The Nijmegen Inception Cohort of Early Rheumatoid Arthritis

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ABSTRACT. Rheumatoid arthritis is a heterogeneous chronic disease with an unpredictable disease course. To study such a disease, longterm observational studies are needed, with regular assessment of patients using valid and reproducible measures. This article describes the purpose and design of such a study at the Department of Rheumatology, University Medical Centre Nijmegen. Within this inception cohort, several instruments to assess RA were developed and validated, such as the Disease Activity Score, the European League Against Rheumatism response criteria, and a Dutch version of the Health Assessment Questionnaire disability index. These instruments are described and results of studies are discussed concerning prognostic and predictive factors, disease course, and the relationship between the different process and outcome measures. (J Rheumatol 2004;31 Suppl 69:14–21)

Key Indexing Terms:
RHEUMATOID ARTHRITIS COHORT STUDIES
OUTCOME AND PROCESS ASSESSMENT

Rheumatoid arthritis (RA) is a chronic, inflammatory, systemic disease. It is a heterogeneous disease with an unpredictable course, varying from mild to very severe and disabling[1].

To study the course and (longterm) outcome of such a disease longterm observational studies are needed. To be able to avoid interference of disease modifying treatment when studying prognostic features for disease outcome, patients should be followed from as early in the disease as possible. Patients should be measured at fixed intervals (and not only by indication, since this might give bias toward more serious disease). Further, no stringent selection criteria apart from a diagnosis of RA should be applied, to allow study of all subgroups of patients. Valid and reproducible measures are needed to assess the disease. This article describes the setup and the results of research within such a longitudinal study, the Nijmegen inception cohort in The Netherlands.

PATIENTS AND METHODS

In 1985 the Department of Rheumatology of the University Medical Centre Nijmegen started a longterm observational study (inception cohort study) of early RA. The purposes of initiating this study were:

1. To establish a database to serve as a basis for the development and validation of outcome measures and the evaluation of instruments for clinical trials and daily clinical practice.
2. To collect information on the (longterm) course of RA with respect to the activity of the disease, joint destruction, functional capacity, pharmacotherapy, comorbidity, and socioeconomic consequences.
3. To search for prognostic and predictive factors for the course of the disease and response to treatment.

At this time new patients are still being included, and followup continues.

Patients and methods. The study is designed as an inception cohort study. All patients at our department that satisfy the following criteria are asked to participate: RA according to the 1958 (later 1987) American College of Rheumatology (ACR, formerly American Rheumatism Association) criteria for RA[2]; disease duration less than 1 year; and no prior use of disease modifying antirheumatic drugs (DMARD).

Patients are followed regularly at fixed intervals (not only by indication, to prevent selection bias). No predefined end of followup is determined; patients are followed until they die or until they refuse to participate further.

On May 1, 2003, 492 patients were included in this cohort, with a mean followup of more than 7 years and 3444 patient-years of followup. Over the followup period 13 patients (4.6%) were lost to followup due to moving to another area, 23 patients (4.7%) were lost involuntarily (i.e., comorbidity, hospital admissions), and 58 patients (11.8%) refused to participate further in the study.

Drug treatment decisions are made by rheumatologists according to daily clinical practice standards. DMARD are prescribed usually within the first months, starting as a rule with sulfasalazine as first and methotrexate as second DMARD.

Measures. Patients are assessed at least every 3 months by a research nurse. Three-monthly data are collected concerning process variables: Ritchie Articular Index (53 joints, graded for tenderness, grouped in 26 units, range 0–78); 44-joint count for swelling ungraded or the 28-joint counts for swelling and tenderness; Westergren erythrocyte sedimentation rate (ESR); C-reactive protein (CRP); patient assessment of general health; disease activity and pain on 100 mm visual analog scale (VAS; 0 = best possible, 100 = worst possible); and physician assessment of disease activity.

In the first 3 years, radiographs of hands and feet are taken every 6 months; thereafter patients are assessed once a year, and after 6 years, assessment is every 3 years. This schedule reduces the burden for patients and reflects the gradual progression of radiological damage.

IgM rheumatoid factor (RF > 10 IU/ml is considered positive) is determined at baseline and yearly thereafter. Grip strength is measured using a vigorimeter (mm Hg, range 0–175), and HLA-DR4 status is determined serologically.

