An Early Rheumatoid Arthritis Treatment Evaluation Registry (ERATER) in the United States

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ABSTRACT

An Early Rheumatoid Arthritis Treatment Evaluation Registry (ERATER) was established in 2001 to enroll patients with a disease duration of 3 years or less, in order to analyze treatment patterns in an era of biological therapies and to study the long-term outcomes of rheumatoid arthritis (RA). Patients were assessed at baseline according to a standard protocol to evaluate their rheumatoid arthritis (SPERA). Similar data from earlier cohorts with RAin the same community will allow for comparisons with treatments and outcomes from previous decades. This essay describes the background regarding the identification of the cohort, methods for data collection, and observations to date.

Introduction

Most early rheumatoid arthritis (RA) databases have been established outside the USA. In the US, a database of the Western Consortium of Practicing Rheumatologists (CPR) was created in 1993 to enroll patients with an RA duration of less than one year, positive rheumatoid factor, 6 or more swollen and 9 or more tender joints, and no previous treatment with disease-modifying anti-rheumatic drugs (DMARDs) (1). The aim of the North American Cohort of Patients with Early RA (SONORA) is to examine genetic predictors for outcomes in patients with early RAover 5 years (2). The Consortium for the Longitudinal Evaluation of African-Americans with RA (CLEAR) registry is enrolling African-American patients with early RA for a 5-year prospective study (3).

An Early RA Treatment Evaluation Registry (ERATER) was established in Nashville, Tennessee in 2001 to enroll patients with disease for 3 years or less, with no other exclusion criteria. Patients were assessed at baseline according to a standard protocol to evaluate their rheumatoid arthritis (SPERA) (4). Similar data from earlier cohorts with RA in the same community will allow for comparisons with treatments and outcomes from previous decades.

Early RATreatment Evaluation Registry (ERATER)

Between February 2001 and August 2004, 452 patients with early RA for less than 3 years were enrolled in the ERATER study in Nashville, Tennessee (5), including 336 patients from a private practice of Arthritis Specialists of Nashville, 48 from Vanderbilt University Rheumatology Clinics, and 68 from other sites. The ERATER program has also been adapted in Brooklyn, New York and Burlington, Massachusetts with about 100 patients at each of these sites (6).

Why study the long-term outcomes of RA?

The primary objective of the ERATER study is to evaluate the long-term outcomes of early RA at the present time, when potent new DMARDs including biological agents are available, and to compare these results to previous cohorts. These goals require that observations be made 5-10 years after disease onset. Several studies have indicated that measures of activity may be improved over the first years while progression of joint damage may be seen in radiographs, joint deformity and measures of functional status (7-17). Such damage is most apparent in cohorts with the longest follow-up. In earlier decades, only 10-20% of patients with RA had favorable outcomes 15-20 years after.

Several long-term observational studies have suggested that patients with RAhave enjoy better status at this time compared to previous decades, based on the Ritchie articular index (18), functional capacity (19,20), radiographic scores (21, 22), and several clinical measures (23,24), including lower mortality rates in patients who responded

to methotrexate (25, 26). It should be noted that almost all of these patients were treated prior to the availability of anti-tumor necrosis factor (TNF) agents. Furthermore, some studies suggest that the rates of joint replacement surgery have decreased in recent years in patients with RA (27-29). Improved outcomes have been associated with more active treatment strategies and the wider use of methotrexate. Availability of more powerful treatments and the implementation of more aggressive treatment strategies may lead to further improvement in long-term outcomes that can be studied by means of the ERATER database in the future. While the ERATER database has been established to serve as a baseline for the analysis of long-term outcomes, cross-sectional studies of the baseline data have been informative concerning RA at this time, as reviewed later in this essay.

No exclusion criteria

The only entry criterion for the ERATER study is early disease of less than 3 years' duration. Therefore, the ERATER study differs from many other RA databases, which often require a certain level of disease activity, certain therapies, or other selection criteria. Furthermore, many early RA studies require DMARD naïve patients. The ERATER study enrolled patients with RA of less than 3 years regardless of their prior medications. Information concerning all prior medications is collected from medical records and carefully reviewed with the patients prior to their entry into the database. With no strict exclusion criteria imposed, the ERATER database is designed to provide generalizable data reflecting routine rheumatology care.

