Rheumatoid arthritis databases in Finland

T. Sokka

Tuulikki Sokka, MD, PhD, Research Assistant Professor, Vanderbilt University, Nashville, Tennessee, USA, and Consultant Rheumatologist, Jyväskylä Central Hospital, 40620 Jyväskylä, Finland.

Please address correspondence and reprint requests to: Tuulikki Sokka, MD, PhD, Vanderbilt University / Rheumatology, 203 Oxford House, Nashville, TN 37232-4500, USA.
E-mail: tuulikki.sokka@vanderbilt.edu

Clin Exp Rheumatol 2005; 23 (Suppl. 39): S201-S204.

Key words: Database, rheumatology, rheumatoid arthritis, longitudinal observational studies.

ABSTRACT

A tradition exists in Finland of longitudinal studies to analyze the long-term outcomes of rheumatoid arthritis (RA), including early studies in the 1970s and 1980s of work disability and premature mortality in patients with RA and follow-up studies of early RA cohorts. This article reviews long-term observations from the Finnish RA Combination Therapy Trial (FIN-RACo), a 2-year multicenter randomized controlled trial which has been continued as a longitudinal observational study after the initial two years. We also describe the Central Finland RA Database, which captures most patients who have been diagnosed with RA since 1980 in a district of a quarter of a million people.

Introduction

Longitudinal observational studies are required to supplement clinical trials in order to analyze the long-term outcomes of patients with rheumatoid arthritis (RA). Clinical cohorts may include a limited number of patients, but over many years and even decades of follow-up fundamental observations emerge (1). Available computerized technology and standard measures, developed over the past two decades to document health status and outcomes of RA, provide a basis for data collection from large numbers of subjects to form RAdatabases.

The OMERACT (Outcome Measures in Rheumatology) IV Conference set guidelines for five domains to be included in longitudinal observational studies for RA: health status, disease process, joint damage, mortality, and toxicity/adverse reaction (2). Two additional domains, work disability and costs, were recognized as important but were not included in the "core" set of five domains. In addition, it is desirable that an RAdatabase be representative of the entire underlying patient population (3). RA data banks may be defined as "purposeful, organized, systematic data repositories driven by (usually) unwritten hypotheses or questions" (4).

Several clinical cohorts of patients with early RA have been established in Finland since the 1970s (5). The numbers of patients in these cohorts was limited, but careful and persistent long-term follow-up has proven the value of these cohorts (6). The first Finnish early RA cohort was the Rheumatism Foundation Hospital early RA Cohort (the Heinola Cohort) of 103 patients, established in Heinola in 1973-75. A 25-year follow-up of this cohort confirmed the severity of RAduring an era when only a limited number of treatment options were available (7,8). Other early RA cohorts in Finland were established in Helsinki (9) and Jyvaskyla (10-12). Studies of these cohorts have indicated more favorable long-term outcomes in recent years (13). These clinical cohorts are not described in detail in this essay, but are noted here as background for further detailed description of the Finnish RA Combination Therapy Trial, termed the FIN-RACo study (14), and the Central Finland RADatabase.

The FIN-RACo trial and 5-year outcomes

The FIN-RACo study (14) enrolled 195 patients with early RA in 18 Finnish rheumatology clinics in 1993-1995. The patients were randomized to two treatment arms for two years: 97 received the combination of methotrexate (MTX), sulfasalazine (SSZ), hydroxyhloroquine (HCQ), and prednisolone, while 98 received single-drug therapy with SSZ (with or without prednisolone), with MTX later substituted in 51 patients.

The primary outcome measure in the FIN-RACo study was remission, defined as no tender and no swollen joints, morning stiffness <15 minutes, no pain, and a normal erythrocyte sedimentation rate (ESR). Compared to the ACR criteria, fatigue was excluded, but the patient had to meet all 5/5 criteria in the FIN-RACo study to be considered in re-

mission, while the ACR remission criteria require 5/6. Applying these strict criteria, the frequency of remission was 37% in the combination group, and 18% in the single-drug group at two years ($p = 0.003$) (14).

