# Experiences from a Prospective Early Rheumatoid Arthritis Study in Southern Sweden

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***ABSTRACT.*** Characteristics of an ongoing longitudinal observational study of patients with established rheumatoid arthritis (RA) are described. The sample comprised 183 patients enrolled from 1985 to 1989. Disease duration at inclusion was 1 year. Patients were referred from primary care and were included in the study irrespective of disease severity, with evaluation at a team care unit every 6 to 12 months. The assessment comprised a broad spectrum of standardized measures that covered the potentially most important disease outcomes. After 10 years the dropout rate was only 3%. Results to date from this study are summarized. Findings include disease course and remission rate, physical function, radiographic progression, hip involvement, mortality, work disability, and economic consequences. (J Rheumatol 2004;31 Suppl 69:9-13)

*Key Indexing Terms:*
EARLY RHEUMATOID ARTHRITIS
OUTCOME ASSESSMENT
LONGITUDINAL OBSERVATIONAL STUDY
DISEASE OUTCOME

Prospective observational studies can provide important information about outcome of a disease. However, such studies may have inherent problems making interpretation of results difficult. One major problem is possible biases, for instance, regarding sociodemographic characteristics, patient selection, disease severity, assessment methods, and loss to followup. An adequate and detailed description of different study features is necessary for assessment of the quality and validity of a study. Uniform reporting would facilitate this. Reporting requirements for longitudinal observational studies have therefore been suggested[1]. In the following section characteristics of our study are described, to the extent possible, according to these recommendations.

*Study rationale*. The aim was to investigate disease course and outcome in rheumatoid arthritis (RA) in a longitudinal observational study starting at an early stage of the disease and on a longterm basis.

## METHODS

*Patient selection, inclusion criteria, and study design*. The study was conducted at the Department of Rheumatology at Lund University Hospital in southern Sweden. The patients were mostly referred from primary care units in the surrounding health districts. The population base was about 200,000. A special campaign to recruit cases of recent onset was carried out. The primary care physicians were asked to refer every patient who possibly had contracted RA during the last 2 years. All patients were examined at our department within a few weeks after referral. The recruitment time was 1985 to 1989. Due to the accessibility of the Swedish health care system, there was no socioeconomic bias.

Altogether 183 patients were included in the prospective study. Criteria for inclusion were definite RA[2] with duration of symptoms less than 24 months and age 18 years or more. The patients were enrolled irrespective of disease activity and severity. Table 1 shows demographic data and some disease characteristics at inclusion.

The patients were assessed in a clinical setting. They were evaluated with standardized measures at inclusion and every 6 to 12 months thereafter at an outpatient team care unit. The team consisted of a rheumatologist, a nurse, a physiotherapist, an occupational therapist, and a medical social worker. This study design allowed for continuous registration of a broad spectrum of disease features that could be assessed by different members of the team. To enhance patient compliance in the long term we tried to choose the simplest and least time-consuming measures possible.

*Treatment*. Patients with active disease were offered treatment with disease modifying antirheumatic drugs (DMARD), and 77% of them received such treatment at some time during the first 10 years. Our treatment policy

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*Supported by grants from the Medical Faculty of Lund, The Österlund and Kock Foundations, The King Gustaf V 80-Years Fund, and Reumatikerförbundet.*

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*Table 1.* Demographics and some disease characteristics of the 183 patients at inclusion in the prospective study. Methods for determination of rheumatoid factor (RF) and genetic markers are as described[3,4].

| | |
|---|---|
| Female/male. n | 116/67 |
| Age at onset, yrs, mean (SD) | 51.4 (12.4) |
| Duration of symptoms, mo, mean (SD) | 11.1 (6.1) |
| RF positive, % | 75 |
| Shared epitope, % | 85 |

changed over time. During the first years most patients received chloroquine or D-penicillamine, but 10 years later methotrexate was the most frequently used drug. Forty-four percent were treated with low-dose oral glucocorticosteroids at some point in time.

*Assessment methods*. Our major assessment methods are listed in Table 2.

