Should Anti-citrullinated Protein Antibody and Rheumatoid Factor Status Be Reassessed During the First Year of Followup in Recent-Onset Arthritis? A Longitudinal Study

MARIA D. MJAAVATTEN, DÉSIRÉE M. van der HEIJDE, TILL UHLIG, ANNE J. HAUGEN, HALVOR NYGAARD, OLAV BJØRNEBOE, and TORE K. KVIEN

ABSTRACT. ***Objective.*** Presence and levels of antibodies contribute to the classification of rheumatoid arthritis. We investigated the longitudinal course of anti-citrullinated protein antibodies (ACPA) and immunoglobin M (IgM) rheumatoid factor (RF) during the first year after arthritis onset in patients with very short disease duration.

Methods. Patients (aged 18-75 years) with ≥ 1 swollen joint of ≤ 16 weeks' duration had assessments of ACPA (2nd generation anti-cyclic citrullinated peptide antibodies, anti-CCP2) and IgM RF at inclusion and after 3, 6, and 12 months. Frequencies of seroconversions (negative to positive and vice versa) and changes in antibody levels during followup were determined.

Results. A total of 281 early arthritis patients (median duration of joint swelling 32 days, 14.2% ACPA positives, 12.8% IgM RF positives) with 978 longitudinally collected serum samples were included. Only 5 patients (1.8%) negative for both antibodies at baseline turned antibody-positive during followup, while 9 antibody-positive patients (3.2%) turned antibody-negative. ACPA was more stable than RF regarding both status and levels.

Conclusion. Antibody status (ACPA/RF) is a stable phenotype in very early arthritis, as seroconversion was only found in 5% of patients. Repeated measurement of ACPA or RF during the first year after onset of arthritis does not offer major additional information. (First Release Oct 1 2011; J Rheumatol 2011;38:2336–41; doi:10.3899/jrheum.110234)

Key Indexing Terms:
ANTICYCLIC CITRULLINATED ANTIBODIES RHEUMATOID FACTOR
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The presence and levels of rheumatoid factor (RF) and antibodies against citrullinated proteins (ACPA) are important predictors of a poor outcome in patients with early arthritis, in terms of development of rheumatoid arthritis (RA)[1], persistence of arthritis[2], and development of erosive disease[3]. Early treatment with disease-modifying antirheumatic drugs (DMARD) improves outcome in early RA[4], especially in ACPA-positive patients[5].

Because presence or absence of ACPA or RF will influence classification and treatment decisions in patients with recent-onset arthritis, determination of antibody status is a central part of the initial investigation. Seroconversions from negative to positive antibody status over time are of special interest, as this will influence decision-making for diagnosis and choice of treatment. RF and ACPA seroconversion during followup in patients with early inflammatory arthritis was addressed in a recent review[6]. Although RF and ACPA seemed to be stable over time in the studies included in this review, no detailed reports specifically addressing this issue were identified, and the review concluded that further elaboration on this topic was needed.

Both presence and levels of ACPA and RF antibody status affect disease classification in the 2010 American College of Rheumatology (ACR)/European League Against

From the Department of Rheumatology, Diakonhjemmet Hospital, Oslo; Department of Rheumatology, Østfold Hospital Trust, Fredrikstad; Lillehammer Hospital for Rheumatic Diseases, Lillehammer; and Martina Hansen's Hospital, Baerum, Norway; and the Department of Rheumatology, Leiden University Medical Center, Leiden, The Netherlands.

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M.D. Mjaavatten, MD, Department of Rheumatology, Diakonhjemmet Hospital; D.M. van der Heijde, MD, PhD, Professor, Department of Rheumatology, Diakonhjemmet Hospital, Department of Rheumatology, Leiden University Medical Center; T. Uhlig, MD, PhD, Department of Rheumatology, Diakonhjemmet Hospital; A.J. Haugen, MD, Department of Rheumatology, Østfold Hospital Trust; H. Nygaard, MD, Lillehammer Hospital for Rheumatic Diseases; O. Bjørneboe, MD, Martina Hansen's Hospital; T.K. Kvien, MD, PhD, Professor, Department of Rheumatology, Diakonhjemmet Hospital.