Analyses of delay in treatment are of considerable interest. In the combination group, the frequency of remission was similar in patients with short (0-4 months) and long delays (>4 months) in the institution of therapy. However, in the single-drug group, 35% of patients with a short delay (0-4 months) were in remission at two years compared to only 11% in patients with a long delay (> 4 months) ($p = 0.021$).

The 5-year outcomes of radiographic scores and work disability favored early combination treatments, although therapies were at physicians'discretion after two years. After 5 years, the median Larsen score was 11 in the initial combination group versus 24 in the single-drug group ($p < 0.01$) (15).

Patients in the initial combination group were more likely to maintain their capacity to continue paid employment over 5 years compared to patients in the single-drug group (16). Furthermore, 54% of patients who did not have ACR 20% responses over 6 months became permanently work disabled over five years, compared to 22% of those who had ACR 20% or 50% responses. If inflammation was controlled to a status of remission at 6 months, no patient was receiving work disability payments at 5 years (17, 18). This observation indicates that improvement rates of ACR 20% or 50% appear to be sub-optimal goals for therapies in patients with early RA.

The Central Finland RADatabase

Jyväskylä Central Hospital is the only rheumatology center in the Central Finland District and serves a population of 264.000 (19). All new patients with RA are referred to this center for diagnostic studies and the initiation of therapy.

The Central Finland RA database was established in the mid 1990s, and began enrolling patients prospectively in January 1997. Therefore, all patients with early RA since 1997 are included in the database; more than 100 patients with early RA are enrolled every year. Data concerning most patients with RA from 1980 to 1997 were collected retrospectively using hospital databases to identify patients with RA, and these have also been entered into the database. More than 2.500 patients with RA are included in the database as of 2005.

The database includes demographic variables, year of symptom onset, date of diagnosis, laboratory tests, and questionnaire scores (joint counts are included in the prospective subset of patients) prior to the initiation of therapies. The date of initiation and discontinuation of each disease-modifying anti-rheumatic drug (DMARD) or combination of DMARDs is recorded; reasons for discontinuation are classified as inefficacy, adverse events, remission, improved status, and other reasons. Data concerning functional capacity according to the Health Assessment Questionnaire (HAQ) and laboratory tests are entered in a time-oriented database. Comorbidities, extra-articular manifestations, radiographic erosions, rheumatoid factor status, orthopedic surgery, work status, and vital status are recorded.

A research assistant updates the database daily with data collected at clinic visits. Further data have also been collected by annual mailed self-report questionnaires since 1998 with a response rate of 71-73% (19).

To utilize the RA database more extensively, 2,000 age- and sex-matched subjects were randomly selected from the general population of Central Finland. These people were mailed in 2000 and 2005 a self-report questionnaire similar to the one mailed to patients in the RAdatabase.

The Central Finland RA Database constitutes a component of the official hospital records, compiling clinically relevant information concerning the course of the disease, comorbidities, and DMARD therapies on one summary sheet, to be utilized in clinical care. The other objective of the database is to collect data for scientific research.

Some observations which have emerged from the Central Finland RA Database are reviewed below.

Disability in patients with RA compared to the community population. Results of a mailed questionnaire which included the HAQ, pain, education level, comorbidities, height, weight, smoking, and exercise habits in 1.095 patients with RA identified in the Central Finland RA Database were compared to 1.533 age- and sex-matched subjects in the general population in a cross-sectional analysis in June 2000. Although the HAQ has been used in clinical trials in clinical research for more than 20 years in numerous countries, this was the first study that compared the HAQ scores in patients with RA to those of the general population including all age groups (19), and the first to benchmark disability according to the HAQ in the general population (20).

