Mortality in Rheumatoid Disease

William R. Finch, MD

This paper provides an overview of rheumatoid disease from the perspective of its impact on mortality. The term, rheumatoid arthritis, may promote the misconception that this disease is relatively trivial and easily managed; therefore, “rheumatoid disease” is preferred. Numerous long-term studies in many settings have established that significant excess mortality is associated with rheumatoid disease, and that this excess mortality is related to cardiovascular disease deaths. Inflammation in rheumatoid and cardiovascular diseases shares the same biologic mechanisms. Severity of extraarticular disease, decline in functional level, and level of inflammatory activity are associated with increased risk of mortality.

Detection and measurement of novel inflammatory biomarkers may provide tools to assess prognosis and to monitor therapy. Close attention to the management of traditional cardiovascular risk factors is essential in these patients. Whether disease modifying anti-rheumatic drug (DMARD) therapy will reduce all-cause and cardiovascular disease mortality in rheumatoid disease is the subject of ongoing studies.

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INTRODUCTION

The title of this overview is “Mortality in Rheumatoid Disease” not rheumatoid arthritis. There are two reasons for this. First, if we think about rheumatoid disease, we realize that this is a multi-system disorder. It is easier to identify organ systems not involved in rheumatoid disease than those that are. Secondly, if we refer to it as rheumatoid disease, we tend to avoid the trivialization that the word arthritis seems to invoke. As I will argue in this paper, this is not a benign or trivial disease. Considering the illness as rheumatoid disease gives one a better understanding of its scope and consequences.

FEATURES OF RHEUMATOID DISEASE

Rheumatoid disease is common with a prevalence rate of about 1% in the adult population of the United States. There are some populations where it is much more frequent. For instance, as many as 5% of the Pima Indians in Arizona have rheumatoid disease.

The peak onset of rheumatoid disease is generally between the ages of 30–50 years. The oldest person that I have ever seen who developed an overt rheumatoid disease was a lady with seropositive nodular rheumatoid arthritis, which developed at age 85. Rheumatoid disease is more common in women than men; frequently it is chronic, progressive, and in many cases, a disabling disease.
It is well recognized that a majority of patients with rheumatoid disease will develop evidence of joint space narrowing and erosions within the first 2 years of the disease. We believe that joint space narrowing and erosions are evidence of irreversible disease. The joint disease is a symmetrical small and large joint polyarthritis, often manifest by swelling in the 2nd and 3rd metacarpal phalangeal (MCP) and proximal interphalangeal (PIP) joints. In an adult, it may present as mono- or oligoarticular disease, but generally progresses quite rapidly into a symmetrical small and large joint polyarthritis.

Unfortunately, prior to the availability of newer therapy, many patients developed significant deformities. Changes that result in hand deformity include synovial proliferation at the wrist, MCPs, PIPs, and the common extensor tendon sheath, interosseous atrophy, ligamentous laxity, extensor tendon damage, and ulnar deviation. In addition to the usual aspects of disability, patients have trouble eating, trouble dressing and performing personal care. It is critical that individuals receive treatment before significant deformities develop.

The impact of rheumatoid disease can be measured in many ways. In the United States, the care of rheumatoid disease cost $14 billion in 1992. That is about 3 times the cost of care for people who do not have rheumatoid disease. Unfortunately, between 50%-70% of people with rheumatoid disease will become disabled from work within the first 10 years. The disability from work tends to be associated with high sedimentation rate, elevated C-reactive protein (CRP), and severe joint swelling. Rheumatoid disease decreases earning potential substantially, and again, the fastest decline seems to be in the first 3-5 years. If disease is not controlled early, patients and their families will suffer economically, as well as socially and physically.

The etiology of rheumatoid disease is unknown, but there is substantial understanding of the pathogenesis of the illness. It is believed to start in the synovial tissue. Under normal circumstances, synovium is 2-3 cell layers thick. In rheumatoid disease, it may be 20, 30 or 40 cell layers thick and is infiltrated with a variety of cells, particularly mononuclear cells. Currently, it is believed that the macrophage is the cell most responsible for perpetuating the inflammatory process. Macrophage derived cytokines, including interleukins IL-1 and IL-6, and tumor necrosis factor α, are found in large amounts in the synovial fluid. T-lymphocytes are present, particularly long-term memory cells. Fibroblasts in the synovium synthesize matrix metalloproteinases, which are responsible for cartilage and bone destruction, and prostaglandin E2, also a potent mediator of bone resorption. In the synovial fluid, there is also activation of complement, resulting in chemotaxis of neutrophils, and increasing vascular permeability. Overall, rheumatoid disease involves a highly active inflammatory process.

