

A Cohort Study of Clinical Care in Rheumatoid Arthritis: the IORRA study

JMAJ 52(1): 54–56, 2009

Hisashi YAMANAKA *1

Continuing advances have been seen in the field of medical care, and progress in the treatment of rheumatoid arthritis (RA) during the past decade has been particularly impressive.

Rheumatoid arthritis is especially frequent in women, and the prevalence of this disease is about 0.5–1.0% in ethnic groups worldwide. Patients with RA suffer the progressive destruction of joints throughout the body, gradually leading to difficulty in performing the activities of daily living. If the disease is left untreated, the patient eventually may be confined to bed, thereby creating a marked decline in his or her quality of life (QOL). Although RA is an intractable disease that can occur in almost anyone, a treatment effective in preventing joint destruction was not available until the 1990s, and the mainstay of treatment consisted of short-term improvement in QOL by relieving joint pain through the use of non-steroidal anti-inflammatory drugs (NSAIDs) and orthotic devices. However, in the 1990s, disease-modifying antirheumatic drugs (DMARDs) that were able to prevent joint destruction began to be developed. After 2000, biologic products that would improve clinical symptoms greatly and suppress joint destruction almost completely were introduced to clinical practice, causing a dramatic change in the clinical field. The introduction of a new treatment can cause the treatment strategy itself to change significantly. The treatment of RA over the past 10 years is a perfect example of such change. Namely, there was a significant change in the goal of treatment, from short-term improvement in QOL to long-term improvement in QOL during the past 10 years. More specifically, modest treatment aimed only at maintaining the patient's current functioning has been changed to more

aggressive treatment to completely control disease activity and to prevent joint destruction, placing a cure for the disease itself in perspective.

However, it is extremely difficult to quantitatively evaluate such changes in daily practice. Attention to variations in the consumption of old and new drugs may reveal an overall change in drug therapy. It is, however, not possible to determine which group of patients has received the new therapy, how well disease activity has been controlled, and what benefit the new therapy bestows upon the patient. Although analysis of changes in outcome resulting from the altered therapeutic strategy or procedure is a critical piece of information in determining whether the new therapy is truly safe and effective, a good system is necessary for the verification of such information. To this end, a long-term survey within a patient cohort is necessary.

In order to investigate the current status of and changes in the treatment of RA in Japan, we launched the IORRA (Institute of Rheumatology, Rheumatoid Arthritis) study. The Institute of Rheumatology, Tokyo Women's Medical University, is Japan's foremost clinical institute for the treatment of rheumatic diseases, and treats 5,000 patients with RA, 3,000 with gout, and 2,000 with connective tissue diseases. Since the total number of RA patients in Japan is said to be 500,000, this institute treats approximately 1% of all RA patients in the country. The IORRA study is a clinical study of all ambulatory RA patients treated in the Institute of Rheumatology, Tokyo Women's Medical University.

In the IORRA study, patients undergo an evaluation of swollen or painful joints by physicians twice annually (in spring and autumn) upon the occasion of patient visits to the Institute of

*1 Director and Professor, Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan (yamanaka@ior.twmu.ac.jp).

Rheumatology. After blood tests, patients are given a survey form comprising about 30 pages. Patients are requested to take the form home, fill in the necessary information, and return the form to the Institute by mail. The results of a physician's evaluation, laboratory tests, and patient self-evaluation are integrated into a database to provide various analyses. The first survey was conducted in October 2000, and, thereafter, two surveys per year have been carried out, with the ongoing survey the 17th. Data on the clinical outcomes of 5,000 RA patients treated over the past 8 years have been included in the database.

This study has a number of features that deserve particular mention. First, the quality of the patient survey is very high. All RA patients who visit our institute during a certain period of time are asked to participate in this research by the physicians in charge. More than 99% of patients have consented to participate in surveys, and more than 98% have filled in and returned the 30-page survey form. This indicates that patients have placed a high degree of trust and great expectations in this study. We believe that our providing feedback to the patients has contributed greatly to their trust in the study. Specifically, we have calculated the disease activity for each patient based on the information given in the survey form, and have handed each patient a report of his or her individual results and a newsletter that contains the findings obtained in the study. This is an important element of the success of this study.