An active joint was defined as swollen and either tender or painful on motion. Fifty peripheral joints were assessed. Remission was defined according to the American Rheumatism Association (American College of Rheumatology) criteria[5]. Functional impairment was evaluated with the SOFI performance index, which consists of 3 parts with simple range of motion movements for hand, lower limb, and upper limb[6].

Functional class was estimated according to Steinbrocker[7].

Disability was measured by a validated Swedish version of the Stanford Health Assessment Questionnaire Disability Index (HAQ)[6].

Overall health related quality of life was assessed by EuroQol[8].

Radiographs of hands and feet were taken at baseline, years 1–5, and year 10. Findings in 32 joints were evaluated according to Larsen with a total range of the score 0–200[9,10]. Erosive disease was defined as a score of at least 2 in one joint.

Major extraarticular manifestations were registered continuously. Only manifestations that could be objectively verified by, for example, biopsy, radiography, or electromyography were documented.

Work status was recorded at each followup visit.

Economic consequences were estimated using a Markov simulation model[11]. In this model progression of a disease is reflected by transition from one Markov state to another during a certain time cycle. The Markov states are defined by disease severity, and the model is divided into cycles of equal length. Spending one cycle in a particular state is associated with a certain cost and quality of life (utility). Utility is quantified on a scale ranging from 0 to 1.

*Table 2*. Major assessment methods.

| |
|---|
| Disease activity and disease course |
| Number of active joints |
| Acute phase reactants |
| Remission |
| Physical function |
| Signals of functioning impairment (SOFI) |
| Functional class |
| HAQ |
| Health related quality of life |
| EuroQol |
| Damage |
| Radiographic |
| Total joint replacement |
| Extraarticular manifestations |
| Mortality |
| Number and causes of death |
| Standardized mortality rate (SMR) |
| Work disability — economic consequences |
| Markov model |

## RESULTS

We have produced a number of specific reports. A short summary of selected results from our clinical studies is given below.

The dropout rate during the first 10 years was 3%.

As shown in Table 3, disease activity decreased continuously during the study time[12].

We made detailed observations regarding remission periods that occurred during the first 5 years. Twenty percent of the patients had achieved remission periods of at least 6 months' duration, with an average length of remission of almost 2 years. Point prevalence of remission at the 10-year followup was 18%[12,13].

Fifty-six percent had a relapsing–remitting disease pattern during the first 5 years. After 10 years this number had increased to 80%. Not unexpectedly, persistently active disease was a bad prognostic sign[12,13].

To a great extent functional impairment of different joints as assessed by SOFI occurred early in the disease course. Already at the start of the study almost half the patients had impaired hand function, mostly affecting finger flexion and pincer grip. After 2 years' observation, hand impairment was mainly unchanged, but the frequency of impairment in other joints had increased. The deterioration was most marked for metatarsophalangeal joints (55%), elbow joints (35%), ankle joints (30%), shoulder joints (28%), and hip joints (25%). SOFI correlated more strongly than HAQ to radiographic damage, implying that SOFI reflected structural changes more closely[14].

After 10 years, 94% of the patients managed daily life activities independently (functional class I–II). The median HAQ scores had increased from 0.8 to 1.1. One-fifth of the patients had almost no disability at all (score < 0.5) and 1/10 were seriously disabled (score > 2.0). The 6 patients who had a score > 2.5 all had other serious diseases, influencing their functional capacity considerably[12]. The individual variation of HAQ scores over time was substantial. The maximum decrease and increase counted over 5 years was –1.0 and +1.0, respectively[14].

The series of radiographs was fairly complete. After 10

*Table 3*. Development of disease activity over time.

| | Year | | | |
|---|---|---|---|---|
| | 0 | 1 | 5 | 10 |
| Active joint count, 0–50 | 6 (4–10) | 4 (2–8) | 3 (1–5) | 2 (0–5)* |
| ESR, mm/h | 29 (15–50) | 25 (12–46) | 22 (10–38) | 18 (10–40)* |

* $p < 0.001$ Wilcoxon test for paired data (difference between study start and finish).

years the mean number of available examinations for each patient was 6.2 (out of a maximum of 7).