It is possible that rheumatoid disease is declining in frequency. Figure 1 illustrates a study by Doran et al of the Mayo Clinic, which examines the incidence of rheumatoid disease in Rochester, Minn, from 1955-1995. They noted a decline in the incidence of the disease over the last 4 decades, 1950s through 1990s.

Hochberg and Spector studied the incidence and prevalence of rheumatoid disease in Wales. They compared age-adjusted incidence and prevalence between the periods of 1970-72 and 1980-82. Over periods about a
decade apart, there was a decline in the incidence for women but not for men. Since oral contraceptives were introduced in the United States and worldwide in approximately 1960, it is quite possible that oral contraceptives reduced either the frequency or the severity of rheumatoid disease.

Buchanan and Murdoch from McMaster University speculated that there was an epidemic of rheumatoid disease, perhaps caused by an infection in the mid 1900s, and as it gradually moves through the population, frequency is declining.

Silman and Hochberg from the United Kingdom found that rheumatoid disease seems to be becoming more benign over time after following a large number of patients over multiple decades. The disease is less severe as assessed by seropositivity, extraarticular features, and bony erosions. Therefore, we may be witnessing a disease that is declining both in frequency and severity.

RHEUMATOID DISEASE AND MORTALITY

Having completed an overview of rheumatoid disease, how does it impact mortality? There are 4 key questions:

1. Are mortality rates increased in rheumatoid disease?
2. Can we predict the increased mortality rate?
3. How do we explain the increased mortality?
4. What can we do as clinicians to improve the outcome?

Are Mortality Rates Increased in Rheumatoid Disease?

There has been a major change in thinking in rheumatology in the past 20 years concerning the nature of rheumatoid disease. Kelly’s *Textbook of Rheumatology* in 1985 stated that in the majority of instances, rheumatoid arthritis is a disease with a good prognosis. This statement did not reflect the patients seen in practice, yet this idea was commonly reflected in the literature. In the same textbook in 1989 (4 years later), a sentence appeared that reflected the change in thinking: “rheumatoid arthritis is a chronic and progressive disease, and it is likely that once it becomes active and chronic in a given individual, it will become progressively worse.” Rheumatoid disease is not a benign illness.

Unfortunately, a paraphrased sequence of medical notes from a rheumatoid clinic patient’s chart often states, “doing well, doing well, doing well, in a wheelchair, dead.” This occurs because for any one physician and in any one patient, it is very difficult to recognize the increased mortality with this disease. This may be the record of an older female patient with very severe rheumatoid arthritis and a myocardial infarction. This may not be a terribly surprising course of events, except that she had her myocardial infarction 5 years “early” because of the presence of the risk factor of rheumatoid disease.

Table 1 lists 21 studies that have examined standardized mortality rates in people with rheumatoid disease. These studies were conducted in multiple sites around the world. In a variety of settings (some clinical, some community), most studies show an increase in standardized mortality rate (SMR), anywhere from 1.28–3.0. People with rheumatoid disease die at accelerated rates. A most astonishing listing in this table is that in 1953, Cobb et al from Boston first demonstrated that people with rheumatoid disease had an increased mortality rate. We seem to have failed to recognize the significance of this study until recently.

It is difficult to compare the various mortality studies for several reasons. In incidence studies, data recording will be more complete. Disease onset will be known exactly, but many times follow-up is short. If the increased mortality rate does not begin for 8–10 years after onset, it might be missed in an incidence study.

Conversely, in established disease cohorts, if individuals entered into the study have already had rheumatoid disease for many years, those who had severe coronary artery