In addition, it is noteworthy that data on medications are obtained not from the medical records but from patients' own descriptions. Many patients do not take drugs exactly as they are prescribed, particularly in the case of NSAIDs, which can be reduced as symptoms improve. In the IORRA study, attention was given to the actual status of medication from the very beginning of the study, and the efficacy and safety of treatment have been evaluated on the basis of patients' information on drug consumption.

The year 2000, when the IORRA study was initiated, had yet to see any significant change in the treatment of RA. At that time, none of the biologic products, bisphosphonate preparations, or coxibs had been introduced for the treatment

of this disease in Japan. Therefore, it was possible for the IORRA study to determine in detail the influence of these drugs on the treatment of RA following their introduction.

Analyses of the IORRA cohort have yielded 36 papers issued in English. The memorable first paper dealt with scientific validation of a Japanese version of the Stanford Health Assessment Questionnaire (HAQ).¹ Thus, all analyses in the IORRA study have used validated indices. An analysis of data on disease activity and functional impairment in the IORRA cohort from 2000 to 2006² revealed that there was marked improvement in the disease activity score DAS28 (from 4.15 to 3.45 on average), the Japanese Health Assessment Questionnaire (JHAQ) score for functional impairment (from 0.80 to 0.76 on average), and CRP (from 1.43 mg/dl to 0.99 mg/dl on average). The most prominent change in treatment during this period was that of methotrexate therapy; the dosing percentage increased markedly from 34% to 59%, with a distinct increase in mean dose from 5.5 mg/week to 6.9 mg/week.² In addition, it became apparent that insufficient control of disease activity led to subsequent aggravation of the JHAQ functional impairment score,² and that maintenance of the remission status (DAS28 < 2.6) could effectively prevent the progression of functional impairment.³

Other studies have addressed issues including the frequency of various complications and the influences of drug therapy in RA patients,^{4,5} disease sensitivity and the patient's genomic information,⁶ severity of the disease,⁷ and the surgical risks of RA patients,⁸ all of which have received high commendation.

This series of investigations has provided only a summation of data from a single institute, and may not reflect the overall picture of clinical practice for rheumatic disease. However, since our data correspond to more than 1% of all RA patients in Japan, we believe that the results of the data analyses can certainly provide feedback as to clinical practice for this disease.

We intend to continue to collect and compile data devoid of selection bias, carry out scientifically precise analyses, and offer feedback and information to patients.

References

1. Matsuda Y, Singh G, Yamanaka H, et al. Validation of a Japanese version of the Stanford Health Assessment Questionnaire in 3,763 patients with rheumatoid arthritis. *Arthritis Rheum.* 2003;49(6):784–748.
2. Yamanaka H, Inoue E, Singh G, et al. Improvement of disease activity of rheumatoid arthritis patients from 2000 to 2006 in a large observational cohort study IORRA in Japan. *Mod Rheumatol.* 2007;17(4):283–289.
3. Tanaka E, Mannalithara A, Inoue E, et al. Efficient management of rheumatoid arthritis significantly reduces long-term functional disability. *Ann Rheum Dis.* 2008;67(8):1153–1158.
4. Furuya T, Kotake S, Inoue E, et al. Risk factors associated with incident fractures in Japanese men with rheumatoid arthritis: a prospective observational cohort study. *J Bone Miner Metab.* 2008;26(5):499–505. Epub 2008 Aug 30.
5. Yamada T, Nakajima A, Inoue E, et al. Increased risk of tuberculosis in patients with rheumatoid arthritis in Japan. *Ann Rheum Dis.* 2006;65(12):1661–1663.
6. Kobayashi S, Ikari K, Kaneko H, et al. Association of STAT4 with susceptibility to rheumatoid arthritis and systemic lupus erythematosus in the Japanese population. *Arthritis Rheum.* 2008; 58(7):1940–1946.
7. Tsukahara S, Shinozaki M, Ikari K, et al. Effect of matrix metalloproteinase-3 functional SNP on serum matrix metalloproteinase-3 level and outcome measures in Japanese RA patients. *Rheumatology (Oxford).* 2008;47(1):41–44.
8. Momohara S, Inoue E, Ikari K, et al. Risk factors for wrist surgery in rheumatoid arthritis. *Clin Rheumatol.* 2008;27(11):1387–1391.