Development of erosive disease occurred early in the disease course. Already at inclusion, 49% of the patients had erosions and this number had increased to 90% after 2 years. Between years 5 and 10 another 5% became erosive. Radiographic progression was most rapid during the first 2 years, and 75% of all damage occurred during the first 5 years. The median Larsen score increased from 6 at inclusion to 41 after 5 years and 54 after 10 years. Only 5% of all evaluated joints became maximally eroded[15]. The individual rate of progression was highly variable. This is illustrated in Figure 1, where we have plotted progression rate each year for 10 patients, ending up within the same range of progression over 5 years[10].

At some time during the first 5 years 121 patients had received DMARD treatment and 62 had not. Figure 2A shows radiographic progression over this period of time among patients treated with DMARD, and Figure 2B shows the same among patients not getting such treatment. As a group, the untreated ones had much less radiographic progression, implying that some RA patients even with established disease can manage without DMARD treatment. The rapid progression among the treated patients may have been slower with the more aggressive treatment available today.

Large joint destruction leading to joint replacement occurred in 19% of the patients during the first 10 years. Hip joint replacement was most common, being more than twice as frequent as knee joint replacement[12]. Early hip involvement and usefulness of ultrasonography was therefore the focus for a special study of 2 subgroups of patients within the cohort. We found that hip joint destruction usually gave symptoms at a very late stage, emphasizing the need for earlier detection of hip joint involvement. We demonstrated that ultrasonography rather than signs and symptoms could identify patients with hip involvement and provide a rationale for early treatment[16].

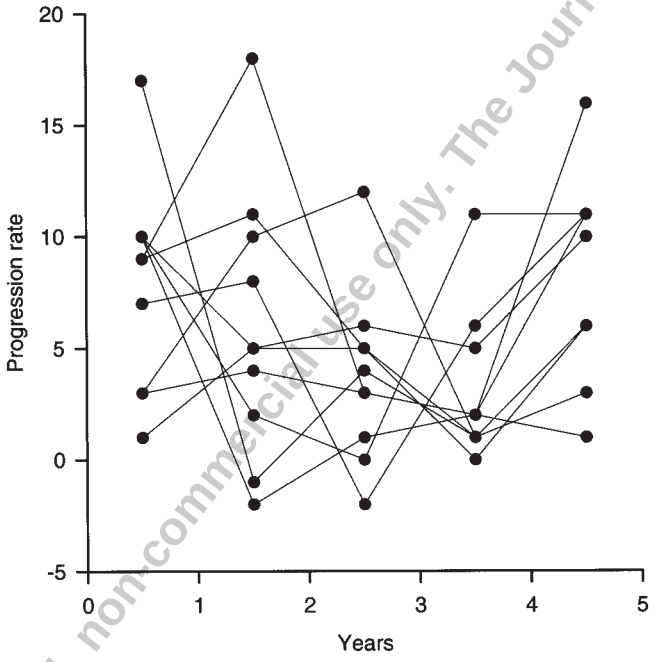


*Figure 1.* Annual rate of progression in 10 patients with a 5 year total around the median (range 31–47). From Fex, *et al*, Br J Rheumatol 1996;35:1106-15[10], with permission.

Nine percent of the patients had developed serious extraarticular manifestations during 10 years of observation[12]. Despite this, we found no increased mortality during the first 8 to 13 years of disease. Eighteen patients (11 men and 7 women) had died. The expected number of deaths was 20.6. Standardized mortality rate (SMR) for our cohort was 87. RA was not the main cause of death in any case, but may have contributed to death in 2 cases. The causes of death were cardiovascular disease in 9 individuals and malignancy in 7. Significant risk factors for death, estimated by the Cox proportional hazards model, were older age at onset and male sex. Thus at this stage of the disease no clinical variable contributed to an increased risk of death[17].