Address correspondence to Dr. M.D. Mjaavatten, Department of Rheumatology, Diakonhjemmet Hospital, PO Box 23 Vinderen, N-0319 Oslo, Norway. E-mail: maria_mjaavatten@hotmail.com

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Rheumatism (EULAR) classification criteria for RA[7]. Thus, both seroconversion and changes in antibody level from low positive [above the upper limit of normal (ULN)] to high positive (> 3 x ULN) are of interest for the classification of early RA.

The aim of our study was to investigate the longitudinal course of ACPA [measured by anti-cyclic citrullinated peptide antibodies (anti-CCP)] and immunoglobin M (IgM) RF during the first year after onset of arthritis in patients with ≤ 16 weeks' disease duration at inclusion to the study.

MATERIALS AND METHODS

Very Early Arthritis Clinic. The Norwegian Very Early Arthritis Clinic (NOR-VEAC) study was started in 2004 as a multicenter observational study. The cohort includes patients (aged 18–75 yrs) presenting with at least 1 clinically swollen joint of ≤ 16 weeks' duration, and patients are followed longitudinally for 2 years (visits at 0, 3, 6, 12, and 24 months). The details of the data collection have been described elsewhere[8]. One-year followup was our study focus, but data from the visit after 2 years were used if available. The study was approved by the regional Ethics Board and the Data Inspectorate, and patients gave written informed consent.

Laboratory markers. Sera were frozen at –70°C at baseline and used to analyze ACPA (anti-CCP2; Inova Diagnostics, San Diego, CA, USA) and IgM RF (in-house enzyme-linked immunosorbent assay) in 1 batch. As recommended by the manufacturer of the assay used for anti-CCP2, a local standard for the cutoff level determining a positive status was employed. The cutoff levels recommended by the central laboratory for positivity of the serologic markers were ACPA ≥ 25 units/ml, IgM RF ≥ 25 units/ml. These levels are also used in clinical practice, and have been used in previous reports[9,10,11].

Patient selection. All patients with 1-year followup time and with ACPA and IgM RF results from baseline plus 1 or more followup visits during the first year after enrollment were included in the analyses.

Statistical analysis. ACPA and IgM RF antibody status (positive/negative) was assessed at baseline and at subsequent visits, and the numbers and proportions of patients switching antibody status from negative to positive and vice versa during followup were determined. The number and proportion of patients switching from a low positive (25–74 U/ml) to a high positive (≥ 75 U/ml) antibody status were also determined. Disease activity measures were compared between seroconverters and nonconverters with independent-samples t tests/Mann-Whitney U tests according to the distribution of data. Wilcoxon signed-rank test was used to investigate if antibody levels changed significantly from baseline to 1 year. Longitudinal changes in antibody levels were compared between patients who had received and those who had not received DMARD treatment (Mann-Whitney U tests).

RESULTS

Baseline characteristics and completeness of data. Two hundred eighty-one patients (median duration of joint swelling 32 days) with 978 longitudinally collected serum samples were included in our study. One hundred sixty-nine patients (60.1%) had complete antibody data available (baseline and all 3 followup visits) and an additional 78 patients (27.8%) had data from baseline and 2 followup visits, while the remaining 34 patients (12.1%) had antibody data only from baseline and 1 followup visit. Sixty-five of the 281 patients (23%) also had antibody data from the 2-year visit. Patient selection and reasons for missing data are shown in Figure 1.

Baseline characteristics and outcome after 1 year are shown in Table 1. Forty patients (14.2%) were ACPA-positive, while 36 (12.8%) were IgM RF-positive at baseline. Twenty-three patients (8.2%) were positive for both ACPA and IgM RF; 53 patients (18.9%) were positive for one of the 2.

