

Repeated Anticitrullinated Protein Antibody and Rheumatoid Factor Assessment Is Not Necessary in Early Arthritis: Results from the ESPOIR Cohort

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ABSTRACT. Objective. Presence and levels of anticyclic citrullinated peptide antibodies (anti-CCP) and rheumatoid factor (RF) contribute to the classification and prognosis of rheumatoid arthritis (RA). The objective was to determine the usefulness of repeating anti-CCP/RF measurements during the first 2 years of followup in patients with early arthritis.

Methods. In patients with early undifferentiated arthritis, serial anti-CCP and RF were measured using automated second-generation assays every 6 months for 2 years. Frequencies of seroconversions (from negative to positive or the reverse) and changes in antibody levels during followup were determined.

Results. In all, 775 patients, mean (SD) age 48.2 (12.5) years, mean symptom duration 3.4 (1.7) months, 76.6% female, were analyzed; 614 (79.2%) satisfied the American College of Rheumatology/European League Against Rheumatism 2010 classification criteria for RA at baseline. At baseline, respectively for anti-CCP and RF, 318 (41.0%) and 181 (23.4%) patients were positive, of whom 298 (93.7% of the positive) and 111 (61.3% of the positive) were highly positive (above 3 × upper limit of the norm). There were only 12 anti-CCP seroconversions toward the positive (i.e., 2.6% of the anti-CCP-negative), 21 seroconversions toward the negative (6.6% of the anti-CCP-positive), and 8 (1.0%) changes to a higher anti-CCP level category during the 2-year followup; respectively for RF, 27 (4.6%), 95 (52.5%), and 13 (1.7%).

Conclusion. In this cohort of patients with early arthritis, including in the subset of patients who did not fulfill the RA criteria, antibody status showed little increase over a 2-year period. Repeated measurements of anti-CCP/RF very infrequently offer significant additional information. (First Release Nov 15 2013; J Rheumatol 2014;41:41–6; doi:10.3899/jrheum.121313)

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Accumulating evidence that early therapeutic interventions can positively influence the disease course of rheumatoid arthritis (RA) and improve individual patient outcomes has prompted a growing medical need for early diagnosis of RA¹. Further, the development of expensive treatment strategies favoring an early start of therapy has also increased the interest in prognostic tools that could trigger patient stratification and adjusted treatment decisions. However, performing unnecessary tests may lead to higher costs and delayed decisions². Therefore, determining the most effective diagnostic strategy in early arthritis is important.

The presence and level of anticyclic citrullinated peptide antibodies (anti-CCP) and of rheumatoid factor (RF) are part of the 2010 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) classification criteria for RA³. In these criteria, anti-CCP and RF titers are analyzed as negative, “low titer” if inferior to 3 × the upper limit of the norm (ULN), or “high titer” if above 3 × ULN³. Further, anti-CCP are established

prognostic markers in early RA and early undifferentiated arthritis^{4,5}. Therefore, determination of anti-CCP and RF status is of great interest in the initial investigation of early arthritis, for both classification and prognosis.

Although change in anti-CCP and RF status over time in patients with recent-onset inflammatory arthritis has been studied, there was heterogeneity in the results^{6,7}. The clinical question is whether antibody levels should be periodically reassessed over time in patients with early inflammatory arthritis. Reassessment of anti-CCP/RF would be useful if it could be shown that a significant number of patients “switch” from a negative antibody status to a positive status (seroconversion) or if it were shown that a significant number of patients change status from low to high titer.

The objective of our study was to determine the proportion of patients with early inflammatory arthritis who change anti-CCP/RF status during the first 2 years of followup, and therefore the usefulness of repeated measures. To answer these questions, we used data from the ESPOIR cohort, a prospective observational study.

MATERIALS AND METHODS

Participants. The early inflammatory arthritis cohort ESPOIR is an ongoing French multicenter national prospective observational cohort⁸. After approval by the Montpellier ethical committee, 16 university hospital rheumatology departments included patients drawn from a large part of France. In our study, the data analyzed pertain to baseline and the first 2 years of followup. The following inclusion criteria were used: signed informed consent, age 18–70 years, 2 or more swollen joints with a duration of joint swelling of > 6 weeks and < 6 months, no previous disease-modifying drugs and no previous steroids, and no definite diagnosis of a disease other than RA or undifferentiated arthritis⁸. Thus, the ESPOIR cohort is composed of both early undifferentiated inflammatory arthritis and recently developed RA.

A total of 775 patients were analyzed; 510 (65.8%) satisfied the ACR 1987 criteria for RA at baseline.

Followup. Patients were followed longitudinally with clinical and laboratory examinations at baseline and after 6, 12, 18, and 24 months (followup is ongoing). For this study, only those patients with anti-CCP/RF levels available both for the initial assessment and for at least 1 followup visit during the first 2 years were analyzed.

