

Association of Anticyclic Citrullinated Peptide Antibodies and/or Rheumatoid Factor Status and Clinical Presentation in Early Arthritis: Results from the ESPOIR Cohort

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ABSTRACT. Objective. To compare the initial clinical, biological, and radiographic findings of early arthritis by positivity for rheumatoid factor (RF) and/or anticyclic citrullinated peptide antibodies (anti-CCP), and to validate a patient profile based on this serologic information.

Methods. The ESPOIR cohort comprises patients presenting synovitis of at least 2 joints for 6 weeks to 6 months. Patients underwent testing for IgM rheumatoid factor (IgM-RF) and anti-CCP2 antibodies and were divided into 4 groups: RF– and anti-CCP– (group 1), RF+ and anti-CCP– (group 2), RF– and anti-CCP+ (group 3), RF+ and anti-CCP+ (group 4). We compared the groups in terms of clinical, biological, and radiographic features (baseline scores and 6-month and 12-month progression).

Results. Of the 813 recruited patients, 406 (50%) were in group 1, 91 (11.2%) in group 2, 34 (4.1%) in group 3, and 281 (34.6%) in group 4. Mean baseline erythrocyte sedimentation rate and C-reactive protein were higher for anti-CCP+ groups (groups 3 and 4) than for other groups ($p < 0.001$), and van der Heijde-modified Sharp score for radiographs was higher for group 4 than for other groups ($p < 0.001$). Clinical presentation was not consistently associated with serologic profile. Radiographic progression at 1 year was higher for anti-CCP+ groups than other groups ($p < 0.001$).

Conclusion. The phenotype of patients with early arthritis with or without anti-CCP and/or RF positivity did not correspond to a particular clinical presentation. However, baseline acute-phase reactants and short-term radiographic progression were high in patients with anti-CCP positivity, which may be associated with the inflammatory process and progressive disease in patients with early arthritis. (First Release July 15 2014; J Rheumatol 2014;41:1614–22; doi:10.3899/jrheum.130884)

Key Indexing Terms:

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Early arthritis has variable clinical presentations and disease courses. For some patients, the course is persistent and erosive, and for others, it spontaneously resolves^{1,2}. No test is sufficiently specific to identify early rheumatoid arthritis (RA) with certainty. Diagnosis is made on the basis of a range of clinical, biological, and radiographic data, with initial erosions being considered sufficient if their locations, aspect, and numbers are typical of the disease. Thus, testing for autoantibodies such as rheumatoid factor (RF) and anticitrullinated protein antibodies (ACPA) is useful for physicians.

ACPA such as anticyclic citrullinated peptide antibodies (anti-CCP) are highly specific to RA³, have good predictive validity in undifferentiated RA⁴, and are associated with radiographic progression in early RA^{5,6,7,8,9}. Although RF is considered less specific, it is still important, with the same weight as ACPA in the 2010 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) classification criteria for RA^{10,11} and is

therefore useful for RA diagnosis³. RF is also associated with severe radiographic outcome^{5,12,13,14}.

RA has major genetic risk factors. The gene-environment interaction of smoking and HLA-DRB1* polymorphism is associated with ACPA-positive RA¹⁵. Distinct genetic risk factors are associated with ACPA-positive or -negative disease. Anti-CCP-positive (anti-CCP+) RA was found to be associated with HLA-DRB1, HLA-DP, PTPN22, C5-TRAF1, and TNFAIP3-OLIG3 polymorphisms^{16,17,18}, whereas anti-CCP-negative (anti-CCP-) RA was found to be associated with genes such as *HLA-DR3* and *IRF-5*^{18,19}. These data might indicate distinct pathogenic mechanisms underlying ACPA-positive and -negative RA. Given these reported genetic differences, the 2 serological states may result in different phenotypical properties and may be closely related but different diseases in terms of pathogenesis, clinical profile, and outcome. However, apart from extraarticular manifestations²⁰, few data support a relationship between immunological and clinical profiles. In this context of uncertainty, we assumed that comparing risk factors, clinical manifestations, disease activity, and severity according to ACPA status might be relevant.

RF and anti-CCP autoantibodies are important in both the diagnosis and prognosis of RA^{21,22}, but few studies have described the role of either in the distribution and degree of symptoms and signs in early RA^{23,24}. Further, few studies were designed with unselected patients presenting early arthritis, and published results differ in prognosis factors evaluated, heterogeneity of samples, and followup duration.