<table>
<thead>
<tr>
<th>Study, Year</th>
<th>n</th>
<th>SMR*</th>
<th>95% CI or $P^{\dagger}$</th>
<th>Country</th>
<th>Duration (years)</th>
<th>Setting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior et al, 1984</td>
<td>448</td>
<td>3.0</td>
<td>&lt;0.001</td>
<td>UK</td>
<td>11.2</td>
<td>Clinical</td>
</tr>
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<td>Symmons et al, 1998</td>
<td>448</td>
<td>2.7</td>
<td>2.4–3.1</td>
<td>UK</td>
<td>16–22</td>
<td>Clinical</td>
</tr>
<tr>
<td>Krause et al, 2000</td>
<td>256</td>
<td>2.6</td>
<td>2.05–3.15</td>
<td>Germany</td>
<td>7.5–15.3</td>
<td>Clinical</td>
</tr>
<tr>
<td>Allebeck, 1982</td>
<td>1,165</td>
<td>2.48</td>
<td>2.27–2.71</td>
<td>Sweden</td>
<td>7.5</td>
<td>Clinical</td>
</tr>
<tr>
<td>Monson and Hall, 1976</td>
<td>1,035</td>
<td>1.85</td>
<td>NA</td>
<td>US</td>
<td>12–42</td>
<td>Clinical</td>
</tr>
<tr>
<td>Mutru et al, 1985</td>
<td>1,000</td>
<td>1.73</td>
<td>&lt;0.0001</td>
<td>Finland</td>
<td>10</td>
<td>Clinical</td>
</tr>
<tr>
<td>Wallberg-Jonsson et al, 1997</td>
<td>606</td>
<td>1.57</td>
<td>&lt;0.001</td>
<td>Sweden</td>
<td>15</td>
<td>Clinical</td>
</tr>
<tr>
<td>Mitchell et al, 1986</td>
<td>805</td>
<td>1.51</td>
<td>$\dagger$</td>
<td>Canada</td>
<td>12</td>
<td>Clinical</td>
</tr>
<tr>
<td>Kvalvik et al, 2000</td>
<td>147</td>
<td>1.49</td>
<td>1.15–1.88</td>
<td>Norway</td>
<td>15</td>
<td>Clinical</td>
</tr>
<tr>
<td>Reilly et al, 1990</td>
<td>100</td>
<td>1.4</td>
<td>NA</td>
<td>UK</td>
<td>25</td>
<td>Clinical</td>
</tr>
<tr>
<td>Myllykangas-Luosujarvi et al, 1995</td>
<td>1,186</td>
<td>1.37</td>
<td>1.35–1.4</td>
<td>Finland</td>
<td>—</td>
<td>Community</td>
</tr>
<tr>
<td>Cobb et al, 1953</td>
<td>583</td>
<td>1.32</td>
<td>NA</td>
<td>US</td>
<td>9.6</td>
<td>Clinical</td>
</tr>
<tr>
<td>Allebeck et al, 1981</td>
<td>293</td>
<td>1.32</td>
<td>NA</td>
<td>Sweden</td>
<td>11</td>
<td>Community</td>
</tr>
<tr>
<td>Pincus et al, 1984</td>
<td>75</td>
<td>1.31</td>
<td>NA</td>
<td>US</td>
<td>9</td>
<td>Clinical</td>
</tr>
<tr>
<td>Uddin et al, 1970</td>
<td>475</td>
<td>1.29</td>
<td>&lt;0.01</td>
<td>Canada</td>
<td>10</td>
<td>Clinical</td>
</tr>
<tr>
<td>Sokka et al, 1999</td>
<td>135</td>
<td>1.28</td>
<td>0.83–1.89</td>
<td>Finland</td>
<td>8–14</td>
<td>Clinical</td>
</tr>
<tr>
<td>Jacobsson et al, 1993</td>
<td>2,979</td>
<td>1.28</td>
<td>1.01–1.62</td>
<td>US</td>
<td>2–25</td>
<td>Community</td>
</tr>
<tr>
<td>Lewis et al, 1980</td>
<td>311</td>
<td>1.28</td>
<td>NA</td>
<td>UK</td>
<td>11</td>
<td>Clinical</td>
</tr>
<tr>
<td>Linos et al, 1980</td>
<td>521</td>
<td>1.16</td>
<td>&gt;0.05</td>
<td>US</td>
<td>24</td>
<td>Community</td>
</tr>
<tr>
<td>Lindqvist and Eberhardt, 1999</td>
<td>183</td>
<td>0.87</td>
<td>0.53–1.36</td>
<td>Sweden</td>
<td>9.8</td>
<td>Clinical</td>
</tr>
</tbody>
</table>

* RA = rheumatoid arthritis; SMR = standardized mortality ratio; 95% CI = 95% confidence interval; NA = not available.
† $P$ value for observed vs expected mortality.
‡ 95% CI and/or $P$ value were not given, but the report states that statistical significance was achieved.
disease may be missed due to early death. Data recording may not have been as complete for these patients.

