Universiteit
Leiden
The Netherlands

Determinants of disease course in rheumatoid arthritis

Linn-Rasker, S.P.

Chapter 2

Auto-antibodies to cyclic citrullinated peptides predict progression in rheumatoid arthritis patients with undifferentiated arthritis

Arthritis and Rheumatism 2004; 50(3): 709-715

Autoantibodies to Cyclic Citrullinated Peptides Predict Progression to Rheumatoid Arthritis in Patients With Undifferentiated Arthritis

A Prospective Cohort Study

F. A. van Gaalen, S. P. Linn-Rasker, W. J. van Venrooij, B. A. de Jong, F. C. Breedveld, C. L. Verweij, R. E. M. Toes, and T. W. J. Huizinga

Arthritis and Rheumatism 2004; 50(3): 709-715

Abstract

Objective **Rheumatoid arthritis (RA) is a common, severe, chronic inflammatory joint disease. Since the disease may initially be indistinguishable from other forms of arthritis, early diagnosis can be difficult. Autoantibodies seen in RA can be detected years before clinical symptoms develop. In an inception cohort of patients with recent-onset arthritis, we undertook this study to assess the predictive value of RA-specific autoantibodies to cyclic citrullinated peptides (CCPs) in patients with undifferentiated arthritis (UA).**

Methods **Anti-CCP2 antibody tests were performed at baseline in 936 consecutive, newly referred patients with recent-onset arthritis. Patients who could not be properly classified 2 weeks after inclusion were categorized as having UA. Patients with UA were followed up for 3 years and evaluated for progression of their disease to RA as defined by the American College of Rheumatology (ACR) 1987 revised criteria.**

Results **Three hundred eighteen of 936 patients with recent-onset arthritis were classified as having UA and were available for analysis. After 3 years of followup, 127 of 318 UA patients (40%) had been classified as having RA. RA had developed in 63 of 249 patients (25%) with a negative anti-CCP test and in 64 of 69 patients (93%) with a positive anti-CCP test (odds ratio 37.8 [95% confidence interval 13.8–111.9]). Multivariate analysis of the presence of anti-CCP antibodies and parameters from the ACR criteria identified polyarthritis, symmetric arthritis, erosions on radiographs, and anti-CCP antibodies as significant predictors of RA.**

Conclusion **Testing for anti-CCP antibodies in UA allows accurate prediction of a substantial number of patients who will fulfill the ACR criteria for RA.**

Rheumatoid arthritis (RA) is a chronic inflammatory joint disease affecting 1% of the population. Recognition of RA as early as possible seems important, because a significant proportion of the patients develop irreversible joint damage shortly after disease onset[1].

Although not developed to support the diagnostic process, the American College of Rheumatology (ACR; formerly, the American Rheumatism Association) 1987 revised criteria are commonly used for disease classification[2]. According to these criteria, patients can be classified as having RA when at least 4 of 7 criteria are met using patient history, physical examination, and laboratory and radiographic findings. The classification criteria reach a sensitivity of 90% if patients are observed over a period of several years, but such a cumulative approach has been shown to be insufficient for early diagnosis of RA in patients with arthritis of recent onset[3-6]. Therefore, since early RA is often indistinguishable from other inflammatory joint diseases, arthritis of recent onset poses a diagnostic and prognostic problem[3-5]. This is relevant, since RA must be differentiated from self-limiting arthritis not only because of the different prognosis, but also because of the risks associated with treatment of RA[6].

A hallmark of RA is the presence of autoantibodies. In established disease, IgM rheumatoid factors (IgM-RF) can be detected with a sensitivity of 60–70% and a specificity of 80–90%. However, recently developed assays detecting antibodies against cyclic citrullinated peptide (anti-CCP antibodies) have a higher specificity of 98% at a similar sensitivity of 68–80%[7,8]. Anti-CCP antibodies are antibodies against antigens containing the unusual amino acid citrulline[9], including modified fibrin[10], which is present in the rheumatoid joint[11,12].