Figure 3 shows the changes in work status during the first 5 years. The prevalence of work disability at year 5 was 37%. A striking finding was that the majority of the patients, who eventually got disability pension, had already stopped working in the first year after RA onset even before attending the rheumatology unit. Early referral is very important to help avoid permanent work disability. Over the course of the disease it is also essential to identify possible measures to make it easier for a patient to stay employed. This is illustrated in our cohort, where almost 80% of the patients who continued to work had taken such measures. A logistic regression analysis showed that the 3 most important predictors for work disability were higher HAQ at study start, lower education level, and older age[18].

The prevalence of work disability remained mainly unchanged for years 5 to 10 (unpublished observation).

Cohort data were used to develop an economic Markov model with the aim to analyze cost effectiveness of treatments that affect progression of RA, regarding both costs and quality of life (utility). The patients were classified into 6 Markov states defined by HAQ level. Each time cycle was one year and the model ran for 5 years. The costs for spending one year in a certain state were divided into direct costs including number of hospital days due to RA, outpatient visits, and DMARD treatment, and indirect costs due to work disability. Indirect costs constituted about 85% of all costs in this study. Mean utility values for each Markov state were derived from the EuroQoL, based on good agreement between utility values obtained by EuroQol and our HAQ-derived Markov states as reported by us elsewhere[19].

The cohort distribution among the 6 Markov states showed disease progression over time. Costs increased with increasing severity of the Markov states. Thus the model

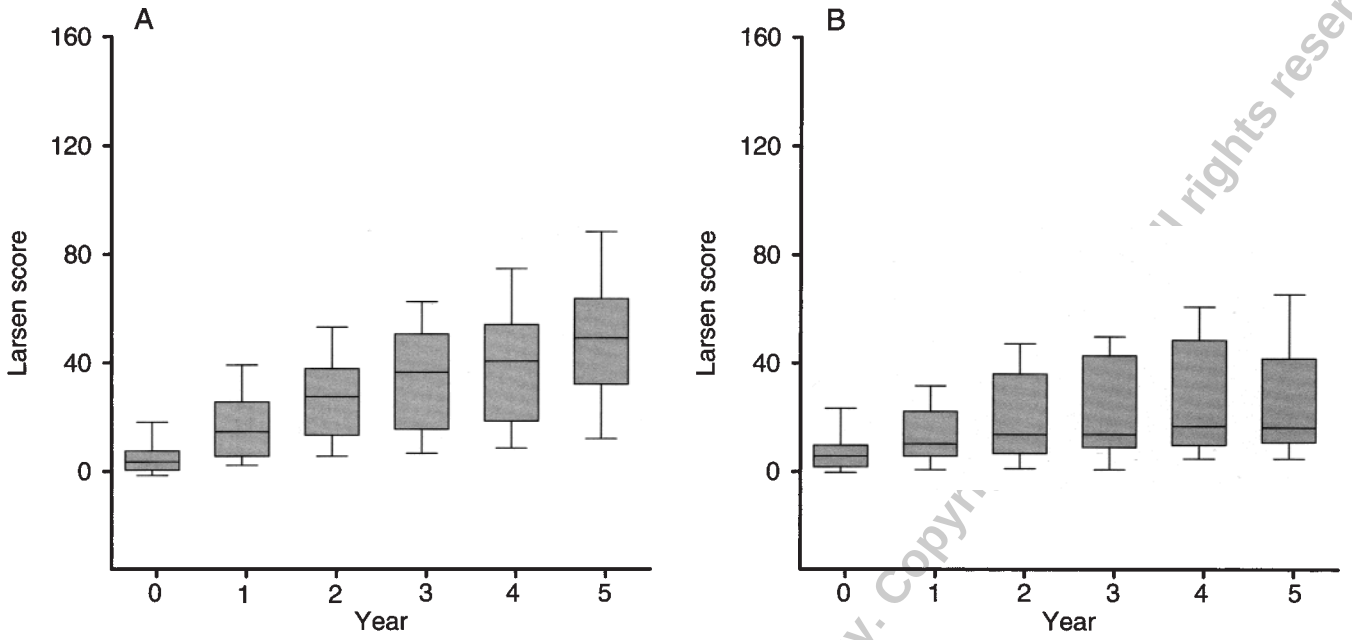


*Figure 2*. A. Development of radiographic damage over 5 years among the 121 DMARD recipients. Box plots show the median and percentiles 10, 25, 75, and 90. B. As in A, with results for 62 nonrecipients of DMARD.