Studies that come from hospitals or tertiary referral centers tend to show higher mortality rates than community centers. This reflects more severely ill patients in hospitals or referred to tertiary care facilities. Duration of follow-up is very important. For an incidence study, two generations of investigators may be needed to follow these people long enough to really understand mortality rate. Practice styles may impact mortality, especially if the study involves a group where a very large percentage of physicians prescribe methotrexate and the anti-tumor necrosis factor \( \alpha (\text{TNF}_\alpha) \) drugs. These patients may have different mortality rate than individuals who are receiving nonsteroids only.

To illustrate these points, the standardized mortality rates (SMR) for an inception cohort are lower than SMR for a non-inception cohort, 1.22 vs 1.89. Examining community-based vs clinic-based studies, lower SMR rates are seen for community (SMR = 1.47) vs clinic (SMR = 1.79). There have been several recent studies that have reported a decline in the mortality rate of rheumatoid disease in the last 10–15 years. Some of these more recent studies have been inception cohorts in community settings in which patients may represent a group with milder disease. In fact, this is probably not the case. Data from the Mayo Clinic suggests there had been no substantial decline in mortality rate in rheumatoid disease over the last 40 years. This is in spite of the fact that we would like to think that we have improved prognosis with current therapy.

Finally, when evaluating survival studies, it is important to be aware of the criteria used for study entry. The value of studies done before 1980 is limited because the 1958 American College of Rheumatology classification criteria were used. The 1958 criteria had 4 categories: classic, definite, probable, and possible rheumatoid disease. Many of these studies included cases classified as “probable.” In retrospect, a large percentage of people classified as probable rheumatoid disease never had rheumatoid disease. As a result, early studies are very difficult to interpret. Therefore, when examining mortality rates, it is best to focus on studies that apply to the 1987 American College of Rheumatology classification criteria.

Wolfe and colleagues conducted the largest study of mortality in rheumatoid arthritis to date. They used the ARAMIS (Arthritis, Rheumatism and Aging Medical Information) database to review mortality rates in 3500 patients including 922 deaths from 4 centers. The first 3 centers, Saskatoon, Wichita and Stanford, included consecutively enrolled patients; whereas Santa Clara advertised to recruit patients. Saskatoon is a referral center in Canada for people of Saskatchewan; they saw virtually all the rheumatoid patients from the province. Wichita is a large community-based rheumatology practice. Stanford is a tertiary referral center, where they tend to get more severe disease. With patients from a variety of centers, the bottom line is similar. The standardized mortality rates from all are higher than expected; on average a little over 2 (Table 2). As discussed previously, the community-based center had the lowest mortality, whereas the tertiary care center had the highest.

In the Saskatoon and Stanford centers, females had higher SMRs, and in the Wichita and Santa Clara centers males had higher SMRs. This made it difficult to assess whether there is higher mortality risk in males or females.

There may be several reasons why increased mortality in rheumatoid disease was not recognized earlier. The fact that rheumatoid disease was depicted as easily controlled and did not need aggressive therapy has been discussed previously. Most early studies were short-term, 6 weeks to 3 months, and considered clinical endpoints rather than mortality. Clinical endpoints included joint swelling, morning stiffness, night pain, and sedimentation rate, but not bone and joint destruction, disability or mortality. There has been very little long-term clinical research done until re-

<table>
<thead>
<tr>
<th>Center</th>
<th>No. of Deaths</th>
<th>Total</th>
<th>Standardized Mortality Ratio (SEM)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Females</td>
<td>Males</td>
</tr>
<tr>
<td>Saskatoon</td>
<td>459</td>
<td>2.24 (0.07)</td>
<td>2.44 (0.09) 2.04 (0.09)</td>
</tr>
<tr>
<td>Wichita</td>
<td>228</td>
<td>1.98 (0.11)</td>
<td>1.94 (0.14) 2.05 (0.17)</td>
</tr>
<tr>
<td>Stanford</td>
<td>175</td>
<td>3.08 (0.16)</td>
<td>3.29 (0.23) 2.77 (0.22)</td>
</tr>
<tr>
<td>Santa Clara</td>
<td>60</td>
<td>2.18 (0.24)</td>
<td>1.98 (0.28) 2.83 (0.46)</td>
</tr>
<tr>
<td>All Centers</td>
<td>922</td>
<td>2.26 (0.05)</td>
<td>2.36 (0.07) 2.14 (0.07)</td>
</tr>
</tbody>
</table>

Standardized mortality ratios for 3501 rheumatoid arthritis patients at 4 Arthritis, Rheumatism and Aging Medical Information System (ARAMIS) centers. The standardized mortality ratio is the ratio of observed deaths in the group under study to expected deaths in the general populations.