Previous retrospective studies in different countries have shown that autoantibodies, including anti-CCP antibodies and IgM-RF, can be detected in RA patients several years before clinical symptoms occur[13-16]. Given the low prevalence of RA, autoantibody testing in the general population is of no clinical benefit. However, in individuals at a higher risk of RA, this may not hold true. For instance, a substantial proportion of patients with recent-onset arthritis who are initially categorized as having undifferentiated arthritis (UA) will have their disease progress to RA in subsequent years. Therefore, we performed a prospective study in patients enrolled in a recent-onset arthritis cohort to investigate the value of anti-CCP antibodies in predicting the development of RA in patients with UA.

Patients and methods

Patients

In 1993, after approval of the Institutional Review Board, a special Early Arthritis Clinic (EAC) was started at the Department of Rheumatology of the Leiden University Medical Center, the primary referral center for patients with rheumatic disease in an area with 300,000 inhabitants in the west of The Netherlands. General practitioners were encouraged to refer patients directly when arthritis was suspected. Patients referred to the EAC could be seen within 2 weeks and were included in the program when the physician's examination of the patient revealed arthritis and the symptoms had lasted 2 years. Second opinions were excluded [16].

Methods

A standard diagnostic evaluation was performed at the first visit, consisting of patient history, physical examination, laboratory testing, and radiographs of hands and feet [16]. Baseline laboratory testing included an IgM-RF enzyme-linked immunosorbent assay (ELISA), as previously described [17]. An anti-CCP2 antibody ELISA (Immunoscan RA Mark 2; Euro-Diagnostica, Arnhem, The Netherlands) was performed according to the manufacturer's instructions with the cutoff at 25 units (sensitivity 74%, specificity 97–99%). Clinicians were blinded to patients' anti-CCP status, but not to their IgM-RF status, since IgM-RF positivity is part of the classification criteria for RA.

After evaluation, 2 weeks after inclusion, a diagnosis was made according to international classification criteria, and, in particular, RA was defined according to the 1987 ACR criteria with the 6-weeks criteria established from patient history[2]. For instance, a patient's history of symptoms of morning stiffness of 8 weeks was sufficient, but a history of 2 weeks was not. This modification of the criteria did not affect the performance of the criteria, since 96% of patients with RA at 2 weeks continued to have RA after 1 year. When a diagnosis could not be made, the condition was classified as UA. After 1, 2, and 3 years of followup, patients with UA were reassessed until a definite diagnosis was made. Patients lost to follow-up for unknown reasons were excluded from analysis. Patients were not allowed to reenter the study.

Statistical analysis

The occurrence of RA in patients with UA tested for anti-CCP antibodies was used to calculate univariate odds ratio (OR) and test sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and likelihood ratio for a positive result. To assess anti-CCP antibody testing in conjunction with the ACR classification criteria, variables recorded at baseline were used for logistic regression modeling. Model 1 contained variables derived from the ACR criteria: morning stiffness for 1 hour, arthritis in 3 joint groups, arthritis of wrist or metacarpophalangeal or proximal interphalangeal joints, symmetric arthritis of joints, rheumatoid nodules, IgM-RF positivity, and erosions on hand and/or foot radiographs. Model 2 contained the same variables as model 1, with the addition of anti-CCP antibodies. The information content of the models was compared using the –2 log likelihood and the area under the curve (AUC) of receiver operating characteristic (ROC) curves. The Statistical Package for the Social Sciences (SPSS), version 10.0 (SPSS, Chicago, IL) was used to analyze the data. In all tests, P values less than 0.05 were considered significant.

Results

UA in an early arthritis cohort. Nine hundred thirty-six patients were included in a recent-onset arthritis cohort, and after 2 weeks a diagnosis was made (Table 1). Of these 936 patients, 590 (63.0%) could be readily diagnosed, and the largest proportion had RA (205 patients [21.9%]). Other common diagnoses were psoriatic arthritis, mixed connective tissue disease, crystal-induced arthritis, reactive arthritis, spondylarthropathy, and osteoarthritis. A total of 346 patients (37%) were categorized as having UA (Tables 1 and 2). In UA patients, there was a median of 2 swollen joints at baseline (range 1–14), and 39% of patients had a polyarthritis (arthritis in 3 joints). Forty-six percent of UA patients had a symmetric arthritis, 1% had rheumatoid nodules, and 11% had bone erosions on radiographs of hands or feet. IgM-RF and anti-CCP antibodies were each detected in 21% of patients, and 14% of patients had both autoantibodies. Of the 346 UA patients, 28 were lost to followup and were excluded from the analysis (Table 3).