Antibody assessment. Anti-CCP were measured from frozen sera using an automated second-generation anti-CCP assay (Elecsys Anti-CCP, Roche Diagnostics GmbH) and RF was similarly measured using Roche Cobas RFII. The measurements were blindly made by Roche Diagnostics. Concentrations ≥ 17 U/ml (for anti-CCP) and ≥ 14 U/ml (for RF) were considered positive (manufacturer cutoff). Thus, levels of anti-CCP were interpreted on successive sera (baseline, 6 mos, 12 mos, 18 mos, and 24 mos) as negative, positive (17 to < 3 × ULN, i.e., 51 U/ml), and highly positive (≥ 3 × ULN), and similar analyses were conducted for RF (cutoffs, 14 and 42 U/ml, respectively).

Other data collection. At baseline, variables collected included demographic variables, clinical history and clinical examination, health assessment questionnaire⁹, acute-phase reactants, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP; positivity cutoff 10 mg/l). After 2 years, the data used were fulfillment of the ACR/EULAR classification criteria for RA³.

Statistical analyses. To assess the usefulness of repeated anti-CCP/RF measures, the percentage of patients going from one antibody status at

baseline to another status at any timepoint over followup (i.e., over 5 assessments, 1 every 6 mos for 2 yrs) was analyzed. For patients changing anti-CCP/RF status, the ACR/EULAR criteria for RA were applied before and after the anti-CCP/RF status change.

Finally, to assess situations where repeating anti-CCP and RF measurements would be relevant in a real-life situation, we also performed a sensitivity analysis only in patients who did not fulfill the ACR/EULAR 2010 criteria for RA at baseline.

RESULTS

In all, 775 of the 813 patients in the cohort were analyzed. They had anti-CCP or RF levels available both for the initial assessment and for at least 1 followup visit during the first 2 years. Of them, 772 had data available for both anti-CCP and RF. A maximum of 5 followup visits were analyzed from each patient; thus, 3613 samples were analyzed.

Characteristics were typical for early arthritis cohorts (Table 1): mean (SD) age was 48.2 (12.5) years, mean (SD) duration of symptoms was 3.4 (1.7) months; and 76.6% were female. Of the 775 patients, 614 (79.2%) satisfied the ACR/EULAR 2010 classification criteria^{3,10}. No differences in baseline measurements apart from antibody status were identified when comparing individuals who fulfilled the RA criteria at baseline with those who did not.

Anti-CCP/RF positivity at baseline. At baseline, 457 of 775 patients (59.0%) were anti-CCP negative and 591 of 772 (76.6%) were RF-negative. Among the positive patients, 298 (93.7%) were highly anti-CCP-positive and 111 (61.3%) were highly RF-positive. Figure 1 shows the distribution of the titers of anti-CCP and RF at baseline.

Change in anti-CCP status over time. Anti-CCP status was available for 775, 753, 721, 690, and 674 patients at each timepoint, respectively. Anti-CCP status was stable over time. Only 12 patients (2.6% of 457 negative patients) changed status from negative to positive at any timepoint during the 2-year followup, whereas 8 (40.0% of 20 low-positive patients) changed from positive to highly

Table 1. Baseline characteristics of 775 early arthritis patients included in the ESPOIR cohort and analyzed for the present study.

Characteristic	Result
Age, yrs, mean (SD)	48.2 (12.5)
Joint swelling duration, mos, mean (SD)	3.4 (1.7)
Women, n (%)	594 (76.7)
Tender joint count (0–28), mean (SD)	8.5 (7.0)
Swollen joint count (0–28), mean (SD)	7.2 (5.4)
Health Assessment Questionnaire, mean (SD)	0.97 (0.68)
Erosive status, yes, n (%)	106 (13.7)
ESR, mm/h, mean (SD)	22 (24)
CRP, mg/l, mean (SD)	22.2 (33.9)
Anti-CCP positivity, n (%)	318 (41.0)
RF positivity, n (%)	181 (23.4)

ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; anti-CCP: anticyclic citrullinated peptide antibodies; RF: rheumatoid factor.