Table 3. Death in Rheumatoid Arthritis (RA) percent of deaths by cause compared to US population. Based on Pincus T. *J Rheumatol.* 1986;13:841–845. (reference 10)

<table>
<thead>
<tr>
<th>Cause</th>
<th>RA %</th>
<th>U.S. Population %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
<td>42.1</td>
<td>41.0</td>
</tr>
<tr>
<td>Cancer</td>
<td>14.1</td>
<td>20.4</td>
</tr>
<tr>
<td>Infection</td>
<td>9.4</td>
<td>1.0</td>
</tr>
<tr>
<td>Renal</td>
<td>7.8</td>
<td>1.1</td>
</tr>
<tr>
<td>Respiratory</td>
<td>7.2</td>
<td>3.9</td>
</tr>
<tr>
<td>RA</td>
<td>5.3</td>
<td>NC</td>
</tr>
<tr>
<td>GI</td>
<td>4.2</td>
<td>2.4</td>
</tr>
<tr>
<td>CNS</td>
<td>4.2</td>
<td>9.6</td>
</tr>
<tr>
<td>Accidents</td>
<td>1.0</td>
<td>5.4</td>
</tr>
<tr>
<td>Other</td>
<td>7.0</td>
<td>15.2</td>
</tr>
</tbody>
</table>

Recently. Additionally, criteria that exclude individuals with multiple comorbidities, multiple medications or the elderly, result in a study that will be limited in favor of relatively milder disease.

Pincus and Callahan studied the cause of death in people with rheumatoid disease in their 1986 review of patient experience in the 1960s and 1970s. (Table 3) These results have been reproduced in multiple other studies. Interestingly, persons with rheumatoid disease die of the same illnesses as the general population—cardiovascular disease; they just die earlier than an age- and sex-matched population. Cardiovascular disease accounted for 42.1% of all cause mortality in rheumatoid disease vs 41% in the population. In a survey of 14 studies, del Rincon and Escalante verified what one would expect to see from standardized mortality rates in larger studies; significantly, these represent mortality strictly from cardiovascular disease in patients with rheumatoid disease. Over these 14 studies, the observed-to-expected cardiovascular death ratio ranged from 0.9 to 3.85, with 9 between 1.24–2.7. This suggests the majority of excess mortality in rheumatoid disease is related to cardiovascular illness.

Patients may die as a direct result of rheumatoid disease, but this is not common. The incidence of death directly attributed to rheumatoid disease is probably about 5%. Necrotizing vasculitis occurs in rheumatoid disease, but it is seen in fewer than 1% of rheumatoid patients. Some investigators feel that subclinical vasculitis is far more common. It may well be that subclinical vasculitis contributes to endothelial dysfunction and thus accelerates cardiovascular disease. Atlantoaxial subluxation of the cervical spine is associated with an 8-fold greater risk for mortality compared to those rheumatoid individuals who do not have atlantoaxial subluxation. For reasons that are not well understood, atlantoaxial subluxation is declining in frequency. This change is attributed to better therapy, although this may not be the true explanation.
There is an increased risk of infection in patients with rheumatoid disease; three studies show that the relative risk of death from infection in rheumatoid disease to be between 5 and 15. The majority of these people die of pulmonary infection or sepsis. Risk of infection has been attributed to immunosuppression, although methotrexate, the most commonly used disease modifying antirheumatic drugs (DMARD), does not greatly increase the risk of opportunistic infections. The problem may be subclinical lung disease in rheumatoid disease. It has been estimated by pulmonary function testing, such as diffusion capacity (DLCO), that at least 30% of rheumatoid patients have evidence of interstitial disease. Additionally, studies have suggested that rheumatoid patients have a much higher incidence of bronchiectasis than the normal population. With a background of abnormal lung function and bronchiectasis, it is not surprising that if these people are even modestly immunosuppressed, there is a higher incidence of pulmonary complications.

There is no evidence that rheumatoid disease causes gastrointestinal (GI) disease. In the Arthritis, Rheumatism and Aging Medical Information System (ARAMIS) database, there is a relative risk of GI disease as a cause of death in rheumatoid disease of 1.5. The probable explanation is direct toxicity of non-steroidal anti-inflammatory drugs (NSAID).