Anti-CCP antibodies as a risk factor

As shown in Table 3, after 1 year, 103 of 318 UA patients (32%) fulfilled the ACR classification criteria for RA. This percentage rose to 38% (122 of 318 patients) after 2 years and to 40% (127 of 318 patients) after 3 years. Sixty-nine UA patients tested positive for anti-CCP antibodies. After 1 year, 57 of these patients (83%) fulfilled the criteria for RA, and after 3 years this value had risen to 93% (64 patients). Of the remaining 249 UA patients who were negative for anti-CCP antibodies, 46 (18%) met the criteria for RA after 1 year, and 63 (25%) did so after 3 years.

Table 1

Diagnoses at 2 weeks for patients with recent-onset arthritis enrolled in an early arthritis cohort*

Rheumatoid arthritis	205 (21.9)
Psoriatic arthritis	57 (6.1)
Mixed connective tissue disease	54 (5.8)
Crystal-induced arthritis	52 (5.6)
Reactive arthritis	51 (5.4)
Spondylarthropathy	46 (4.9)
Osteoarthritis	41 (4.4)
Sarcoidosis	22 (2.4)
Palindromic rheumatism	14 (1.5)
Posttraumatic arthritis	10 (1.1)
Malignancy-related arthritis	10 (1.1)
Septic arthritis	7 (0.7)
Lyme arthritis	6 (0.6)
Systemic lupus erythematosus	6 (0.6)
Juvenile chronic arthritis	4 (0.4)
Other	5 (0.5)
Undifferentiated arthritis	346 (37.0)
Total	**936 (100)**

* Values are the number (%) of patients.

With these results we calculated the OR (risk) for disease as well as the test performance (sensitivity and specificity) and the predictive values for baseline testing with 3 years of followup. As could be expected from the data, the presence of anti-CCP antibodies was a significant risk factor for RA, with an OR of 37.8 (95% confidence interval [95% CI] 13.8–111.9).

As shown in Table 4, in this group of patients, the sensitivity of the anti-CCP antibody test was 50% (95% CI 41–59), with a specificity of 97% (95% CI 95–99), a PPV of 93% (95% CI 87–99), and an NPV of 75% (95% CI 69–80). Since 93% of UA patients with anti-CCP anti-bodies had disease that progressed to RA (PPV), and 75% of patients without anti-CCP antibodies did not (NPV), it can be calculated that anti-CCP antibodies are 16.7 times more likely to be detected in patients with UA that progresses to RA than in those with UA that does not (likelihood ratio for a positive result).

Table 2

Baseline characteristics of 346 patients with undifferentiated arthritis enrolled in an early arthritis cohort*

Age, median (range) years	49 (16–93)
Female	55
Duration of symptoms at baseline, median(range) months†	3 (0–24)
Morning stiffness > 1 hour	22
Swollen joints, median (range)	2 (1–14)
Arthritis of ≥ 3 joints	39
Symmetric arthritis	46
Rheumatoid nodules	1
Erosions in hands and/or feet	11
IgM-RF positive	21
Anti-CCP antibody positive	21
IgM-RF positive and anti-CCP antibody positive	14
IgM-RF positive only	7
Anti-CCP antibody positive only	7

* Except where indicated otherwise, values are the percent of patients with a given characteristic. RF = rheumatoid factor; CCP = cyclic citrullinated peptide. † Information from patient history.

In the present study, 28 patients with UA (4 with anti-CCP antibodies and 24 without) were excluded from the analysis, since they were lost to followup due to unknown reasons (Table 3). To assess possible selection bias resulting from differential loss to followup, we performed best- and worst-case analyses. In the worst case, all excluded anti-CCP–negative patients would have disease that progressed to RA, and all excluded anti-CCP–positive patients would have disease that did not. This would have yielded a sensitivity of 42% (95% CI 0.35–0.42), a specificity of 95% (95% CI 92–98), a PPV of 87% (95% CI 80–94), and an NPV of 68% (95% CI 63–73). In the best case, no anti-CCP–negative patients would have disease that progressed to RA, and all anti-CCP–positive patients would have disease that did progress. This case would have yielded a sensitivity of 52% (95% CI 43–60), a specificity of 98% (95% CI 96–100), a PPV of 93% (95% CI 87–99), and an NPV of 77% (95% CI 72–82).