For this prospective followup study, we used part of the database from a French longitudinal prospective cohort of adult patients with early arthritis, the Etude et Suivi des Polyarthrites Indifférenciées Récentes (ESPOIR) cohort²⁵, to compare initial clinical, biological, and radiological features of patients with early arthritis in terms of RF and/or ACPA status and to validate a patient profile based on these serological data.

MATERIALS AND METHODS

Study population. The ESPOIR cohort is a nationwide prospective cohort study of adults conducted under the umbrella of the French Society of Rheumatology. The cohort was constituted by asking general practitioners and rheumatologists to refer patients with early arthritis to one of the 14 university hospitals participating in the ESPOIR cohort project. The protocol has been described in detail elsewhere²⁵. Briefly, patients were eligible if they had a definitive or probable clinical diagnosis of RA or a diagnosis of undifferentiated arthritis with potential for progression to RA. Patients were included if they met the following criteria: age > 18 and < 70 years, swelling of ≥ 2 joints for 6 weeks, symptom duration < 6 months, and no prior treatment with disease-modifying antirheumatic drugs or glucocorticoids. Patients with another definite diagnosis of an inflammatory rheumatic disease at the baseline visit were excluded. Included patients were evaluated every 6 months for 2 years and then once a year for at least 10 years. Each center acted as an observational center and did not interfere with patient treatment, unless in charge of the patient. The patients were routinely monitored and followed by private rheumatologists in the geographical area. Between November 2002 and April 2005, 813 consecutive patients were included in the ESPOIR cohort.

Autoantibodies. For the present study, patients were tested for anti-CCP antibodies and IgM-RF and then divided into 4 groups: RF- and anti-CCP- (group 1), RF+ and anti-CCP- (group 2), RF- and anti-CCP+ (group 3), and RF+ and anti-CCP+ (group 4). Anti-CCP antibodies were analyzed by use of an ELISA kit for CCP2 (DiaSorin), with titers > 50 units/ml considered positive. RF was analyzed using an ELISA kit (Ménarini), with titers > 9 IU/ml considered positive. The analyses of RF and anti-CCP status were centralized and carried out in the Department of Immunology, Bichat University Hospital, Paris.

Baseline assessment. A standard diagnostic evaluation was performed at the first visit. We collected data on demographics (age, sex, ethnic group), socioeconomic status, comorbidities, tobacco exposure, family history of RA, duration of symptoms at first visit (defined by the first fixed swollen joint), presence of a triggering factor, clinical features [duration of morning stiffness, 28-joint Disease Activity Score using erythrocyte sedimentation rate (DAS28-ESR)²⁶, topography of the joint(s) with arthritis (hands joints and large joints, i.e., shoulder, elbow, and knee), global health, and pain assessed on 0–100 mm visual analog scale, functional disability by the Health Assessment Questionnaire (HAQ)²⁷, rheumatoid nodules and other extraarticular manifestations, squeeze test in the metacarpophalangeal (MCP) and/or metatarsophalangeal (MTP) joints], biological features [including ESR (mm/h), level of C-reactive protein (CRP; mg/l) by standard laboratory methods, autoantibodies, and HLA-DRB1* genotype], and radiographs of hands, wrists, and feet in the posteroanterior view. RA was defined according to the 1987 ACR criteria²⁸ or to the 2010 ACR/EULAR criteria¹⁰.

Radiographs of the wrists, hands, and feet were stored in the Department of Rheumatology, Brest Hospital (Brest, France) and scored for presence of erosions and joint space narrowing (JSN) according to the van der Heijde-modified Sharp score (mTSS)²⁹ by an experienced rheumatologist (CL) who was blinded to the patient's other data. An erosive disease for use in the 2010 ACR/EULAR RA classification criteria was defined when an erosion (defined as a cortical break) was seen in at least 3 separate joints at any of the following sites: the proximal interphalangeal, the MCP, the wrist (counted as 1 joint), and the MTP joints on radiographs of both hands and feet³⁰.

Followup assessment. All patients were followed for at least 1 year. Radiographs were obtained and scored at 6 and 12 months in a chronological order using the same technique. Radiographic progression was defined as an increase in at least 1 point of the mTSS or the erosion score assessed at baseline and after 6 and 12 months. An increase in 1 point of the mTSS indicated 1 new bone erosion or JSN or worsening of existing erosion or JSN.

Statistical analysis. Data are presented as mean (SD) for quantitative variables and were compared by Kruskal-Wallis test and were considered significant with $p = 0.15$. In that case, aggregate groups were created and compared by a Newman-Keuls-like method and considered statistically significant if $p < 0.05$. Categorical variables were compared by chi-square test. Categorical variables were considered significant with $p = 0.15$, then data were reanalyzed by chi-square test to pool data. Statistical analysis involved use of SAS 8.1 for Windows (SAS Institute).

