The Predictive Value of Anti-Cyclic Citrullinated Peptide Antibodies in Early Arthritis

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ABSTRACT. ***Objective.*** To assess the additional predictive value of anti-cyclic citrullinated peptide (anti-CCP) antibodies above conventional variables for progressive erosive or disabling disease in a cohort of patients with early inflammatory oligo- and polyarthritis.

Methods. Consecutive new patients with peripheral arthritis of > 2 joints and < 2 years of symptom duration, referred between 1995 and 1999 were studied. Excluded were patients with bacterial, psoriatic, crystal-induced arthritis or spondyloarthropathy. Optimal cut-off values for serum IgM-rheumatoid factor (RF) and anti-CCP were deduced from receiver operating characteristics curves. At 2 year followup, progressive erosive disease was defined as: radiographic progression > 5 (Sharp-van der Heijde units) and low functional capacity as a Health Assessment Questionnaire score > 1. For the statistical analysis, a logistic regression model was used.

Results. A total of 282 patients [68% female, median age 56 yrs (18–83)] were included. Thirty-two percent of the patients were positive for anti-CCP at baseline. Anti-CCP correlated significantly ($p < 0.001$) with a progressive erosive disease after 2 years, but not with a low functional capacity. The combination of a positive anti-CCP status and radiographic damage at baseline could predict the radiographic progression with a sensitivity, specificity, and accuracy of 78%, 82%, and 81%, respectively. The positive predictive value (PPV) for radiographic progressive disease was 63%, while the negative predictive value (NPV) was 90%. The accuracy of the model decreased from 81 to 76% after leaving out anti-CCP from the model. In a subgroup of 178 IgM-RF negative patients, the PPV for radiographic progressive disease was 40%, while the NPV was 95%.

Conclusion. Anti-CCP positivity has a small additional value above the conventional prognostic variables for progressive erosive disease in a cohort of patients with early inflammatory oligo- and polyarthritis. The prognostic value of anti-CCP lies mainly in its ability to predict mild disease. This effect is accentuated in the subgroup of IgM-RF negative patients. (J Rheumatol 2003;30:1691–5)

Key Indexing Terms:
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Recent reports highlight the early onset of structural joint damage in patients with rheumatoid arthritis (RA)[1,2]. Antirheumatic therapy has become more aggressive and is started earlier[3-5]. As a consequence, there is a risk that patients with benign, self-limiting polyarthritis will be treated unnecessarily with antirheumatic drugs. It would be desirable to separate such patients from those who will develop persistent and destructive disease. Attempts to base this separation on the presence or absence of the diagnosis RA are hampered by the lack of a clear definition of early RA. There is no distinct clinical, laboratory or radiological marker to support an early diagnosis of RA. At present, the diagnosis RA is defined by the 1987 criteria of the American College of Rheumatology (ACR)[6]. However, these classification criteria have low sensitivity in early RA[7,8].

More important than a correct diagnosis is the ability to predict a severe disease outcome. Although more than half the patients with undifferentiated polyarthritis (UPA) have a good prognosis, a substantial minority develops a severe disease that may not be recognized and treated in time[9].

Established prognostic markers for a severe outcome of early RA are: female sex[10,11]; serum IgM-RF positivity[12-14]; initial radiographic damage[14-16]; number of swollen joints[17], and other markers of disease activity[12,13,18,19]. Combinations of these predictors reach an accuracy of maximum 82% in predicting mild or progressive disease. Unfortunately, this is not sufficient for decision making at the individual level[14]. Therefore, a more specific and sensitive marker for progressive RA is needed, which ideally should be present at an early stage of the disease.

The antiperinuclear factor (APF) was first described in

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1964[20]. APF is reactive to keratohyaline granules surrounding the nucleus in human buccal mucosa cells. It was put forward both as a diagnostic tool and as a prognostic marker for severe RA, especially in IgM-rheumatoid factor (RF) negative patients. The APF test, although specific for RA, is rather time-consuming and complicated to carry out and therefore unsuitable for general use[21,22].

