A paradigm shift in studies based on rheumatoid arthritis clinical registries

Soo-Kyung Cho and Yoon-Kyoung Sung

Clinical research is the study of aspects of patient health or illness that are closely related to clinical practice. In the late 20th and early 21st century, outcomes for patients with rheumatoid arthritis (RA) improved dramatically due to breakthroughs in new drugs. Patient-reported outcome measures now play a significant role in the drug development process as study endpoints in clinical trials of new therapies, and this has led to increased interest in the patient's perspective, drug safety and treatment outcomes in clinical practice. In accordance with these needs, many prospective cohorts for RA patients and registries of biologic disease modifying anti-rheumatic drugs have been actively conducted in the United States and European and Asian countries. A gradual shift is taking place in the major outcomes of clinical research using these prospective cohorts and registries. This article will introduce representative registries for RA in each country set up in the early 2000s and will discuss future perspectives in clinical research on RA patients using such clinical registries.

Keywords: Arthritis, rheumatoid; Cohort studies; Registries; Patients reported outcomes; Big data

INTRODUCTION

Rheumatoid arthritis (RA) is a long-term chronic disease whose symptoms include joint pain and difficulty with daily tasks and can progress to joint deformity and reduced quality of life (QoL) [1]. With the advance of years these features can lead to many comorbid conditions in patients. Because of the complexity of the clinical manifestations of RA and the different experiences of patients, long-term observational studies are crucial for understanding treatment outcomes and predicting the prognosis of RA patients [2].

Since the introduction of biologic disease modifying anti-rheumatic drugs (DMARDs) for treating RA in the early 2000s [3], there have been improvements in disease outcomes and patients’ QoL. Various outcome measures including disease activity and patient-reported outcomes (PROs) have been developed and used widely to estimate the efficacy or safety of new drugs in randomized clinical trials (RCTs) [4]. Eventually, treat to target (T2T) strategies and evidence-based clinical practice guidelines were developed based on these indices [5]. Although these RCTs can reveal the efficacy and safety of drugs, they are still limited by the characteristics of the particular study population in terms of limited exposure, fewer comorbidities and inclusion and exclusion criteria not considered to be exclusionary in general practice [6]. Therefore, many prospective cohort of RA patients and registries of biologic DMARDs have been established in the United States (US) and European and Asian countries [7]. The observational studies recorded provide a great deal of information on the clinical features and long-term outcomes of RA patients and the comparative effectiveness and responsiveness...
of innovative treatments [8-10].

Over the last decades, the main issues examined in studies using these prospective cohorts and registries of RA patients have changed. In this article, we intend to review representative cohort and registries of RA patients in various countries and to describe recent changes in the research issues confronted in these observational studies.

ESTABLISHED RA REGISTRIES AND THEIR MAIN OUTCOMES

To date, prospective RA cohorts and registries have been established to observe the natural course of the disease, changes in disease activity in response to the various treatment options, and the safety of conventional and innovative treatments. Representative RA cohorts and registries are listed in Table 1 [6,11-17].

In the US, a nationwide cohort using a computer system for collecting data was established in 2002: the Consortium of Rheumatology Researchers of North America (CORRONA) [8]. This database collected clinical information, PRO, toxicities and new medical problems facing RA patients. CORRONA extended the patient spectrum enrolled to psoriatic arthritis (PsA), spondyloarthritis, psoriasis, inflammatory bowel disease in 2015, and is now expanding into the realm of patient-derived data based on applications of mobile devices [6]. Treatment patterns [18], disability [19], and drug safety [20] were the main outcomes of the early studies from the CORRONA. However, over time, studies have come to focus on remission [21], comorbidities [22], and PROs [23].

Cohorts from single centers can have strengths that differ from nationwide cohorts in terms of quality of data, with less missing data and less attrition of participants, even though their generalizability is limited. The Brigham and Women’s Hospital Rheumatoid Arthritis Sequential Study (BRASS) cohort was established in a single center in the USA in 2003, and many important results were obtained using this cohort [24]. These included genetic factors influencing disease phenotype and drug responses [9,25], remission [26,27], and predictors of radiographic progression [28,29]. Thereafter, multimorbidities became the main focus of studies [30-34].

In European countries, several nationwide registries for biologic DMARDs were established early by government: the Swedish Biologics Register [35] in 1999 [36], a nationwide registry of biological therapies in Denmark [35] in 2000 [37], the Norwegian NOR-DMARD register also in 2000 [38], and the British Society for Rheumatology Biologics Register (BSRBR) in 2001 [39]. A distinctive characteristic of these registries is the ability to retrieve important outcomes by linkage to other nationwide databases for claims or statistics within the individual countries, since they were promoted by government. These registries provided valuable evidence concerning effectiveness and safety issues related to biologic DMARD [40-42] and as long-term observations with registries became possible, malignancy and mortality data have also been reported [43-45].

Recently international collaborative studies have been conducted between countries [46-48], as well as between registries, especially European ones [35,49]. Such collaborations can produce more reliable information because of the greater numbers of patients and generalizability, and they make it possible to identify different patterns of drug use and disease progression in the specific medical environments of each nation.