Further, data are collected concerning age at onset of disease,

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complaints at baseline, medical consumption, family history concerning rheumatoid arthritis and health related quality of life (using the Arthritis Impact Measurement Scale) throughout followup. Every year a sample of serum and plasma is stored.

A deviation of 1 month from the assessment timepoints according to the protocol was allowed.

The research nurses were trained prior to participation in the study, and they are reevaluated once a year.

In the early phase of the study (the first 100 patients included) patients were assessed every month. This was done to obtain a dataset to determine variability and measurement qualities (reliability and validity) of the measures, which were largely unknown in 1985. This knowledge was also used to determine the proper followup frequency for the different variables in the study.

During the early phase of the Nijmegen inception cohort a similar protocol was established at the Department of Rheumatolgy of Groningen University Hospital in The Netherlands and data were combined for collaborative analyses. In 1991 a similar protocol was started at the Department of Rheumatology of the St. Maartens Clinic in Nijmegen in cooperation with our department. The results presented here are mainly based on data from the Nijmegen cohort.

RESULTS

To date the work using data from the inception cohort study has resulted in the development and validation of several instruments to assess disease course in patients with RA. Examples of these instruments are the Disease Activity Score (DAS), the European League Against Rheumatism (EULAR) response criteria, the Modified Sharp method to assess radiological damage, and the validation of the Dutch Health Assessment Questionnaire. Numerous articles in peer-reviewed journals and many PhD theses have resulted. Below the instruments are briefly described:

Disease Activity Score. A core set of disease activity measures was selected based on their measurement qualities as assessed during the early phase of the study. The DAS was developed based on treatment decisions of rheumatologists[3]. The decision of a rheumatologist to start (another) DMARD treatment was used as the gold standard for high disease activity, and if DMARD treatment was not started, or remained unchanged for at least one year, or was stopped because of remission, this was equated with periods of low disease activity. The derived index consists of the following core set variables (in order of importance): Ritchie Articular Index, 44-joint count for swelling ungraded, Westergren ESR, and patient assessment of general health based on 100 mm VAS. The DAS can also be calculated without VAS for general health (see Appendix A for formulae). The instrument produces a score from 0 (totally inactive disease) to 10 (very active disease). It has been found to be valid ($r > 0.60$ with other measurements of disease activity)[4] and reproducible (measurement–remeasurement correlation from 0.70 to 0.94)[3,4]. The DAS can be useful to monitor the disease process[5,6].

The DAS was divided into low, moderate, and high disease activity, based on the above noted treatment decisions of rheumatologists[7]. A cutoff point for the DAS was defined, whereby RA patients were in remission according to ACR criteria for remission of RA[8] (see Figures 1 and 2).

A study on validity and reliability of joint counts by Prevoo, *et al* using data from this cohort demonstrated that a 28-joint count without weighting or grading was as valid and reproducible as a more complicated joint count, and therefore is preferable to these more complicated joint counts[9]. A modified DAS (DAS28) including 28-joint count was developed and validated in a fashion similar to that of the original DAS (see Appendix A). A program to calculate the DAS is available at the website http://www.das-score.nl. Recently DAS formulae were developed using the CRP instead of the ESR. These formulae are also present at the DAS website and are shown in Appendix A.

EULAR response criteria. The EULAR response criteria were developed for evaluation of disease activity and response to treatment in clinical trials[7,10]. These criteria are based on the DAS (or DAS28) and combine a change in the DAS(28) (larger than the expected change due to measurement error) and the achieved value of the DAS(28). These criteria are illustrated in Table 1. The EULAR response criteria were extensively validated, and several studies have shown them to be as valid as ACR improvement criteria in the evaluation of clinical trials[7,10-12].

Modified Sharp method. A modified Sharp method for the evaluation of joint damage as seen on radiographs has been developed and validated[13,14]. This method counts erosions and joint space narrowing in joints of hands and feet on radiographs. It produces a score from 0 (no damage) to 448 (very much damage). The modified Sharp score is currently one of the most frequently used for quantifying joint destruction on radiographs. The method has been found to be valid (correlation above 0.5 with other scoring methods and scores of physical joint deformity and limited motion)[15] and reproducible (interobserver correlation coefficients of 0.92 to 0.94)[14-16].