Ethics approval. The study was approved by the Institutional Review Board of the Montpellier University Hospital, the coordinating center for this nationwide study. Before inclusion, all patients gave their written informed consent to participate.

RESULTS

Patient characteristics. The baseline characteristics of the 813 patients with data for analysis are given in Table 1. Patients presented active, recent-onset disease: mean DAS28 5.11 (1.30) and mean disease symptom duration 3.38 months (1.72).

Autoantibodies. In total, 406 patients (50%) were negative

Table 1. Baseline characteristics of patients with early arthritis in the ESPOIR cohort (n = 813).

Characteristic	Values
Female, n (%)	623 (76.7)
Age, yrs, mean (SD)	48.1 (12.5)
White, n (%)	749 (92.2)
Symptom duration at first visit, mo, mean (SD)	3.4 (1.7)
IgM rheumatoid factor–positive, n (%)	372 (45.8)
Anti-CCP–positive, n (%)	315 (38.8)
ESR, mm/h, mean (SD)	29.5 (24.6)
CRP level, mg/l, mean (SD)	22.2 (33.6)
DAS28, mean (SD)	5.11 (1.30)
HAQ score, mean (SD)	0.98 (0.68)
mTSS, mean (SD)	5.76 (7.70)
Modified Sharp erosion score, mean (SD)	2.76 (4.68)
Modified Sharp joint-space-narrowing score, mean (SD)	3.00 (4.42)
“Typical” erosive disease [#] , n (%)	185 (25.1)
HLA-DRB1*01 or *04 gene, n (%)	438 (57.6)
1987 ACR criteria, n (%)	579 (71.3)
2010 ACR/EULAR criteria, n (%)	641 (79)

[#]According to 2010 ACR/EULAR RA classification criteria. ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; DAS28: Disease Activity Score in 28 joints; HAQ: Health Assessment Questionnaire; mTSS: van der Heijde-modified total Sharp score; anti-CCP: anticyclic citrullinated peptide antibodies; ACR: American College of Rheumatology; EULAR: European League Against Rheumatism; RA: rheumatoid arthritis.

for both autoantibodies (group 1), 91 (11.2%) were RF+ and anti-CCP– (group 2), 34 (4.1%) were RF– and anti-CCP+ (group 3), and 281 (34.6%) were positive for both autoantibodies (group 4). K coefficient for the association of RF and anti-CCP at baseline was 0.69 (95% CI 0.64–0.74). Among the 34 patients with RF–IgM– and anti-CCP+ (group 3), 17 (50%) were RF–IgA+. This subclass of RF was also present in 39 (9.6%), 41 (45.1%), and 262 (93.2%) patients in groups 1, 2, and 4, respectively.

Radiographic data. Complete sets of hand and feet radiographs were available for 736 patients from the first visit and for 719 and 673 patients at 6 and 12 months, respectively. Baseline characteristics of these patients and the whole cohort were similar.

Clinical characteristics of groups at baseline. Clinical presentation was not consistently associated with serologic profile. Patients positive for both antibodies (group 4) more frequently fulfilled the 1987 ACR criteria for RA than did the other groups (89% vs 76.5%, 68.1% and 59.5% for groups 3, 2, and 1, respectively, $p < 0.001$) even when RF was left out of the set of criteria ($p < 0.001$; Table 2). Patients negative for both factors (group 1; anti-CCP– and RF–) less often had positive results of the squeeze test for MTP joints (48.8% vs 66.3% for the other groups, $p < 0.001$) and arthritis of hand joints (89.4% vs 97%, $p < 0.001$). This group fulfilled the 2010 ACR/EULAR criteria

Table 2. Differences in clinical presentation between the 4 groups at baseline.

Group	Comparison	
CCP+RF+ vs 3 other groups	More frequent 1987 ACR criteria for RA	$p < 0.001$
CCP–RF– vs 3 other groups	Less frequent arthritis of hand joints	$p < 0.001$
	Less frequent positive squeeze test on metatarsophalangeal joints	$p < 0.001$
	Less frequent 2010 ACR/EULAR criteria for RA	$p < 0.001$
CCP+ vs CCP–	More frequent rheumatoid nodules	$p = 0.001$
	At least 1 HLA-DRB1*01 or 04 gene	$p < 0.001$
RF+ compared with RF–	More frequent arthritis of metacarpophalangeal and interphalangeal 2 and 3 joints	$p < 0.001$