Data collection

Patients were evaluated according to a standard protocol to evaluate rheumatoid arthritis (SPERA) (4), which includes four one-page questionnaires, 3 completed by a physician or assessor and one completed by the patient:

A. Assessor questionnaires

1. Clinical features – Classification criteria, comorbidities, extra-articular manifestations, surgeries, laboratory results, and work status.
2. All medications used for RA.
3. A 42-joint count which includes 10 proximal interphalangeal (PIP) and 10 metacarpophalangeal (MCP) joints of the hand, 2 wrists, 2 elbows, 2 shoulders, 2 hips, 2 knees, 2 ankles and 10 metatarsophalangeal (MTP) joints. All joints are scored for tenderness, swelling (except hips and shoulders), limited motion, and surgery, with a space to indicate that a joint is normal.

B. Patient questionnaires

4. A patient self-report Multi-Dimensional Health Assessment Questionnaire (MDHAQ) including the modified Health Assessment Questionnaire (MHAQ) for functional capacity, visual analog scales to assess pain, global health, and fatigue, minutes of morning stiffness, and symptom list (30). The MDHAQ is completed at each visit to the rheumatologist as well as twice a year by mail.

   (The SPERA protocol is presented in detail elsewhere in this Supplement.)

Reports concerning the EARTER database

DMARDs used in the ERATER Cohort. Data concerning the first 232 ERATER patients were analyzed to determine which DMARDs were used in early RA in standard clinical care (Table I) (5). Methotrexate (MTX) was the first DMARD used in 192 patients (82.8%), in 3 of whom in combination therapy. During the first year of drug treatment, 89.2% of the patients had taken MTX, 15.9% hydroxychloroquine (HCQ), 3.9% sulfasalazine (SSZ), 22.0% leflunomide, 9.5% etanercept, 4.3% infliximab, and 87.0% prednisone. Thus, MTX appeared to be the anchor drug taken by almost 90% of patients during the first year, while 30% took leflunomide, etanercept, or infliximab, usually in combination with MTX (5, 31).

Eligibility of patients in routine care for contemporary clinical trials of biological agents in RA. Data concerning the 232 first patients in the ERATER database were analyzed to identify the proportion of patients who met criteria for inclusion in the early rheumatoid arthritis (ERA) clinical trial of etanercept versus MTX (32,33). Only 16% of all patients met inclusion criteria for this clinical trial (Table II) (34). In another report, it was observed that only 34% of ERATER patients met four of the common criteria for inclusion in RA clinical trials, i.e. 6 or more swollen joints, 6 or more tender joints, a erythrocyte sedimentation rate of 28 or more, and/or morning stiffness of 45 minutes or more (35). Inclusion criteria for RA clinical trials have hardly changed over the last 20 years, despite evidence of a better status of many patients at this time than in previous decades (23). It appears that re-examination of inclusion criteria might be of value, as data in recent RA clinical trials may not be generalizable (35).

Morning stiffness in patients with early RA. Morning stiffness is included as a marker of inflammatory activity in classification criteria for RA, in inclusion criteria for most clinical trials in RA, and in RAremission criteria. Analyses of the ERATER cohort call attention for reassessment of the role of morning stiffness in these criteria (36).

Coronary artery atherosclerosis in RA. A subset of patients from the ERATER study was enrolled to review risk factors for coronary artery disease, including electron-beam computed tomography to assess the extent of coronary artery calcification (37). Three groups were included in the study: patients with early RA (mostly from the ERATER study), patients with long-standing RA, and healthy controls. The extent of coronary artery calcification was greatest in patients with long-standing RA. Among patients with RA, smoking and an elevated erythrocyte sedimentation rate were associated with more severe coronary artery calcification, while many known risk factors such as elevated blood pressure or the serum lipid profile were not significant in multivariable analyses (37). This study indicates that coronary artery calcification is substantially increased in patients with long-standing RA, but not in patients with early RA.

Work disability in early RA in Nashville, TN, and in Jyvaskyla, Finland.

Table I. Percentage of patients taking DMARDs in a cohort of 232 patients with recent onset rheumatoid arthritis in the Early Rheumatoid Arthritis Treatment Evaluation Registry (ERATER).