Recently, a peptide-based ELISA was developed using citrullinated cyclic peptides (CCP) as a substrate, which is easier to use in clinical practice to assess APF[23]. In a study of early arthritis, the anti-CCP ELISA appeared to be highly specific for RA (96%)[24]. Since a part of the IgM-RF negative patients is positive for anti-CCP, the combination of anti-CCP and IgM-RF testing has additional diagnostic value over anti-CCP testing or IgM-RF alone in patients with early UPA[25].

We assessed the predictive value of anti-CCP antibodies for progressive erosive or disabling disease in a cohort of patients with early oligo- or polyarthritis.

MATERIALS AND METHODS

Patients. As part of an ongoing study, early arthritis patients seen at a large rheumatology outpatient clinic[25], referred between September 1995 and March 1999, aged > 18 years, with peripheral arthritis of > 2 joints and < 2 years symptom duration were included. Excluded were patients who were previously treated with a disease modifying antirheumatic drug (DMARD) or patients with bacterial, psoriatic, and crystal-induced arthritis, as well as patients with osteoarthritis. After 1 year of followup the clinical diagnosis (RA or UPA) was made by an experienced rheumatologist. The diagnosis RA was as well defined according to the ACR criteria for RA[6].

Disease variables. Baseline variables included: demographic characteristics, time of onset of complaints (defined as persistent pain and/or swelling), the Disease Activity Score (DAS28: a composite score based on erythrocyte sedimentation rate (ESR), number of painful and number of swollen joints (both by 28 joint count) and patient global assessment by visual analog scale (VAS)[26], C-reactive protein (CRP), anti-CCP status[25] and serum rheumatoid factor (IgM-RF)[25]. Anti-CCP activity was measured using the CCP1 test (Immunoscan RA-Mark 1, Euro Diagnostica, Arnhem, The Netherlands). Optimal cut-off values for serum IgM-RF and anti-CCP were deduced from receiver operating characteristics curves. These were 40 IU/ml for IgM RF and 50 AU/ml for anti-CCP. Also measured: damage score on radiographs of hands and feet[1] and functional status by the validated Dutch version of the Health Assessment Questionnaire (HAQ)[27]. The maximum HAQ score for disability was 3.

Outcome variables at 2 years were the radiographic damage and functional capacity. Joints were scored for erosion and joint space narrowing according to the method of Sharp/van der Heijde[1]. The maximum total score was 448. An experienced trained rheumatologist (DvS), who was blind to the clinical status of the patients, scored the radiographs. Radiographic progression, expressed as the delta Sharp/van der Heijde score, was computed by subtracting the initial radiographic damage score from the 2-year score.

Analysis. To analyze the outcome measures, we used a measure of change for the radiographic score and a measure of state for the disability score, as these are the usual methods of analysis for these variables. The patients were divided into radiographic progressive and mild disease group after 2 years. Radiographic progressive disease was defined as: Sharp/van der Heijde change score after 2 years of followup > 5; the remainder was classified as mild. The cut-off value of > 5 Sharp score units for radiographic progressive disease was chosen as this is the minimal clinically important change according to Bruynesteyn, *et al*[28]. Low functional capacity was defined as: HAQ score > 1 at 2 year followup as this is defined by Hakala, *et al* as moderate-severe disability[29].

Baseline characteristics for radiographic progressive and disabling disease were univariately tested by Student's t test or chi-square test where appropriate.

Multivariate logistic regression analyses were performed to analyze the prognostic value of anti-CCP for radiographic progressive or disabling disease. Variables significantly correlated ($p < 0.10$) with radiographic progressive or disabling disease were used as independent variables. The ability of the logistic regression model to predict radiographic progressive disease or disability after 2 years of followup was evaluated and expressed in terms of sensitivity (the proportion of true positives), specificity (the proportion of true negatives), PPV (the number of diseased patients with positive tests divided by the number of patients with positive test) and negative predictive value (NPV: the number of non-diseased patients with negative tests divided by the number of patients with negative tests).

Additional logistic regression analyses were performed for a subgroup of IgM-RF negative patients and for a subgroup of patients clinically diagnosed by the rheumatologist as RA after one year of followup.

All analyses were carried out with SPSS 10.0.

RESULTS

Of the 362 patients who were included in the study, complete data of 2 years followup were available of 282 patients (78%). The reasons for loss to followup were: noncompliance (40%), moving home (14%), death (11%), and miscellaneous (35%). Patients lost to followup compared to patients who completed followup were less often diagnosed as RA (46% vs 73%) and were less often positive for IgM-RF (24% vs 40%) and anti-CCP (19% vs 33%) ($p < 0.001$ for all variables). Nevertheless, the group of non-completers had a higher median baseline Sharp score compared to the completers (6 vs 4, $P < 0.001$).

Thirty percent of the patients completing 2 years of followup were anti-CCP positive. The baseline characteristics of mild and severe radiographic disease and high and low functional capacity in patients with early arthritis is shown in Table 1. Patients from the severe radiographic disease group were significantly more often clinically diagnosed as RA, were anti-CCP and IgM-RF positive, and had a higher disease activity and mean radiographic damage score compared to the mild disease group ($p < 0.001$). Patients with a low functional capacity had a significantly worse functional status and higher disease activity ($p < 0.001$), were more often female ($p < 0.01$), were more often clinically diagnosed as RA, and were anti-CCP and IgM-RF positive ($p < 0.05$) compared to patients with a high functional capacity. Based on the 2 year outcome, 97 (34%) patients were categorized into the radiographically progressive and 185 (66%) into the radiographically mild disease group. The mean number of DMARD used during the first year of followup was significantly higher ($p < 0.001$) in the radiographically progressive disease (1.4; SD 0.7) than in the mild disease group (1.1; SD 0.6). Anti-CCP+, IgM-RF+, joint damage at entry, ESR, CRP, and DAS28 and HAQ score correlated significantly ($p < 0.001$) with higher radiographic progression (data not shown).

Table 1. Baseline characteristics of mild and severe radiographic disease and mild and severe disabling disease in patients with early arthritis. Data are mean (SD) or median (range) unless otherwise stated.

Baseline Characteristics	Radiographically Progressive Disease (0–2 yrs Sharp ≥ 5), N = 97	Radiographically Mild Disease, N = 185	p	Low Functional Capacity (2yrs HAQ ≥ 1), N = 56	High Functional Capacity, N = 203	p
Age, yrs	59 (27–81)	56 (18–82)	NS	54 (23–82)	57 (18–81)	NS
Female, %	70	66	NS	80	63	**
Disease duration, mo	4.3 (0.4–24)	3.3 (0.4–24)	NS	4.4 (0.6–24)	3.4 (0.4–24)	NS
Clinical diagnosis RA, %	94	62	***	84	72	*
IgM-RF +, %	64	23	***	50	34	*
Anti-CCP +, %	65	17	***	50	31	*
ESR, mm/h	43 (22)	28 (22)	***	37 (24)	32 (23)	NS
CRP, mg/dl	41 (45)	22 (33)	***	32 (43)	28 (37)	NS
DAS28 score	5.3 (1.1)	4.6 (1.3)	***	5.3 (1.1)	4.7 (1.3)	***
Sharp/van der Heijde score	3 (0–86)	0 (0–40)	***	1 (0–86)	1 (0–49)	*
HAQ score	1.1 (0.9)	0.7 (0.6)	***	1.2 (0.9)	0.7 (0.7)	***

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$, NS: not significant.

Classification of patients according to their functional capacity at 2 years resulted in 64 patients (22%) in the low functional capacity group. Anti-CCP positivity was not correlated with a low functional capacity at 2 years; therefore logistic regression analysis was not performed.

To determine the additional value of anti-CCP for radiographically progressive disease, all variables correlated ($p < 0.10$) with radiographically progressive disease in the univariate analysis were entered into a logistic regression model (Table 2). Variables most predictive for radiographically progressive disease at 2 years were anti-CCP positivity and joint damage at entry. The sensitivity, specificity, and accuracy of this model for predicting radiographically progressive disease were: 78%, 82%, and 81%, respectively. The PPV for radiographically progressive disease was 63%, while the NPV was 90%. When anti-CCP was excluded from the model, the accuracy decreased to 76% (PPV 55% and NPV 87%) (data not shown).

The analysis was repeated in the subgroup of 178 IgM-RF negative patients. Nineteen patients (11%) of this subgroup were anti-CCP positive, they had a significantly ($p < 0.001$) higher mean radiographically progression score (19; SD 17) compared to the anti-CCP negative group (3; SD 9). No differences were found in terms of functional capacity between the anti-CCP positive and negative group (data not shown).

The results of the logistic regression analysis are shown in Table 3. Only anti-CCP positivity was selected as a significant prognostic variable for radiographically progressive disease at 2 years. The sensitivity, specificity, and accuracy of this model for predicting radiographically progressive disease were 67%, 86%, and 83%, respectively. The PPV for radiographically progressive disease was 40%, while the NPV was 95%. In other words, in the IgM-RF negative subgroup, radiographically mild disease can be predicted with 95% certainty by the baseline anti-CCP status. When anti-CCP was excluded from the subgroup model, the accuracy decreased to 80% (PPV 11% and NPV 99%) (data not shown).

Logistic regression analysis was repeated for the subgroup of 206 patients clinically diagnosed as RA by the rheumatologist. Entry variables most predictive for radiographically progressive disease after 2 years of followup in this subgroup were anti-CCP positivity (odds ratio, OR = 5.3; $p < 0.001$; 95% CI 2.3 to 11.9) and joint damage at entry (OR = 1.1; $p < 0.01$; 95% CI 1.0 to 1.2). The sensitivity, specificity, and accuracy to predict radiographically progressive disease of this subgroup model were: 76%, 75% and 76%, respectively. The PPV for radiographically progressive disease in patients with RA was 66%, while the NPV was 84%. When anti-CCP was excluded from the subgroup model, the accuracy decreased to 72% (PPV 59%; NPV 82%). There was no relation between serologic variables and low functional capacity in this RA subgroup (data not shown).

Table 2. Results of logistic regression analysis of baseline variables to predict radiographic progressive disease at 2 years in 282 patients with oligo-/polyarthritis. Variables without a significant relation with radiographic progressive disease in the logistic regression analysis: IgM-RF+, ESR, CRP, DAS28, HAQ.

Criterion Predictor	Coefficient (ß)	Standard Error	OR (Exp ß)	95% CI	Accuracy
(Constant)	–3.3	0.8			
Anti-CCP+	1.81	0.4	6.1	2.7 to 13	81%
Joint damage at entry	0.09	0.03	1.1	1.0 to 1.2	

Table 3. Results of logistic regression analysis of baseline variables to predict radiographic progressive disease at 2 years in the subgroup of 178 IgM-RF negative patients. Variables without a significant relation with radiographic progressive disease in the logistic regression analysis: joint damage at entry, ESR, CRP, DAS28, HAQ.

Criterion Predictor	Coefficient (ß)	Standard Error	OR (Exp ß)	95% CI	Accuracy
(Constant)	–3.6	1.1			
Anti-CCP+	3.06	0.7	21	6 to 79	83%

The analysis was repeated when defining RA according to the ACR criteria, resulting in a subgroup of 194 patients fulfilling the ACR criteria. Entry variables most predictive for radiographically progressive disease after 2 years of followup in this subgroup were anti-CCP positivity (OR = 4.7; $p < 0.001$; 95% CI 2.0 to 10.8) and joint damage at entry (OR = 1.1; $p < 0.01$; 95% CI 1.0 to 1.2). The sensitivity, specificity and accuracy to predict radiographically progressive disease of this subgroup model were: 72%, 75%, and 74% respectively. The PPV for radiographically progressive disease in patients with RA was 68%, while the NPV was 79%.

DISCUSSION

Anti-CCP positivity was recorded in 32% of the early arthritis patients and correlated significantly with radiographic progression at 2 years. Anti-CCP positivity combined with radiographic damage at baseline was the best predictor for radiographic progressive disease at 2 years. Anti-CCP was not of significant weight in the prediction of functional capacity. The small additional value of anti-CCP+ above the conventional prognostic variables for progressive erosive disease in a cohort of patients with early inflammatory oligo- and polyarthritis is due to its power to predict mild disease. This effect is accentuated in the subgroup of IgM-RF negative patients.

The results of the stepwise logistic regression suggest that some variables are superior to others in the prediction of outcome. However, more variables than the ones selected in the stepwise logistic regression were strongly related to the outcome variables in the univariate analysis. The choice of variables in stepwise logistic regression is also dependent upon their interrelations. From the variables with high mutual correlations, the statistical analysis will make a selection. Further, some known prognostic variables, such as the genetic marker HLA-DR4, were not part of the analysis, which impeded a complete evaluation of the surplus value of anti-CCP. Radiographic progressive disease as well as anti-CCP positivity were associated with increased use of DMARD during the first year of followup. The consequence might be that the measured impact of being positive for anti-CCP on disease progression was reduced with increased use of DMARD.

Our study differs from previous studies on the prognostic value of anti-CCP in the selection of the study population. Besides RA patients, also patients with undifferentiated oligo- and polyarthritis were included in our cohort. The merged cohort resulted in higher sensitivity and specificity levels than were found in the subgroup diagnosed as RA regardless of whether RA was defined by the ACR criteria or by the opinion of the rheumatologist. This may be related to the fact that the anti-CCP test performs best in the IgM-RF negative subgroup.

The observation that anti-CCP positivity was associated with radiographic damage whereas the additional predictive value of anti-CCP was rather moderate confirms previous studies[19,22-24,30]. Kroot[19] found almost the same predictors for radiographic damage (after 6 yrs) in patients with early RA as in our study: IgM-RF status, baseline joint damage, and anti-CCP positivity. Further, the anti-CCP status was not of significant influence either on the functional capacity in the study of Kroot, although the followup period in this study was 6 years. A followup period of 2 years, as was the case in our study, is rather short to determine predictive factors at baseline for functional decline. The HAQ score is labile in early RA and only stabilizes after 5 years[31]. Nevertheless, we believe that the measurement of functional status is important at all stages of the disease and should therefore not be omitted from the analysis.

In accordance with our study, van Jaarsveld, *et al*[23] concluded that the prognostic value of the APF test was due to the ability to predict radiographically mild disease at 3 years in patients with RA, considering the high NPV of 94%. Schellekens, *et al*[24], however, found that anti-CCP had a PPV of 91% for erosive disease at 2 years of followup in patients with RA. In that study the predictive value for radiographically severe disease was higher than in our study.

In our study, anti-CCP performed best in the subgroup of IgM-RF negative patients. This is in accordance with the study of Westgeest, *et al*[22]: APF in serum of patients with RA was associated with more radiographic progression, especially in IgM-RF negative patients. In the study of Kroot, *et al*[19], however, no difference in radiographic damage was found in the subgroup of IgM-RF negative patients.

In conclusion, anti-CCP has a small additional value above the conventional prognostic variables to predict mild erosive disease in a cohort of patients with early inflammatory oligo- and polyarthritis. The prognostic value of anti-CCP lies mainly in its ability to predict mild disease,

considering the high NPV. This effect is accentuated in the subgroup of IgM-RF negative patients.

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