The HAQ is a strong predictor of mortality in the general population. It was reported in 1984 (1) and has been repeatedly confirmed that functional status is a powerful predictor of mortality in RA(21). A study of patients with RA and individuals matched for age and sex in the general population indicated that people with higher levels of disability according to the HAQ have a higher likelihood of mortality over two years (22). This observation adds to the increasing body of data concerning the importance of functional status as a predictor of mortality in general. Patient functional status has been reported to predict mortality in patients with congestive heart failure as strongly as the ejection fraction on cardiac catherization (23) and in patients with AIDS as strongly as T4/T8 lymphocyte ratios (24, 25).

Non-response as a cause of possible bias in mail surveys. The use of mailed questionnaires has become widely incorporated into longitudinal observational clinical research. Possible non-response bias may affect the results, but has not been addressed extensively in the rheumatology literature. We found that non-responders to mailed surveys were two to three times more likely to die over the following two years compared to the responders (26). This observation should be borne in mind in the interpretation of studies that collect mail survey data only.

Smoking and RA. Smoking is a risk factor for RA, and a specific association has been reported between smoking and rheumatoid factor-positive RA (27). Current and past smoking status was queried in the self-report questionnaire that was mailed to patients with RAand controls in 2000 (28). A past smoking history was associated with a 2.3-fold higher risk of rheumatoid factor-positive RAin men, but such an association was not seen in women (28).

Frequency of remissions using different criteria. The remission rate in the prospective part of the RA database in patients with early RA since 1997 was 17% according to the ACR remission criteria (31) in a 5-year follow-up (29, 30). Clinical remission criteria were defined as no tender and no swollen joints and a normal ESR, according to which 37% of the patients were in remission. These data suggest that ACR remission criteria may actually exclude a proportion of patients who are in clinical remission (29). The criterion of having "no joint pain" (VAS < 10 mm on a 100 mm pain visual analog scale) may lead to misclassification, as musculoskeletal pain is common in the general population (32) (see Pain Chapter in this Supplement). The estimated average level of pain was 20 on a 100 mm VAS in the population sample from Central Finland (33). Therefore, it appears that a score for pain of 10–25 mm on a 100 mm VAS may indicate a "normal" score for pain in an actual patient > 55 years of age.

It was observed that a 28-joint disease activity score (DAS28) of less than 2.6 might be too liberal to detect remission. A substantial proportion of patients who met this criterion, proposed as the DAS28 cutoff value for remission, had tender and/or swollen joints. Overall, 7-9% of patients had tender or swollen joints on a 28-joint count and 3-4% had both tender and swollen joints. The corresponding percentages using a 68-joint count were 8-24% and 6-7% (30).

Yttrium radiosynovectomy and risk of cancer. The long-term risk of cancer was studied in patients with RA who had been treated with yttrium for knee synovectomy in Jyvaskyla Central Hospital during the period 1970-1985. The incidence of cancer was not increased after yttrium treatment over a period of 30 years (34).

Avision of a uniform database

No existing RA database meets criteria for a "perfect" longitudinal observational study, nor will that ever be achieved. However, regardless of the extent of the database in terms of the number of patients, the data collected, or the broadness of the goals, any longitudinal observational study has the potential to provide clinically important information concerning long-term outcomes of RAto supplement the data from randomized clinical trials.

A common feature of longitudinal databases is the unflagging enthusiasm of the initiators of these databases and their indefatigable belief in the genuine importance of long-term data collection to improve the long-term outcomes of patients with RAand to document changes over time. Available computerized technology and standard measures developed over the past two decades to document the health status and outcomes of RAprovide a baseline that could be used by all rheumatologists for uniform data collection. Although the observations emerging from individual databases are valuable, standardized data collected world-wide in rheumatology clinics would provide a strong platform for "evidence-based" rheumatology.

Acknowledgments

The author would like to acknowledge Dr. Theodore Pincus for his helpful comments.