DMARD	No. (%) of pts. taking as their 1st DMARD	No. (%) of pts. taking DMARD at study entry	No. (%) of pts. who had ever taken this drug alone or in combination
MTX only	189 (81.5%)	130 (56.0%)	207 (89.2%)
HCQ only	15 (6.5%)	4 (1.7%)	37 (15.9%)
SSZ only	2 (0.9%)	1 (0.4%)	9 (3.9%)
LEF only	6 (2.6%)	14 (6.0%)	51 (22.0%)
ETAN only	0	2 (0.9%)	22 (9.5%)
INFLIX only	0	1 (0.4%)	10 (4.3%)
MTX + HCQ and/or SSZ	2 (0.9%)	16 (6.9%)	
MTX + LEF	0	20 (8.6%)	
MTX + ETAN	1 (0.4%)	8 (3.4%)	
MTX + ETAN + HCQ	0	3 (1.3%)	
MTX + INFLIX	0	8 (3.4%)	
LEF + ETAN	0	3 (1.3%)	
Other DMARDs	0	1 (0.4%)	
No DMARDs	17 (7.3%)	21 (9.1%)	

DMARD: disease-modifying anti-rheumatic drug; MTX: methotrexate; HCQ: hydroxychloroquine; SSZ: sulfasalazine; LEF: leflunomide; ETAN: etanercept; INFLIX: infliximab. Source: (5).

Table II. Analysis of patients who met criteria for inclusion in early rheumatoid arthritis (ERA) clinical trial, according to therapies taken in patients enrolled in the Early Rheumatoid Arthritis Treatment Evaluation Registry (ERATER).

	No. of patients	≥ 12 tender joints & ≥ 10 swollen joints	Positive Rh factor or radiographic erosions	Morning stiffness ≥ 45 minutes or ESR ≥ 28 mm/hr
No prior methotrexate, first visit	19	10 (53%)	8 (42%)	8 (42%)
No prior methotrexate, not first visit	17	3 (18%)	3 (18%)	3 (18%)
No prior methotrexate, any visit	36	13 (36%)	11 (31%)	11 (31%)
Prior methotrexate	135	25 (19%)	20 (15%)	17 (13%)
Prior leflunomide, etanercept, infliximab (± methotrexate)	61	10 (16%)	10 (16%)	9 (15%)
Prior methotrexate, leflunomide, etanercept or infliximab	196	35 (18%)	30 (15%)	26 (13%)
All patients	232	48 (21%)	41 (18%)	37 (16%)

Source: (34).

Patients who were working and were less than 65 years of age at their first symptoms of RA, and therefore potential candidates for work disability were identified in the ERATER database. The probability of working at 3 years was 0.89 (0.84–0.92) for the patients in Nashville, suggesting that rates of work disability in patients with RAare lower at this time compared to previous decades (38).

The 269 ERATER patients were compared to a similar group of 364 patients with early RA from Jyväskylä, Finland to analyze rates and predictors of work disability in early RA at two sites with different economic, social, and health care systems (38). The probability of their still working at three years was 0.84 (0.80-0.88) for patients from Jyväskylä ($p = 0.02$) compared to patients from Nashville. A 2.6-fold increased likelihood of being permanently work disabled was seen in Jyväskylä compared to Nashville (95% CI 1.44–4.59, $p = 0.001$), when adjusted for several demographic, work, and disease-related variables, although patients from Jyväskylä had significantly better scores for pain and global status at their last observation. This analysis suggested that differences in rates of work disability are explained by differences in social policies rather than disease severity, although rates of work disability appear to have declined in both countries.

Collaboration with other researchers is an important feature of the ERATER program. Many ERATER patients have volunteered to participate in genetic studies conducted at Vanderbilt University and elsewhere. Microarray analyses suggest that a gene expression signature in the peripheral blood mononuclear cells identifies patients with early RA(39).

Conclusion

Early RA databases in the USA, such as ERATER, will provide an opportunity to study the long-term outcomes of early RA over several years, including functional status, radiographic damage, work disability, and mortality, in an era when several new therapies have become available for RA, some within the last few years. Certain unique data will be collected in these early RA databases in the USA that will not be available from any other sources over the next decade.

First, the new expensive biologic agents are being used to treat early RA in the USA, whereas different social and health care systems in many European countries have designated these new DMARDs for use primarily in patients with more advanced RA. Second, disparities in patient populations in terms of social, economic, educational, cultural, and racial background as well as differences in treatment strategies between clinics in the USA are broad, facilitating research concerning various approaches in various types of patients. Finally, longitudinal observational studies supplementing clinical trials will be required to evaluate the influence of aggressive treatment on the long-term outcome of RA, as well as the issues of long-term usage, continuation, effectiveness, and possible rare serious adverse events of the new DMARDs and biologic agents.

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