Table 3

Anti-CCP antibodies and prediction of RA in patients with UA*

	Patients fulfilling ACR RA criteria, no. (%)		
	After 1 year	After 2 years	After 3 years
Anti-CCP positive (n = 69)	57 (83)	62 (90)	64 (93)†
Anti-CCP negative (n = 249)	46 (18)	60 (24)	63 (25)
Total (n = 318)	**103 (32)**	**122 (38)**	**127 (40)**

* Of 346 patients with undifferentiated arthritis (UA) at baseline, were lost to followup for unknown reasons (24 had tested negative 4 had tested positive for antibodies to cyclic citrullinated peptide (anti-CCP2 [anti-CCP]). The remaining 318 patients, grouped by anti-CCP status, were followed up to determine how many of would fulfill the American College of Rheumatology (ACR) criteria for rheumatoid arthritis (RA) after 1, 2, and 3 years.
† The presence of anti-CCP antibodies was a significant risk factor RA (odds ratio 37.8 [95% confidence interval 13.8–111.9]).

Table 4

Diagnostic properties of the anti-CCP2 antibody test*

	Percent (95% confidence interval)
Sensitivity	50 (41–59)
Specificity	97 (95–99)
Positive predictive value	93 (87–99)
Negative predictive value	75 (69–80)

* It was determined that anti-CCP antibodies are 16.7 times more likely to be detected in patients with UA that progresses to RA than in those with UA that does not (likelihood ratio for a positive result) (see Results). See Table 3 for definitions.

In order to assess how anti-CCP testing performs in conjunction with commonly used clinical variables, we performed multivariate analysis with fulfillment of the ACR RA criteria at 1 year as the dependent variable and baseline assessment of the ACR RA criteria and anti-CCP antibodies as possible explanatory variables (Table 5). The first model (model 1) contained items from the ACR criteria for RA. Table 5 shows that within model 1, 5 items had significant ORs: morning stiffness, poly-arthritis, symmetric arthritis, IgM-RF positivity, and erosions on radiographs. The highest OR (9.8 [95% CI 4.1–23.4]) was found for IgM-RF positivity.

Adding anti-CCP antibody testing to the items in model 1 generated the second model (model 2). Again, poly-arthritis, symmetric arthritis, and erosions on radiographs were significant predictors. Remarkably, IgM-RF positivity had an OR of 1.7 (95% CI 0.5–5.6), which was not significant (P = 0.4). Anti-CCP antibody positivity, however, proved to be the most important predictor in this multivariate analysis, with an OR of 38.6 (95% CI 9.9–151.0), which was highly significant (P < 0.001). Logistic regression analysis of the 2- and 3-year data using the same models gave similar results (data not shown).

Table 5

Multivariate model analysis of factors predictive of progression from UA to RA after 1 year*

	Model 1: ACR criteria		Model 2: ACR criteria plus anti-CCP antibody	
	OR (95% CI)	P	OR (95% CI)	P
Morning stiffness 1 hour	2.9 (1.2–6.5)	0.013	2.1 (0.8–5.3)	0.108
Arthritis of 3 joints	5.8 (2.4–13.6)	< 0.001	5.0 (1.8–13.2)	0.001
Arthritis of wrist or MCP or PIP joint	1.8 (0.7–4.5)	0.24	1.2 (0.4–3.3)	0.762
Symmetric involvement of joints	2.6 (1.1–6.0)	0.028	6.1 (2.0–19.0)	0.002
Rheumatoid nodules	0.002 (0.0–∞)	0.787	0.003 (0.0–∞)	0.795
IgM-RF positivity	9.8 (4.1–23.4)	< 0.001	1.7 (0.5–5.6)	0.406
Erosions on radiographs	7.6 (2.4–24.4)	0.001	8.7 (2.4–31.2)	0.001
Anti-CCP antibody positivity	–	–	38.6 (9.9–151.0)	0.001

* Analysis of 2- and 3-year data gave similar results. OR = odds ratio; 95% CI = 95% confidence interval; MCP = metacarpophalangeal; PIP = proximal interphalangeal; RF = rheumatoid factor (see Table 3 for other definitions).