References

1. PINCUS T, CALLAHAN LF, SALE WG, BROOKS AL, PAYNE LE, VAUGHN WK: Severe functional declines, work disability, and increased mortality in seventy-five rheumatoid arthritis patients studied over nine years. *Arthritis Rheum* 1984; 27: 864-72.
2. WOLFE F, LASSERE M, VAN DER HEIJDE D *et al.*: Preliminary core set of domains and reporting requirements for longitudinal observational studies in rheumatology. Omeract IV: Outcome measures in rheumatology. Cancun, Mexico, April 16-20, 1998. *J Rheumatol* 1999; 26: 484-9.
3. KVIEN TK, UHLIG T: The Oslo experience with arthritis registries. *Clin Exp Rheumatol* 2003; 21: S118-S122.
4. Dr. Frederick Wolfe, personal communication, 2004.
5. SOKKA T: Early rheumatoid arthritis in Finland. *Clin Exp Rheumatol* 2003; 21: S133-S137.
6. SOKKA T, HANNONEN P, MOTTONEN T: Conventional DMARDs in early arthritis. *Rheum Dis Clin North Am* (in press).
7. JANTTI JK, KAARELA K, BELT EA, KAUTIAINEN HJ: Incidence of severe outcome in rheumatoid arthritis during 20 years. *J Rheumatol* 2002; 29: 688-92.
8. PALM TM, KAARELA K, HAKALA MS, KAUTIAINEN HJ, KROGER HPJ, BELT EA: Need and sequence of large joint replacements in rheumatoid arthritis. A 25-year follow-up study. *Clin Exp Rheumatol* 2002; 20: 392-4.
9. PELTOMAAR, LEIRISALO-REPO M, HELVE T, PAIMELA L: Effect of age on 3 year outcome in early rheumatoid arthritis. *J Rheumatol* 2000; 27: 638-43.
10. MÖTTÖNEN TT: Prediction of erosiveness and rate of development of new erosions in early rheumatoid arthritis. *Ann Rheum Dis* 1988; 47:648-53.
11. HANNONEN P, MÖTTÖNEN T, HAKOLA M, OKA M: Sulfasalazine in early rheumatoid arthritis. *Arthritis Rheum* 1993; 36: 1501-9.
12. SOKKA T, MÖTTÖNEN T, HANNONEN P: Disease-modifying anti-rheumatic drug use according to the 'sawtooth'treatment strategy improves the functional outcome in rheumatoid arthritis: Results of a long-term follow-up study with review of the literature. *Rheumatology* 2000; 39: 34-42.
13. SOKKA T, KAUTIAINEN H, HÄKKINEN K, HANNONEN P: Radiographic progression is getting milder in patients with early rheumatoid arthritis. Results of 3 cohorts over 5 years. *J Rheumatol* 2004; 31: 1073-82.
14. MÖTTÖNEN T, HANNONEN P, LEIRISALO-REPO M *et al.*: Comparison of combination therapy with single-drug therapy in early rheumatoid arthritis: A randomised trial. FIN-RACo trial group. *Lancet* 1999; 353: 1568-73.
15. KORPELA M, LAASONEN L, HANNONEN P *et al.*: Retardation of joint damage in patients with early rheumatoid arthritis by initial aggressive treatment with disease-modifying antirheumatic drugs: five-year experience from the FIN-RACo study. *Arthritis Rheum* 2004; 50: 2072-81.
16. PUOLAKKA K, KAUTIAINEN H, MÖTTÖNEN T *et al.*: Impact of initial aggressive drug treatment with a combination of disease-modifying antirheumatic drugs on the development of work disability in early rheumatoid arthritis. A five-year randomized followup trial. *Arthritis Rheum* 2004; 50: 55-62.
17. PUOLAKKA K, KAUTIAINEN H, MÖTTÖNEN T *et al*.: Predictors of productivity loss in early rheumatoid arthritis: a 5 year follow up study. *Ann Rheum Dis* 2005; 64: 130-3.
18. PUOLAKKA K, KAUTIAINEN H, MÖTTÖNEN T, HANNONEN P, KORPELA M: Early suppression of disease activity is essential for maintenance of work capacity in patients with recent-onset rheumatoid arthritis: five-year experience from the FIN-RACo trial. *Arthritis Rheum* 2005; 52: 36-41.
19. SOKKA T, KRISHNAN E, HÄKKINEN A, HANNONEN P: Functional disability in rheu-

matoid arthritis patients compared with a community population in Finland. *Arthritis Rheum* 2003; 48: 59-63.