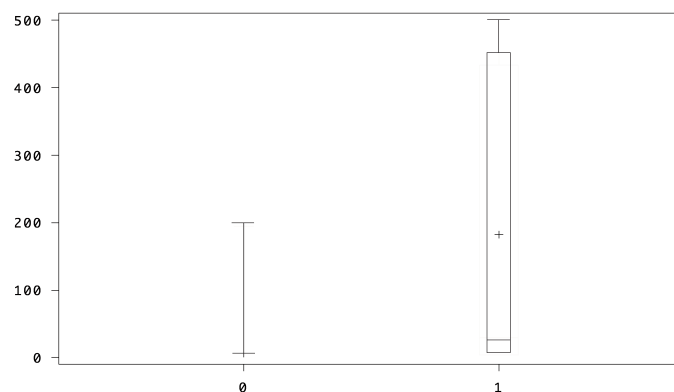
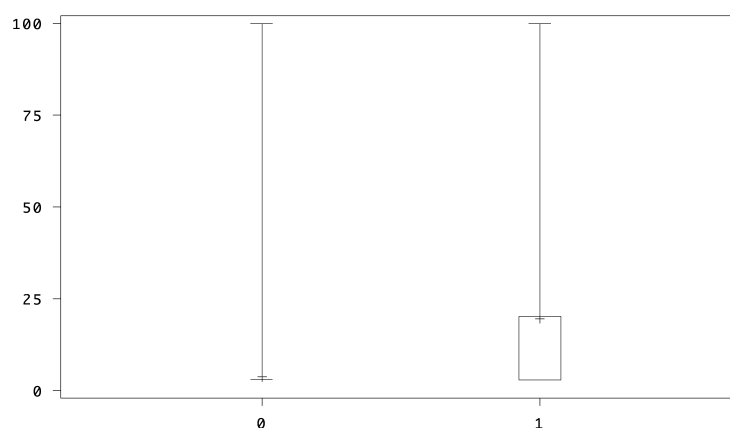
A**B**

Figure 1. Box plot distribution of anticyclic citrullinated peptide antibodies (anti-CCP) and rheumatoid factor (RF) status at baseline. Column 0 is patients not fulfilling the American College of Rheumatology/European League Against Rheumatism classification criteria, and column 1 is patients who do fulfill the criteria. A. Anti-CCP. B. RF. Y axis: antibody blood value.

positive. Conversely, 21 patients (6.6% of 318 positive patients) became negative over followup.

For the 12 patients who became anti-CCP positive over time, 5 became positive at the 6-month visit; of the 5, only 2 were positive at the next visits; 3 became positive at the 1-year visit; and 4 became positive during the second year (Supplementary Table 1 available from the author on request). In all, 9 of these 12 patients were positive for anti-CCP at only 1 of the 5 assessments, and 5, when they were positive, had very low positive levels of anti-CCP (< 27 U/ml).

The symptom duration of the 20 patients who changed anti-CCP status toward greater positivity was no shorter than in the rest of the cohort [3.0 mos (1.4), extremes

1.1–5.9] and there were no differences between the 20 patients who changed anti-CCP category toward greater positivity and those patients who remained CCP-negative/CCP low (Supplementary Table 2 available from the author on request).

The mean value of anti-CCP titers also remained very stable (mean titer fluctuating between 142.4 and 145.7 U/ml over the 2 yrs of assessment).

Among the 21 patients who became negative for anti-CCP over the followup, 14 (66.6%) had very low anti-CCP levels at baseline and the seroconversion was for all succeeding visits for 7 patients (33.3%), whereas 14 then became positive again at some of the next visits.

Change in RF status over time. RF status was available for

Table 2. Anti-CCP and RF status at baseline and during 2-year followup in 772 early arthritis patients. Data are number (% of total). Followup refers to the last available assessment: either at 2 years (for anti-CCP, 674 patients and for RF, 673 patients) or at the last available timepoint.

		Baseline		Total
		Anti-CCP and/or RF-positive	Anti-CCP and RF-negative	
Followup	Anti-CCP			
	and/or RF-positive	321 (41.6)	7 (0.9)	328 (42.5)
	Anti-CCP and RF-negative	14 (1.8)	430 (55.7)	444 (57.5)
	Total	335 (43.4)	437 (56.6)	772

Anti-CCP: anticyclic citrullinated peptide antibodies; RF: rheumatoid factor.

772, 751, 719, 688, and 673 patients at each timepoint, respectively. RF status was also globally stable over time. Only 27 patients (i.e., 4.6% of the 591 RF-negative) changed status from negative to positive at any timepoint during the 2-year followup, whereas 13 (18.6% of the 70 low-positive) changed from positive to highly positive. Conversely, however, 95 patients (12.3% of the cohort and 52.5% of the 181 positive patients) became negative over followup. The mean value of RF titers remained quite stable (mean titer fluctuating between 10.4 and 16.3 U/ml over the 2 yrs of assessment).

Among the 95 patients who became negative for RF over the followup, the mean (SD) level of RF titer at baseline was 41.1 U (28.6), versus 74.4 U (29.9) for patients who were positive and remained positive.

Change in RA classification. Changes in anti-CCP and RF titers did not always occur in the same patients (Supplementary Table 3 available from the author on request); because the ACR/EULAR 2010 criteria take into account both titers, there were few changes in antibody category according to the ACR/EULAR criteria (in particular, 7 patients, 0.9%, becoming positive and 14 patients, 1.8%, becoming negative; Table 2).

Among the patients who changed antibody titer category, when analyzing both anti-CCP and RF and comparing the baseline visit to the last visit with data available, this change in itself would have changed the patient's classification at baseline according to the ACR/EULAR RA criteria in 8 cases (1.0%): 1 by a positive change in the criteria related to a positive change in antibody status, and 7 by a negative change.

Results in the subpopulation who did not fulfill the ACR/EULAR 2010 criteria for RA at baseline. In this smaller population (n = 161), 157 (97.5%) were anti-CCP negative at baseline and 159 (98.8%) were RF negative at baseline.

Results in terms of change in status were similar to the

total population, with only 4 patients (2.5%) going from negative to positive or very positive for anti-CCP over followup (of whom 3 switched status at the 6-mos visit). For RF, there were 2 patients (1.2%) going from negative to positive or very positive, 1 at the 6-month and 1 at the 18-month visit. Only 1 individual changed in terms of disease classification (i.e., fulfilled the RA criteria) owing to change in antibody status.

DISCUSSION

In this cohort of patients with recent onset arthritis, anti-CCP and to a lesser extent RF status was generally stable over time, and only 2.6% of patients changed status from anti-CCP-negative to anti-CCP-positive over followup. Similar results were found for RF, with 4.6% increasing from negative to positive, but more patients having decreasing titers over time. Further, results were similar (with < 3% patients changing status) in the subpopulation of patients who did not fulfill the 2010 ACR/EULAR criteria for RA at baseline.

The results suggested that repeated measurements of antibodies and in particular anti-CCP over a 2-year period in patients with arthritis of short duration very rarely offer additional important information, as compared to a single measurement in the first months of early arthritis.

Our study has major strengths. The ESPOIR cohort is a national cohort of early arthritis⁸. Because the entry criteria (> 2 swollen joints for 6 weeks to 6 mos) are close to clinical practice and because of its large number of participants, this cohort is well-adapted to the present study objective, with a good representation of patients with early arthritis. An early arthritis cohort, such as ESPOIR, is better adapted to assess diagnostic/classification values than an undifferentiated arthritis cohort excluding patients with RA¹¹ because the ESPOIR cohort corresponds to real-life situations. ESPOIR mimics natural conditions closely because of its observational nature, which leads to better generalizability of the results. However, it should be noted that one limit of the present study is that the percentage of positivity for antibodies is low in the ESPOIR cohort, as has been previously observed². Anti-CCP titers were assessed using a second-generation assay widely used in rheumatology and shown to have strong measurement properties¹². The test for RF is also widely used. However, some of the seroconversions could be the result of human error during the analyses rather than actual seroconversions, because all blood samples were tested at once and the samples showing seroconversion were not retested. In our study, we assessed titers of antibodies and also the effect of these titers on classification of the patients. In this way, antibody titers may be translated into practical and applicable information for the rheumatologist. We showed that the infrequent changes in anti-CCP titers did not alter these patients' classification; changes in RF titer (toward a lower category) did alter 7

patients' classification (from RA to undifferentiated arthritis).

It may be thought that only 1 measure of anti-CCP titer is sufficient, if that first assessment is performed late in the disease process. However, in our study, patients were included after a mean duration of synovitis of only 3.3 months. This often corresponds to the point in time when early arthritis patients see a rheumatologist for the first time; thus our results are transposable to clinical practice.

There is much interest in determining biomarkers, which could be important for diagnosis/classification or for prognosis in RA. Recent studies of smaller groups of patients showed results very similar to ours^{6,7,13,14,15,16,17}; however, several of those patients did not have conditions that evolved mainly into RA but instead had other rheumatic diseases, although this question is mainly of interest in early RA cases. RF was shown here to be less stable than anti-CCP in early arthritis, as has been previously observed^{18,19,20,21,22}. One explanation may be that RF titers would fluctuate with disease activity, though this should be investigated further¹².

We assessed the diagnostic role of repeated measurements; however, we did not assess prediction of "hard outcomes" such as radiographic progression²³.

Anti-CCP titers have been shown to be predictive of joint destruction^{4,23} as have some other biomarkers, such as C-terminal crosslinked telopeptide of type I collagen generated by matrix metalloproteinases, anti-interleukin 1 α , anti-CRP antibodies, or cartilage oligomeric matrix protein^{24,25,26,27}. However, we did not assess those biomarkers.

Measuring antibody titers when faced with a patient with early arthritis is helpful for the clinician; however, our study showed that very little additional information was gained by repeating this measure, even when patients had "unclear" symptoms and did not fulfill the ACR/EULAR RA criteria. Therefore, we recommend that such an assessment be performed only once, when the patient first presents with synovitis.

Future studies should focus on the usefulness of repeating the measurement of these biomarkers in borderline situations of very low titers, and of assessing other biomarkers, as a means to improve the prognostic assessment of early arthritis.

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