Rheumatoid arthritis registries in Sweden

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ABSTRACT

Patient registries provide valuable contributions to the field of rheumatology for both quality control and scientific purposes. With respect to the latter, patient registries are among the most important datasets used for longitudinal observational studies in rheumatic diseases, which are in turn an essential complement to data obtained from randomized, controlled trials.

In Sweden a number of registries are available for such studies, ranging from general medical registries such as the in-patient registry, to rheumatoid arthritis (RA)-specific inception cohorts and biologics registries focusing on a specific patient population defined by a group of treatments. In recent years it has become particularly clear that questions regarding new therapies, their use in practice and their long-term safety, as well as aspects such as pharmacoeconomics, cannot fully be assessed using the data from clinical trials, and that registries are indispensible to obtain accurate answers to such questions.

In this review we describe the Swedish rheumatology registries, including the Swedish RA registry and the Swedish biologics registries ARTIS (Antirheumatic Therapies Iin Sweden), SSATG (Southern Sweden Antirheumatic Therapy Group), and STURE (Stockholm Tumor Necrosis Factor-a Follow-up Registry). Data obtained from analyses based on these registries are reviewed.

It is concluded that rheumatology registries are excellent tools for improving our knowledge base regarding rheumatic diseases.

Scientific rationale: The case for registries as the basis of longitudinal observational studies

Randomized, placebo-controlled clinical trials (RCTs) are arguably the most scientifically sound method of addressing specific clinical questions relating to therapy. In recent years it has become almost axiomatic to equate "evidence-based medicine" with medical decision-making based on the results of RCTs. However, it has also been recognized that RCTs possess inherent limitations (1, 2). Thus, RCTs by their very nature primarily address one specific question, the primary endpoint of the study. For instance, the primary endpoint of ATTRACT (Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis (RA) with Concomitant Therapy) was achieving the ACR20 improvement criterion at 30-weeks of follow-up, and the trial successfully showed that giving infliximab as combination therapy to patients with partial or no response to methotrexate (MTX) enabled significantly more patients to achieve ACR20 than giving placebo + MTX (3). However, there are many more questions one would like to ask, such as: What about patients who have favorable response to methotrexate ? Who benefits from infliximab?

- Is therapy with infliximab able to maintain such a positive response over longer periods of time?
- Do patients with early-onset RA achieve the same, or even better results?
- Does the dosage of infliximab matter?
- Is the background use of MTX necessary, and if so, could it be replaced by other immunosuppressive medications?

Some of these additional questions were addressed by secondary endpoints within the same trial (4). However, while secondary endpoints provide valuable information and carry a certain amount of weight, they do not have the same level of reliability or validity as the primary endpoint. Some of the other important questions above were not featured as secondary endpoints, although some inferences can still be made in a *post hoc* analysis. For example, post hoc analyses for ATTRACT have been published by St Clair *et al*. (5) with regard to different dosage and frequency combinations of infliximab, and by Breedveld *et al*. (6) addressing

the question of early RA. Furthermore, some questions that could be asked about a given therapy are not addressed at all in the design of RCTs such as, for example, in ATTRACT the question of other immunosuppressives.

RCTs have also been criticized on the grounds of restrictive inclusion and exclusion criteria. A recent study showed that only 4.1% of patients in a typical rheumatology practice would have been able to participate in RAtrials (7). Similar results were seen in a Swedish cohort (8). This observation raises concerns about the generalizability of RCT results; how can we be certain that treating the vast majority of our patients will provide similar results as those from RCTs ?

Another important concern is that RCTs deal with the means of observations, treating patients in groups rather than as individuals. When studying the effects of a drug on a clearly defined, single disease entity with a "gold standard" for measurement (such as hypertension) this is probably not a concern, but when dealing with rheumatic diseases we may in fact be treating groups of clinical syndromes that meet similar criteria, but which may have different pathophysiologies, and clinical features.