ACR: American College of Rheumatology; EULAR: European League Against Rheumatism; CCP: cyclic citrullinated peptide; RF: rheumatoid factor; RA: rheumatoid arthritis.

for RA less frequently than did the other groups at baseline (59.3% vs 99.3%, 100%, and 96.7% for groups 3, 2, and 1, respectively, $p < 0.001$) and at 1 year (70.1% vs 99.6%, 100%, and 97.8% for groups 3, 2, and 1, respectively, $p < 0.001$). Patients who were RF+ (groups 2 and 4) had arthritis of the MCP and interphalangeal 2 and 3 joints more frequently than did those who were RF– (91.1% vs 81.4%, $p < 0.001$). Rheumatoid nodules were rare at baseline and were associated with anti-CCP antibodies: they were present in 4.1% of anti-CCP+ patients (groups 3 and 4) versus 0.8% of anti-CCP– patients (groups 1 and 2; $p < 0.001$). The groups did not differ in age, smoking, morning stiffness, DAS28, or HAQ score, symptom duration at first visit, and delay to initiation of a first disease-modifying antirheumatic drug (DMARD).

Biological and genetic characteristics at baseline. Mean baseline ESR was higher in anti-CCP+ patients (32.1 and 34.9 in groups 3 and 4 vs 26.3 and 26.1 in groups 1 and 2, respectively, $p < 0.001$; Figure 1). The same was found regarding baseline CRP (mean values: 23.62, 22.71, 16.31, 18.64 in groups 4 to 1 respectively, $p < 0.001$, groups 3 and 4 vs groups 1 and 2). Controlling for RF did not strongly influence acute-phase values.

In total, 72.9% of anti-CCP+ patients (groups 3 and 4) were positive for at least 1 HLA-DRB1*01 or *04 RA-associated gene as compared with 45.1% of anti-CCP– patients (groups 1 and 2, $p < 0.001$).

Radiographic features at baseline. Mean mTSS, erosion score, and JSN score were respectively 5.8 (7.7), 2.8 (4.7), and 3.0 (4.4) at baseline. The mTSS score was higher for group 4 than for other patients ($p = 0.002$; Figure 2). The difference was mainly due to the forefeet score ($p < 0.001$). By contrast, groups did not differ for the hands score ($p = 0.31$). The JSN score was not significantly different between

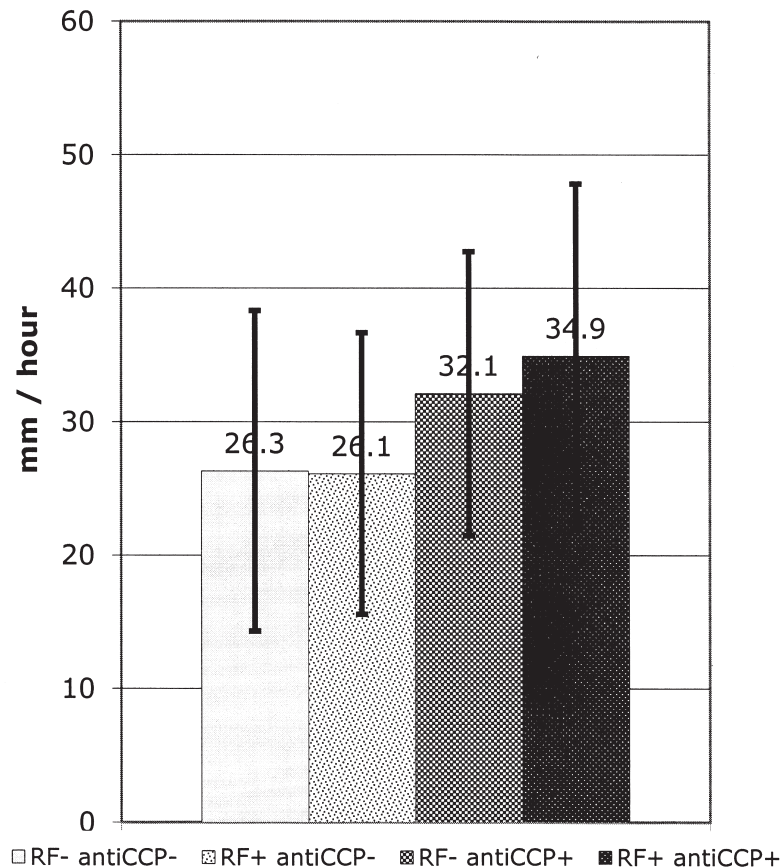


Figure 1. Mean erythrocyte sedimentation rate in 4 groups at baseline. Error bars represent SD. RF: rheumatoid factor; anti-CCP: anticyclic citrullinated peptide antibodies.