Fear of increased mortality with use of aggressive use of DMARD has hindered the aggressive therapy of rheumatoid disease. In a study from Finland of 1666 deaths in people with rheumatoid disease treated with methotrexate and sulfasalazine, bone marrow suppression and death were actually quite rare. As expected, deaths from NSAID were fairly common, exceeding those from DMARD. Out of 47 deaths attributed to medications, 37 were attributed to NSAID, while there were only 2 deaths each were attributed to sulfasalazine and methotrexate. These data suggest there has been excess concern over risk from DMARD. Data such as these have changed attitudes toward early prescribing of DMARD.

Potential predictors of mortality in rheumatoid disease include: age, education level, male sex, functional level, rheumatoid factor, presence of nodules, markers of inflammation such as sedimentation rate and C-reactive protein, joint count, and prednisone use. Can we predict mortality in rheumatoid disease? Poor or declining function, rheumatoid factor positivity, presence of nodules or extraarticular disease, elevation of erythrocyte sedimentation rate or C-reactive protein, and total joint count are all predictors of mortality. Together, these may be telling us the same thing, that it is the burden of inflammation that is predictive. The more organs and joints involved, and the higher the level of active inflammation present, the more likely the patient is to die with rheumatoid disease. It has been suggested that prednisone use may also contribute to excess mortality. Early prednisone usage may relate more to a very active inflammatory process. Those patients are treated with prednisone early to suppress this process. Inflammatory activity increases mortality, not low dose prednisone therapy per se.

The oldest available predictor of mortality is rheumatoid factor, originally described in 1948. By 1952 it was recognized that people who were seropositive for IgM rheumatoid factor had a substantially worse prognosis. We now recognize that standardized mortality ratios in men who are seropositive were 1.51 compared to 0.89 for men who were seronegative. Similarly for women, SMR for those who were seropositive was 1.41 compared to 0.80 for those who were seronegative. This suggests that virtually all the excess mortality is in those people who are seropositive.

Extraarticular features of rheumatoid disease include: rheumatoid nodules, lymphadenopathy, episcleritis and scleritis, pulmonary interstitial fibrosis, nodules and pleural effusion, vasculitis, Felty’s syndrome, Sjögren’s syndrome, anemia, cricoarytenoid arthritis,
and neuromuscular manifestations. Most of these extraarticular features are not direct causes of mortality, although some may be, such as vasculitis, Felty’s syndrome and severe pericarditis. Most studies have suggested the excess mortality of rheumatoid disease is entirely in the group that has extraarticular disease. Virtually all of those with extraarticular disease are also seropositive.

A retrospective study of 424 patients from Mayo Clinic examined the effect of extraarticular disease on survival. This compared expected mortality in rheumatoid patients with any extraarticular disease, and more severe extraarticular disease (curve labeled “ExRA 1–8” in Figure 2) such as pericarditis, pleurisy, Felty’s syndrome, vasculitis. Figure 2 shows that extraarticular disease, particularly certain types of extraarticular disease predicts very poor prognosis.

Formal education seems to impact survival. Patients with less than 12 years of education experience substantially higher mortality rates than those who have completed high school or college. The explanation for this finding is unclear. An obvious answer could be that these people did not get appropriate medical care. However, Pincus and Callahan retrospectively reviewed charts and divided those people who they thought got adequate medical care from those who did not. Care quality did not seem to make a difference, suggesting that lack of formal education does impact survival independent of medical care.

The extent of arthritis also is predictive of mortality. If more than 48 joints are involved, survival is poor. With severe seropositive extraarticular disease with many joints involved, the 5-year prognosis is about the same as 3-vessel coronary artery disease or stage 4 Hodgkin’s lymphoma.

In addition to the negative impact of disability on quality of life, disability may predict mortality. A study of 1269 patients from northern California evaluated the impact of progression of disability on survival. Health assessment questionnaire (HAQ) scores were used to measure disability. HAQ is a series of questions covering activities of daily living. Patients indicate if they can do each with ease, help, or not at all. HAQ was measured at baseline and follow-up assessments were

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**Figure 2.** Effect of Extraarticular Disease on Survival. ExRA(1–8) denotes more severe extraarticular disease. From: Turesson C, O’Fallon W, Crowson C, Gabriel S, Matteson E. Occurrence of extraarticular disease manifestations is associated with excess mortality in a community based cohort of patients with rheumatoid arthritis. J Rheumatol. 29:62–67. Permission to reproduce figure granted by the editor of the Journal of Rheumatology and Carl Turesson, MD, PhD.
performed for up to 20 years. They found that patients in the 4th quartile of HAQ scores had a very poor prognosis. The same study (Figure 3) also looked at individuals with declining levels of function based on HAQ scores. Of the 1269 patients in this study, 40% experienced declining function over the course of this study. With unchanging or improving function, the prognosis is much better than in patients with declining level of function. (Figure 4) Patients with declining functional ability are more likely to die with rheumatoid disease.