Longitudinal observational studies (LOS) avoid some of the problems associated with RCTs. The basic idea of LOS is to systematically follow cohorts of patients who are allowed to behave as patients do in real life and who are being treated in the same way that their own physicians would treat them. Interventions are not prescribed, but measurements are made in a systematic and – hopefully – thorough and scientific manner. LOS allow researchers to address a wide range of issues, not only regarding therapeutic efficacy and safety, but also the everyday use of medications, complex interactions, pharmacoeconomics, quality of life, and so on. Thus, LOS can simultaneously address many questions, all patients can be included, and there is no demand to treat the results at the group level (although this is, of course, done as well). The main advantages and disadvantages of RCTs and LOS are listed in Table I.

Table I. The pro's and con's of randomized controlled trials and longitudinal observational studies.

Randomized controlled trials	Longitudinal observational studies
Pro's • Experimental design allows for maximal control over variables that may differ between groups • Primary analysis is relatively straightforward	Pro's • Mirrors "real-life" situation • All patients can be included – generalizable results • Multiple questions can be addressed • Affordable
Con's • Limited generalizability • Limited number of questions addressed • Expensive • Often address short-term changes in performance (of surrogate measures) when long-term outcome is more important in chronic diseases • Ill-suited to address rare or insidious side-effects • Study protocol may fix and limit dosages, thereby moving away from clinical practice • In typical RCTs group-level changes are measured in preference to individual variation	Con's • Observational design opens the way for more threats to a study's validity • More complex analyses may be required • Rapid changes in practice may decrease the relevance of the data

The principal limitation of LOS is that they do not match the level of scientific certainty that can be achieved by RCTs. For instance, when comparing the results obtained in clinical practice on two different medications, one of the most common reasons for misleading results is the fact that the treatments are given to different kinds of patients. This type of bias is always hard to circumvent completely, but several studies such as the Norfolk Arthritis Register (9,10) have suggested that a method called "propensity modeling" might lead to a greater degree of reliability (11).

Despite such methodological advances, LOS may never be able to unequivocally state that treatment A is superior to treatment B, simply because the treatments are never given prospectively to similarly defined patient groups. For example, the question as to whether etanercept is superior to hydroxychloroquine would be a very straightforward one to address in an RCT by randomizing patients to one or the other therapy over a given period of time. However, in an LOS this question could only be addressed if comparisons were made between patients receiving one or the other treatment while controlling for differences in the patient groups. Because hydroxychloroquine is generally perceived to be a relatively weak agent appropriate for patients with mild RA, while etanercept is perceived to be a strong agent appropriate for patients with moderate to severe RA, the differences between these patient groups is likely to be very substantial. It is possible that LOS would not be able to identify patients sufficiently similar in baseline characteristics to allow a meaningful comparison.

International examples of registries in the rheumatic diseases

One of the first large-scale registries was ARAMIS (the "American Rheumatism Association Medical Information System", later changed to the "Arthritis, Rheumatism, and Aging Medical Information System"), which was established at Stanford University (Stanford, CA, USA) in conjunction with several other centers (12,13) (see chapter in this supplement by Fries). The registry aimed to include all patients with rheumatic diseases at the participating clinics, and has in many ways served as the model for later efforts, having proved to be highly productive in terms of scientific output. The registry can be viewed as a 3-dimensional matrix of data points, with patients on the x-axis, the different observations made on each patient along the y-axis, and the time (t) represented by the third axis. Theoretically, this type of design