Dutch HAQ disability index. The HAQ-DI has been validated for use in The Netherlands[17,18]. The most recent version of the HAQ-DI is equal to the original version and was translated and backtranslated by 2 rheumatology researchers and an English teacher and native English speaker, respectively[18]. Differences were discussed and a consensus was reached on the translation that best matched the original Stanford HAQ. Further, the consequences of the different calculation methods of the HAQ-DI in use in the literature were described. This indicated that the calculation with correction for aids and devices leads to significantly higher HAQ-DI score, and that taking the mean per category rather than the maximum per category leads to lower HAQ-DI scores[16]. For international comparison of study results this is not preferable and a standard way to calculate the HAQ-DI score should be used.

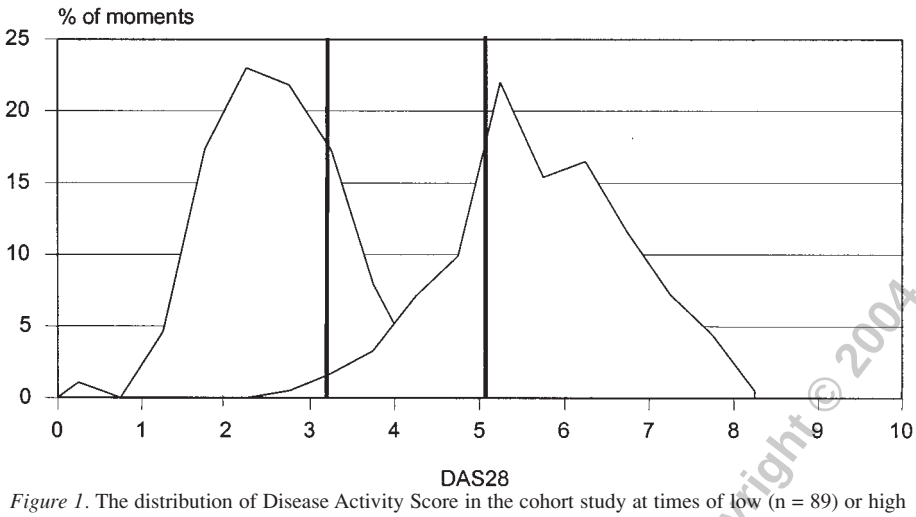

Figure 1. The distribution of Disease Activity Score in the cohort study at times of low (n = 89) or high (n = 189) disease activity according to treatment decisions by rheumatologists. The vertical lines divide the DAS28 into low (≤ 3.2), moderate (> 3.2 and ≤ 5.1), and high disease activity (> 5.1).

Disease outcome. Although research of the department focuses mainly on development and validation of outcome and process measures, the dataset of the inception cohort has also been used to gain insight into disease course in patients with early RA during the first years. This indicated that damage starts early in disease[19,20]. This (together with work from many other groups) has had an impact on the therapeutic strategies of patients with early RA: Treat patients as soon as possible as aggressively as needed in order to prevent joint damage[21]. Further, it was shown that RA has a socioeconomic impact already in the first years of disease[22]. In this cohort no increased mortality was present in the first decade of the disease[23].

Since RA has an unpredictable disease course, many groups have performed studies on prognostic and predictive factors. Within our cohort several studies have been performed looking at factors that predict course of disease as well as response to antirheumatic therapies, with respect to both effectiveness and toxicity[24-30].

With the continuing followup of patients and established measurement instruments it also became possible (1) to study the course of disease in established RA using followup data, and (2) to describe the relationship between the most important process and outcome measures in RA (disease activity, radiological progression, and functional disability) over the course of disease.

A recent study within our cohort has shown that on average the functional capacity of patients as measured by HAQ-DI worsened over the first 9 years of disease after initial improvement[31]. Moreover, after initial reduction in disease activity, mean DAS remained more or less stable over the disease course and mean modified Sharp score worsened over the course of disease, with a slower progression rate later in the disease (see Figure 3). Using regression analysis it was also found that the effect of disease activity and joint destruction on functional capacity changed over the course of disease. In early RA, functional capacity was mostly associated with disease activity, and in late disease, with joint damage.