The performance of an entire prediction model can be expressed by a –2 log likelihood, which is a quantity that indicates how well the model fits with the explanatory variables, and by an ROC curve, in which the sensitivity is plotted against the specificity. In such models, the performance has improved when the AUC of the ROC curve is higher and the –2 log likelihood is lower (18). The model summary (Table 6) shows that overall performance in predicting fulfillment of the ACR criteria after 1 year, as expressed by the –2 log likelihood and the AUC, improved when anti-CCP antibody testing was added to the items in model 1. A third model made by adding symptom duration 3 months (Table 2) as a variable performed equally well, but symptom duration was not a significant predictor (not shown).

To assess which UA patients would benefit most from anti-CCP testing, UA patients were stratified according to the number of ACR criteria they fulfilled at baseline (Table 7). Significantly more patients with anti-CCP antibodies had disease that progressed to RA in groups meeting 1, 2, or 3 criteria at baseline. In 42 patients meeting ≥4 criteria, all 17 patients who were positive for anti-CCP antibodies and 19 of the 25 anti-CCP–negative patients had disease that progressed to RA ($P = 0.06$). Anti-CCP antibody testing was of little value in UA patients who fulfilled none of the ACR criteria. Of the 43 UA patients fulfilling none of the criteria, 2 (5%) had disease that progressed to RA, and neither of these patients had anti-CCP antibodies.

At 2 weeks, 205 patients with early arthritis were diagnosed as having RA, and these patients were excluded from the UA group (Table 1). Followup data were available for 204 of these patients. At baseline, 105 had anti-CCP antibodies and 99 did not. At the end of followup, 104 of 105 anti-CCP–positive patients (99%) and 92 of 99 anti-CCP–negative patients (93%) were still classified as having RA.

In patients with rheumatic diseases other than RA or UA, anti-CCP antibodies were detected in 30 of 385 patients, 2 of whom were lost to followup for unknown reasons. In 17 of the remaining 28 patients, a (co)diagnosis of criteria-defined RA was made during the study.
Of the remaining 11 patients, after 3 years, 1 had gout, 1 was diagnosed as having osteoarthritis, 2 had sarcoid arthritis, 3 had palindromic rheumatism, and 4 had psoriatic arthritis.

Table 6

Model summary*

	–2 log likelihood	AUC (95% CI)
Model 1: ACR criteria	205.1	0.881 (0.836–0.922)
Model 2: ACR criteria plus anti-CCP antibody	164.3	0.923 (0.885–0.956)

* AUC = area under the curve of the receiver operating characteristic curve; 95% CI = 95% confidence interval (see Table 3 for other definitions).

Discussion

Predicting disease requires specific tests as well as a population in which a reasonable proportion of patients will develop disease. The data from blood donors who developed RA demonstrated that anti-CCP autoantibodies, which have a high specificity in established disease, are present years before clinical symptoms occur[14,15]. However, given the low prevalence of RA, screening of the population is not likely to be of clinical benefit. The predictive value of these autoantibodies was tested in a group of UA patients, who are at risk for RA. After 3 years, 40% of these patients had disease that progressed to RA. The presence of anti-CCP autoantibodies was an important predictor for RA, since within 3 years, 93% of the patients who tested positive for anti-CCP antibodies were classified as having RA, most of them in the first year of followup.

Multivariate analysis confirmed anti-CCP antibodies as an important independent predictor of RA. Moreover, adding anti-CCP antibodies to a model consisting of the individual items from the ACR criteria improved the overall performance of the model.

It is remarkable that the laboratory variables and radiographs performed so well in both models. This is probably partly due to the background of the cohort in which the models were tested. In a cohort of UA patients, clinical variables such as polyarthritis and arthritis of hand joints are commonly found in other arthritides such as reactive arthritis. This observation underlines the value of objective and (semi)specific markers in daily practice. Another example of this is that in UA patients without anti-CCP antibodies, the chance of disease progressing to RA increased with the number of ACR criteria present at baseline, but this was not so for UA patients with anti-CCP antibodies (Table 7).