Antibody status and levels during followup. Only 5 patients (1.8%) who were negative for both antibodies at baseline turned antibody-positive during the first year of followup (Table 2). One of these patients became positive for both RF and ACPA, while the remaining 4 developed only IgM RF antibodies (Table 3). One additional patient who was already positive for IgM RF at baseline also became ACPA-positive (i.e., double-positive) during followup, while 2 initially ACPA-positive/RF-negative patients became RF-positive. Of the 65 patients with 2-year sera samples available, 1 baseline antibody-negative patient turned marginally RF-positive at 2 years.

Nine antibody-positive patients (3.2%) became antibody-negative during followup (Table 2). One patient switched from positive to negative status for ACPA and RF, 4 patients switched from positive to negative RF status, and 4 switched from positive to negative ACPA status. Baseline levels in the ACPA switchers were all in the low-positive range, with levels from 27 to 37 U/ml, while baseline levels in the RF-positive to RF-negative switchers ranged from 27 to 63 U/ml (Table 3). Three additional patients switched from positive to negative RF status, but remained ACPA-positive throughout followup. The seroconversion rates were consistently low across subgroups of patients according to outcome at 1 year (Tables 1 and 3). No statistical differences could be found for measures of disease activity in converters compared to nonconverters.

If alternative cutoff levels for positivity of the serologic markers, e.g., 20 U/ml and 30 U/ml, had been used, the following total numbers of patients switching antibody status would have been found: 30 U/ml: 4 negative-to-positive switchers, 5 positive-to-negative switchers; 20 U/ml: 6 negative-to-positive switchers, 8 positive-to-negative switchers (data not shown).

ACPA levels were stable during followup, but RF levels decreased significantly in baseline RF-positive patients (Table 4). Only 2 patients switched from the 2010 ACR/EULAR criteria for RA "low positive" to the "high positive" antibody category during followup (Table 5). One of these patients would theoretically have been reclassified as RA after 1 year based on this finding; the other was already classifiable at baseline.

Antibody status and DMARD treatment. Ninety patients (32%) were treated with DMARD during followup: methotrexate (MTX; n = 59), sulfasalazine (n = 11), leflunomide (n = 1), sequential synthetic DMARD/DMARD combination (n = 9), or MTX plus tumor necrosis factor-α (TNF-α) antagonist (n = 10). None of the 10 patients treat-

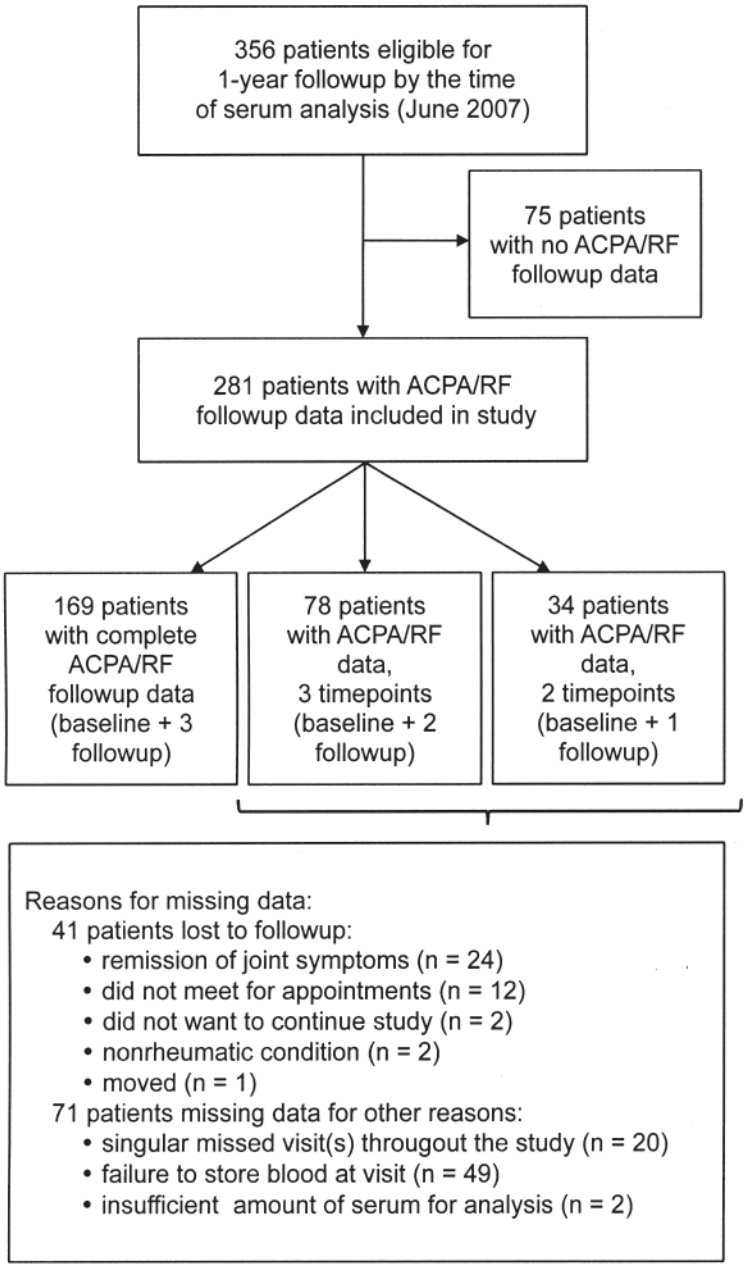

Figure 1. The patient selection procedure.

ed with TNF inhibitors switched antibody status. Details of treatment in patients switching antibody status are given in Table 3. There were no statistically significant differences in change in levels for either ACPA or RF in patients who had received DMARD treatment compared to those who had not received DMARD treatment.

DISCUSSION

The clinician has to consider the balance between cost and usefulness when ordering specific tests for patients with recent-onset arthritis. In our study we show that patients rarely change antibody status within the first year after onset of joint swelling. Most patients with qualitative changes had marginally positive/negative samples at baseline and were thus probably not true "switchers." Of special clinical interest is that very few antibody-negative patients became positive during followup. This finding is in accord with previous studies showing that both ACPA and RF can be found in premorbid sera in a proportion of RA patients several years before diagnosis[12].

The previous evidence regarding the longitudinal course of ACPA/RF in early arthritis is limited, as recognized in a recent review[6]. Published studies have had relatively low sample sizes and have not addressed this issue specifically

Table 1. Baseline characteristics and 1 year outcome in 281 patients with very early arthritis. Values are n (%) unless stated otherwise.

Characteristics	
Age, median yrs (25; 75 percentile)	46 (35; 59)
Female, n (%)	164 (58.4)
Duration of symptoms, median days (25; 75 percentile)	32 (10; 62)
ACPA-positive	40 (14.2)
Low-positive, 25–74 U/ml	12 (4.2)
High-positive, ≥ 75 U/ml	28 (10.0)
IgM RF positive	36 (12.8)
Low-positive, 25–74 U/ml	14 (5.0)
High-positive, ≥ 75 U/ml	22 (7.8)
ACPA and/or IgM RF-positive	53 (18.9)
Both ACPA and IgM RF-positive	23 (8.2)
Only ACPA-positive	17 (6.0)
Only RF-positive	13 (4.6)
One-year outcome	
Rheumatoid arthritis* (RA)	55 (19.6)
Undifferentiated arthritis	94 (33.5)
Non-RA rheumatic disease (ReA, Löfgren's, PsA, other)	87 (30.9)
Noninflammatory joint condition	9 (3.2)
Transient arthritis (no joint-related diagnosis or symptoms at final followup)	36 (12.8)

* Clinical diagnosis. ACPA: anti-citrullinated protein antibody; IgM RF: immunoglobulin M rheumatoid factor; ReA: reactive arthritis; PsA: psoriatic arthritis.

Table 2. Antibody status (ACPA/RF) at baseline and during followup in 281 patients with early arthritis. Data are number (%).

