Editorial

Rheumatoid Arthritis: Is the Disease Becoming Milder or Is Treatment Improving?

Rheumatoid arthritis (RA) is a chronic, systemic, inflammatory disease leading to joint destruction and disability. There is a general consensus that over the past few decades a change in the presentation of our patients with RA has occurred, including fewer extraarticular manifestations and improved longterm outcomes. It has been suggested that both the incidence and severity of this disorder are decreasing[1-3]. Although there is no published literature to support this, there is agreement that complications such as rheumatoid vasculitis, Felty's syndrome, and rheumatoid nodules are becoming less frequent. Is this due to early, aggressive and improved treatment, or is the disease itself becoming less severe?

Radiologic progression has been shown to correlate with cumulative disease activity and overall disability in RA[4,5]. In this issue of *The Journal*, Sokka, *et al* present a comparison of 5-year radiographic progression in 3 cohorts of patients with RA monitored prospectively from 1983–85, 1988–89, and 1995–96[6]. All 3 cohorts included patients with early RA, median duration of symptoms between 6 and 7 months, and no previous use of disease modifying antirheumatic drugs (DMARD). Although the cohorts were assembled separately to test different hypotheses, patients in all 3 were ultimately treated with DMARD, with the exception of one patient in Cohort B. Radiographs of the hands and feet were done at baseline and annually thereafter and graded using the Larsen score[7].

Five-year median radiographic progression decreased with each cohort where the Larsen score increase was 12, 6, and 4 for cohorts A, B, and C, respectively. The proportion of patients who were rheumatoid factor positive with erosive disease at 5 years was similar in all 3 cohorts. The authors concluded that despite similar potential for erosive disease, patients in the most recent cohort have the mildest disease, with the least radiographic progression at 5 years.

The authors' explanations of their conclusions include improved treatment, patient selection, and milder disease. Multiple studies have shown that aggressive treatment can slow radiographic progression in RA[8-11]. In their study, although almost all the patients received DMARD therapy, the type and dose of drug differed in the 3 cohorts. Only a few patients in Cohort A received methotrexate over the study period, as compared to 20% of patients in Cohort B and almost 70% of patients in Cohort C at 5 years. Further, more patients in Cohort C than in Cohorts A and B received combination therapy.

In an attempt to standardize for the difference in treatment received, the authors assigned a "DMARD score" to each patient. DMARD were coded from hypothetically weakest to strongest, and the sum of a patient's DMARD use over 5 years was combined to yield a score. Drug dose, duration of therapy, route of administration, biologic therapy, and DMARD use between set times of recording were not included in the score. If a patient was receiving a minimal dose of methotrexate (e.g., 5.0 mg per week), the DMARD score would be higher than a maximal dose of sulfasalazine. As drug dosage can influence the aggressiveness of the intervention[12], an effective DMARD score should consider this in its calculation. Development of a DMARD score would have clear potential utility given the recent and expected change in treatment paradigms for RA. However, the tool used in the study by Sokka, *et al* has not been validated, and no tool with which to compare DMARD use between patients or cohorts has been developed. In their study, we can observe that patients in the most recent cohort were treated more aggressively than those in earlier cohorts. Whether differences in DMARD regimens alone can explain the difference in radiographic progression is inconclusive.

Perhaps the most interesting concept presented by this

See Radiographic progression is getting milder in patients with early rheumatoid arthritis, *page 1073*

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study is that RA is becoming a milder disease. Certainly, we have all noticed that today's patients have less severe disease than those of 30 years ago. Many would argue that this change in severity of patients predated the shift in treatment paradigm for RA and the widespread use of methotrexate. Therefore, it may not be related to earlier and more aggressive treatment. In their study, Sokka, *et al* demonstrate that more recent cohorts of early RA have less radiographic progression over 5 years than earlier cohorts.

Although the cohorts have similar symptom duration prior to presentation, the authors observe that baseline characteristics are different. Patients in the earlier cohort had longer duration of morning stiffness, higher inflammatory markers (erythrocyte sedimentation rate, C-reactive protein), and higher rates of rheumatoid factor positivity than more recent cohorts, suggesting more active disease at baseline. Although this may have biased their results, the authors point out that it also supports the argument that earlier patients had more aggressive disease, independent of treatment.

The concept that RA is becoming milder is not new. It has been well documented that both incidence and severity of disease are decreasing. Such changes over time may be due to differences in patient selection, early diagnosis, improved treatment, or other environmental factors including cohort or period effects[13]. A decline in incidence of RA over 4 decades was reported in Rochester, Minnesota, USA[14]. This decrease was found to be substantially greater in women. Findings are consistent with observed declines in other populations including cohorts in Japan[15] and Finland[16] and the Pima Indians in Arizona, USA[17]. From this information it may be concluded that the fall in incidence of RA seems to be a worldwide phenomenon[18].

Trends in severity of RA can be determined by assessing radiographic progression, disability, extraarticular manifestations, and mortality. These are more difficult to evaluate than incidence rates as they may be influenced by early diagnosis and treatment. Silman, *et al* found that the severity of RA, as measured by seropositivity, erosions, and nodules, decreased in patients attending the Rheumatology Department at the London Hospital between 1970 and 1980[2]. Similarly, the average level of disability decreased between 1978 and 1989 in a Finnish population of patients with seropositive RA[19].

However, similar studies evaluating trends in extraarticular manifestations and mortality in RA have not shown a decline in incidence. Turesson, *et al* from the Rochester Epidemiology Project found no decrease in the incidence of extraarticular manifestations in patients with RA between 1955 and 1995[13]. Similarly, Watts, *et al* did not find a decrease in rheumatoid vasculitis in the 1990s in Norfolk, UK[20]. Mortality in patients with RA is higher than that in the general population and correlates with extraarticular manifestations and comorbidities[21,22]. Disease severity is significantly associated with mortality regardless of the presence of comorbid disease[23]. Assessment of mortality rates in 3 population based cohorts in Rochester, Minnesota, found no change in relative or absolute mortality rates over 4 decades[22]. Moreover, a review of survival studies in RA concluded that any apparent improvement in survival might be due to referral selection bias rather than aggressive treatment or trend in disease[24].

So what does this all mean? Can we really argue that RA is becoming milder? Incidence and severity of RA seem to be decreasing, but mortality and extraarticular manifestation rates remain unchanged. Why is there discordance? One possibility is delay of effect. Conceivably, we will see the decrease in severity of disease reflected in future studies of survival. Unfortunately, it will be difficult to eliminate the confounding of early diagnosis and improved treatment from these assessments of trends in disease. The change in therapeutic approach for RA emerged in the mid to late 1980s and has continued to evolve since then, particularly with the advent of the biologic agents. Treatment focus has shifted from symptom control to halting joint destruction, and in some cases induction of disease remission. Perhaps the effect of this change in treatment paradigm will have a delayed effect on survival and that is yet to come.

The data presented by Sokka, *et al* raise the same questions as previous studies with regard to trends in RA. The authors present a decrease in radiographic progression and milder disease in newer cohorts versus older ones. Studies of longterm radiographic outcomes, which control more precisely for changes in treatment paradigms and disease duration, are needed to confirm these results. The benefit of improved radiographic outcomes should also correlate to a reduction in other clinical manifestations, disability, and mortality. It will be of interest to see if these changes in the epidemiology of RA will translate into improved clinical and survival outcomes in the 21st century.

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