the 4 groups ($p = 0.33$). Regarding the erosion score, the 4 groups could not be clearly differentiated. Nevertheless, group 4 was distinguished from the 2 anti-CCP- groups [mean erosion score 4.08 (6.13), 1.66 (2.58), and 2.02 (3.38) in groups 4, 2, and 1, respectively, $p < 0.001$]. Again, 162 (44.8%) in group 1, 42 (50.6%) in group 2, 13 (41.9%) in group 3 and 155 (60.3%) in group 4 showed feet erosion at baseline ($p < 0.001$, group 4 vs the 3 other groups). The proportions of patients with hand erosion at baseline were fairly distributed in all 4 groups ($p = 0.54$). Overall, 185 patients (25.1%) had an erosive disease according to the 2010 ACR/EULAR RA classification criteria. Anti-CCP+ groups (groups 3 and 4) more frequently had a “typical” erosive disease than did the 2 other groups (34.1%, 31.3%, 20.5%, and 19.1% in group 4 to 1 respectively, $p = 0.001$ group 3 and 4 vs group 1 and 2). RF+ and RF- patients did not differ in radiographic scores.

Radiographic progression at 6 and 12 months. Mean mTSS were 6.6 (8.9) and 7.3 (10.4) at 6 and 12 months, respectively. Mean erosion scores were 3.4 (5.8) and 4.0 (7.1) at 6 and 12 months, respectively. Overall, 150 patients (20.9%) showed a mean increase of at least 1 unit in mTSS at 6 months and 189 (28.1%) at 1 year; 140 patients (19.5%)

showed a mean increase of at least 1 unit in the erosion score at 6 months and 181 (26.9%) at 1 year. During the first year, the mean increase in mTSS was greater for the 2 anti-CCP+ groups [$+2.57$ (5.48) for group 4 and $+2.14$ (4.20) for group 3] than for the 2 anti-CCP- groups [$+0.59$ (1.75) for group 2 and $+0.81$ (3.40) for group 1, $p < 0.001$]. Similar results were found for progression of erosion score at 1 year ($p < 0.001$, data not shown). At Month 6, progression of the mTSS and erosion score was greater for group 4 than for groups 1 and 2 ($p < 0.001$, data not shown).

Fifty-four patients (16.6%) in group 1, 14 (18.7%) in group 2, 14 (48.3%) in group 3, and 107 (44.2%) in group 4 showed progression of at least 1 unit in the mTSS at 12 months ($p < 0.001$ anti-CCP+ groups vs anti-CCP- groups; Figure 3). A similar contrast (anti-CCP+ vs anti-CCP-) was made regarding the percentage of progressors (mTSS) at 6 months and regarding the percentage of patients with a new erosion or worsening of existing erosion at 6 and 12 months (Figure 3). An additional multivariate analysis was conducted by the means of logistic regression to investigate the weight of immunologic and clinical characteristics at baseline on the 12 months radiographic progression. The results are summarized in Appendix 1 and show that high