A possible limitation to the generalizability of these results is that the study was performed in a population in which general practitioners were encouraged to refer arthritis patients to a rheumatologist. Patients with recent-onset arthritis may visit different specialists (general internists, orthopedists, geriatricians, etc.) and probably even at different time points. This may affect the prevalence of RA in patients with recent-onset UA. Nonetheless, even if the prevalence of RA was 50% lower (20%) than that in our cohort, the calculated PPV for anti-CCP antibodies would still be 87%.

Other groups at risk of developing RA, such as family members of RA patients or even the general public, are less likely to benefit from anti-CCP testing due to the low prevalence of RA. For instance, in our cohort, with a 40% prevalence of RA (Table 3) and a likelihood ratio of 16.7, the posttest probability of a positive test result is 92%, but in the unselected general population, with a prevalence of 1%, the posttest probability of a positive test result would only be 14%.

Table 7

Progression to RA in patients with UA stratified by number of ACR criteria fulfilled at baseline*

No. of ACR criteria fulfilled, anti-CCP antibody status	No. of patients	Patients with RA after 3 years, no. (%)	P†
0			
All	43	2 (5)	–
Positive	1	0 (0)	
Negative	42	2 (5)	
1			
All	64	9 (14)	> 0,001
Positive	8	6 (75)	
Negative	56	3 (5)	
2			
All	43	16 (37)	> 0,001
Positive	9	9 (100)	
Negative	34	7 (21)	
3			
All	46	32 (70)	0,03
Positive	13	12 (92)	
Negative	33	20 (61)	
≥4			
All	42	36 (86)	0,06
Positive	17	17 (100)	
Negative	25	19 (76)	
Total			
All	**239**	**95 (40)**	
Positive	**48**	**44 (92)**	
Negative	**191**	**51 (27)**	

* For symptoms (morning stiffness, polyarthritis, symmetric arthritis, and arthritis of wrist or MCP or PIP joints) to be counted, a 6-week duration observed or established from the patient's history was not required. Of the 346 patients in the cohort, 28 were excluded due to incomplete followup and 79 were excluded because of incomplete data regarding fulfillment of ACR criteria at baseline. See Tables 3 and 5 for definitions.
† By Fisher's exact test.

At the end of the study, we individually reviewed the 5 anti-CCP–positive UA patients whose disease had not progressed to RA. All 5 patients were still visiting the outpatient clinic on a regular basis, since 1 was diagnosed as having palindromic rheumatism, which is an independent risk factor for RA, and 4 still had UA (3 with erosive disease). These unclassified patients reflect an important issue of this study. Since there is no independent standard or test for RA, the ACR criteria are widely used as the “gold standard.” However, using an imperfect standard to evaluate a new diagnostic test is not ideal[19]. One possible solution is to frame the diagnostic problem

in terms of clinical outcome instead of using the ACR criteria. In an earlier study with 40% of the same patients as those in the present study, Visser et al developed a prediction model for early arthritis in which outcome of arthritis was used. In that study, anti-CCP antibodies were a predictor of both erosive and persistent arthritis[20]. However, studies on the efficacy of interventions that improve functional outcome and retard joint damage are nearly always performed in patients fulfilling the ACR criteria for RA[21–23]. Therefore, we chose fulfillment of the criteria as the main outcome. This was also reflected in clinical practice, since only 4% (8 of 191) of the UA patients who did not meet the ACR criteria for RA had ever used disease-modifying antirheumatic drugs during the study (data not shown). Moreover, this eliminated a possible source of experimental artifact, because early treatment might reduce symptoms, which in turn could prevent patients from meeting the classification criteria.

The role of anti-CCP autoantibodies in the pathogenesis of RA is unclear. Possible clues are the association of citrullination with apoptosis, the appearance of anti-CCP antibodies before the occurrence of clinical symptoms, the specificity for RA, and the fact that a genetic risk factor that leads to increased citrullination is associated with RA[24].

With these clues in mind, RA may be analogous to celiac disease. Celiac disease is a chronic intestinal disease caused by an immune response to antigens in wheat gluten. It is thought that the disease occurs after the antigen gliadin has been changed by the enzyme tissue transglutaminase, which allows subsequent presentation in the context of specific HLA molecules[25]. In RA, citrullination may lead to the modification of an (auto)antigen which unmasks a "cryptic" epitope, creating a fitting motif for binding to HLA class II molecules, leading to the initiation of an autoimmune response.

