Editorial

Changes in disease activity, disability and mortality of inflammatory arthritis in in the new millennium compared with the 10 years before

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Inflammatory polyarthritis and its subset rheumatoid arthritis (RA) are characterized by synovial inflammation and hyperplasia, autoantibody production, cartilage and bone destruction, and systemic features, including cardiovascular, pulmonary, psychological, and skeletal disorders (1,2). In contrast to osteoarthritis, which is also associated with cartilage and bone destruction but generally considered as noninflammatory arthritis and with hardly any treatment options that modify the course (3-5), outcomes of inflammatory polyarthritis and RA can be improved by administration of appropriate therapy. Nevertheless, a number of studies comparing changes in the long-term outcome of treatment for patients with inflammatory polyarthritis during the mid-1990s have achieved inconsistent conclusions (6,7). Furthermore, there are suggestions that RA is becoming less severe (8,9). Thus, it would be of interest to investigate whether any improvements in long-term outcome are associated with less severe disease or with the changes in treatment strategy.

Against that background, the study by Gwinnutt *et al.* is very welcome: they showed that activity of inflammatory polyarthritis is significantly improved (17% decrease as evaluated by a 51 swollen and tender joint count) in the new millennium compared with the decade before, whereas disability and mortality are unchanged (10).

How strong are the data? Is bias fully excluded?

Gwinnutt *et al.* used the Norfolk Arthritis Register (NOAR) database, in which data were collected by general practitioner or rheumatologists in UK (10). Patients with inflammatory polyarthritis were recruited from 1990 to 1994 [cohort 1 (C1), n=1,022] and from 2000 to 2004 [cohort 2 (C2), n=631]. Only patients with 2 or more swollen joints lasting for 4 or more weeks were included while those were excluded if their baseline assessment took place >2 years after symptom onset. After a follow-up of 10 years, they found that patients in C2 had 17% lower swollen 51 joint counts than C1, whereas tender 51 joint counts and Health Assessment Questionnaire were comparable. C2 patients had reduced risk of all-cause and cardiovascular disease mortality than C1. However, the difference in mortality was no longer significant after adjustment by mortality risk in the general population. Obviously, the key question is whether unknown confounding factors might have led to the bias of the results. For example, do patients in cohort 2 have a healthier lifestyle, or take some medications not listed in the study [i.e., not disease-modifying antirheumatic drugs (DMARDs)], or have a higher socioeconomic status, and so on?

Without doubt, the authors tried to minimize the effect of confounding on the outcomes by performing a number of statistical analyses. For example, they used population-average negative binomial regression and generalized estimating equation analysis to compare the longitudinal disease activity and disability between cohorts. In addition, they compared risk of 10-year mortality between cohorts using Cox models and compared risk of cardiovascular disease mortality using competing risks analysis. They also calculated mortality rate ratios using Poisson regression.

The variables (age, gender, symptom duration at baseline, smoking status, etc.) were included in the tenth year outcome models and in those for comparison of longitudinal disease activity and disability. Nevertheless, although these all seem to be optimal and robust, it is still impossible to completely rule out the risk of bias, because unknown bias cannot be detected and thus not calculated.

Another thing that should be noticed is that both inflammatory polyarthritis and RA are autoimmune diseases that affect joints, bones, muscles and other organs (2). For different patients, their body resistance and tolerance to inflammatory polyarthritis may vary greatly. Therefore, it may be difficult to judge the severity of the disease from patients with the same clinical symptoms using some currently available examinations or tests. For example, the evaluation of disability was conducted by a form of self-reported questionnaire (Health Assessment Questionnaire) at each assessment. This means that the results were determined by the patients' subjective satisfaction, which may have impaired the strength of the data. Furthermore, sometimes it is even difficult to judge whether the treatment effect is really good or not, for example, when the patients' expectations are taken into account.

Are these data in line with other studies?

The finding of no significant change in mortality of the study was comparable with results from a previous study of patients with RA from Ontario, Canada (6). Widdifield *et al.* computed all-cause mortality rates among residents with RA (n>46,961) versus without RA (n>8,903,118) from 1996 to 2009 (6). They found that the standardized mortality ratios for RA patients in 1996–1997, 2000–2001, 2004–2005, and 2008–2009 were 1.51 (95% CI, 1.43–1.59), 1.50 (95% CI, 1.43–1.57), 1.43 (95% CI, 1.37–1.50), and 1.41 (95% CI, 1.35–1.47), respectively. They also did not find a significant change in the mortality rate ratios by calendar time.

Because the study by Gwinnutt *et al.* is probably the first one to directly compare the longitudinal clinical outcome over 10 years between two cohorts of patients recruited 10 years apart, the results of the disease activity and disability analyses extend that of previous studies in some aspects (7,9). For example, the average ages of symptom onset of inflammatory polyarthritis patients in C2 (58 years; range, 47–70 years) was higher (95% CI, 2.00 to 6.00) than C1 (54 years; range, 41–67 years). Additionally, the number of patients recruited in C2 (n=631) was much less (–38.3%) than that of C1 (n=1,022). These results more or less demonstrated that with the improvement of medical conditions (e.g., treatment of DMARDs), the incidence and onset of inflammatory polyarthritis might be controlled to some extent.

What are the consequences?

Since the study suggests that disability and mortality of inflammatory polyarthritis remain unchanged with 10 years ago, this might indicate that the new treatment (like biologic DMARDs) of the disease since the new millennium is still far from satisfied. Probably, not all patients with inflammatory polyarthritis had benefited from the new therapy. Of course, it is too early to conclude that these medications should be stopped from prescribing to patients with inflammatory polyarthritis, because prospective data on randomized control studies are still lacking.

We hold the opinion that, the next steps for research in this specific field should not only focus on improving the treatment and nursing of the disease, but also pay more attention to the in-depth study of the cause of the disease so as to reveal the pathogenesis fundamentally, and to evaluate the progression and prognosis of the disease effectively. For example, a number of questions should be answered: Is the progression of disease beyond our awareness? Is it still difficult to cure this disease with our current medical technology? Or are our expectations of disease prognosis exceeding the extent of its recovery? With answers to these questions, we might be able to find out which persons would have the better or worse outcomes after therapy, based on for example gender, age, activity level, severity and subtype of inflammatory polyarthritis syndrome among other factors.

In summary, the data from a high-quality natural history study presented by Gwinnutt and colleagues have documented and suggested that the activity (assessed by a 51 swollen and tender joint count) of inflammatory polyarthritis has significantly improved in the new millennium, whereas disability and mortality were unchanged. This study hopefully might stimulate further research on pathogenesis and evaluation of inflammatory polyarthritis. Substantial further prospective work needs to be carried out to confirm these findings.

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Footnote

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