In Japan, a single center in Tokyo Women’s Medical University launched the Institute of Rheumatology Rheumatoid Arthritis (IORRA) cohort in 2000 to improve the management of Japanese RA patients [10]. Early on, the main outcomes of this Japanese cohort were disability [50,51] and fragility, including osteoporosis and fracture [52,53]. On one hand, the Registry of Japanese Rheumatoid Arthritis Patients on Biologics for Long-term safety (REAL) was started in 2005 [54] and reported on drug safety issues, especially infection risks associated with biologic DMARDs [55].

Meanwhile in Korea, a nationwide cohort for RA, the Korean Observational Study Network for Arthritis (KORONA), was created in 2009 by Clinical Research Center for Rheumatoid Arthritis in Hanyang University and funded by the Ministry of Health and Affairs of Korea [56]. A total of 5,371 RA patients over the age of 18 who satisfied the 1987 American College of Rheumatology (ACR) classification criteria for RA were recruited by rheumatologists from 23 centers across Korea as part of KORONA. Through this prospective cohort study, researchers published studies on various outcomes in...
Korean RA patients: disability [57,58], comorbidity [59], and mortality [60]. The Biologics Pharmacoepidemiology Study (BIOPY) for RA patients which can be merged with the KORONA database was established in 2011, and produced a study of the comparative effectiveness of biologic and conventional DMARDs [61]. In 2012, the Korean nationwide registry, Korean College of Rheumatology Biologics and targeted therapy Registry (KOBIO) for several rheumatic diseases such as RA, ankylosing spondylitis (AS), and PsA was launched by Korean College of Rheumatology [62]. This registry is a multi-centre, prospective, observational program that gathers and analyzes data on patients being treated with biologic agents and small molecules in Korea. As of September 10, 2018, those patients who were requested by each rheumatologist had consented to participate in the cohort and a total of 1,881 RA, 1,731 AS, and 62 PsA patients had been included in KOBIO (http://rheum.inforang.co.kr/kobio/).

### PUBLISHED TOPICS IN STUDIES FROM MAJOR PROSPECTIVE RA COHORTS AND REGISTRIES

To identify research topics derived from data in cohorts and registries, articles were extracted from PubMed as search words ‘the name of cohort’ AND ‘rheumatoid arthritis’ using a total of six cohorts and registries. We reviewed individual articles selected from each cohort and registry as of September 2018: CORRONA (n =Table 1. Characteristics of RA cohorts and registries in various countries

| Cohort or registry | Start date | Country | Population | No. of RA patients | Main outcome |
|--------------------|------------|---------|------------|--------------------|-------------|
| CORRONA            | 2002       | USA     | RA (2001–), SpA, PsA, Psoriasis (2015–) | Over 42,000 [6] | Clinical information |
| BRASS              | 2003       | USA, single center (The Brigham and Women's Hospital) | RA | 1,309 [11] | Drug response and toxicity, disease activity and prognosis |
| DANBIO             | 2000       | Denmark | Biologics users with RA, AS, PsA | 14,249 [12] | Drug safety |
| BSRBR              | 2001       | UK      | Biologics users and non-users with RA; biologic users with SpA, PsA | 19,282 RA biologics users [13] | Drug safety |
| IORRA              | 2000       | Japan, single center (Tokyo Women’s Medical University) | RA | 5,637 [14] | Clinical information |
| REAL               | 2005       | Japan   | Biologics users and non-users with RA | 1,068 TNF inhibitor users [15] | Drug safety |
| KORONA             | 2008       | South Korea | RA | 5,317 [16] | Clinical information |
| KOBIO              | 2012       | South Korea | Biologics users and non-users with RA; biologics users with AS, PsA | 1,227 RA [17] | Drug safety and effectiveness |

RA, rheumatoid arthritis; CORRONA, consortium of Rheumatology Researchers of North America; BRASS, Brigham and Women’s Hospital Rheumatoid Arthritis Sequential Study; DANBIO, nationwide registry of biological therapies in Denmark; AS, ankylosing spondylitis; PsA, psoriatic arthritis; BSRBR, British Society for Rheumatology Biologics Register; SpA, spondyloarthropathy; IORRA, Institute of Rheumatology Rheumatoid Arthritis by Tokyo Women's Medical University; REAL, Registry of Japanese Rheumatoid Arthritis Patients on Biologics for Long-term safety; TNF, tumor necrosis factor; KORONA, Korean Observational Study Network for Arthritis; KOBIO, Korean nationwide Biologics.

a Number of patients based on the last published article.
96), IORRA (n = 54), KORONA (n = 11), BSRBR (n = 44), DANBIO (nationwide registry of biological therapies in Denmark; n = 98), and KOBIO (n = 3), to identify the clinical research performed using each database. Then the main topics of studies using these databases were classified into 10 categories: (1) RA disease activity and remission, (2) disability and quality of life, (3) comparative effectiveness of drugs, (4) comorbidities, (5) PRO, (6) compliance, (7) drug effectiveness, (8) drug safety, (9) mortality, and (10) “other” including description of the database, methodologic issues, economic analysis, medical accessibility, and pathogenesis. (Table 2).