Testing for anti-CCP antibodies in UA allows accurate prediction of a substantial number of patients who will fulfill the ACR criteria for RA.

At baseline, all patients in the cohort were tested for anti-CCP antibodies. Anti-CCP antibodies were present in approximately half of the patients who were excluded at 2 weeks from the UA group with a diagnosis of RA, and nearly all patients with RA at 2 weeks had RA at the end of followup. During the course of the study, a (co)diagnosis of RA was eventually made in 17 of 28 anti-CCP–positive patients (61%) who had originally been excluded from the UA group as having differentiated rheumatic diseases other than RA. Of the 11 remaining anti-CCP–positive patients, 3 were diagnosed as having palindromic rheumatism and 4 as having psoriatic arthritis; both diseases are often difficult to distinguish from RA using the current classification criteria[21,26].

One may wonder whether anti-CCP testing will replace IgM-RF testing in the diagnosis of RA. This study does not provide the answer because it was not designed to do so. The present study asked whether anti-CCP testing would be informative when a standard diagnostic evaluation was insufficient. However, if one has to choose, it is important to take into account that although anti-CCP tests are more specific than IgM-RF tests, they are probably more expensive and currently not as commonly available.

At present, our group is analyzing the association between HLA genes and the presence of anti-CCP antibodies in RA. This may reveal additional factors involved in generating the anti-CCP response and may also help to identify the antigen(s) targeted in RA. For now, we conclude that in patients with UA, the presence of anti-CCP antibodies predicts progression to RA independently of other known predictors.

Acknowledgment

We thank Dr. F. W. Dekker for his help reviewing the statistical methods.

References

1 **Bukhari M,** Harrison B, Lunt M, Scott DGI, Symmons DPM, Silman AJ. Time to first occurrence of erosions in inflammatory polyarthritis: results from a prospective community-based study. Arthritis Rheum 2001;44:1248–53.

2 **Arnett FC,** Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988;31:315–24.

3 **Harrison BJ,** Symmons DP, Barrett EM, Silman AJ. The performance of the 1987 ARA classification criteria for rheumatoid arthritis in a population based cohort of patients with early inflammatory polyarthritis. American Rheumatism Association. J Rheumatol 1998;25:2324–30.

4 **Huizinga TWJ,** Machold KP, Breedveld FC, Lipsky PE, Smolen JS. Criteria for early rheumatoid arthritis: from Bayes' law revisited to new thoughts on pathogenesis. Arthritis Rheum 2002;46: 1155–9.

5 **El-Gabalawy HS,** Duray P, Goldbach-Mansky R. Evaluating patients with arthritis of recent onset: studies in pathogenesis and prognosis. JAMA 2000;284:2368–73.

6 **Tunn EJ,** Bacon PA. Differentiating persistent from self-limiting symmetrical synovitis in an early arthritis clinic. Br J Rheumatol 1993;32:97–103.

7 **Van Boekel MA,** Vossenaar ER, van den Hoogen FH, van Venrooij WJ. Autoantibody systems in rheumatoid arthritis: specificity, sensitivity and diagnostic value. Arthritis Res 2002;4:87–93.

8 **Schellekens GA,** Visser H, de Jong BAW, van den Hoogen FHJ, Hazes JMW, Breedveld FC, et al. The diagnostic properties of rheumatoid arthritis antibodies recognizing a cyclic citrullinated peptide. Arthritis Rheum 2000;43: 155–63.

9 **Schellekens GA,** de Jong BA, van den Hoogen FH, van de Putte LB, van Venrooij WJ. Citrulline is an essential constituent of antigenic determinants recognized by rheumatoid arthritis-specific autoantibodies. J Clin Invest 1998;101:273–81.

10 **Masson-Bessiere C,** Sebbag M, Girbal-Neuhauser E, Nogueira L, Vincent C, Senshu T, et al. The major synovial targets of the rheumatoid arthritis-specific antifilaggrin autoantibodies are deiminated forms of the alpha- and beta-chains of fibrin. J Immunol 2001;166:4177–84.

11 **Baeten D,** Peene I, Union A, Meheus L, Sebbag M, Serre G, et al. Specific presence of intracellular citrullinated proteins in rheumatoid arthritis synovium: relevance to antifilaggrin autoantibodies. Arthritis Rheum 2001;44:2255–62.