Recently the relationship between inflammatory disease activity, using the DAS, and progression of radiological damage (modified Sharp score) over the course of disease was studied within the cohort. It was shown that disease activity [DAS(28)] was longitudinally related to radiological progression of joint damage (modified Sharp method), meaning that a change in disease activity in individual patients is related to a change in radiological progression. Not only was the mean value of the DAS related over a 3-year period to radiological progression but also the fluctuation of the DAS (SD-DAS) over the 3-year period proved important. This relationship seemed to be stronger in RF positive patients[32]. In Figure 4, expected Sharp scores over time are shown for (1) a patient that remains in remission after a period of moderate disease activity (mean DAS 2.4, SD 0.4, in the first 3 years, and mean DAS 1.5, SD 0.3, in the years thereafter); (2) a patient with persistent high disease activity (mean DAS 4.2, SD 0.4, in the first 3 years, and mean DAS 3.8, SD 0.3, in the years thereafter); (3) a patient with fluctuating remission after a period of fluctuating moderate disease activity (mean DAS 2.4, SD 0.9, in the first 3 years, and mean DAS 1.5, SD 0.8, in the years thereafter); and (4) a patient with fluctuating high disease activity (mean DAS 4.2, SD 0.9, in the first 3 years, and mean DAS 3.8 with SD 0.8 in the years thereafter). There are separate figures representing patients with a positive RF test, a negative RF test, no baseline damage, and baseline Sharp score of 20 units. The figures are derived from a regression model using generalized estimating equations.

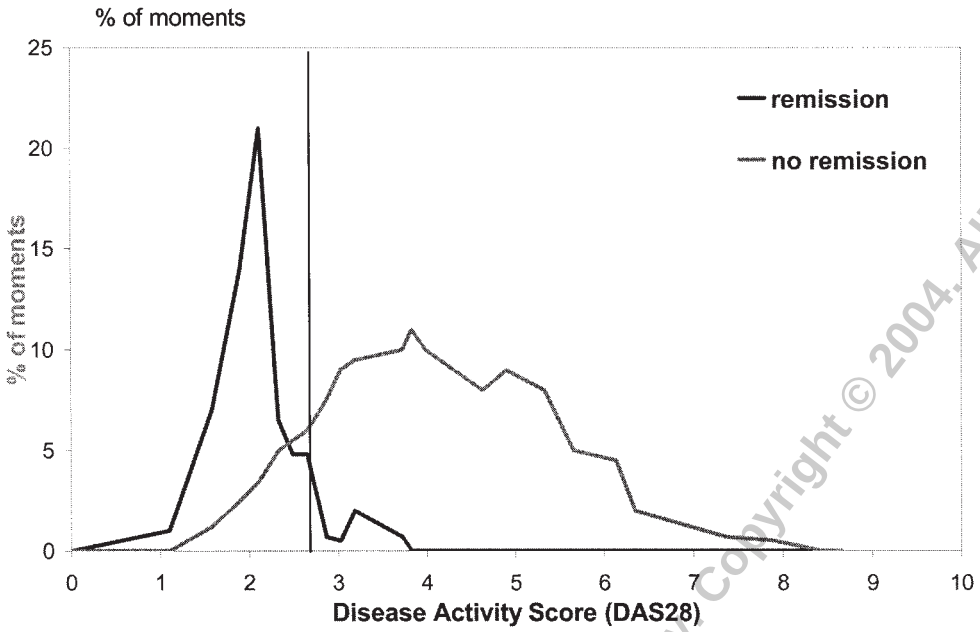

Figure 2. Comparison of Disease Activity Score values with ARA preliminary remission criteria. The distribution of Disease Activity Score at the time patients fulfilled ARA preliminary remission criteria (n = 196) or did not (n = 2636). Vertical line denotes the cutoff value for the DAS28 (2.6).

Table 1. EULAR response criteria.

DAS at endpoint	DAS28 at endpoint:	Improvement in DAS or DAS28 from baseline: > 1.2	> 0.6 and ≤ 1.2	≤ 0.6
≤ 2.4	≤ 3.2	Good		
> 2.4 and ≤ 3.7	> 3.2 and ≤ 5.1		Moderate	
> 3.7	> 5.1			None

The followup data have also been used as a retrospective control group for patients treated with tumor necrosis factor-blocking treatment[33] and frequently (part of) the followup data are used for studies looking at several aspects of RA that need a well described population with longitudinally collected data and then perform some extra measurements (i.e., a biological marker) on these patients

With longer followup more patients withdraw from study. This can be a problem when studying the longterm course of disease or prognostic factors when dropping out is selective. Further, including patients over a long time might give rise to cohort effects when patients included in the early phases of study are different (or are assessed differently) from ones included later due to, for example, a change in disease presentation or treatment, earlier referral to rheumatologists, or a change in the target population for the hospital, or due to use of other measurement instruments. Using all patient data together might therefore introduce bias in studies investigating the course of disease or prognostic factors, since patients included early and late are different due to the above mentioned cohort effects. However, comparing these patients might also yield data on time trends in (the outcome of) the disease. These factors should also be studied in the future when the inclusion of patients and followup continues.

DISCUSSION AND CONCLUSION

This article describes the setup of the Nijmegen inception cohort and results of the main research using followup data from the study. Several instruments to assess course of disease in patients with RA were developed and validated within the study, making use of the followup data. Examples are the DAS(28), the EULAR response criteria, the Modified Sharp method, and the Dutch HAQ-DI. These instruments are widely accepted and used, making comparisons between different studies more feasible. Using these

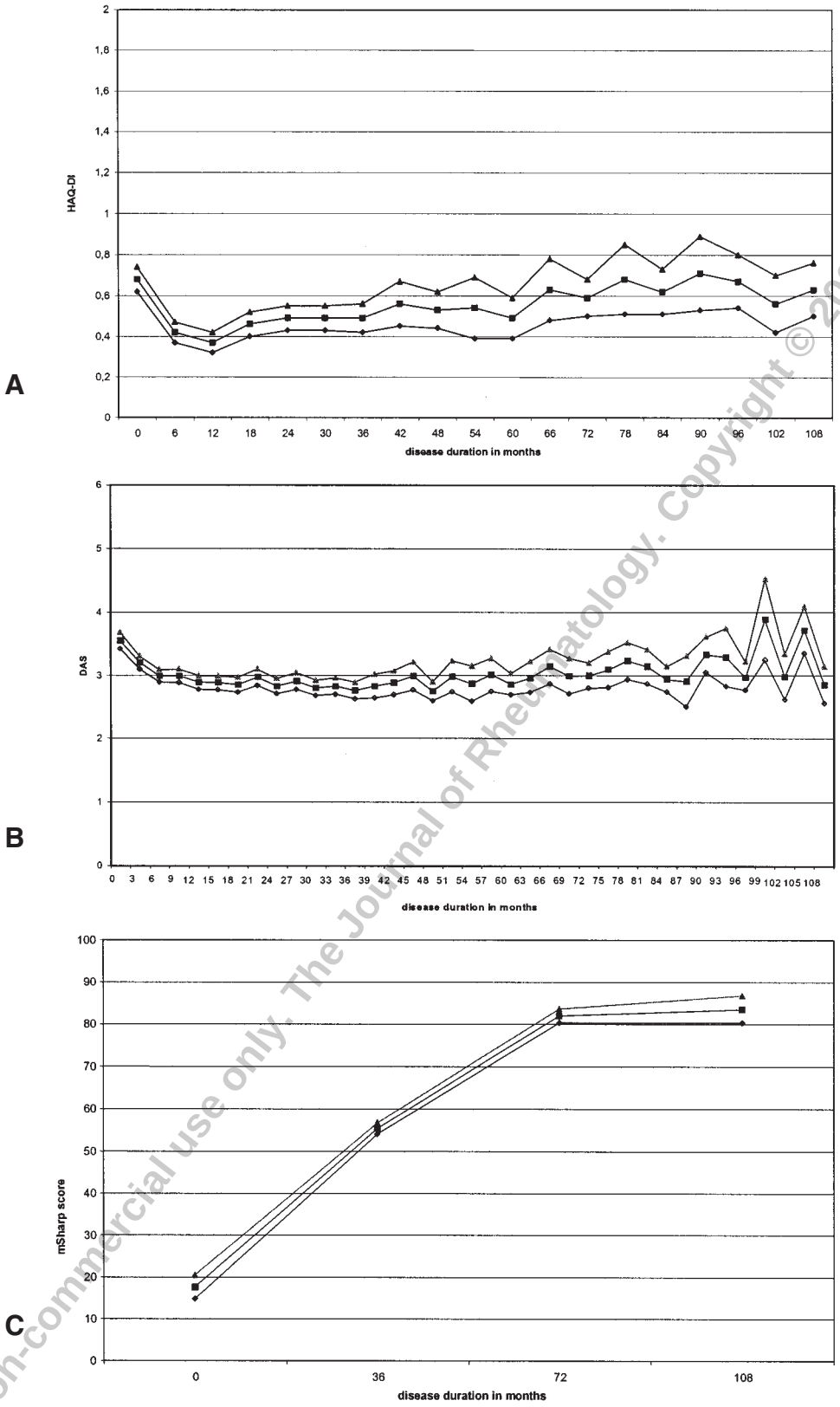

Figure 3. Functional capacity, disease activity, and joint destruction over the course of disease. Upper and lower lines represent the upper and lower limits of the 95% CI. A: functional capacity; B: disease activity; C: joint destruction.

measurement instruments the course of the disease, prognostic and predictive factors, and relationships between process and outcome measures can be studied, as was done within this cohort. Inclusion and followup of the Nijmegen inception cohort is ongoing and data will continue to be used to study the course and outcome of RA. Studying time