How Do We Explain the Increased Mortality?

What is the evidence that shows that people with rheumatoid disease have excessive amounts of cardiovascular disease? Using adenosine cardiac stress SPECT scans, 50% of patients with rheumatoid disease show evidence of ischemic heart disease, compared to only 27% of osteoarthritis patients matched for age and sex. There is an increased frequency of silent myocardial ischemia on 24-hour Holter monitors in people with rheumatoid disease compared to normal individuals. It is interesting that patients with rheumatoid arthritis are more likely to suffer silent myocardial ischemia than are normal individuals, similar to diabetics.

Rheumatoid patients demonstrate evidence of diastolic dysfunction, based on left ventricular end diastolic diameter measured on echocardiography. In normal individuals (non-rheumatoid individuals), diastolic dysfunction does correlate with cardiovascular events, which reflects myocardial ischemia. Carotid artery intima-media thickness has also been correlated with future cardiovascular events in otherwise normal individuals. When measured in people with rheumatoid disease, carotid artery intima-media thickness is much greater than in normal individuals. Therefore, multiple lines of evidence suggest that rheumatoid patients do have excess cardiovascular pathology.

This association should probably not be a surprise. An editorial published in Circulation compared arthrosclerosis to rheumatoid disease. There is evidence of macrophage activation in the synovial tissue. Macrophages are also activated in arthrosclerosis. This re-


Results in produce increased amounts of tumor necrosis factor α, matrix metalloproteinase, and interleukin IL-6 in both processes. There is also evidence of T-cell activation in people who have unstable angina. People who have unstable angina and rheumatoid disease have expanded populations of CD4+CD28– cells. CD4+CD28– cells produce high levels of gamma interferon. This leads to up-regulation of C-reactive protein synthesis, an up-regulation of adhesion molecules, and to neoangiogenesis, all process are common to the inflammatory pathogenesis of both atherosclerosis and rheumatoid disease.

While the risk factors for cardiovascular disease in rheumatoid disease include the classic risk factors, hypertension, smoking, diabetes, and dyslipidemia, these probably do not account for the majority of excess cardiovascular disease in rheumatoid patients. There is not good evidence that rheumatoid patients differ from the normal population with respect to these factors. To find the cause of the increased cardiovascular disease in rheumatoid disease, it is necessary to assess the role of certain novel risk factors. These novel markers include C-reactive protein (CRP), serum amyloid A (SAA), tumor necrosis factor alpha (TNF-α), IL-6, IL-1, homocysteine, and prothrombotic factors.

Most rheumatologists believe tumor necrosis factor alpha (TNF-α) is a major inflammatory cytokine in rheumatoid disease. Many of the newest therapies for rheumatoid disease are directed against TNF-α. TNF-α stimulates production of IL-6 as well as more TNF-α, and acts in part by increasing adhesion molecule expression on white blood cells and endothelial cells. This leads to endothelial dysfunction. Endothelial dysfunction probably predisposes to atherosclerotic coronary vascular disease. TNF-α increases matrix metalloproteinase production, including collagenase. For plaque to rupture and cause thrombosis, its fibrous cap must break. Rheumatoid patients produce increased amounts of metalloproteinases, which may promote plaque rupture leading to myocardial events.

Interleukin IL-6 stimulates immunoglobulin synthesis, as well as B-cell and cytotoxic T-cell differentiation. It also stimulates the liver to synthesize CRP and SAA, two acute-phase reactants. There is a clear correlation between CRP and SAA levels and future car-
diovascular events in rheumatoid individuals. Persons with rheumatoid disease have substantially elevated CRP levels.

Ridker showed that CRP is at least as predictive of a future myocardial infarction as fibrinogen, tissue plasminogen activating antigen (tPA), total to HDL cholesterol ratio. CRP level is also predictive of survival. For many years, it was thought that CRP might be an epi-phenomenon, an acute phase reactant produced by the liver of questionable importance. That is probably not true. There are multiple proposed atherogenic effects of CRP. CRP induces monocyte chemotaxis; the first cell to arrive in a developing plaque is a monocyte. The monocyte moves through the endothelium, matures into a macrophage, ingests LDL, becomes a foam cell, and begins the process of plaque synthesis.