12 **Masson-Bessiere C,** Sebbag M, Durieux JJ, Nogueira L, Vincent C, Girbal-Neuhauser E, et al. In the rheumatoid pannus, antifilaggrin autoantibodies are produced by local plasma cells and constitute a higher proportion of IgG than in synovial fluid and serum. Clin Exp Immunol 2000;119:544–52.

13 **Aho K,** Palosuo T, Heliovaara M, Knekt P, Alha P, von Essen R. Antifilaggrin antibodies within "normal" range predict rheumatoid arthritis in a linear fashion. J Rheumatol 2000;27:2743–6.

14 **Rantapaa-Dahlqvist S,** de Jong BA, Berglin E, Hallmans G, Wadell G, Stenlund H, et al. Antibodies against cyclic citrullinated peptide and IgA rheumatoid factor predict the development of rheumatoid arthritis. Arthritis Rheum 2003;48:2741–9.

15 **Nielen MMJ,** van Schaardenburg D, van de Stadt RJ, van der Horst-Bruinsma IE, de Koning MHM, Habibuw M, et al. Autoantibodies in serum of blood donors precede symptoms of rheumatoid arthritis (RA) by 1 to 6 years [abstract]. Arthritis Rheum 2002;46 Suppl 9:S370.

16 **Van der Horst-Bruinsma IE,** Speyer I, Visser H, Breedveld FC, Hazes JM. Diagnosis and course of early-onset arthritis: results of a special early arthritis clinic compared to routine patient care. Br J Rheumatol 1998;37:1084–8.

17 **Visser H,** Gelinck LB, Kampfraath AH, Breedveld FC, Hazes JM. Diagnostic and prognostic characteristics of the enzyme linked immunosorbent rheumatoid factor assays in rheumatoid arthritis. Ann Rheum Dis 1996;55:157–61.

18 **Kienstra GE,** Terwee CB, Dekker FW, Canta LR, Borstlap AC, Tijssen CC, et al. Prediction of spinal epidural metastases. Arch Neurol 2000;57:690–5.

19 **Valenstein PN.** Evaluating diagnostic tests with imperfect standards. Am J Clin Pathol 1990;93:252–8.

20 **Visser H,** le Cessie S, Vos K, Breedveld FC, Hazes JMW. How to diagnose rheumatoid arthritis early: a prediction model for persistent (erosive) arthritis. Arthritis Rheum 2002;46:357–65.

21 **Boers M,** Verhoeven AC, Markusse HM, van de Laar MA, Westhovens R, van Denderen JC, et al. Randomised comparison of combined step-down prednisolone, methotrexate and sulphasalazine with sulphasalazine alone in early rheumatoid arthritis. Lancet 1997;350:309–18.

22 **Mottonen T,** Hannonen P, Leirisalo-Repo M, Nissila M, Kautiainen H, Korpela M, et al. Comparison of combination therapy with single-drug therapy in early rheumatoid arthritis: a randomised trial. FIN-RACo trial group. Lancet 1999;353:1568–73.

23 **Bathon JM,** Martin RW, Fleischmann RM, Tesser JR, Schiff MH, Keystone EC, et al. A comparison of etanercept and methotrexate in patients with early rheumatoid arthritis. N Engl J Med 2000; 343:1586–93.

24 **Guerne PA,** Weisman MH. Palindromic rheumatism: part of or apart from the spectrum of rheumatoid arthritis. Am J Med 1992;93:451–60.

25 **Palazzi C,** Olivieri I, Petricca A, Salvarani C. Rheumatoid arthritis or psoriatic symmetric polyarthritis? A difficult differential diagnosis. Clin Exp Rheumatol 2002;20:3–4.

26 **Suzuki A, Yamada R,** Chang X, Tokuhiro S, Sawada T, Suzuki M, et al. Functional haplotypes of PADI4, encoding citrullinating enzyme peptidylarginine deiminase 4, are associated with rheumatoid arthritis. Nat Genet 2003;34:395–402.

27 **Mowat AM.** Coeliac disease—a meeting point for genetics, immunology, and protein chemistry. Lancet 2003;361:1290–2.