20. KRISHNAN E, SOKKA T, HÄKKINEN A, HUBERT H, HANNONEN P: Normative values for the Health Assessment Questionnaire disability index: benchmarking disability in the general population. *Arthritis Rheum* 2004; 50: 953-60.
21. PINCUS T, SOKKA T: Quantitative target values of predictors of mortality in rheumatoid arthritis as possible goals for therapeutic interventions: an alternative approach to remission or ACR20 responses? *J Rheumatol* 2001; 28: 1723-34.
22. SOKKA T, HÄKKINEN A, KRISHNAN E, HANNONEN P: Similar prediction of mortality by the health assessment questionnaire in patients with rheumatoid arthritis and the general population. *Ann Rheum Dis* 2004; 63: 494-7.
23. KONSTAM V, SALEM D, POULEUR H *et al.*: Baseline quality of life as a predictor of mortality and hospitalization in 5,025 patients with congestive heart failure. *Am J Cardiol* 1996; 78: 890-5.
24. JUSTICE AC, AIKEN LH, SMITH HL, TURNER BJ: The role of functional status in predicating inpatient mortality with AIDS: A comparison with current predictors. *J Clin Epidemiol* 1996; 49: 193-201.
25. CUNNINGHAM WE, CRYSTAL S, BOZZETTE S, HAYS RD: The association of health-related quality of life with survival among persons with HIVinfection in the United States. *J Gen Intern Med* 2005; 20: 21-7.
26. KAUPPI M, SOKKA T, HANNONEN P: Survey nonresponse is associated with increased mortality in patients with rheumatoid arthritis and in a community population. *J Rheumatol* 2005; 32: 807-10.
27. HELIÖVAARA M, AHO K, AROMAA A, KNEKT P, REUNANEN A: Smoking and risk of rheumatoid arthritis. *J Rheumatol* 1993; 20: 1830-5.
28. KRISHNAN E, SOKKA T, HANNONEN P: Smoking-gender interaction and risk for rheumatoid arthritis. *Arthritis Res Ther* 2003; 5: R158-R162.
29. MÄKINEN H, KAUTIAINEN H, HANNONEN P, SOKKA T: Frequency of remissions in early rheumatoid arthritis defined by 3 sets of criteria. A 5-year follow-up study. *J Rheumatol* 2005; 32: 796-800.
30. MÄKINEN H, KAUTIAINEN H, HANNONEN P, SOKKA T: Is DAS28 an appropriate tool to assess remission in rheumatoid arthritis? *Ann Rheum Dis* 2005.
31. PINALS RS, MASI AT, LARSEN RA *et al.*: Preliminary criteria for clinical remission in rheumatoid arthritis. *Arthritis Rheum* 1981; 24: 1308-15.
32. HARKNESS EF, MACFARLANE GJ, SILMAN AJ, MCBETH J: Is musculoskeletal pain more common now than 40 years ago ? Two population-based cross-sectional studies. *Rheumatology (Oxford)* 2005; 44: 890-5.
33. KRISHNAN E, HÄKKINIEN A, SOKKA T, HANNONEN P: Impact of age and comorbidities on the criteria for remission and response in rheumatoid arthritis. *Ann Rheum Dis* 2005; 64: 1350-2 (E-pub 2005 March 10).
34. VUORELA J, SOKKA T, PUKKALA E, HANNONEN P: Does Yttrium radiosynovectomy increase the risk of cancer in patients with rheumatoid arthritis ? *Ann Rheum Dis* 2003; 62: 251-3.