It has been suggested that elevated levels of homocysteine are associated with accelerated atherosclerosis. Homocysteine is directly toxic to endothelial cells, producing endothelial dysfunction. Homocysteine also has prethrombotic effects, increases oxidation of LDL (oxidized LDL is a much more atherogenic particle) and decreases the availability of nitric oxide, a vasodilator. Fasting levels of homocysteine are significantly higher in patients with rheumatoid arthritis when compared to normal controls. Methotrexate has been shown to increase levels of homocysteine. It is very important that when rheumatoid patients are treated with methotrexate they also receive folic acid. Without folic acid, methotrexate may increase cardiovascular disease risk.

The pro-thrombotic state is also associated with future cardiovascular events. Pro-thrombotic factors that are increased in rheumatoid patients including fibrinogen, von Willebrand factor, tPA, and D-dimer.

Does treatment of rheumatoid patients increase cardiovascular risk? The answer is possibly. Nonsteroidal anti-inflammatory drugs are associated with the development of or worsening hypertension. A mistake made by clinicians is the prescription of nonsteroids without monitoring blood pressure. Modest elevations of both systolic and diastolic blood pressure are associated with an increase in cardiovascular and cerebrovascular events. COX-2 inhibitors may have a pro-thrombotic effect, shifting the ratio of prostacyclin to thromboxane. Prostacyclin had a platelet inhibitory vasodilatory effect, while thromboxane has a platelet activator and vasoconstrictor effect. Whether or not COX-2 inhibitor NSAID drugs actually increase the risk of cardiovascular disease is still uncertain and is the subject of 3 ongoing studies.

Does therapy improve mortality? Again, the answer is possibly. A study by Krause et al analyzed survival of rheumatoid patients who responded to methotrexate therapy vs those who did not. Patients were followed up to 12 years. Patients who responded to methotrexate, showing improved rheumatoid disease manifestations, had improved survival. Choi et al reported a larger prospective but nonrandomized group of rheumatoid patients taking methotrexate. Those on methotrexate generally had more severe disease, and they should have had a worse prognosis. They found that the individuals given methotrexate had an overall 60% reduction in mortality, and a 70% reduction in cardiovascular mortality. Evidence is growing that with methotrexate and perhaps the TNF-α inhibitors, treatment may improve survival of patients with rheumatoid arthritis.

What Can Clinicians Do to Improve the Outcome?

Clinicians must understand the natural history of rheumatoid disease; it is not the benign disease once thought. It may be useful to borrow a practice of oncologists and stage those with rheumatoid disease. Those who have severe functional disability, are seropositive, have extensive extraarticular disease, and have persistently elevated C-reactive protein and sedimentation rate are at highest risk. They should receive special attention in treatment planning. Clinicians need to recognize the importance of the “classic” cardiovascular risk factors, but also the novel
cardiovascular risk factors previously discussed. In dealing with the classic risk factors, I feel rheumatologists need to accept more of a primary care role. Rheumatologists should no longer send a patient with persistently elevated systolic blood pressure out to a general internist. Other risk factors such as smoking and obesity must be addressed. Rheumatologists have the opportunity to contribute to improved mortality with careful attention to these risk factors. Modifications of the novel risk factors will depend on the development of therapies that can alter underlying pathophysiology.

SUMMARY

Treatment of rheumatoid disease is currently where treatment of hypertension and diabetes were 20 years ago. We must aggressively treat the inflammatory process, or we will not prevent functional decline and increased mortality in affected individuals. A few nonsteroidal tablets, a pat on the back and some physical therapy are no longer adequate therapy for rheumatoid disease.

Rheumatoid disease is a systemic illness, not simply arthritis. Rheumatoid disease leads to disability in many patients and that disability tends to be predicted by the overall inflammatory burden. Mortality is clearly increased in rheumatoid disease, and there are factors such as seropositivity, progressive disability, and the level of inflammation that probably predict this increased mortality. These are factors, which can be identified and measured. Cardiovascular disease is the major cause of death in rheumatoid disease, and we are beginning to understand the relationship between inflammation and atherosclerosis. Hopefully, in the next 10 years we will be able to prove that therapy with methotrexate and new anti-cytokines will improve the overall prognosis and survival of rheumatoid disease patients.

Based on a presentation to the American Academy of Insurance Medicine, Scottsdale, Ariz, on October 13, 2003.

REFERENCES

16. Turesson C, O'Fallon W, Crowson C, Gabriel S,


Editor’s note: Interested readers may also wish to review these articles, which have appeared in insurance literature: