Clinically suspect arthralgia and early rheumatoid arthritis: advances in imaging and impact on daily life

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Impact on daily life

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Is ACPA-Positive Rheumatoid Arthritis Still a More Severe Disease Than ACPA-Negative Rheumatoid Arthritis? A Longitudinal Cohort Study in Rheumatoid Arthritis Patients Diagnosed From 2000 Onward

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Abstract

Objective

Because of its association with joint destruction, anti-citrullinated protein antibody (ACPA)-positive rheumatoid arthritis (RA) is considered to be more severe than ACPA-negative RA. Clinically relevant joint destruction is now infrequent thanks to adequate disease suppression. According to patients, important outcomes are pain, fatigue, and independence. We evaluated whether ACPA-positive RA patients diagnosed during or after 2000 have more severe self-reported limitations and impairments, including restrictions at work, than ACPA-negative RA patients.

Methods

A total of 492 ACPA-positive and 450 ACPA-negative RA patients who fulfilled the 2010 criteria and were included in the Leiden Early Arthritis Clinic cohort during or after 2000 were compared for self-reported pain, fatigue, disease activity, general well-being (measured by numerical rating scales), physical function (measured by the Health Assessment Questionnaire), and work restrictions, including absenteeism at baseline and during the 4-year follow-up. Linear mixed models were used.

Results

At disease presentation, ACPA-negative patients had more severe pain, fatigue, self-reported disease activity scores, and functional disability ($p<0.05$), although absolute differences were small. During follow-up, ACPA-negative patients remained somewhat more fatigued ($p=0.002$), whereas other patient-reported impairments and limitations were similar. Thirty-eight percent of ACPA-negative and 48% of ACPA-positive patients reported absenteeism ($p=0.30$), with median 4 days missed in both groups in the last 3 months. Also, restrictions at work among employed patients and restrictions with household work were not statistically different at baseline and during follow-up.

Conclusion

In current rheumatology practice, ACPA-positive RA is not more severe than ACPA-negative RA in terms of patients' relevant outcomes, including physical functioning and restrictions at work. This implies that efforts to further improve the disease course should be proportional to both disease subsets.

Introduction

Anti-citrullinated protein antibody (ACPA)-positive and ACPA-negative rheumatoid arthritis (RA) patients are considered as having different disease entities with differences in etiopathology, as both subsets have differences in genetic and environmental risk factors.[1] ACPA-positive RA has always been considered as a more severe subset of RA, as the presence of ACPA is associated with more severe joint destruction and a higher mortality rate.[2–4]

During the last decade treatment strategies have improved, and earlier treatment initiation and treat-to-target approaches have resulted in better disease outcomes.[5] Especially from the year 2000 onward, early treatment with methotrexate (MTX) has become key and, at present, clinically relevant joint destruction has become infrequent.[6–10] In addition, RA patients no longer have an evidently increased mortality rate.[11–13] Therefore, these traditional outcomes of RA have become less important. This leads to the consideration of what should be the current essential disease outcomes.

A recent study emphasized determining these outcomes, and according to patients, the important outcomes are pain, fatigue, and independence.[14] Independence strongly relates to physical functioning and the ability to perform one's tasks at home and at work.[15] It is still unknown if ACPA-positive patients in current rheumatology practice have a worse disease than ACPA-negative RA patients, as evaluated with the abovementioned patient-reported outcomes (PROs). Therefore, this study assessed, in RA patients who were diagnosed from 2000 onward and were treated with up-to-date treatment strategies, whether ACPA-positive patients have more severe PROs, including functional disability and work restrictions, than ACPA-negative RA patients.

Patients and methods

Longitudinal cohort

Patients were included in the Leiden Early Arthritis Clinic (EAC) cohort, a population-based inception cohort in The Netherlands that started in 1993. Inclusion required the presence of arthritis confirmed at physical examination and symptom duration <2 years. Baseline visit was at first presentation of arthritis at the outpatient clinic. Follow-up visits were performed yearly with questionnaires, 66 swollen (SJC66) and 68 tender joint counts (TJC68), and laboratory investigations (including C-reactive protein (CRP)-level; immunoglobulin M-rheumatoid factor (RF, positive if ≥3.5 IU/ml); and ACPA, anti-cyclic citrullinated peptide (anti-CCP2), Eurodiagnostica, positive if ≥25 U/ml; from 2009 EliA CCP, Phadia, positive if ≥7 U/ml), as described in detail elsewhere.[16] For the present study, RA patients included in the Leiden EAC cohort during or after 2000 were analyzed. Patients were treated according to routine care. According to local and national protocols, patients were treated initially with MTX; in case of failure a second conventional disease-modifying antirheumatic drug (DMARD) was started or added, and in case of subsequent failure a biologic DMARD was allowed. The strategy of treatment adjustment changed over time, as in our hospital Disease Activity Score

(DAS)-steered treatment adjustments became standard as of 2005.[17, 18]

To measure experienced pain, fatigue, disease activity, and general well-being, patients were asked by trained research nurses to indicate on single-item numerical rating scales (NRS), ranging from 0 (no symptoms) to 10 (extreme symptoms), the grade that best reflected how they felt affected by arthritis during the last 24 hours. To measure limitations in physical functioning, the multi-item Health Assessment Questionnaire (HAQ), expressed as a disability index (DI) from 0 (no disability) to 3 (severe disability), was used. A questionnaire on work ability was added to the study protocol in 2010. It contained questions from 1) the RA-specific Work Productivity Survey, addressing work status and type of work; 2) the Work Productivity and Activity Impairment Rheumatoid Arthritis questionnaire, assessing influence of disease on productivity at a paid job (presenteeism) or during nonpaid work in the past 7 days, ranging from 0 (no restrictions) to 10 (severe restrictions); and 3) additional questions on the number of days patients had worked with these restrictions in the past 7 days, as well as work days absent in the past 3 months (see Supplementary Table 6.3).

Among employed patients at baseline, we analyzed absenteeism and the number of patients that reported absenteeism; we also analyzed presenteeism (level of restrictions at work) and the number of days employed patients had worked with restrictions in the last week due to arthritis, as well as restrictions with household activities for all patients. Data were gathered at baseline and at the yearly follow-up visits. Written informed consent was obtained from all patients. The study was approved by the local medical ethics committee.

Patient selection

From all early arthritis patients included between 1993 and 2016 (n=3,722), 2,615 were included during or after 2000; of these, 982 fulfilled the 2010 classification criteria for RA at baseline [19] (see Supplementary Figure 6.5).

RA patients with missing ACPA status were excluded (n = 40); they did not differ in age, sex, SJC66, CRP level, RF positivity, or symptom duration from patients with available ACPA data (see Table S2, *online available*). In total, 450 ACPA-negative and 492 ACPA-positive patients were studied. To evaluate whether the choice of classification criteria affected the results, analyses were repeated with RA defined as fulfilling the 1987 criteria.[20] Of the 2,615 patients included from 2000 onward, 563 fulfilled the 1987 criteria at baseline (225 ACPA-negative patients, 338 ACPA-positive patients). A portion of the patients that fulfilled the 1987 criteria did not fulfill the 2010 criteria and vice versa.

Since the introduction of the questionnaire on work ability in 2010, 130 ACPA-negative and 152 ACPA-positive RA patients fulfilling the 2010 criteria were included (see Supplementary Figure 6.5). Of these 282 patients, 24 ACPA-negative and 36 ACPA-positive patients did not fill in the work ability questionnaire at baseline. These 60 patients did not differ in age, sex, symptom duration, SJC66, CRP level, or RF positivity

from those who did complete the work ability questionnaire (see Table S3, available on the Arthritis Care & Research web site). The addition of this questionnaire later in the study does not cause a bias, as missingness is completely at random.

Statistical analyses

We presented median levels and corresponding interquartile ranges. Baseline data were analyzed with a t-test, the Mann-Whitney U test, and chi-square test as appropriate.

For longitudinal analyses between ACPA-negative and ACPA-positive patients, linear mixed models were used. Although PROs were non-normally distributed, the residuals were normally distributed and thus fulfilled the requirement for linear mixed models. Patients were censored after 4 years of follow-up because the number of patients with follow-up longer than this period decreased. No random effects were added to the model.[21, 22] This model has the advantage that all patient information, including those who had missing data of PROs, was used, as it assumes that missing outcomes can be estimated using available measurements. Also, to prevent bias due to selective dropout of patients, we did not apply a minimum follow-up duration for inclusion in the analyses. To determine the best-fitting covariance matrix, the matrices available in SPSS were considered. Akaike information criterion was used to measure the goodness-of-fit, as this was best for the compound symmetry matrix. We obtained estimates of the main effect of ACPAs. Because the target variables are known to vary with age and sex, adjustments were made in all longitudinal analyses. For PROs of impairments and limitations, adjustments for the year of inclusion were also made.[23–25] In analyses, median values of estimated coefficients of the longitudinal analyses are shown. IBM SPSS, version 23, was used, and values less than 0.05 were considered significant.

Sensitivity analyses

In sensitivity analyses, it was first evaluated whether results would be different when ACPA-negative and RF-negative patients were compared to patients with positive ACPA and/or RF, as part of the ACPA-negative patients were RF positive. Second, analyses were repeated in patients that were included during or after 2005. This was done as this study aimed to evaluate patients who were treated according to current treatment strategies. Although an early start of MTX was common from 2000 onward, DAS-steered treatment adjustments became fully integrated in daily practice in our hospital from 2005 onward.[18]

Finally, as a reference showing that patients treated according to up-to-date treatment strategies were different from patients who were treated in the past, we performed similar analyses for patients who were included in the EAC between 1993 and 1999. In this era, DMARDs were initiated with delay, and/or mild DMARDs (such as hydroxychloroquine) were started as initial therapy, as described elsewhere.[5]

Results

Patient characteristics

(Table 6.1) presents baseline characteristics of included RA patients (fulfilling the 2010 criteria). ACPA-negative patients were older (mean age 63 versus 54 years; p<0.001), had more swollen joints than ACPA-positive patients (median 9 versus 5; p<0.001), more tender joints (median 16 versus 10; p<0.001), and a shorter disease duration (median 103 versus 144 days; p<0.001). Over time a similar proportion (70-80%) of patients achieved DAS-remission (44 joints assessed, DAS≤2.4) (Figure 6.1), indicating that despite differences in characteristics between both groups the disease activity was equally suppressed in both groups.

Table 6.1: Baseline characteristics of RA patients (fulfilling 2010 criteria) for analyses on patient-reported impairments and limitations, and work restrictions

	ACPA-negative (n=450)	ACPA-positive (n=492)	P-value
Age, mean (SD)	60 (16)	54 (14)	<0.001
Female, n (%)	295 (66)	333 (68)	0.49
68-Tender joint count, median (IQR)	16 (10-24)	10 (5-17)	<0.001
66-Swollen joint count, median (IQR)	9 (4-14)	5 (3-10)	<0.001
CRP (mg/L), median (IQR)	12 (3-32)	11 (4-24)	0.40
RF positive (≥3.5 IU/mL), n (%)	154 (34)	431 (88)	<0.001
Symptom duration in days, median (IQR)	103 (58-194)	144 (72-294)	<0.001
	ACPA-negative (n=130)	ACPA-positive (n=152)	P-value
Age, mean (SD)	59 (16)	54 (14)	0.009
Female, n (%)	90 (69)	99 (65)	0.47
68-Tender joint count, median (IQR)	13 (8-21)	8 (4-12)	<0.001
66-Swollen joint count, median (IQR)	7 (3-12)	5 (2-8)	0.005
CRP (mg/L), median (IQR)	11 (3-32)	8 (3-18)	0.12
RF positive (≥3.5 IU/mL), n (%)	58 (45)	129 (85)	<0.001
Symptom duration in days, median (IQR)	94 (46-210)	121 (68-280)	0.035

ACPA, anti-citrullinated peptide antibody (anti-CCP2, EliA CCP, Phadia, the Netherlands, positive if ≥7 U/mL); RF, immunoglobulin M-rheumatoid factor (RF) (positive if ≥3.5 IU/mL); CRP, c-reactive protein (positive if ≥5mg/L); SD, standard deviation; IQR, Inter quartile range.

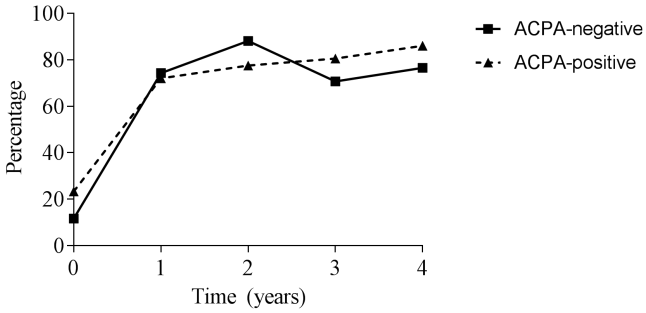

Figure 6.1: The percentages of ACPA-negative and ACPA-positive RA-patients (2010-criteria) achieving DAS-remission (DAS44<2.4) during 4-years follow-up.

Patient-reported impairments and limitations at baseline

ACPA-negative patients reported statistically significant more pain than ACPA-positive patients (median 5.8 versus 5.2, p=0.045), more severe fatigue (median 5.5 versus 5.0, p=0.003), more severe disease activity (median 6.1 versus 5.6, p=0.006) and more functional disability (1.0 versus 0.9, p=0.001), although absolute differences were small (Figure 6.2). General wellbeing was equal for both groups of patients (median 4.3 versus 4.0, p=0.25). As, due to the composition of the 2010-criteria ACPA-negative patients can only fulfill the criteria in case of >10 involved joints and ACPA-negative patients indeed had more swollen joints, we hypothesized that the patient selection by the criteria used might explain the higher PROs in ACPA-negative patients. Therefore analyses were repeated in 1987-criteria positive RA-patients. Baseline characteristics are shown in Supplementary Table 6.4. Here, no significant differences were observed between ACPA-negative and ACPA-positive RA-patients (6.2).

Course of patient-reported impairments and limitations during 4 years of disease

The 450 ACPA-negative and 492 ACPA-positive RA-patients (2010-criteria) were studied during 4-years follow-up, as shown in Figure 6.1, which shows the predicted values adjusted for age, gender and year of inclusion. For all measured variables, the largest improvement was seen during the first year. Both patient groups had equal amounts of pain over time. ACPA-negative patients remained more severely fatigued over time (p=0.002; β=0.53; this β indicates that on a NRS ranging 0-10 ACPA-negative patients were 0.5 more severely fatigued). The self-reported disease activity and the HAQ were equal between both groups. We corrected for age in all analyses and this had only a significant effect in the longitudinal analysis of the HAQ (β=0.008; p<0.001 on a scale ranging from 0-3). When the 1987-criteria positive RA-patients were studied over time, no statistically significant differences were found for all variables (Figure S2, *online available*). Repeating the analyses in RA-patients (both if defined by the 2010- or the 1987-criteria) with additional correction for RF-factor positivity, SJC and symptom duration, resulted in no significant differences between ACPA-negative and

ACPA-positive patients.

Patient-reported restrictions with work and household activities at baseline

Baseline characteristics of the 130 ACPA-negative and 152 ACPA-positive patients that completed questionnaires on work restrictions are presented in Table 6.1. Absenteeism and presenteeism among patients with paid work were not different at disease presentation as shown in Table 6.2. 38% ACPA-negative versus 48% of ACPA-positive employed patients reported absenteeism in the last 3 months (p=0.30), with median 4 days missed at work for both groups. Presenteeism due to arthritis was equal, median 3 versus 5, and the days worked with restrictions due to arthritis was median 4 versus 3

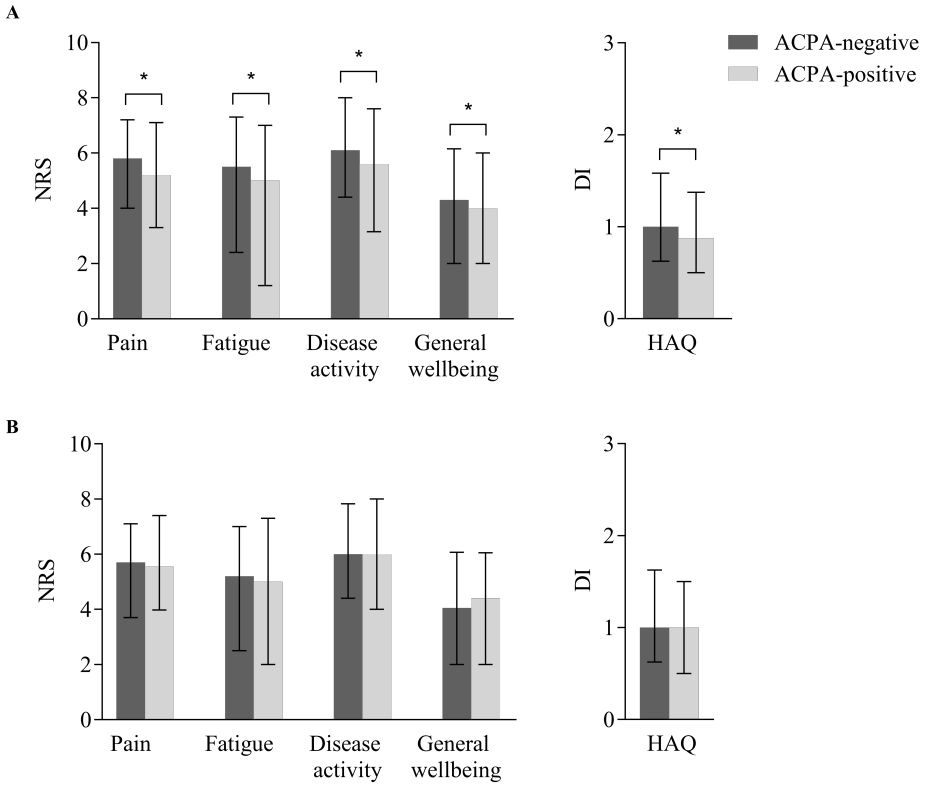

Figure 6.2: Patient-reported outcomes of impairments and limitations of ACPA-negative and ACPA-positive patients for the 2010-criteria (A) and 1987-criteria (B) at baseline.
Legend. Median values and corresponding interquartile ranges are shown for severity of self-reported pain, fatigue, disease activity and general wellbeing measured by NRS (numerical rating scale) ranging from 0-10, and physical function by the health assessment questionnaire-disability index (HAQ-DI) ranging from 0-3 in the last 24 hours. *p-values<0.05 with Mann-Whitney U test.

days for ACPA-negative and ACPA-positive patients, respectively. Also, restrictions due to arthritis at home were similar. The median level of restriction was 6 versus 7 in ACPA-negative and ACPA-positive patients and median days restrictions due to arthritis was 7 versus 6, respectively. Statistically, differences were non-significant for all analyses.

Table 6.2: Baseline data of ACPA-negative and ACPA-positive RA-patients (1987-criteria) on restrictions with work and household activities

	ACPA-negative (n=130)	ACPA-positive (n=152)	P-value
Productivity at home			
Level of restrictions in household work productivity past 7 days, median (IQR)	6 (2-8)	7 (3-8)	0.84
Days restricted in household productivity past 7 days, median (IQR)	7 (2-7)	6 (2-7)	0.25
Employed, n (%)	40 (31)	69 (45)	0.001
Age, mean (SD) years	47 (13)	49 (11)	0.31
Type of work:			0.48
Physical, n (%)	7 (18)	16 (23)	
Physical and mental, n (%)	19 (48)	25 (36)	
Mental, n (%)	13 (33)	27 (39)	
Productivity in the work place			
Work hours per week, median (IQR)	32 (20-38)	28 (20-40)	0.80
Work days per week, median (IQR)	5 (4-5)	5 (3-5)	0.31
Missed any work in last 3 months, n (%)	15 (38)	33 (48)	0.30
Days missed at work in last 3 months (absenteeism), median (IQR)	4 (2-21)	4 (2-12)	0.92
Level of restrictions in work productivity (presenteeism) past 7 days, median (IQR)	5 (2-8)	3 (2-8)	0.41
Days restricted while at work past 7 days, median (IQR)	4 (2-7)	3 (0-5)	0.20

*Analysed in employed patients only. 0-10 scale, where 0 means no restrictions and 10 means complete restrictions. Percentages were calculated on non-missing data. There were no statistically significant differences. ACPA, anti-citrullinated peptide antibody; RA, Rheumatoid Arthritis; SD, standard deviation; IQR, Inter quartile range.

When the 1987-criteria positive RA-patients were studied, no statistically significant differences were observed for all analyses (Supplementary Table 6.5).

Course of patient-reported restrictions with work and household activities during 4 years of disease

Presenteeism was assessed during 4-years follow-up and was equal between both groups (p = 0.89). ACPA-negative 2010-criteria positive patients had more days with restrictions at work (p=0.02; β=0.89, this β indicates that ACPA-negative patients had 0.89 days more restrictions) than ACPA-positive patients. Both restrictions at home (p=0.17) and the days restrictions at home (p=0.64) were equal, as illustrated by Figure 6.4. Evaluating

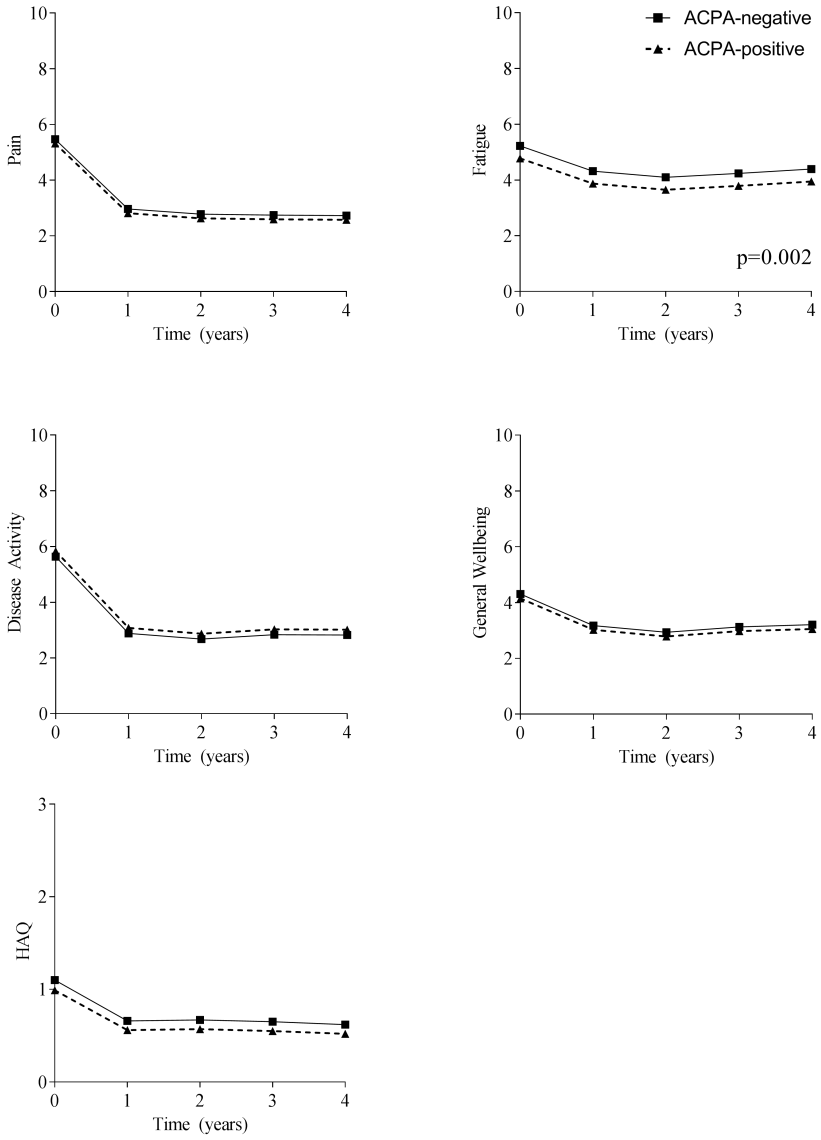

Figure 6.3: Patient-reported outcomes of impairments and limitations of ACPA-negative and ACPA-positive RA-patients for the 2010-criteria during 4-years follow-up.
Legend. Presented are median predicted values obtained by linear mixed models adjusted for age at inclusion, gender and year of inclusion. In case of significance of the interaction between ACPA and time, this was added to the modeled figures. Pain, fatigue, disease activity and general wellbeing were measured by a 0-10 NRS scale. Physical function was measured by the HAQ with a disability index from 0-3. Both groups experienced equal pain; ACPA-negative patients were more severely fatigued (p=0.002; β=0.53) than ACPA-positive patients; both groups had equal self-reported disease activity, general wellbeing and HAQ. The number of available data per follow-up year for ACPA-positive patients for pain: 457, 316, 224, 240, 209; fatigue: 447, 276, 187, 202, 176; disease activity: 457, 315, 224, 239, 209; general wellbeing: 449, 316, 223, 242, 210; HAQ: 430, 268, 140, 221, 197. For ACPA-negative patients for pain: 404, 257, 177, 165, 138; fatigue: 400, 232, 150, 143, 114; disease activity: 403, 257, 177, 166, 138; general wellbeing: 401, 257, 175, 166, 139; HAQ: 382, 224, 105, 147, 120.

the 1987-positive RA-patients over time revealed no significant differences in all these analyses (Figure S3, *online available*).

Sensitivity analyses

Because 33% of the ACPA-negative 2010-criteria positive RA-patients were RF-positive, patients without ACPA or RF (n=296) were compared to patients with ACPA and/or RF (n=646). At baseline, patients without ACPA and/or RF had more self-reported pain (p=0.003), were more severely fatigued (p=0.045), had a more severe disease activity (p<0.001) and more severe functional disability (p=0.001). General wellbeing was equal (p=0.17). Thus, these findings were similar to the results of the main analyses. Over 4-years follow-up patients without ACPA and/or RF had more severe pain (p=0.007; β=0.37), were more severely fatigued (p=0.001; β=0.60), had more severe disease activity (p=0.001; β=0.44) and more severe general wellbeing (p=0.026; β=0.29). The HAQ over time was not statistically different between both groups (p=0.08). RA-patients (2010-criteria) without ACPA or RF (n=72) and patients with ACPA and/or RF (n=210) were evaluated for restrictions at work and at home. At baseline patients with and without ACPA and/or RF had equal absenteeism (p=0.21), presenteeism (p=0.75), number of days restrictions at work (p=0.31), level of restrictions at home (p=0.91) and number of days restrictions at home (p=0.97). Over 4-years follow-up both groups had equal presenteeism (p=0.78). ACPA- and RF-negative patients had more days restrictions at work due to arthritis (p=0.043; β=1.2). The level of restrictions at home (p=0.77) and days restrictions at home (p=0.50) were equal between the groups. Because DAS-steered treatment became regular as of 2005, analyses were repeated for 2010-RA-patients included ≥2005. This showed similar results as that of the total group. At baseline ACPA-negative patients reported more severe pain than ACPA-positive patients (p=0.016; β=0.20), more severe fatigue (p=0.003; β=0.45), more severe disease activity (p<0.001; β=0.39), more severe general wellbeing (p=0.029; β=0.14) and more functional disability (p=0.001; β=0.08 on a scale ranging from 0-3). Also follow-up data showed similar results as that of the total group, as shown in Figure S4 (*online available*). Finally, to compare the main findings with those obtained on RA-patients that were treated in earlier time periods and thus with different treatment strategies, the analyses of patient-reported impairments and limitations in ACPA-positive and ACPA-negative patients were also performed on RA-patients included in the EAC between 1993 and 1999 (n=335). As shown in Figure S5 (*online available*), several PROs were more severe in ACPA-positive RA-patients during 4-years follow-up; statistical significance was reached for general wellbeing (p=0.020; β=0.10) and a tendency towards significance for patient-reported disease activity (p = 0.06; β=0.05).

Discussion

This large longitudinal study assessed if at present ACPA-positive RA-patients are still more severely affected than ACPA-negative RA-patients, using self-reported impairments and limitations including functional disability and restrictions at work as outcomes. The current availability of treatment strategies to suppress inflammation

drastically reduced the frequency and degree of joint damage, which makes that prospects of RA-patients have changed substantially.[10] Consequently, other disease outcomes have become central and patients have rated pain, fatigue, wellbeing and independence, items which have been studied here, as most important.[14] In addition, physical functioning and work ability, the key component of independence in RA are important from a socio-economic perspective. We did not observe a more severe disease patient burden in ACPA-positive RA. Evidently, the present data require validation in an independent cohort. Nonetheless, the assumption that ACPA-positive RA is a

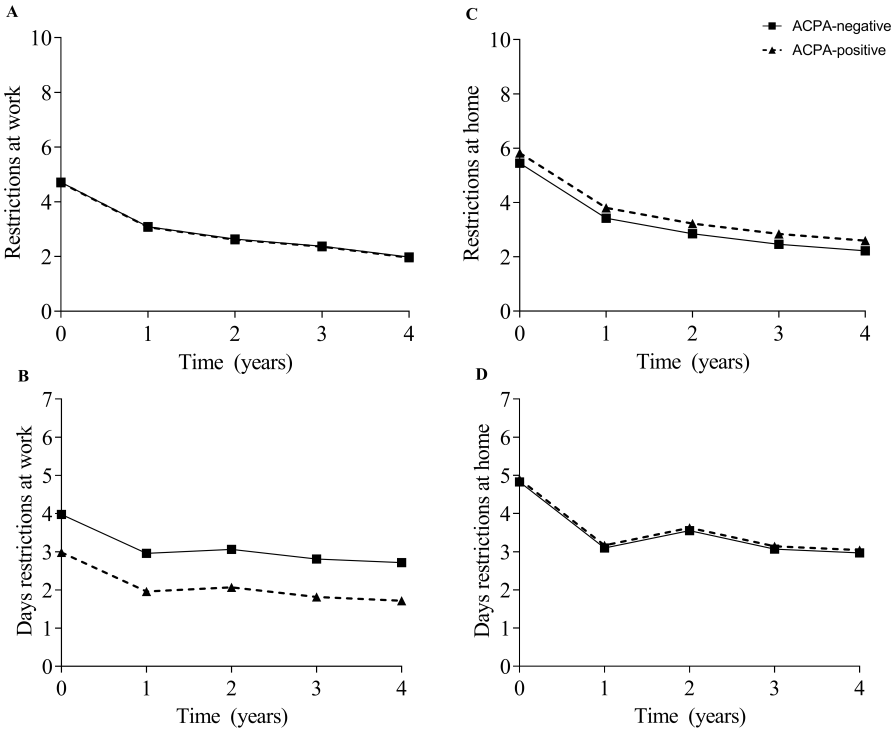

Figure 6.4: Presented are median predicted values obtained by linear mixed models adjusted for age at inclusion and gender of ACPA-negative and ACPA-positive RA-patients according to the 2010-criteria. Presenteeism (level of restrictions at work) (A), number of days restrictions at work (B) and level of restrictions (C) and days restrictions with household activities (at home) (D) over 4-years follow-up. Level of restrictions was measured on a scale of 0-10. Days restrictions due to arthritis ranged from 0-7 days. Presenteeism was equal (p=0.89). ACPA-negative patients had a significantly higher number of days restrictions at work due to arthritis (p=0.02; β=0.89). Level of restrictions (p=0.17) and number of days they had restrictions at home (p=0.64) were equal.
The number of available data per follow-up year for ACPA-positive patients for level of restrictions at work: 63, 52, 44, 31, 19; for days restrictions at work: 53, 50, 36, 27, 17; level of restrictions at home: 103, 83, 75, 59, 37; for days restrictions at home: 89, 69, 63, 51, 28. For ACPA-negative patients for level of restrictions at work: 38, 20, 12, 9, 5; for days restrictions at work: 36, 17, 10, 9, 4; for level of restrictions at home: 82, 58, 39, 24, 12; for days restrictions at home: 71, 44, 26, 16, 8.

more severe disease seems no longer true in current rheumatology practice when the mentioned patient-reported outcomes are considered.

Contrary to the hypothesis tested, we actually observed some differences to the detriment of ACPA-negative patients. However, these differences were small and clinically irrelevant. As ACPA-negative patients were older, which was also shown in previously performed studies, we corrected for age in all longitudinal analyses.[26] Also when analyses were additionally adjusted for comorbidities, similar results were obtained (data not shown). We hypothesized that the small differences found were most likely caused by the fact that RA-patients without ACPA or RF need > 10 joints involved to fulfill the criteria and ACPA-negative patients with positive RF required 4-10 joints involved as reflected by the patient characteristics which showed that ACPA-negative RA-patients (according to the 2010-criteria) had a higher tender- and swollen joint count than ACPA-positive patients. This effect has been observed before.[27, 28] For this reason we repeated the analyses in patients classified according to the 1987-criteria, with a more similar joint count between ACPA-negative and ACPA-positive patients. Then, we did not observe the somewhat higher disease burden for ACPA-negative RA, when treated with current treatment strategies and considering patient-reported impairments and limitations. Thus, although this study was not set up to compare the 2010- and 1987-criteria, the presented data do confirm previously reported observations that ACPA-positive 2010-RA consists of a less severe subset of patients than ACPA-positive 1987-RA and that ACPA-negative 2010-RA consist of a more severe subset of patients compared to ACPA-negative 1978-RA.[27, 28]

In current research, there is a tendency to concentrate more on ACPA-positive than on ACPA-negative RA. For example, much more whole genome genetic studies were performed on ACPA-positive RA.[29] This focus in etiopathologic studies is possibly explained by the paradigm that ACPA-negative RA might represent a more heterogeneous subset of patients, and that current research has revealed fewer clues on the possible causes or mediators of ACPA-negative RA. This could have resulted in ACPA having conquered a more prominent position in the identification of RA within the 2010-criteria. This study however does not intend to address the issue on the classification criteria. The data presented clearly demonstrate that at present ACPA-negative RA is equally severe as ACPA-positive RA when patient-reported impairments and limitations are studied as outcomes. This has implications for future research, both for etiopathophysiological and clinical studies. The present data highlights the importance of keeping the scope set on ACPA-negative RA as well, because it has become an equally severe disease. Moreover the prevalence of ACPA-negative RA like measured in early arthritis cohorts, concerns up to half of the total RA-population.[26, 30]

The risk of misdiagnosis is often estimated higher for ACPA-negative RA than for ACPA-positive RA. In this study, patients were diagnosed with RA according to the treating rheumatologist and this clinical diagnosis was verified after 1 year of disease in the medical files of all patients. Hence, patients that evolved to have other diseases were no longer in the data set. Thereafter patients were checked on fulfilling the 2010-criteria

(or 1987-criteria for sub-analyses). When all these conditions were met, patients were included. Because of this stringent selection, we think that the risk of misdiagnosis of ACPA-negative RA is low.

Secondary comorbidities like fibromyalgia (FM) could also influence the PROs, like pain and fatigue.[31] Data on secondary FM was not collected in our cohort. However, we have no reason to believe that secondary FM would have influenced our comparisons between autoantibody-positive and autoantibody-negative patients, as previous studies have demonstrated that RA-patients with and without concomitant FM have an equal prevalence of RF-positivity.[31–34]

Measuring patients' perceptions of health is a standard approach in observational studies and epidemiological research. Measurements of PROs have proven to be valid and responsive and are sensitive to detect differences between patient groups.[28, 35–38] This is the first study to extensively compare several PROs and work ability among ACPA-positive and ACPA-negative RA-patients during 4-years follow-up. Other studies have included the HAQ or DAS in their analyses and sometimes other patient-reported outcomes.[28, 36–39] However, these measurements were mainly performed at baseline and were not conducted to find differences between ACPA-positive and negative patients over time. Further, it was shown that patients with RA in countries with higher welfare score worse on PROs despite lower levels of objectively measured disease outcomes.[8, 25, 40] However, this study is conducted in only one country.

PROs may be influenced by secular trends.[23–25] Patients studied were included between 2000 and 2014. To prevent confounding effects we did correct the analyses for the year of inclusion. There is no reason to believe that personal contextual factors such as education or self-efficacy are different between ACPA-positive and ACPA-negative patients.

A limitation of PROs could be that reproducibility is sometimes not very satisfactory [41] and the difficulty of any study using self-reported outcomes can be that they may be susceptible to non-response and recall bias. We do not expect this to cause a difference for the comparison made. Also, we are aware that absenteeism is calculated with a recall period of 3 months and some patients present with symptom durations shorter than this. However, if this had any effect, it would have led only to an underestimation of absenteeism in ACPA-negative patients, as they more often had a shorter symptom duration at presentation.

Our frequencies of employment, absenteeism and presenteeism are in accordance with previous studies in RA that also showed that RA-patients are interfered considerably by means of work restrictions even despite improved treatment strategies.[42–44] Data of the Dutch reference population was obtained from the Dutch 'Centraal Bureau voor Statistiek'.[45] Here 45% of the persons aged 45-55 years (this was the most prevalent age category in the patients' cohort) had missed days at work due to sickness during 12 months of the year 2016. The average sick leave was 8 days per year. In comparison,

38-48% of the employed ACPA-negative and ACPA-positive RA-patients missed days at work during 3 months period. In both ACPA-groups the median days missed at work were 4 per 3-months, extrapolation to a 12 months period would result in an estimated sick leave of 16 days per year. This is evidently more than the sick leave in the reference population and these data confirm that RA patients currently still have increased work restrictions. Furthermore, this study adds that no differences were found between ACPA-positive and ACPA-negative patients. Notably the number of working patients was relatively small in our data-set, but findings that the results on restrictions at work were similar to those of the patient-reported impairments and limitations show face-validity.

This study was conducted to evaluate patients that were diagnosed early and were treated according to up-to-date treatment strategies, consisting of early initiation of methotrexate and DAS-steered treatment adjustments. We cannot compare the actual DMARDs used over time in both groups as these data were not collected sufficiently accurate. According to local guidelines initial treatment of ACPA-positive and ACPA-negative RA was similar: treatment regimen consisted of initial treatment with a DMARD (preferably MTX), in case of failure a second conventional DMARD was started and in case of failure a biologic DMARD was allowed. From 2005 onwards, in our hospital DAS-steered treatment became standard,[18] meaning that treatment regimens were adjusted based on the individuals' disease activity. Analysis of biologic DMARDs used after 2-years follow-up revealed that these were used by 9% of ACPA-positive patients and 1% for ACPA-negative patients. Furthermore, the disease activity measured during follow-up was similar in both groups. Hence it is possible that the ACPA-positive patients required more, or more aggressive DMARDs to achieve a similar DAS. Our results could therefore be considered as the consequence of improved treatment strategies.

In line with this notion, we evaluated if PROs were different between ACPA-positive and ACPA-negative patients that were treated in earlier periods with treatment strategies that are now considered outdated. Although the number of patients in this group was smaller, ACPA-positive patients indeed had some PROs that were worse than those of ACPA-negative patients. Results of the present study therefore imply that thanks to improved treatment strategies, not only differences between ACPA-positive and ACPA-negative RA in outcomes such as joint damage severity diminished or disappeared, but that this applied for differences in patient-reported outcomes.

In conclusion, this study thoroughly compared various PROs and restrictions with work during follow-up in ACPA-positive and ACPA-negative RA-patients. It demonstrated that ACPA-positive and ACPA-negative RA managed with nowadays treatment strategy represent an equally severe subset of disease. We do not know if rheumatologists take PROs into account when making treatment decisions. However, as joint damage becomes less relevant as outcome, in the future we should explore if PROs can be considered. Further research is required, but the important personal health impact as well as the socio-economic burden highlighted by the present study imply that effort to further improve the disease course should be proportional to ACPA-positive and ACPA-negative RA.

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Supplementary data

Supplementary data are available at *Arthritis Care & Research Online*.

Supplementary figure

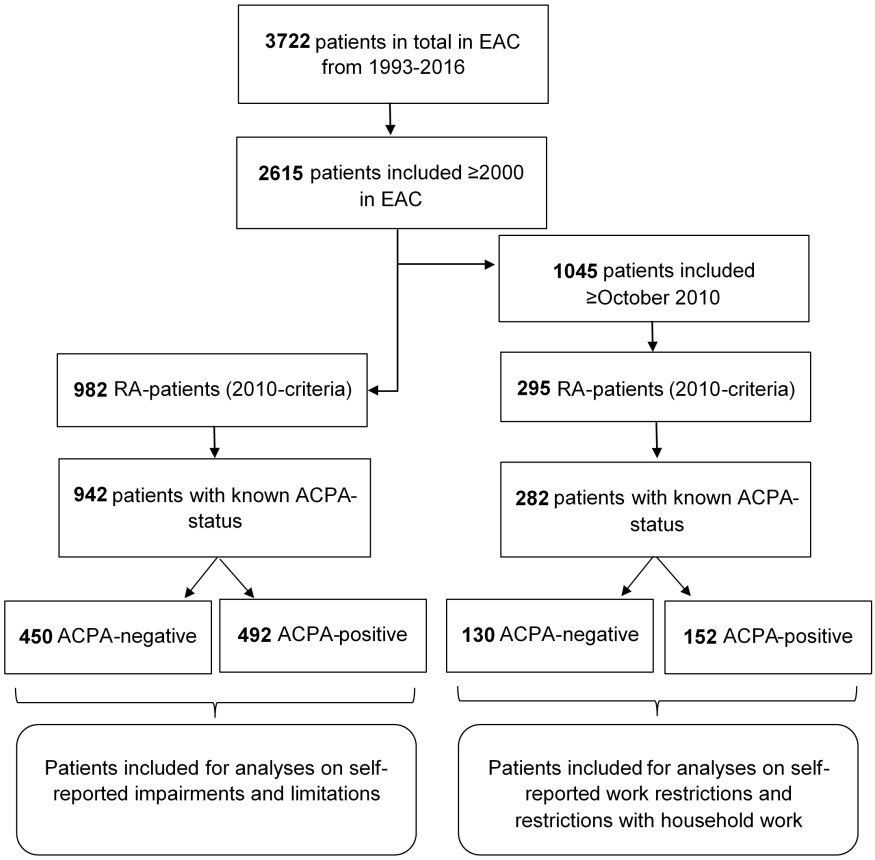

Figure 6.5: Flowchart of patient selection. Legend. Flowchart of patient selection from the Leiden Early Arthritis Clinic (EAC) cohort. The questionnaire on work ability was added to the protocol in 2010. All patients studied for analyses on self-reported work restrictions are part of the patients included for analyses on self-reported impairments and limitations. Analyses were also done in RA-patients included ≥2000 that met 1987-criteria. For self-reported impairments and limitations there were 225 were ACPA-negative and 338 ACPA-positive RA-patients; for work restrictions there were 57 ACPA-negative and 125 ACPA-positive RA-patients.

Supplementary tables

Table 6.3: Work ability questionnaire.

From WPS-RA
Is the patient currently employed outside of home: yes/no *If employed:* What is your occupation: Which box describes their job function best: non-manual, mixed, manual. *If unemployed:* Please check the box that describes their status best: homemaker (voluntary), retired, student, unable to work (due to arthritis or not), jobless.
Other questions
If employed: Absence from work during the last 3 months: yes/no. If yes, how many days have you missed during the last 3 months. How many days did rheumatic complaints affect your productivity during the past 7 days while you were working (0-7). *All patients:* How many days did your rheumatoid arthritis affect your productivity of your normal daily activities, other than work at a job during the past 7 days (0-7).
From WPAI-RA:
If employed: How much did your rheumatic complaints restrict your productivity during the past 7 days while you were working (0-10; 10 unable to work). *All patients:* How much did your rheumatic complaints restrict your productivity of your normal daily activities, other than work at a job during the past 7 days (0-10; 10 unable to work).

Table 6.4: Baseline characteristics of ACPA-negative and ACPA-positive RA-patients (according to the 1987-criteria) for analyses on patient-reported impairments and limitations

	ACPA-negative (n=225)	ACPA-positive (n=338)	P-value
Age, mean (SD)	62 (15)	55 (14)	<0.001
Female, n (%)	142 (63)	226 (67)	0.36
68-Tender joint count, median (IQR)	14 (7-23)	10 (6-17)	0.002
66-Swollen joint count, median (IQR)	8 (4-15)	7 (3-11)	0.001
CRP (mg/L), median (IQR)	15 (5-33)	12 (5-27)	0.34
RF positive (≥3.5 IU/mL), n (%)	66 (29)	296 (88)	<0.001
Symptom duration in days, median (IQR)	86 (49-155)	136 (70-263)	<0.001

ACPA, anti-citrullinated peptide antibody (anti-CCP2, EliA CCP, Phadia, the Netherlands, positive if ≥7 U/mL); RF, immunoglobulin M-rheumatoid factor (RF) (positive if ≥3.5 IU/mL); CRP, c-reactive protein (positive if ≥5mg/L); SD, standard deviation; IQR, Inter quartile range.

Table 6.5: Baseline data of ACPA-negative and ACPA-positive RA-patients (1987-criteria) on restrictions with work and household activities

	ACPA-negative (n=57)	ACPA-positive (n=125)	P-value
Productivity at home			
Level of restrictions in household work productivity past 7 days, median (IQR)	7 (3-8)	7 (3-8)	0.63
Days restricted in household productivity past 7 days, median (IQR)	7 (2-7)	5 (3-7)	0.29
Employed, n (%)	19	55	0.016
Age, mean (SD) years	50 (13)	49 (11)	0.90
Type of work:			
Physical, n (%)	5 (26)	11 (20)	
Physical and mental, n (%)	11 (58)	18 (33)	
Mental, n (%)	3 (17)	25 (45)	
Productivity in the work place			
Work hours per week, median (IQR)	36 (28-40)	26 (20-40)	0.86
Work days per week, median (IQR)	5 (5-5)	4 (3-5)	0.19
Missed any work in last 3 months, n (%)	9 (47)	28 (51)	0.79
Days missed at work in last 3 months (absenteeism), median (IQR)	9 (2-31)	5 (2-12)	0.32
Level of restrictions in work productivity (presenteeism) past 7 days, median (IQR)	6 (3-10)	4 (2-8)	0.38
Days restricted while at work past 7 days, median (IQR)	3 (1-7)	3 (0-5)	0.53

*Analysed in employed patients only. 0-10 scale, where 0 means no restrictions and 10 means complete restrictions. Percentages were calculated on non-missing data. There were no statistically significant differences. ACPA, anti-citrullinated peptide antibody; RA, Rheumatoid Arthritis; SD, standard deviation; IQR, Inter quartile range.