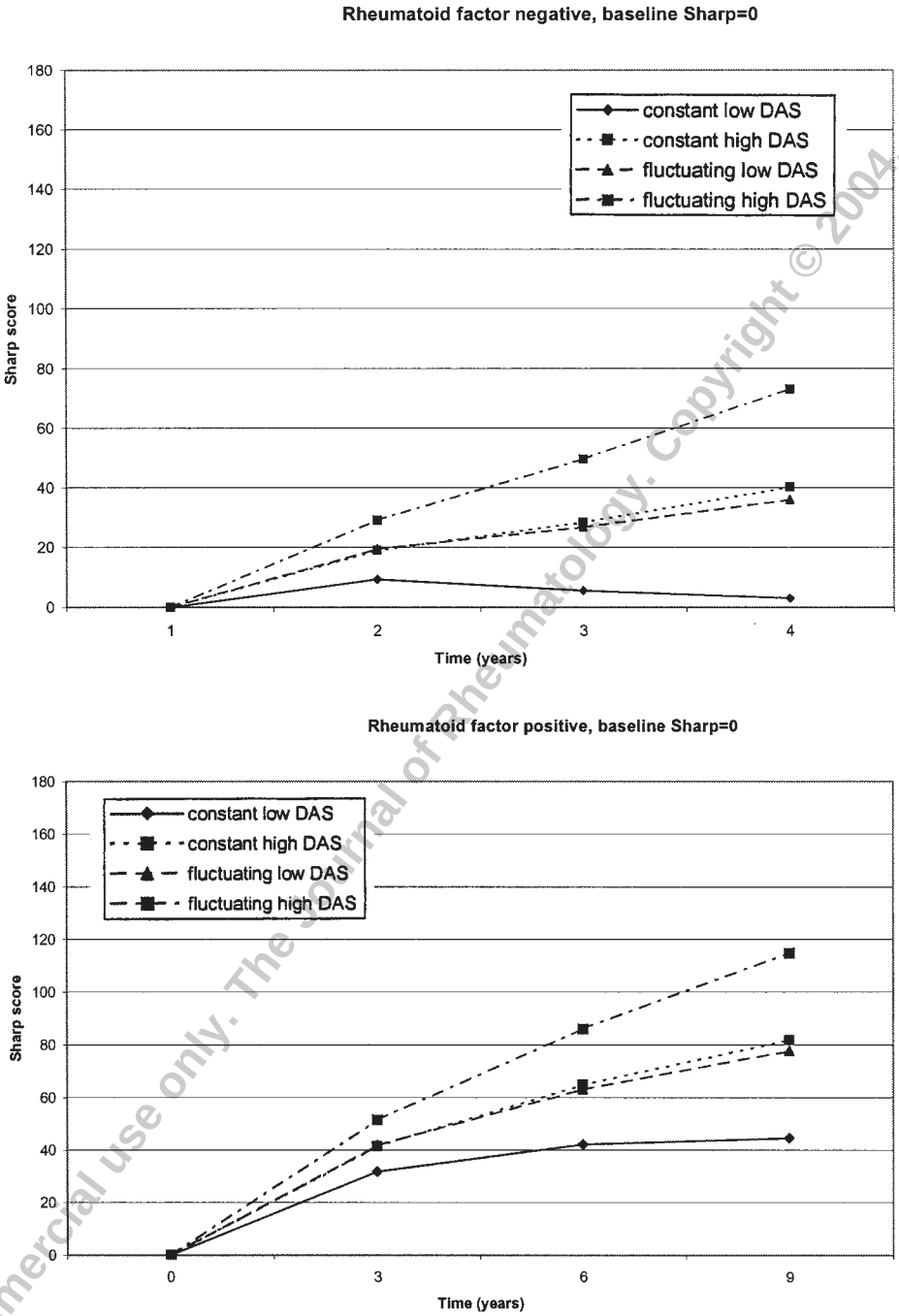

Figure 4. Prediction of radiological damage for patients with different prognostic makeup and patterns of disease activity. Progression of radiological damage as calculated from the generalized estimating equations model 4 for patients with a constant low DAS (mean DAS 2.4, SD 0.4, in the first 3 years, and mean DAS 1.5, SD 0.3, in the years thereafter), constant high DAS (mean DAS 4.2, SD 0.4, in the first 3 years, and mean DAS 3.8, SD 0.3, in the years thereafter), fluctuating high DAS (mean DAS 4.2, SD 0.9, in the first 3 years, and mean DAS 1.5, SD 0.8, in the years thereafter), and a fluctuating remission (mean DAS 2.4, SD 0.9, in the first 3 years, and mean DAS 1.5, SD 0.8, in the years thereafter) for RF positive and negative patients and patients with no baseline damage or a baseline Sharp score of 20. —▲—▲—: constant low DAS; ·····■····· : constant high DAS; --▲--▲--: fluctuating low DAS; ——■——: fluctuating high DAS.

trends in an inception cohort with inclusion and followup continuing over a long period might be interesting. The followup data have proved very useful for many purposes.

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Appendix A. Disease Activity Score (DAS) formulae. LnESR: natural logarithm of Westergren ESR; GH: general health or patient global assessment of disease activity on 100 mm VAS; RAI: Ritchie Articular Index (53 joints in 26 units, graded for tenderness); W44: 44-joint count for swelling; CRP: C-reactive protein. For obtaining sensitive results in the case of low disease activity, it is advised to make general use of a CRP test with a lower detection level of 1.0 mg/l. The CRP test should have been calibrated by the laboratory using a standardized method, either CRM 470 of the International Federation of Clinical Chemistry, or the WHO reference standard for CRP immunoassay 85/506.

DAS28 with four variables:

$$DAS28 = 0.56\sqrt{(TEN28)} + 0.28\sqrt{(SW28)} + 0.70\ln(ESR) + 0.014(GH)$$

DAS28 with three variables:

$$DAS28 = (0.56\sqrt{(TEN28)} + 0.28\sqrt{(SW28)} + 0.70\ln(ESR))1.08 + 0.16$$

Transformation formula:

$$DAS28 = 1.072(DAS) + 0.938$$

Original DAS with four variables:

$$DAS = 0.53938\sqrt{(RAI)} + 0.06465(SW44) + 0.330\ln(ESR) + 0.00722(GH)$$

Original DAS with three variables:

$$DAS = 0.53938\sqrt{(RAI)} + 0.06465(SW44) + 0.330\ln(ESR) + 0.224$$

The following formulae to calculate the DAS or DAS28 using CRP (mg/L) give good estimations of the original DAS or DAS28 values on a group level. It is strongly advised to adhere either to ESR or to CRP determinations.

$$DAS\text{-}4(crp) = 0.54\sqrt{(RAI)} + 0.065(SJC44) + 0.17\ln(CRP+1) + 0.0072GH + 0.45$$

$$DAS\text{-}3(crp) = 0.54\sqrt{(RAI)} + 0.065(SJC44) + 0.17\ln(CRP+1) + 0.65$$

$$DAS28\text{-}4(crp) = 0.56\sqrt{(TJC28)} + 0.28\sqrt{(SJC28)} + 0.36\ln(CRP+1) + 0.014GH + 0.96$$

$$DAS28\text{-}3(crp) = [0.56\sqrt{(TJC28)} + 0.28\sqrt{(SJC28)} + 0.36\ln(CRP+1)]1.10 + 1.15$$

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