortality in a large inception cohort over the first 7 yrs of their disease, and examines whether this relates to disease severity or duration. Detailed assessment of the causes of death offers new insights into the relevance of both cardiovascular and respiratory contributions to mortality and attempts to identify risk factor profiles.

Although increasing age and male gender have been recognized as predictors for an earlier death in RA, few other clues as to an individual’s risk of premature death have been identified. However, recent work has shown direct links between rheumatoid disease activity, increased comorbidity and early death [5, 6]. The Early Rheumatoid Arthritis Study (ERAS) group [4] reports on 1429 patients recruited within 2 yrs of diagnosis over the 11 yrs from 1986. Although 84% received therapy with DMARDs, the all-cause SMR was significantly raised. After increased age, the odds ratios for death were most elevated in those patients with extra-articular disease and in those with established comorbidity.

Early death was most often due to cardiovascular disease or interstitial pulmonary fibrosis, although other vascular and respiratory causes were also over-represented. Cardiovascular disease accounted for 31% of all deaths while pulmonary problems (including respiratory infection and lung cancer) were responsible for almost 29%.

Ischaemic heart disease (IHD) accounted for a quarter of all deaths and carried an SMR of 1.49. It was also the most common cause of death at a young age and had a worse prognosis than in patients without RA. There was a relationship between disease activity as assessed by erythrocyte sedimentation rate (ESR) and probability of death from IHD, a finding consistent with previous reports linking increased markers of inflammation with coronary artery disease [7]. This suggests that DMARD therapy should protect RA patients from developing IHD, and reinforces the need for such therapy to be commenced early in the disease and used aggressively where possible, aiming for remission within the first year of disease.

The link between cardiac disease and other therapeutic agents is less clear. Oral steroids did not have any clear effect on cardiovascular mortality but high-dose or long-term therapy might be expected to adversely affect the traditional risk factor profile by increasing blood pressure and body mass index and worsening the lipid profile. The influence of non-steroidal anti-inflammatory drugs (NSAIDs) on cardiovascular health has been much debated lately. COX-2 drugs especially have been linked with an increase in vascular events (in the order of one additional event per 100 patient years), with the data leading to the ultimate withdrawal of rofecoxib. However, a recent major meta analysis of the data on all NSAIDs report that many non-selective agents such as ibuprofen and diclofenac are also associated with an increased risk of adverse cardiovascular events, although it was unclear as to whether this effect was linked to dose or duration of treatment [8].

Perhaps the most striking aspect of the ERAS report is the high mortality resulting from interstitial pulmonary fibrosis (IPF). This accounted for 6% of all deaths and exceeded the combined number of deaths from all other extra-articular features of RA. It especially affected those patients with a younger age at onset of RA. Given that features of IPF can be shown using high-resolution computed tomography (HRCT) in up to 20% of RA patients [9], this is a significant finding. Although there is some evidence that the natural history of IPF in RA is better than that in cryptogenic fibrosis [10], there is a paucity of data in the literature on this condition. Recent concern has been expressed that the natural history is worse in patients on biological agents following reports linking death from accelerated IPF in patients receiving etanercept, infliximab or adalimumab. Indeed the BSRBR confirms that deaths from IPF are increased nearly 3-fold in patients on anti-tumor necrosis factor (anti-TNF) agents when compared with controls on methotrexate. Methotrexate itself has not been shown to cause deterioration in lung function in large series of patients, but nor does it appear to have any beneficial effect on IPF. Its ability to cause pneumonitis places patients with reduced respiratory reserve at increased risk, and is a cogent argument for the assessment of pulmonary function prior to its use, with patients demonstrating a restrictive defect requiring greater definition using HRCT to identify those patients with significant underlying lung disease [11]. Perhaps the choice of DMARD in patients with proven IPF should be driven by consideration of the lung disease as much as by the degree of articular involvement?

Drug-related deaths were reported in the ERAS report, and these related largely to the use of NSAIDs which were responsible for eight fatalities resulting from upper gastrointestinal haemorrhage or perforation. Most of these patients had been on long-term therapy with NSAIDs but some had only recently commenced these agents. There is good evidence to implicate Helicobacter pylori infection in upper gastrointestinal ulceration, and recent work has shown that the presence of this bacterial agent together with NSAID exposure in RA patients greatly increases their risk of having an endoscopically visualized peptic ulcer [12]. Drugs may also have contributed to the greatly increased SMR (350) recorded for renal failure in the study, given the propensity of NSAIDs to precipitate renal failure in patients with reduced glomerular filtration rates. Taking these findings together with those linking NSAIDs with increased cardiovascular mortality, it is time for rheumatologists and primary care practitioners to reduce dependence on NSAIDs, particularly in patients with a high 10-yr risk of cardiovascular disease, a history of dyspepsia or evidence of reduced renal function.

The risk of death as a result of infection is increased in patients with RA and this is reflected in the ERAS report. Septicaemia had
an SMR of nearly 700, and chest infections were the most common respiratory cause of death. The link between infection and RA has been established for over half a century and chronic infection such as bronchiectasis may predate RA, and has been proposed to precipitate it through the formation of immune complexes. The prevalence of bronchiectasis in RA has been shown to be as high as 20% in some studies using HRCT; although there is little information in the literature as to how to manage this in RA patients. Many other infectious processes and organisms have been putatively linked with the subsequent development of RA and certain antibiotics are reported to have disease-modifying potential. However, the reasons for the increased prevalence of infection in RA are not entirely clear. Drugs have been cited as a contributory factor and the use of anti-TNF agents is contraindicated in patients with chronic infection. However, the ERAS group did not find evidence to implicate DMARDs, although oral steroids were not entirely exonerated. The evidence suggests that active RA is itself associated with a reduced response to infection and that patients failing to mount an adequate leucocyte response to sepsis are at greatest risk of succumbing to it. This may be further compounded by the lack of normal clinical signs of infection, which in turn may result in delays in treatment. This reinforces the need to ensure that all patients with RA are advised to have immunization against influenza annually, and pneumococcal vaccination should be considered 5-yearly (especially for patients on methotrexate who have been shown to have a suboptimal response to vaccination) [13]. Those patients who do develop infection require early assessment and intervention as the risk of atypical infection and adverse outcome is high. Guidelines for ‘surviving sepsis’ [14] and managing pneumonia [15] are proven to reduce mortality and are recommended for use in these settings.

Another area highlighted in the study published in this month’s issue relates to the inadequate recording of RA as a contributory or causative factor on death certificates. In spite of a very high retrieval rate of certification, the presence of RA was recorded only in 18% of all deaths occurring in patients with the disease. This observation has been reported for 20 yrs [16], and the lack of progress over this time highlights the need for all primary and secondary care physicians to recognize the systemic and potentially severe nature of the disorder. Similar issues have been reported with the under-recording of diabetes as a contributory factor in deaths in patients with this condition. Indeed, RA has been compared with diabetes through its association with premature demise as a result of accelerated atherosclerosis, high incidence of renal failure and increased risk of infection, several of the factors confirmed as contributing to death in the ERAS report.

Perhaps rheumatologists should consider revising the approach adopted in the routine assessment of RA patients by using an annual review form to include the systemic aspects of the disease in addition to its articular manifestations. This could be roughly analogous to the approach taken by diabetologists for decades, which has helped to reduce mortality through regularly recording of predictors such as blood lipid profiles, blood pressure, hepatic and renal function, together with a global measurement of disease activity. In diabetes this is usually HbA1c, but with the advent of the Disease Activity Score (DAS), which is now in common use in rheumatology clinics for the identification and assessment of patients who may qualify for anti-TNF treatment, we have the opportunity to use this as our own analogous global measurement of severity in all patients with RA. This approach might go some way to identifying and protecting those RA patients at greatest risk of premature death through reversible causes, and reinforces the need for RA patients to have ongoing specialist input—in contrast to the Government’s latest edict suggesting care for such patients could be undertaken in the community. Much progress has already been made lately in the management of RA but with greater attention to detail, combined with improved partnerships with patients, primary care physicians and secondary care colleagues; the next decade may bring further reductions in mortality.

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