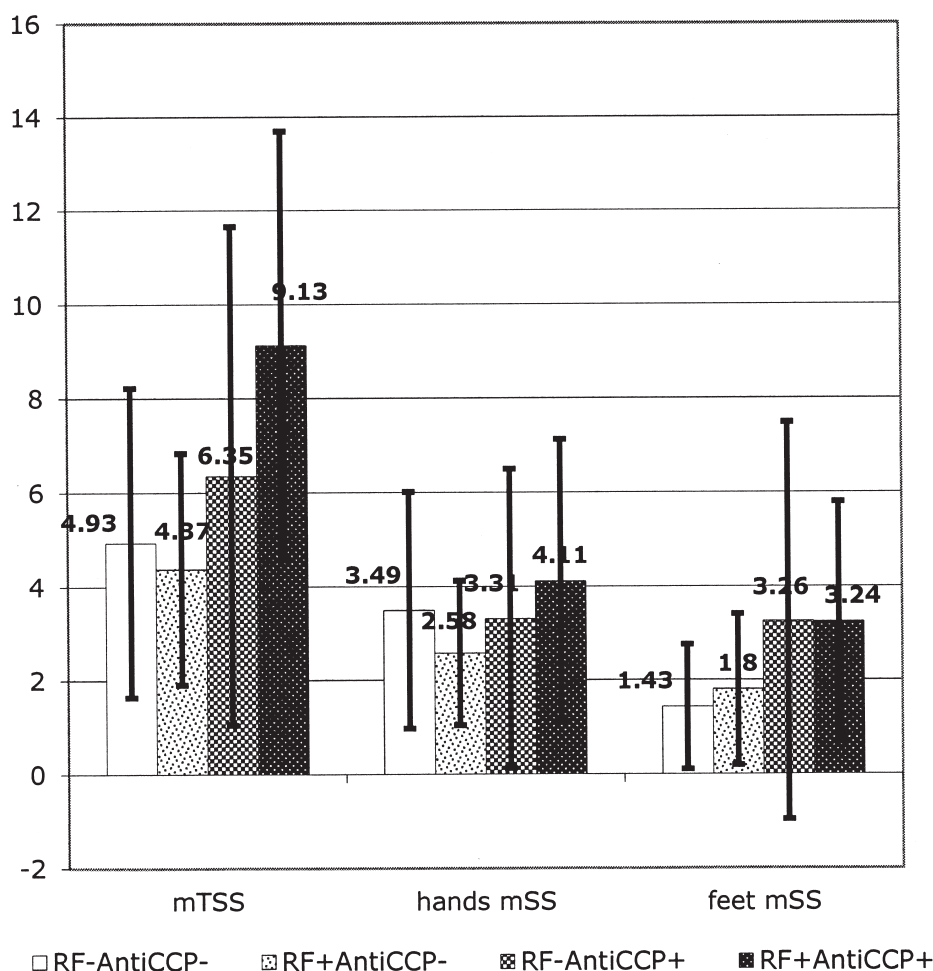


Figure 2. Mean van der Heijde-modified total Sharp score (mTSS) and modified Sharp score for hands and feet for the 4 groups at baseline. Error bars represent SD. RF: rheumatoid factor; anti-CCP: anticyclic citrullinated peptide antibodies.

titers of ACPA have a relevant independent prognostic value. Group 3 could not be distinguished from group 4, or group 1 from 2, which suggests that the prognosis for patients positive for both autoantibodies was not worse than for patients positive for anti-CCP alone, and that controlling for RF did not influence radiographic progression in the short term. Nevertheless, in groups 1 and 3, the percentage of radiographic progressors was higher in patients with IgA-RF versus without IgA-RF, both at 6 months (12.5% vs 11.7% in group 1, 43.8% vs 33.3% in group 3) and 12 months (25% vs 15.8% in group 1, 60% vs 37.5% in group 3).

DISCUSSION

We aimed to compare the initial features of patients with early arthritis according to positivity for RF and/or ACPA. We used a large, prospective, early-arthritis cohort from the community. This situation reflects clinical practice and allowed us to study the clinical value of RF and anti-CCP antibodies in patients selected by symptoms, not diagnosis.

In terms of biological and radiographic data, 2 groups could be separated by anti-CCP status. Patients positive for RF alone (group 2) and patients negative for both autoantibodies (group 1) had similar profiles and differed from anti-CCP+ patients (groups 3 and 4), which suggests that RF had no clear relationship with acute-phase reactant values at baseline or radiographic progression in the short term. The number of patients was heterogeneous among the groups: half the patients were negative for both autoantibodies, one-third were positive for both autoantibodies, and only 15% were positive for only 1 autoantibody, mainly IgM-RF.

Inclusion criteria for patients in early arthritis cohorts often differ, so comparing them is difficult. Few studies have examined patients by both RF and anti-CCP antibody status to determine relationships between these 2 autoantibodies. The proportion of patients with RF and/or anti-CCP antibodies differed in a British early arthritis cohort [Norfolk Arthritis Register (NOAR)]: among 254 patients, 53.3% were negative for both, 8.3% were RF+ and

