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MINIREVIEW

Hisashi Yamanaka · Shigeto Tohma

Potential impact of observational cohort studies in Japan on rheumatoid arthritis research and practice

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Abstract For better management of rheumatoid arthritis (RA) patients, we need information both from well-designed clinical trials, such as randomized controlled trials, and from observational cohorts. Observational cohort study has not been developed in Japanese RA patients; however, two cohorts, IORRA (formerly J-ARAMIS) from 2000 and *NinJa* by iR-net from 2002, have been established. These two cohorts are an important source not only for better management of Japanese RA patients but also for solutions to a variety of issues concerning RA clinical practice in general. In this minireview, necessities of observational cohort studies are discussed.

Key words Cohort study · Prospective · Rheumatoid arthritis (RA)

As a result of intensive research during the last 20 years, new therapeutic tools, including biologic agents, have been developed and introduced into the daily practice of treating patients with rheumatoid arthritis (RA). The effectiveness and safety profile of these new agents are strongly supported by high-quality evidence, primarily from a series of randomized controlled trials (RCTs). However, caution must be observed when applying the results of RCT evidence to RA patients in daily practice, for several reasons.

First, RA is a long-lasting chronic disease to lead patients into a disabled condition; however, it is not realistic to plan a long-term RCT with placebo arm. Disability of patients, an important outcome of treatment, cannot be measured by RCTs conducted for only 1–2 years. For example, even if a drug is demonstrated to prevent joint destruction for 1 year, this does not necessarily mean that it will continue to prevent joint destruction for 10 years.

Second, since many RA clinical trials are designed for patients with active disease, the inclusion criteria of clinical trials are usually very stringent and do not encompass the majority of patients that are seen in daily practice. For example, the percentage of patients who fulfilled all three conditions [number of swollen joints ≥10, number of tender joints ≥12, and C-reactive protein (CRP) ≥2.0 mg/dl] as part of the inclusion criteria of an actual clinical trial of a biologic agent in Japan was only 1.61% among all patients with RA (n = 4338) at the Institute of Rheumatology, Tokyo Women's Medical University. We have to pay attention to the diversity between patients who fulfill the inclusion criteria of RCT and those who will receive the treatment in the real world. This is consistent with the data of Pincus and Sokka,[1] who reported that only a small percentage of RA patients seen in daily practice meet the inclusion criteria of RCTs for infliximab and etanercept. One of the major principles of evidence-based medicine (EBM) is that the results of clinical research can be applied to those patients who meet the inclusion criteria of the study.

Third, as all clinicians recognize, patients in the real world are far more complex and variable than those who participate in clinical trials. Even in patients with similar disease activity, the outcome of RA patients is affected by many factors, including age, sex, disease duration, comorbidities, drug sensitivity, socioeconomic status, and even the treating physician. Although we do not dismiss the value of RCTs, we believe that the evidence generated from RCTs is not always sufficient to provide the basis for decision making for the treatment of RA patients in daily practice.

Finally, it is risky to apply the evidence generated in other ethnicities to Japanese patients, particularly with respect to the safety profile of antirheumatic drugs: ethnic differences in the sensitivity to certain classes of drug, such as leflunomide, have indeed been identified.[2]

One solution to these issues is to use a prospective observational cohort. Data collected from patients seen in daily practice more accurately reflect what occurs in the real

H. Yamanaka (✉)
Institute of Rheumatology, Tokyo Women's Medical University, 10-22 Kawada-cho, Shinjuku-ku, Tokyo 162-0054, Japan
Tel. +81-3-5269-1725; Fax +81-3-5269-1726
e-mail: yamanaka@ior.twmu.ac.jp

S. Tohma
Clinical Research Center for Allergy and Rheumatology, National Hospital Organization, Sagamihara National Hospital, Sagamihara, Japan

Table 1. Two observational cohort studies in Japan

	IORRA cohort (J-ARAMIS)	*NinJa*
Basic concept	Clinical research in Tokyo Women's Medical University	Database of National Institute using iR-net
Headquarter	Institute of Rheumatology, Tokyo Women's Medical University	Sagamihara National Hospital
Study design	Observational cohort	Observational cohort
Institution	One institution	Multiple institutions
Establishment	2000	2002
Measured outcome	Patients > physician, laboratory	Physician > patients, laboratory
Measured disease activity	DAS28, ACR core set	DAS28, ACR core set
Number of patients	Approx. 5000	Approx. 4000
Frequency of investigation	Twice a year	Once a year
Main source of research grant	Consortium of industry	Public grant
Expected advantage	Quality-controlled data	Nationwide data collection
Possible inherent bias	Institutional bias	Patient-selection bias

world. There are lots of difficulties in the establishment and the maintenance of an observational cohort, especially in keeping the data quality high. Furthermore, cohort studies have an inherent bias such as in patient selection or in differences between institutions. Thus, cohort studies require extensive analysis of data using sophisticated statistics to minimize the influence of bias. The pioneering cohort for this type of research in RA is the ARAMIS (Arthritis Rheumatism and Aging Medical Information System)[3] in North America, established in the 1970s. Analysis of this cohort has yielded a plethora of important information, including classification criteria for RA diagnosis and long-term outcomes. Based on this concept, several RA patient cohorts have been established throughout the world, and these have addressed many of the issues encountered in daily practice in the RA clinic.[4–6] Nevertheless, no such cohort has been established in Japan, and we did not previously have the resources to solve specific clinical questions for Japanese RA patients. To better manage RA patients, we need information from both well-designed clinical trials (such as RCTs) as well as from observational cohorts.[7]

One of the authors of this paper (H.Y.) and colleagues established a large observational cohort of RA patients at the Institute of Rheumatology, Tokyo Women's Medical University (IORRA, formerly J-ARAMIS), in 2000.[8] This cohort has been established based on all RA patients seen in an outpatient clinic, and the cohort database is a powerful source not only for clinical research but also for the extensive evaluation of therapeutic strategies under real-life conditions. Later, the other author (S.T.) and colleagues established a multicenter, observational cohort of RA patients (*NinJa* by iR-net) in 2002. As of 2006, 33 institutions located throughout Japan are participating in iR-net. These two cohort studies have been established independently, and differences in the two research systems exist (Table 1); thus, each study has different advantages and disadvantages. We believe that these two cohorts are an important source not only for better management of Japanese RA patients but also for solutions to a variety of issues concerning RA clinical practice in general. As the researchers deeply involved in the establishment of these cohorts, we would like to emphasize the necessity of observational cohort studies of RA patients in Japan, and encourage Japanese researchers to recognize the importance of conducting clinical studies under real-life conditions.

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