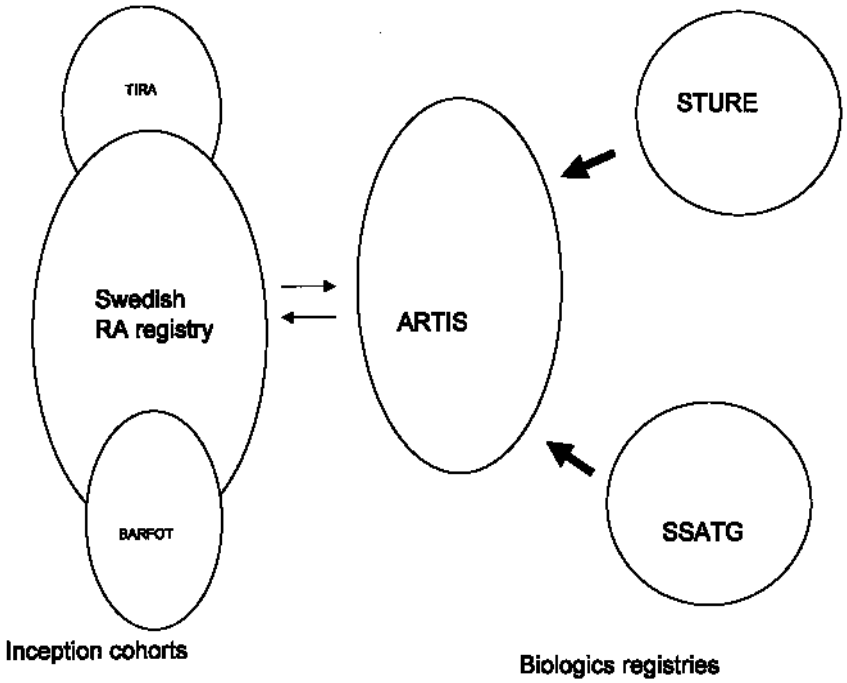

Fig. 1. An illustration of how the Swedish RA inception cohorts and registries for biological agents interrelate. TIRA (therapies in RA), BARFOT (better anti-rheumatic pharmacotherapy), and the Swedish RAregistry have been merged, creating a nation-wide inception cohort.
ARTIS: anti-rheumatic therapies in Sweden. STURE: Stockholm TNF-antagonist follow-up registry. SSATG: Southern Swedish anti-rheumatic therapies group. Both STURE and SSATG are regional registries that aim to include all rheumatological patients treated with biologicals. The data are processed and then submitted to the national registry ARTIS, but scientific analyses at the regional level have been very useful (23-26, 28).

would allow all of the data collected to be used. In recent years, ARAMIS has been extended with a post-marketing surveillance system that has been useful in evaluating drug toxicities (14).

A more recent initiative in the United States, originating from one of the original ARAMIS centers, is the National Data Bank of the Rheumatic Diseases led by Frederick Wolfe (15). This registry gathers information from patients in the form of questionnaires, and some of this information is cross-validated by physicians, or with hospital records and other data.

Some registries aim to include all patients with a given disease within a certain geographic area. A prime example of such an approach is the Norfolk Arthritis Register, which includes all patients with inflammatory polyarthritis in the area of the Norfolk Health Authority in the UK (16). Other registries have also been designed as inception cohorts, for example, the Swedish RA registry (17), which was begun in 1995 as a quality assurance instrument and whose target was to include any patient presenting to one of the participating centers with a diagnosis of RAwithin the preceding 2 years. Thus, patients with a first diagnosis of RA from 1993 onwards are included.

The number of participating centers in the Swedish RARegistry has increased over the years, during which the registry was merged with two similar registries in Sweden, BARFOT (Better Antirheumatic Pharmacotherapy) and TIRA (Therapies In RA). This has in effect resulted in a single inception cohort that covers almost all of Sweden. The decision to create an inception cohort was based primarily on practical considerations, and not including patients with disease onset prior to 1993 creates some limitations. Nonetheless, an inception cohort such as this allows researchers to address many important questions.

Biologics registries

In recent years, a number of registries have been established as a direct result of the considerable impact that biological agents have had on the treatment of RA and other inflammatory arthritides. Thus, in the US databases such as the CORRONA (Consortium of Rheumatology Researchers of North America) registry have been established (18), and the national rheumatology organizations in the United Kingdom (19), Spain (20), Italy (21), and Germany (22) have established similar registries for the systematic follow-up of patients being treated with biologics.

In 1999, when etanercept and infliximab were approved for use in the US, it became possible for Swedish rheumatologists to request a special license from the Swedish Medical Product Agency (MPA) to treat individual patients with these agents. The MPA, when granting these individual licenses (sometimes referred to as “use on a named patient basis”), requested in turn the undertaking of a thorough and systematic follow-up.

Patient demographics, baseline disease characteristics, prior use of disease-modifying antirheumatic drugs (DMARDs), and concurrent medications were all registered at the start of treatment. Systematic follow-up involved every patient returning after 3, 6, and 12 months, and every 6 months thereafter. Each visit was to include the ACR core set of RAoutcomes (swollen joint count, tender joint count, visual analogue scales for global health and pain), the health assessment questionnaire (HAQ), disability index, physician assessment of disease activity, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), medication record, employment status, and any adverse events.

In late 1999, biological agents were approved for use in Sweden, and therefore obtaining a license for their use was no longer required. Nonetheless, the MPA continued to request rheumatologists to provide the same data as before on all patients treated with these agents as a quality-control measure, with particular reference to the fact that the longer-term effects of these agents, despite the RCTs performed to date, remained incompletely understood. This national initiative, which has been

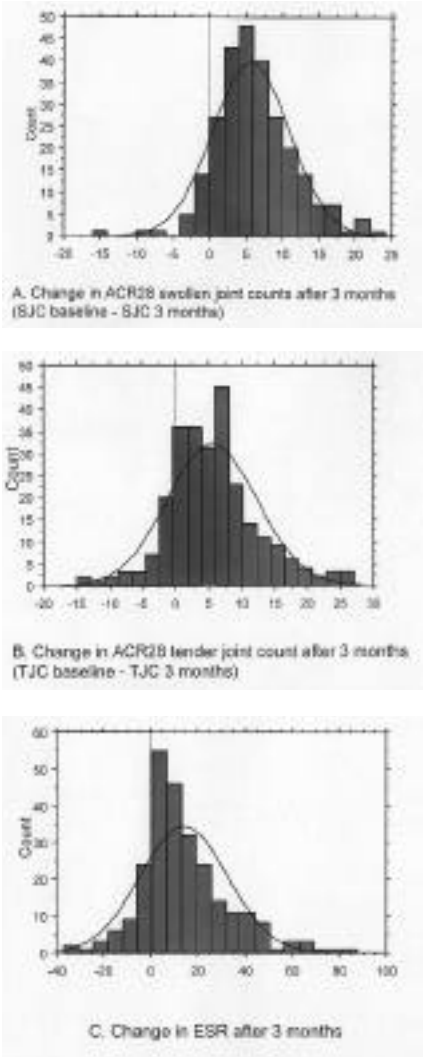

Fig. 2. Absolute changes in ACR core outcomes are normally distributed. The histograms show the distribution of absolute changes in: (**a**) 28-swollen joint counts, (**b**) 28-tender joint count, and (**c**) ESR, each calculated as (value at baseline) – (value at 3 months). The normal curve is computer-generated. Normally distributed histograms are seen without any suggestion of bimodality. Reproduced with permission from (25).

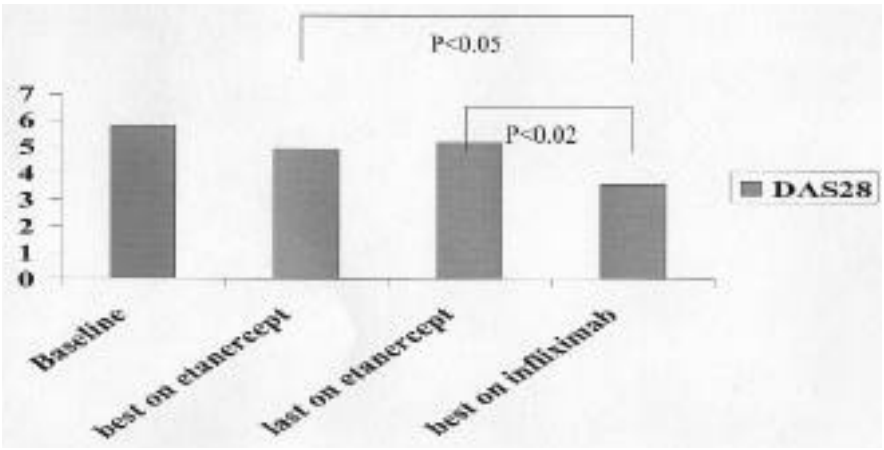

Fig. 3. Disease activity by DAS28 in patients treated first with etanercept, then with infliximab. Values shown are the mean value at baseline (prior to etanercept treatment), mean best value during etanercept therapy, mean value at last visit while on etanercept (when decision to switch was made), and mean best value on infliximab. Comparisons are by paired 2-tailed Student's t-test. Reproduced with permission from (28).

advocated by the large majority of practicing rheumatologists in Sweden, has since been named ARTIS (Antirheumatic Therapies in Sweden).

At the same time, some of the practical organizational aspects associated with the process of gathering the information involved in this registry had been established at a regional level. For instance, in the southern region of Sweden, all follow-up data collected was also gathered in the SSTAG (Southern Swedish Antirheumatic Therapy Group) registry, and, in the Stockholm region, STURE (Stockholm TNF-α Follow-up Registry). While the data gathered in these regional registries is entirely and simultaneously included in the ARTIS registry, it has nonetheless been possible to perform scientific analyses within the regional registries that, owing to economies of scale, were easier to carry out than in the national registry. The relationship between the various Swedish registries is illustrated in Figure 1.

One important function of biologics registries is quality control. In this respect, it is of considerable importance to determine the degree to which the use of biologics in RA is subject to "indication drift". Because the use of biologics in Sweden has been unrestricted, at least administratively, it could have been anticipated that an increasing number of patients with mild RA would be receiving these complex and expensive therapies. However, the databases do not show such a drift in indication; indeed, the level of disease activity for patients included in the first 4 years has remained essentially unchanged (unpublished observations). Nonetheless, a slight change toward the inclusion of patients with lower HAQ scores has been noted, and this could represent an intention to prevent functional loss with such therapies. It is important to point to a restrained and thoughtful use of biologics by practicing rheumatologists in discussions with health care administrators.

A second function of biologics registries is to allow for the detection of potential rare but serious long-term consequences of the use of biological therapies, including cancer, that might not be noticed in controlled clinical trials.

A third function is to provide raw data for analytic studies, a number of which have now been published based on these registries, each addressing a specific question of importance to clinicians and clinical investigators. For example, data from the SSATG regional registry have shown that etanercept or infliximab therapy is significantly better than leflunomide, a non-biologic agent that became available at almost the same time (23). Another study addressed the important question as to whether biologic treatments could result in gains with respect to the direct or indirect costs of RA, that might offset the high costs of the medications themselves (24). This recently published study showed that during the first year of biological therapy, patients underwent significantly fewer surgical operations, most notably fewer hip and knee replacement surgeries, than during the year prior to starting these therapies, resulting in considerable cost savings. It can be argued that these findings were an artifact of the patients preferentially having surgery before starting therapy with biologics. However, it has been shown that the abso-

lute number of operations during the first year after starting biologics was considerably less than the historical average for such patients.

The STURE registry has addressed a number of scientific questions relating to biological therapies. In an early study, the pattern of clinical responses to TNF-α blockers were analyzed. The reporting of clinical trial results have led to a perception that therapy with TNF-α blockers results in a clear distinction between responders and non-responders. However, an analysis of the STURE registry has shown that the responses in terms of any of the ACR core set measures of disease activity display normal (Fig. 2) or skewed distributions, without the appearance of bimodality suggested by the terms "responder" and "non-responder" (25). We have argued that these data have important implications for studies of the biological mechanisms underlying the degree of response to such therapies, and have significant bearing on the development of criteria according to which patients should or should not be allowed to (continue to) receive these agents.

In another study, we compared clinical responses to etanercept monotherapy versus combination therapy with MTX (26). Patients receiving the combination fared slightly better as a group, showing DAS28 values after 3-12 months of therapy that were lower than those in the monotherapy group. A more striking difference was seen in the number of patients achieving DAS-28 remission as defined by EULAR (European League Against Rheumatism). These data, which were obtained not from a controlled trial but from a longitudinal cohort, were confirmed in the large, multicenter TEMPO (Trial of Etanercept and MTX with Radiographic Patient Outcomes) study soon afterwards (27). Although the gains in disease control with combination therapy were small compared with monotherapy, the more impressive gains in the number of patients achieving remission suggested that efforts should be made to treat as many patients as possible with etanercept + MTX rather than with etanercept monotherapy.

We also analyzed the STURE registry to investigate whether patients who failed etanercept should switch to infliximab, or vice versa (28). One might expect that the treatment results would be roughly similar for both agents and that this would simply be a waste of time and expense. Nonetheless, in our patients who changed from one biologic to the other, we saw that treatment with infliximab was significantly better in patients who had discontinued etanercept due to lack of efficacy (Fig. 3), and that etanercept showed at least similar efficacy in patients who had to discontinue infliximab due to adverse events (28).

Safety studies utilizing other Swedish registries

Sweden has a long tradition of maintaining population-based registers, several of which have become important tools to study questions relating to the safety of biologics. Statistics Sweden maintains the Population Register, which provides data on all Swedish residents since 1961. The Cause of Death Register provides information on dates and cause(s) of death for all deceased residents since 1961.

The In-patient Register includes information on every discharge from in-patient care since 1964 (coverage became nationwide in 1987). For each discharge, information on discharge diagnoses and surgical procedures are coded according to the International Classification of Diseases (ICD). General and specific validation surveys suggest that almost 90% of the registered diagnoses are correct when compared to the available information in the medical records. Importantly, in the case of rheumatic diseases secondary diagnoses are registered, so that even diseases that only rarely result in hospital admissions (such as RA) are to a large extent represented in the registry because of patients having been admitted for other reasons (e.g., childbirth, other diseases, and surgery). RA patients identified within this register are referred to as the In-patient Register RA cohort.

The Swedish Cancer Register provides individual-based data on cancer occurrences since 1960. An outstandingly high reporting rate of diagnosed malignancies is maintained through a system of double (and mandatory) reporting by both clinicians and pathologists. Cancers are coded according to a classification system that is applied at their date of registration, but ever since the establishment of the register, cancers have also been coded according to a modified version of ICD-7, which thereby allows the comparison of longitudinal data.

An example of a study using data from various Swedish registries was recently presented (29). In this study, the incidence of malignant lymphomas and other malignancies in 4,160 RA-patients exposed to TNF-antagonists and followed up through 2003 (9,715 person–years, 9 lymphomas) was compared to that of the Early Arthritis cohort (3,703 incident RA–patients, 13,292 person-years, 11 lymphomas), and to that of the In-patient Register RA cohort (53,067 prevalent RA–patients, 297,102 person–years, 319 lymphomas). When these three cohorts were compared to each other, the TNF-antagonist cohort patients were at no risk or only a modestly increased lymphoma risk (relative risk = 1.1, 95% CI 0.6–2.1).

Conclusion

Biologicals registries have been demonstrated to be excellent tools for clinical rheumatology, not only to monitor quality, but also to conduct scientific research that deals with important questions concerning the treatment of patients with rheumatic diseases.

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