According to their main outcomes as shown in Table 1, work based on the CORRONA and IORRA cohorts has focused on RA activity and disability or comorbidity, while work on BSRBR and DANBIO have focused on drug effectiveness and safety.

### A NEW PARADIGM FOR OUTCOMES IN RA COHORTS AND REGISTRIES

Next, the frequency of articles in each research category were arranged in chronologic order to detect trends in the main outcomes of clinical research (Fig. 1). The most significant recent changes have been increasing research on disease remission and PRO. Many studies related to drug safety and effectiveness were published after the introduction of biologic DMARDs and the number of such studies peaked after biologic agents had been in use for a long time. Clinical studies related to these topics will continue to appear due to the introduction of new drugs in clinical practice. In addition, there has recently been a focus on specific comorbidities such as interstitial lung diseases and depression, while papers on well-known comorbidities such as osteoporosis and fracture were published in the early period.

We would now like to discuss possible future initiatives for obtaining valuable evidences for improving patients’ treatment through clinical research using existing cohorts or newly established cohorts. Treatment paradigms have changed in response to evidence from clinical trials and observational data. With the advent of biologic DMARD therapies and T2T approaches we aim to achieve remission and dream of obtaining cures. At the same time, we continue to strive to improve care and better understand treatment choices. The

Table 2. Main outcomes of published papers using representative RA cohorts and registries

| Cohort | CORRONA (n = 81) | IORRA (n = 48) | KORONA (n = 11) | BSRBR (n = 38) | DANBIO (n = 85) | KOBIO (n = 3) |
|--------|------------------|----------------|-----------------|----------------|----------------|--------------|
| Country | US               | Japan          | Korea           | US             | Denmark        | Korea        |
| RA activity and remission | 28              | 3              | 1               | 4              | 14             | 1            |
| Disability and quality of life | 2               | 9              | 2               | 0              | 11             | 0            |
| Comparative effectiveness | 5               | 0              | 1               | 4              | 1              | 0            |
| Comorbidity | 12            | 11             | 2               | 4              | 8              | 0            |
| Patient-reported outcomes | 3               | 0              | 1               | 0              | 3              | 0            |
| Compliance | 1              | 0              | 0               | 0              | 3              | 0            |
| Drug effectiveness | 7               | 7              | 0               | 4              | 22             | 0            |
| Drug safety | 11             | 5              | 0               | 19             | 9              | 1            |
| Mortality | 1               | 2              | 0               | 1              | 0              | 0            |
| Other* | 12              | 11             | 4               | 6              | 15             | 1            |

RA, rheumatoid arthritis; CORRONA, Consortium of Rheumatology Researchers of North America; IORRA, Institute of Rheumatology and Rheumatoid Arthritis of Tokyo Women's Medical University; KORONA, Korean Observational Study Network for Arthritis; BSRBR, British Society for Rheumatology Biologics Register; DANBIO, nationwide registry of biological therapies in Denmark; KOBIO, Korean nationwide Biologics.

*Others: description of the database, descriptive or validation study, methodologic issues, economic analysis, medical accessibility, or pathogenesis.
much greater attention to PRO as the main outcome is one of the significant shifts in clinical research. It is important for physicians to consider the condition of patients outside the hospital, because judging patients’ condition on the basis of single hospital visits may lead to inconsistency between physicians’ and patients’ disease assessments. From this perspective, remote technology-based monitoring systems for PRO are being highlighted in the US and Europe. Such systems can also provide important data that can be integrated into patients’ health records [6,56]. Data are vital for advancing knowledge, and technology has the potential to transform the data we can collect about RA and how it is presented to advance care [63]. In this regard, collaborative studies among national databases and data linkage within individual nations [64] can be crucial. They are now paying great attention to applying databases of patient medical records and laboratory and imaging results not only for research but also for machine learning and ‘artificial intelligence.’ Thus complex clinical data are becoming more meaningful and relevant to decision making in clinical practice. Furthermore, tailored medicine and drug repositioning can also become possible through plentiful clinical studies combined with genetic information on individual patients. In addition, these studies will be useful in preventive research through the study of risk factors and of aggravating factors in the early stages of RA.

**CONCLUSIONS**

In recent decades, enormous prospective RA cohorts and registries have been developed and have generated information about disease activity in patients, disability, and the safety of treatments. These studies have improved the course of disease and contributed significantly to establishing safe and effective treatment strategies. Recently, there has been a gradual shift to PRO and specific comorbidities as the major outcomes of clinical research using cohort databases. In addition, big database that include PRO based on reports from outside the hospital environment as well as wide spectrum clinical information can be put to use in decision making in clinical practice.

In accordance with these changes, efforts to loosen the boundary between PRO in cohort data and electronic medical records and to share information more widely are needed. In this way patient-physician communication and the decision making process will be improved, and should lead to better disease outcomes in RA patients.

**Conflict of interest**

No potential conflict of interest relevant to this article was reported.

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