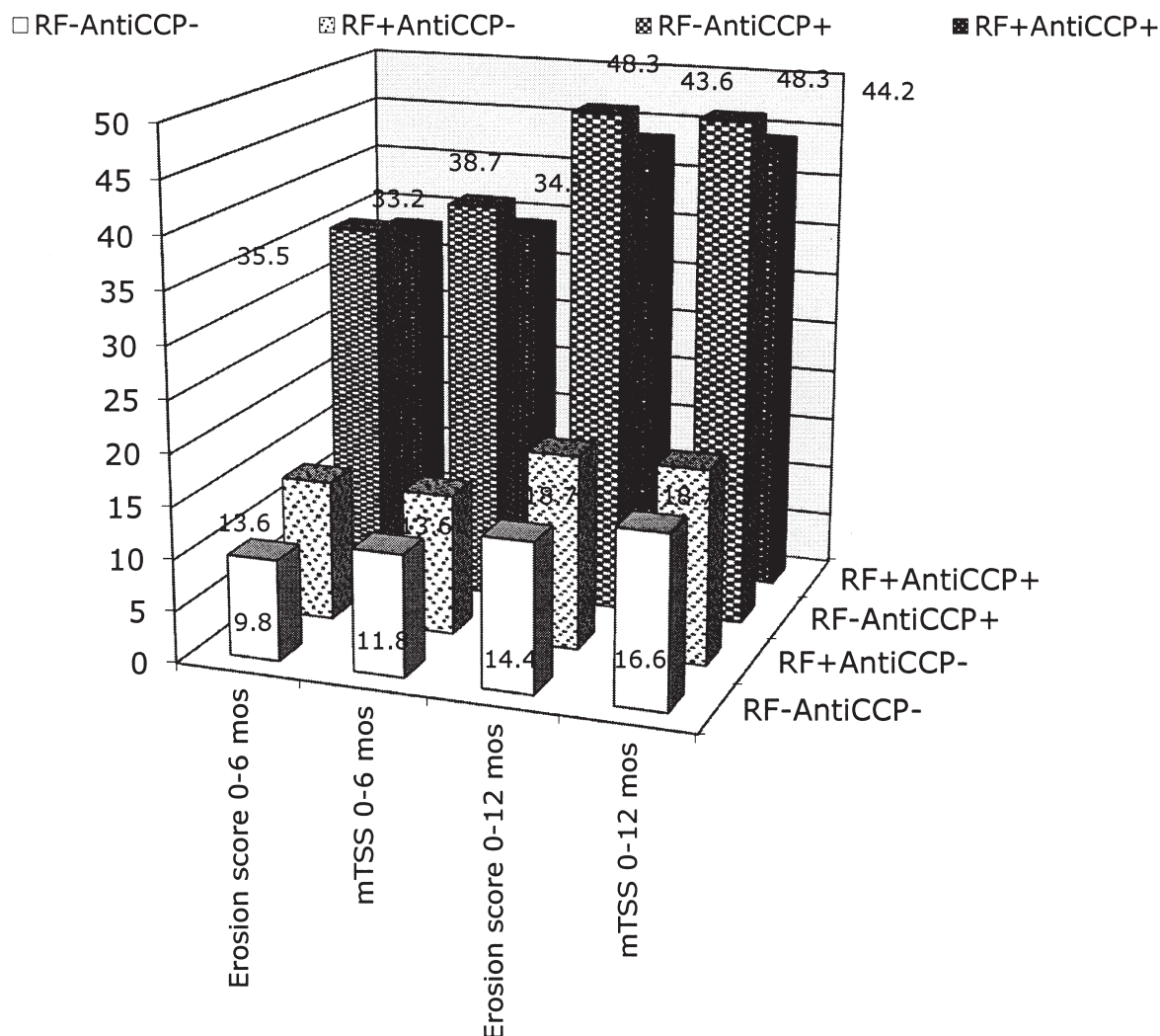


Figure 3. Proportion of patients with radiographic progression at 6 and 12 months. RF: rheumatoid factor; anti-CCP: anticyclic citrullinated peptide antibodies; mTSS: van der Heijde-modified total Sharp score.

anti-CCP-, 18.8% were RF- and anti-CCP+, and 19.6% were positive for both³¹. We found no consistent relationship between clinical presentation and serologic profile in our study. Nevertheless, anti-CCP+ patients more frequently showed rheumatoid nodules. Rheumatoid nodules were associated with RF³² or anti-CCP antibodies³³ in 2 different RA cohorts. Anti-CCP+ and anti-CCP- patients did not differ in localization of arthritis at baseline in a Dutch cohort of 454 patients with early RA²⁴. After a 4-year followup, the mean (SD) number of swollen joint counts, especially MCP 1 and interphalangeal joints 3, 4, and 5, was greater in the anti-CCP+ group [5.3 (6.8) vs 3.1 (4.2), $p = 0.01$]. There was no significant difference in the pattern of joint involvement in an early inflammatory arthritis cohort of 92 patients from Birmingham, except for increased prevalence of knee joint swelling in anti-CCP-positive patients (42.9% vs 22.2%, $p = 0.03$)³⁴.

We found a difference between groups in acute-phase reactants but not DAS28 and HAQ scores at baseline: mean ESR and CRP levels were significantly higher with anti-CCP+, regardless of RF status. Literature results are conflicting regarding the association of these 2 autoantibodies and disease activity. Anti-CCP+ was associated with elevated composite score in 1 study²¹ and with a high DAS28 in another study⁷. Ronnelid, *et al* did not find an association of anti-CCP+ and DAS28 at baseline in a cohort of 279 patients with early arthritis³⁵. Nevertheless, DAS28 was greater after 1 year with anti-CCP+ versus anti-CCP-. In the Dutch study, the number of tender or swollen joints did not differ by anti-CCP+ at baseline²⁴. ESR and/or CRP level were increased with anti-CCP+ in 2 studies^{7,36} but not in others^{24,35,37}.

