Should We Redefine Treatment Targets in Rheumatoid Arthritis? Low Disease Activity Is Sufficiently Strict for Patients Who Are Anticitrullinated Protein Antibody-negative

Yvonne M.R. de Punder, Jos Hendrikx, Alfons A. den Broeder, Elia Valls Pascual, Piet L. van Riel, and Jaap Fransen

ABSTRACT. ***Objective.*** Clinical remission currently is the treatment target for all patients with rheumatoid arthritis (RA). At the same level of inflammation, the prognosis regarding joint damage is believed to be different for anticitrullinated protein antibody (ACPA)-negative and ACPA-positive patients. Our objective was to show the difference in prognosis at similar disease activity levels, and to illustrate how this could be translated to differentiation of treatment targets.

Methods. Data were used from the Nijmegen Early RA Cohort. The relation between the time-averaged disease activity level (by Disease Activity Score; DAS) and joint damage progression over 3 years was analyzed, separately for ACPA-negative and ACPA-positive patients. Joint damage was assessed as change in Ratingen score, and dichotomized as occurrence of erosions in joints that were unaffected at baseline. Linear and logistic multivariable regression models were used.

Results. The regression coefficient of DAS on change in Ratingen score was 3.9 ($p < 0.001$) for ACPA-negative and 4.7 ($p < 0.001$) for ACPA-positive patients, showing less joint damage progression at the same disease activity level in ACPA-negative patients. This difference became greater with increasing disease activity. The probability for erosions in joints unaffected at baseline was 0.35 in ACPA-negative patients when time-averaged DAS was < 2.4 versus 0.80 in ACPA-positive patients.

Conclusion. At the same level of inflammation, ACPA-negative patients have less joint damage and lower probability for damage in newly affected joints than ACPA-positive patients. Low disease activity might be a sufficiently strict treatment target for ACPA-negative patients to prevent progression of joint damage. (First Release June 1 2013; J Rheumatol 2013;40:1268–74; doi:10.3899/jrheum.121438)

Key Indexing Terms:
RHEUMATOID ARTHRITIS ANTICITRULLINATED PROTEIN ANTIBODY
INFLAMMATION JOINT EROSIONS

Rheumatoid arthritis (RA) is a multifactorial disease with joint erosions as a hallmark. Because joint damage is largely irreversible, an important goal of RA treatment is to prevent joint damage[1]. In general, more RA inflammation results in more joint damage[2,3]. Prevention of joint damage can thus be achieved by striving for remission, which is the ultimate treatment goal in RA. A quick switch or addition of medication is advised if remission is not achieved after 3 to 6 months of treatment[4]. However, the probability for future joint damage is not the same for all patients with RA and treatment guidelines advise that factors that predict poor prognosis be taken into account when considering an early or late switch to biologics[5].

One of the main baseline factors predicting worse prognosis regarding joint damage is a positive result for anticitrullinated protein antibody (ACPA)[6,7,8,9]. ACPA-positive and ACPA-negative RA are generally considered 2 different entities of the same disease, because patients who are ACPA-positive are reported to have more progression of joint damage as well as higher levels of inflammation than ACPA-negative patients[10,11]. However, the difference in prognosis cannot be completely explained by the higher inflammation level. The relation between joint damage and inflammation is also different for ACPA-positive and ACPA-negative patients. Consequently,

From the Department of Rheumatology, Radboud University Nijmegen Medical Centre; and Department of Rheumatology, Sint Maartens Kliniek, Nijmegen, The Netherlands.

Y.M.R. de Punder, MD; J. Hendrikx, MSc, Department of Rheumatology, Radboud University Nijmegen Medical Centre; A.A. den Broeder, MD, PhD, Department of Rheumatology, Sint Maartens Kliniek; E. Valls Pascual, MD; P.L.C.M. van Riel, MD, PhD, Professor of Rheumatology; J. Fransen, PhD, Department of Rheumatology, Radboud University Nijmegen Medical Centre.

Address correspondence to J. Fransen, Department of Rheumatology, Radboud University Nijmegen Medical Centre, Postbus 9101, Huispost 470, 6500 HB Nijmegen, The Netherlands.
E-mail: J.Fransen@reuma.umcn.nl

Accepted for publication April 5, 2013.

a level of inflammation that will result in a clinically relevant quantity of joint damage in ACPA-positive patients will have no or little joint damage in ACPA-negative patients. Absence or presence of ACPA in a patient should thus not only be taken into account when considering the intensity of the treatment, but could also result in a refinement of the one-size-fits-all treatment target of remission. This is especially important because sustained remission is still difficult to achieve and patients are often satisfied with a state of low or even moderate disease activity[12,13,14,15]. When the risk for progression of joint damage is limited and the patient is satisfied with his or her symptom state, there remain no strong arguments for remission as a treatment goal for patients with RA.

The objective of our study was to analyze the difference in joint damage progression between ACPA-negative and ACPA-positive patients with RA in the first 3 years of the disease, at the same level of disease activity, and to show that different treatment targets could be used for ACPA-negative as compared to ACPA-positive patients, to prevent progression of joint damage.

MATERIALS AND METHODS

Study design. Data were used from the database of the Nijmegen early RA cohort, an inception cohort in existence since 1985[16]. Because of resource limitations, joint damage scores were available from only a subset of patients, who were included from 1985 until August 2002. For the current analyses, data from the first 3 years of followup of these patients were used.

No formal ethical committee approval was required for this kind of observational study in The Netherlands. All patients provided written informed consent to be included in the cohort.

Patients. Patients were consecutively included in the Nijmegen early RA cohort if they had a diagnosis of RA according to the 1987 American College of Rheumatology criteria for RA, had a disease duration < 1 year, had no prior use of disease-modifying antirheumatic drugs (DMARD) and were age ≥ 18 years. Accuracy of the diagnosis of RA was tested in a random subsample of 30 (34%) ACPA-negative patients, and the diagnosis had been revised in only 2 of the 30, but only after the third year. Therefore, we assumed that misclassification was appropriately low. Because of the high specificity of ACPA for RA, we considered no doubts about the classification of ACPA-positive RA.

Cohort patients were included for the study if scored radiographs of hands and feet were available at baseline and at 2- or 3-year followup; if they had at least 3 visits with assessment of the original Disease Activity Score (DAS), including at least 1 visit in the third year; and if their ACPA status was known. Patients treated with biological response-modifiers during the first 3 years were excluded, because that medication changes the relation between disease activity and joint damage[17,18].

Assessments. Baseline characteristics of all patients were collected, including ACPA and rheumatoid factor (RF). ACPA was assessed using the Anti-CCP2 Enzyme Linked Immuno Assay (ELISA Immunoscan RA Mark 2; Euro-Diagnostica), with a cutoff value > 25 U/ml considered positive. In a subset of patients this was determined posthoc from frozen blood samples, using the fluoroenzyme immunoassay for ACPA (EliA-CCP; Thermo Scientific) with a cutoff value > 10 U/ml considered positive. The correlation between the 2 tests was 0.91. Disease activity was assessed every 3 months by trained research nurses using the 44-joint swollen joint count (SJC), 53-joint tender joint count (TJC), with grading according to Ritchie, erythrocyte sedimentation rate (ESR), and a patient-reported rating of general health on a visual analog scale (VAS) from 0 to 100 mm. The DAS was calculated according to the original formula[19]. Radiographs of hands and feet were taken at baseline and 1, 2, and 3 years' followup.

The radiographs of hands and feet of each patient were read in chronological order by 1 of 4 raters, according to the Ratingen score, using reference pictures[20]. The Ratingen score (range 0–198) is a modification of the Larsen score and evaluates the amount of joint surface destruction, graded from 0 to 5, in 38 hand and foot joints. The interrater reliability (intraclass correlation coefficient; ICC) was 0.85, tested previously with the 4 raters in 10 patients over 9 years of followup.

The primary outcome of the study was the change in Ratingen score between baseline and 3 years' followup, representing the quantity of the progression. However, for the prognosis, not only the quantity of joint damage progression is important, but also if the number of damaged joints increases. This is considered important because it reflects the extent of joint damage and because joints that are already damaged have a higher chance of showing progression in the future[21]. Therefore, occurrence of new erosions in joints unaffected at baseline was the secondary outcome in the study.

Inflammation was assessed using the time-averaged DAS over 3 years, calculated using the area under the curve of the DAS and observation time, divided by observation time.

Analyses. First, we analyzed whether there were baseline differences between ACPA-negative and positive patients, using the chi-square test, independent t test, or Mann-Whitney U test, as appropriate. The relation between inflammation and joint damage progression was analyzed separately for ACPA-negative and ACPA-positive patients, using linear regression, with the change in Ratingen scores as the dependent variable (primary outcome). Ratingen score at baseline was used as a covariate; age and sex were considered as confounders. RF was not considered as a confounder because of its close association with ACPA. Logistic regression was used to analyze the occurrence of newly damaged joints (secondary outcome), with at least 1 newly affected joint considered as progression and the same covariate and confounders. Because, next to ACPA, presence of erosions at baseline itself is an important risk factor for joint damage progression, additional analyses were done, in which the models were not corrected for Ratingen score at baseline, but stratified by presence of erosions at baseline (≥ 1 Ratingen point). A regression coefficient with p value < 0.05 was considered a significant relation.

Missing values for radiograph scores at 3 years' followup were imputed using the last observation carried forward principle, with the obligation that the radiograph was performed during the third year. Missing values for ESR (3%) and VAS for general health (6%) were imputed using single imputation, including a random component, based on sex, age, C-reactive protein, and TJC[22].

The Statistical Package for the Social Sciences (SPSS), version 18.0, was used for all analyses.

RESULTS

Patients. Until August 2002, 448 patients had been included in the Nijmegen early RA cohort. Ratingen scores at baseline and followup were available for 308 patients. Of these patients, 301 (97%) had 3 or more disease activity assessments, with at least 1 visit in the third year. In 281 (91%) of these patients, ACPA status was known; 13 patients had used biological response modifiers during the first 3 years and were excluded. Consequently, 267 (60%) of 448 patients included in the cohort until August 2002 were included for the analyses. The median number of disease activity assessments of these patients was 10 (interquartile range 7–18). Imputation of the radiograph at 3 years was needed in 45 (17%) of 267 patients.

Patient characteristics, disease activity, and joint damage. Baseline characteristics of patients included in the study are presented in Table 1. ACPA-negative patients, compared to ACPA-positive patients, were significantly older and were less frequently positive for RF. There were no differences between the patient groups in measures of disease activity, except for ESR at baseline and followup that were lower in ACPA-negative patients. Presence of joint damage at baseline and progression of joint damage over 3 years was significantly lower in the patients who were ACPA-negative.

Most patients with RA were treated with DMARD monotherapy or in combination (Table 1). Combination therapy was more frequently prescribed for ACPA-positive patients. A few patients were not treated with DMARD but instead with corticosteroids or nonsteroidal antiinflammatory drugs, and this occurred more frequently in ACPA-negative patients. There were no apparent differences in use of corticosteroids between ACPA-negative and positive patients, except for dose of oral corticosteroids. No biologics were used by any patient, as this was an exclusion criterion for the study.

Disease activity score and joint damage progression. The relations between time-averaged DAS and the change in Ratingen score (primary outcome) are presented in Table 2. Linear regression models showed that DAS was strongly associated to joint damage progression in both ACPA-negative and positive patients. In ACPA-negative patients there was an increase (regression coefficient) of 3.9 ($p < 0.001$) Ratingen points per point-increase in average DAS, which was 4.7 ($p < 0.001$) for ACPA-positive patients (Figure 1A). Calculating the mean progression for an example patient with RA, a 55-year-old woman with no baseline erosions with time-averaged DAS < 1.6 over 3 years (remission), would result in no progression of Ratingen score over 3 years for both an ACPA-negative and an ACPA-positive patient. Having an average DAS between 1.6 and 2.4 (low disease activity) would now result in no progression in an ACPA-negative patient and 3 points in an ACPA-positive patient. Having an average DAS between 2.4 and 3.7 (moderate disease activity) results in 6 points progression in ACPA-negative versus 9 points in ACPA-positive patients, while an average DAS > 3.7 (high disease activity) would result in progression of 7 Ratingen

Table 1. Patient characteristics at baseline and during 3 years of followup, by anticitrullinated protein antibody (ACPA) status. Time-averaged SJC, ESR, and DAS measured during 3-year followup. Data are mean (SD), median (25th–75th percentile), or percentage (number).

Characteristic	ACPA-negative n = 87	ACPA-positive, n = 180	p*
Age at diagnosis, yrs	60 (14)	54 (12)	0.001
Female, % (n)	67 (58)	60 (107)	0.255
IgM RF-positive, % (n)	44 (38)	93 (167)	< 0.001
No. visits	10 (8–14)	11 (8–22)	0.297
Baseline SJC	14 (10–23)	14 (10–20)	0.317
Baseline ESR	22 (9–45)	38 (15–56)	0.005
Baseline DAS	3.9 (1.3)	4.0 (1.2)	0.580
Baseline tender joint count	14 (6–21)	12 (6–19)	0.882
Baseline VAS GH	48 (25)	45 (24)	0.386
Time-averaged SJC	9 (5–11)	9 (6–12)	0.137
Time-averaged ESR	14 (8–25)	19 (10–29)	0.042
Time-averaged DAS	2.6 (0.9)	2.9 (0.9)	0.041
Ratingen score at baseline	0 (0–1)	1 (0–3)	0.001
Ratingen score at 3 yrs	1 (0–8)	9 (3–19)	< 0.001
Change in Ratingen, 0–3 years	0 (0–6)	7 (2–16)	< 0.001
Newly damaged joints, 0–3 years, % (n)	48 (42)	82 (148)	< 0.001
DMARD, % (n)			
Combination therapy	76 (66)	75 (135)	0.056
Monotherapy	14 (12)	21 (38)	
None	12 (9)	4 (7)	
Methotrexate use, % (n)	41 (36)	38 (69)	0.351
Corticosteroids, % (n)			
Total	56 (49)	61 (110)	0.455
Oral < 15 mg	9 (8)	15 (27)	0.048
Oral ≥ 15 mg	13 (11)	5 (9)	

* Independent t test, Mann-Whitney U test, and chi-square test, as appropriate. RF: rheumatoid factor; SJC: swollen joint count 44 joints; DAS: Disease Activity Score; ESR: erythrocyte sedimentation rate; TJC: tender joint count 53 joints; VAS GH: general health scored on a visual analog scale; DMARD: disease-modifying antirheumatic drug.

Table 2. Four linear regression models for the relation between time-averaged Disease Activity Score (DAS) and change in Ratingen score, by anticitrullinated protein antibody (ACPA) status. Baseline Ratingen score was added as covariate to both models, age and sex were considered confounders.

Model	Beta (95% CI)	p
ACPA-negative		
DAS	3.32 (1.11–5.53)	0.004
Constant	–3.575 (–9.69–2.55)	0.249
DAS	3.87 (2.01–5.74)	< 0.001
Baseline score	1.36 (0.98–1.75)	< 0.001
Age	–0.11 (–0.24–0.01)	0.068
Sex	–2.58 (–6.23–1.07)	0.163
Constant	3.81 (–6.52–14.15)	0.465
ACPA-positive		
DAS	4.46 (2.70–6.22)	< 0.001
Constant	–2.17 (–7.46–3.31)	0.421
DAS	4.70 (2.96–6.45)	< 0.001
Baseline score	0.81 (0.51–1.11)	< 0.001
Age	–0.11 (–0.24–0.03)	0.120
Sex	–1.77 (–4.98–1.44)	0.278
Constant	3.54 (–5.62–12.69)	0.447

points in the ACPA-negative patient as compared to 14 Ratingen points in the ACPA-positive patient (Figure 2).

In the former analyses Ratingen score at baseline was used as a covariate. Next, the difference in association between DAS and change of Ratingen score between the ACPA-negative and positive group was analyzed for patients with and those without baseline erosions separately. In the subgroup with joint damage at baseline there was a strong association between DAS and change of Ratingen score; however, the difference between ACPA-positive and negative patients disappeared and the regression coefficients were 5.7 and 5.6, respectively. In contrast, in the group of patients without baseline erosions, the difference in association became larger, with a regression coefficient of 2.4 in ACPA-negative patients compared to a regression coefficient of 3.7 in ACPA-positive patients.

DAS and probability for newly damaged joints. The relation between time-averaged DAS and presence of erosions in at least 1 joint unaffected at baseline is presented in Table 3. Disease activity was associated with an increase in affected joints after 3 years in both ACPA-negative and ACPA-positive patients. The group of ACPA-negative patients had a smaller intercept and a larger regression coefficient and OR than the group of ACPA-positive patients. This corresponds with a low baseline risk and strong increase in the probability of newly damaged joints if inflammation is greater in ACPA-negative patients, while the baseline risk in ACPA-positive patients is already high and is not much further increased by an increasing level of inflammation. This resulted in a net lower risk in ACPA-negative patients at low or moderate levels of inflammation than in ACPA-positive patients. Figure 1B illustrates that with an average DAS of 2.4 (low activity), the probability to develop erosive progression in a previously unaffected joint was 0.35 in an ACPA-negative patient and 0.80 in an ACPA-positive patient. When stratified by presence of erosions at baseline, it appeared that the difference between ACPA-negative and ACPA-positive patients was larger in the subgroup of patients without baseline erosions, than in the patients with baseline

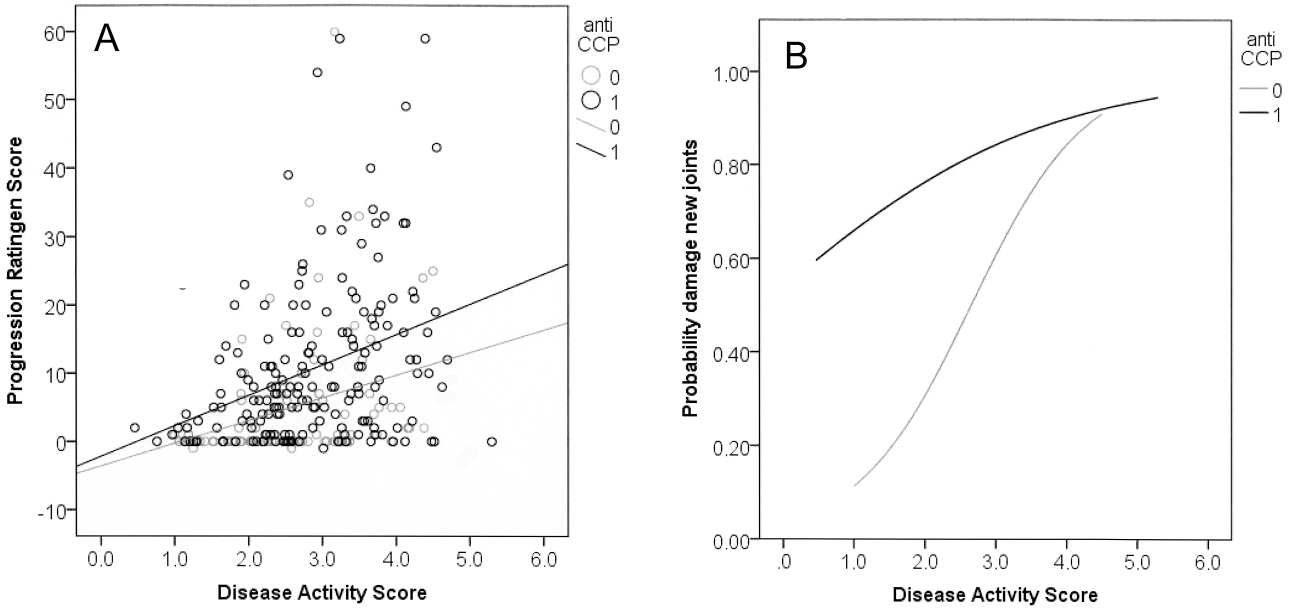

Figure 1. A. Relation between time-averaged Disease Activity Score (DAS) and the amount of joint damage progression, stratified by anticitrullinated protein antibody (ACPA) status (uncorrected model). B. Relation between time-averaged DAS and the probability of occurrence of newly damaged joints (uncorrected model).

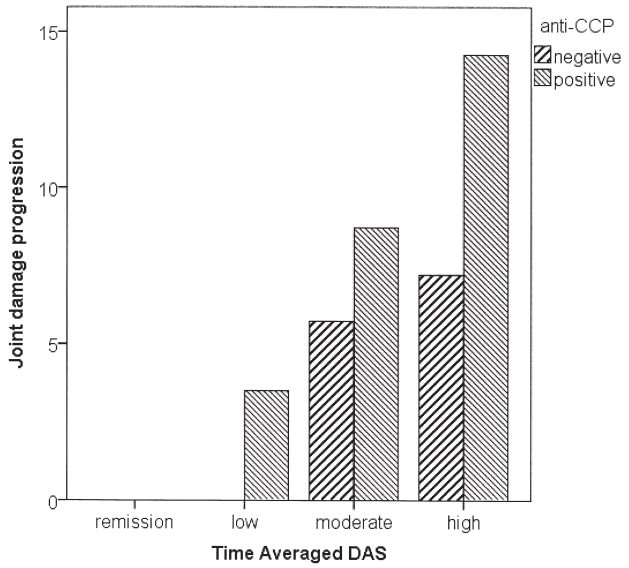

Figure 2. Mean joint damage progression (Ratingen score), calculated for an average patient (female, 55 years old, no baseline erosions), by anti-citrullinated protein antibody (ACPA) status. Remission = Disease Activity Score (DAS) < 1.6, low = DAS 1.6–2.4, moderate = DAS 2.4–3.7, high = DAS > 3.7.

Table 3. Four logistic regression models for the relation between time-averaged Disease Activity Score (DAS) and occurrence of newly damaged joints, by anticitrullinated protein antibody (ACPA) status. Baseline Ratingen score was added as covariate to the models, age and sex were considered confounders.

Model	Beta	OR (95%CI)	p
ACPA-negative			
DAS	1.24	3.47 (1.88–6.40)	< 0.001
Constant	–3.31	0.037	< 0.001
DAS	1.47	4.36 (2.03–9.36)	< 0.001
Baseline erosions	0.69	2.00 (1.19–3.36)	0.009
Age	–0.01	0.99 (0.95–1.03)	0.643
Sex	0.46	1.59 (0.46–5.51)	0.467
Constant	–4.78	0.01	0.008
ACPA-positive			
DAS	0.51	1.66 (1.07–2.56)	0.022
Constant	0.15	1.17	0.801
DAS	0.61	1.85 (1.13–3.02)	0.014
Baseline erosions	0.18	1.20 (0.99–1.46)	0.062
Age	0.01	1.01 (0.76–1.05)	0.571
Sex	–1.20	0.30 (0.12–0.77)	0.012
Constant	0.99	2.69	0.429

erosions. ACPA-positive patients without baseline erosions had a probability of 0.70 at low disease activity (DAS = 2.4), as compared to a probability of 0.25 in ACPA-negative patients. The probabilities in patients with baseline erosions were 0.70 and 0.90 in ACPA-negative and ACPA-positive patients, respectively.

DISCUSSION

According to our results, ACPA-negative patients with RA had less progression of joint damage compared to ACPA-positive patients at the same time-averaged level of disease activity, between baseline and 3-year followup. The difference between the 2 groups increased with an increase in disease activity. It was also shown that at low levels of inflammation, ACPA-positive patients already have a higher probability than ACPA-negative patients to develop erosions in new joints, but there is no difference between the 2 groups if disease activity is high. In the absence of joint damage at diagnosis, these differences between ACPA-positive and negative patients in the development of joint damage at similar levels of disease activity became even more pronounced.

Based on our results, it can be hypothesized that treatment targets in disease activity for the prevention of joint damage progression may be different for ACPA-negative and ACPA-positive patients with RA. It appears that most ACPA-negative patients develop no or little joint damage progression in a state of remission or low disease activity. Within moderate disease activity, joint damage progresses, but the probability for an increase in the number of damaged joints also becomes much higher. Remission and low disease activity both could thus be considered acceptable treatment targets for ACPA-negative RA patients, but moderate disease activity results in progression of joint damage and increase of the number of damaged joints. ACPA-positive RA patients already have measurable progression of joint damage in a low disease activity state, and the probability for joint damage in previously undamaged joints is considerable. Remission may be the most appropriate treatment target to prevent joint damage progression in that group, according to the European League Against Rheumatism treatment guidelines[5].

In the current guidelines, a quick switch to biologics is advised in cases of DMARD failure in patients with risk factors for a bad prognosis. However, as a consequence, the definition of DMARD failure is not equal for all patients, and is notably dependent on ACPA status. The same concept has recently been demonstrated for presence of RF[23]. The ultimate goal of remission in all patients with RA is very hard to achieve in practice, and a state of low disease activity is more feasible[12,13,24]. Therefore, if symptoms are acceptable for patients and the risk for progression of joint damage is limited, the adapted treatment goal in the maintenance phase might be low disease activity instead of remission in ACPA-negative patients[14]. However, before we can generally conclude that joint damage will not progress even in the swollen joints in an ACPA-negative patient with low disease activity, other baseline prognostic factors such as high ESR and presence of erosions should be considered. From a patient's perspective, levels of inflammation that are

unlikely to lead to joint damage may very well be unacceptable or may lead to other negative effects, such as the development of atherosclerosis[25]. Therefore, it is important to discuss prognosis as well as patient preferences in the management of RA.

There are some limitations in our study. The Ratingen score, a variation of the Larsen score[20], was used to score joint erosions. The Ratingen score is used less than the Sharp-van der Heijde score and therefore is harder for rheumatologists to interpret. A difference with the Sharp-van der Heijde score is that the Ratingen score counts only erosions and not joint space narrowing (JSN). However, the same joints are evaluated, and owing to the relative weight given to erosions versus JSN in the Sharp-van der Heijde score, the Ratingen and Sharp-van der Heijde erosion scores are closely correlated[26,27,28,29].

Because radiographic readings for over 300 patients of the cohort included until August 2002 were available, we analyzed this subset. The amount of joint damage progression in this subset was higher than could be expected from patients that have been diagnosed with RA more recently, because of earlier diagnosis, better treatment, and possibly a milder disease course in the last years[30,31]. However, the advantage of an older cohort is that the disease course of patients who are less intensively treated is more reflective of the "natural course." Patients who are diagnosed more recently have joint damage at baseline less often, because of the early diagnosis. The difference between ACPA-positive and negative patients was highest in the subgroup without joint damage at baseline. This is thus especially important in recently diagnosed patients.

There were treatment differences between the ACPA-negative and ACPA-positive groups. The ACPA-positive patients were treated somewhat more intensively with DMARD and corticosteroids. These differences, however, would lead to underestimation rather than overestimation of the differences in radiographic progression that were found.

We observed that ACPA-negative patients have a lower progression rate for joint damage and a lower probability that previously unaffected joints will be damaged after 3 years compared to ACPA-positive patients; this has implications for clinical treatment and for future research. As a result of the higher "tolerable" level of disease activity in ACPA-negative patients, less stringent treatment targets could be used in these patients and low disease activity might be an alternative to remission as a target. Future research is needed to determine the right treatment target for patients with limited risk for progression of joint damage when drug-free remission is not attainable, given the ACPA status and other baseline risk factors, and taking into account safety, medical costs, and patient's perceived effect of disease, for treatment with DMARD as well as with biologics.

ACKNOWLEDGMENT

The authors thank all research nurses and rheumatologists for participation and contribution in data collection; and Thea van Gaalen, Lia Schalkwijk, Carien Versteegden, and Marjon de Lange-Brand for data processing.

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