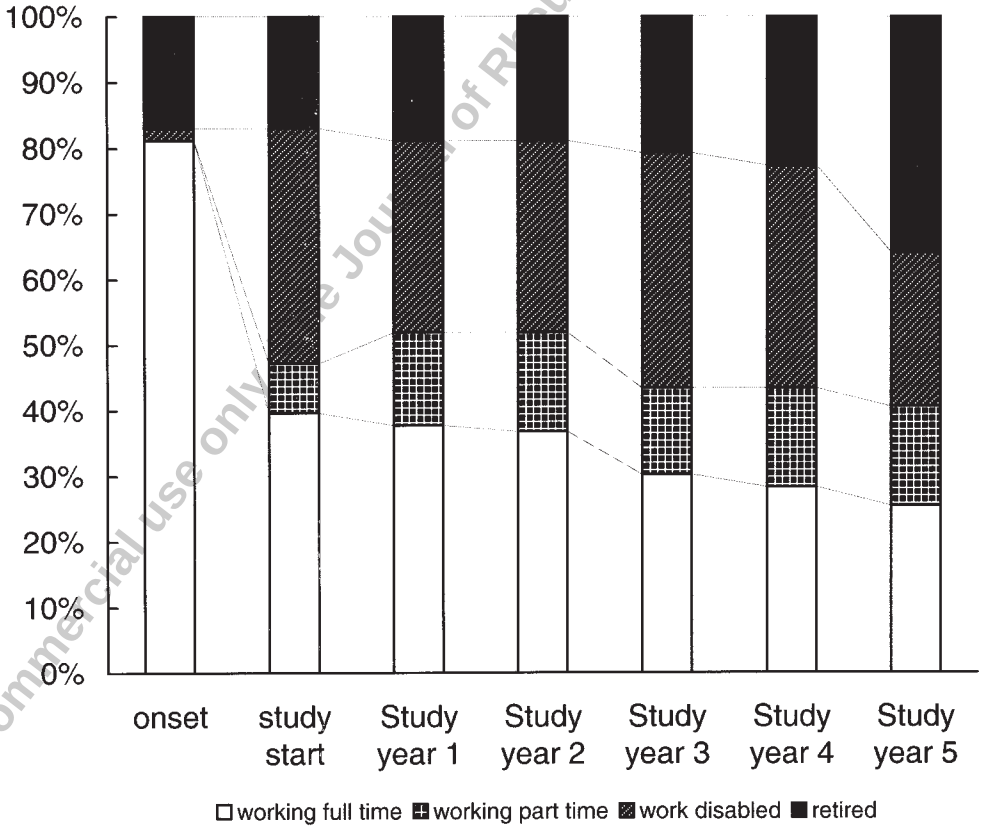


*Figure 3*. Changes of work status over time in the first 106 patients enrolled in the prospective study: conditions at disease onset, at study start on average 1 year later, and for another 5 years thereafter for all patients. From Fex, *et al*, J Rheumatol 1998;25:44-50.

was able to capture the effect of disease progression. It could also estimate differences in cost effectiveness between different treatment alternatives[19].

The economic model has now been further extended using 10 year followup data for all 183 patients. This was used to evaluate economic consequences of the new biological agents[20,21].

## CONCLUSION

Characteristics and selected results from our prospective early RA study have been described here. It was a great advantage that the study could be performed in a clinical setting with access to allied health professionals. This made it possible to assess a broad spectrum of potentially important disease outcomes. The sample size is rather small, but other factors strengthen the relevance of results. We had no obvious selection biases, the number of missing data is small, and the dropout rate is so far only 3%.

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