In our study, radiographic damage findings were more severe for patients with both anti-CCP+ and RF+ at

baseline, and 1-year radiographic progression was greater with anti-CCP+. The addition of RF+ did not change the findings. Radiographic features were similar to those from other studies of early arthritis. In the NOAR cohort, erosions (scored according to Larsen score) at baseline were more frequent with anti-CCP+ [OR ratio 2.53 (95% CI 1.48–4.30)] but not RF+ [1.63 (0.94–2.82)]³¹. Their groups did not differ in erosions when combining RF+ and anti-CCP+ [2.18 (0.77–6.13) vs anti-CCP– and 0.95 (0.40–2.28) vs RF–]³¹. Nevertheless, 7 early arthritis cohorts showed a link between erosions and anti-CCP+ at baseline^{6,7,13,21,38} and for RF+^{6,23,38,39}. Radiographic progression from 2 to 5 years was greater with RF+ and anti-CCP+^{9,31} and anti-CCP+ alone^{5,6,9,13,39,40,41,42,43}. In a Canadian early arthritis cohort in which both RF and ACPA were tested, patients who remained ACPA-positive throughout followup (but not those who remained RF-positive) were more likely to have erosive disease (OR 3.86, 95% CI 1.68, 8.92)⁴⁴. Erosive disease typical of RA was recently defined in light of the ACR/EULAR 2010 criteria for RA, with the outcome measures being initiation of methotrexate therapy or any DMARD therapy within the first year of disease and arthritis persistence over 5 years³⁰. In our study, anti-CCP were associated with a more typical and severe disease at baseline, and these data suggest that the presence of autoantibody should indicate prompt DMARD start in early arthritis patients. We found feet erosion at baseline more frequent in anti-CCP and RF+ patients, whereas this distinction was not observed for hand erosions. As this group more frequently fulfilled 1987 ACR criteria for RA, we can assume that feet erosions have an important weight in predicting RA in patients with early arthritis, as suggested by other authors who demonstrated that the “erosion” criterion at the feet had the best diagnostic performance for RA⁴⁵. As presented, a undeniable proportion of patients were IgA-RF-positive among our groups, even in groups 1 and 3 (i.e., IgM-RF-negative groups). Although these results should be interpreted with caution because of the small patient numbers, we observed a trend toward more radiographic progression in IgA-RF-patients at 6 and 12 months, suggesting that this autoantibody may be associated with more severe disease. Similarly, Berglin, *et al* demonstrated that 2-year radiological progression was predicted by both anti-CCP antibodies and IgA-RF, in combination with clinical data in patients with early arthritis, whereas no significant prediction of structural progression was found with IgM-RF positivity in their model³⁹.

The phenotype of early arthritis patients with or without anti-CCP+ and/or RF+ did not correspond to a particular clinical presentation. However, acute-phase reactant values were higher at baseline, and radiographic progression was greater during the first year with anti-CCP+, which suggests that this autoantibody may be associated with the inflam-

matory process and progressive disease in early arthritis. These data confirm that both RF and ACPA are relevant for purposes of RA diagnosis, with an additional prognostic value conferred by the presence of ACPA. Thus early arthritis with ACPA requires special management, both initially and during followup.

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APPENDIX 1. Stepwise logistic regression analysis of predictive factors of the progression of mTSS at 12 months.

Predictive Factor	OR (95% CI)	p
RF low titer*	0.72 (0.37; 1.40)	0.336
RF high titer [#]	1.11 (0.63; 1.96)	0.727
Anti-CCP, low titer*	2.05 (0.90; 4.70)	0.088
Anti-CCP, high titer [#]	4.67 (2.66; 8.21)	<0.001
DAS28, > 5.1	0.72 (0.48; 1.08)	0.113
Age, > median: 50 yrs	1.86 (1.28; 2.73)	0.001
ESR, > 28 mm/h	1.90 (1.27; 2.84)	0.002

*Titer between 1- and 3-fold the upper limit of normal; [#]titer > 3-fold the upper limit of normal. mTSS: van der Heijde-modified total Sharp score; RF: rheumatoid factor; anti-CCP: anticyclic citrullinated peptide antibodies; DAS28: 28-joint Disease Activity Score; ESR: erythrocyte sedimentation rate.