	Followup		
Baseline	Antibody-positive	Antibody-negative	Total
Antibody-positive*	44 (15.7)	9 (3.2)	53 (18.9)
Antibody-negative†	5 (1.8)	223 (79.3)	228 (81.1)
Total	49 (17.4)	232 (82.6)	281 (100)

* ACPA and/or RF-positive. † ACPA and RF-negative. ACPA: anti-citrullinated protein antibody; RF: rheumatoid factor.

or in detail[13,14,15]. Two recent studies in patients with early arthritis, both with longer symptom duration than in our study, have suggested that both ACPA and RF status are stable during the first years after onset of arthritis[16,17]. In patients with early RA, some longitudinal studies on ACPA/RF have been published and most report a low frequency of ACPA seroconversion (4% to 7%)[18,19,20]. However, one early RA study reported a 15% frequency of ACPA seroconversion[21]. Compared to ACPA, RF status in early RA seems less stable[18,19,20], which is also illustrated by the increase in IgM RF levels with age observed in patients who do not have RA[7,22]. Indeed, in our patients with very early arthritis, RF was also a more unstable phenotype than ACPA, and IgM RF levels decreased significantly in patients who were initially positive for these antibodies.

Some studies in RA have suggested that DMARD treatment (both synthetic and biological drugs) can lead to a decrease in antibody level[20,23]. An effect of treatment was not evident in our study, but the low proportion of patients treated with DMARD does not allow firm conclusions for this issue.

The majority of patients in our study had information available regarding antibody status from all 4 timepoints during the first year of followup. However, in the 267 patients who were nonconverters, 21 (7.9%) had antibody data only from baseline and 3-month followup, while 52 (19.5%) had no antibody data at 1 year (i.e., the last followup visit was at 6 months). We cannot be confident that later samples from these patients would remain unchanged with regard to antibody status. However, if these patients were excluded from the analyses, the seroconversion rate would still have been low: 6.7% instead of 5%.

The determination of which patients could be regarded as converters of antibody status is of course dependent on the cutoff level employed for positivity of the serologic markers. In our study the levels employed in clinical practice in our hospitals were used (25 U/ml for both markers). Changing the cutoff level from 25 U/ml to 30 U/ml or 20 U/ml would have changed the proportion of switchers in this cohort only marginally. This consistency strengthens the main conclusion of our study: that very few patients with early inflammatory arthritis change status for ACPA or RF in the first year after onset of arthritis.

The low frequency of seropositive patients represents a limitation to our study in studying seroconversion from positive to negative, as this could lead to underestimation of change in both antibody levels and status over time. The extremely short duration of joint swelling (median 32 days) in our study sets it apart from the existing studies regarding the longitudinal course of autoantibodies in early arthritis. This gives information on the first year after symptom onset, which is the most critical period for making a diagnosis and starting timely treatment.

Our study shows that antibody status (ACPA/RF) is a stable phenotype in very early arthritis. Repeated measurement of ACPA or RF does not offer important additional information during the first year after onset of joint swelling.

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Table 3. Antibody levels (U/ml) during followup, DMARD treatment, and final diagnosis in the 14 patients switching antibody status. Values representing a new status are shown in bold type. Cutoff for positive antibody status: ACPA: ≥ 25 U/ml, IgM RF ≥ 25 U/ml.

	Patient	Antibody Switching	Baseline	3 Months	6 Months	12 Months	Diagnosis at 1 Year	DMARD Treatment
Negative to	1	ACPA	12	**88**	**210**	**> 250**	Seropositive RA	MTX
positive	1	RF	6	4	23	**44**		
switchers	2	RF	8	11	10	**27**	UA	No
	3	RF	16	22	12	**25**	Gonarthrosis	No
	4	RF	19	22	**37**	**74**	ReA	No
	5	RF	21	9	**40**	**30**	UA	No
Positive to	6	ACPA	28	**23**	**8**	—	Seropositive RA	No
negative	6	RF	28	**5**	**1**	—		
switchers	7	RF	63	—	—	**17**	UA	MTX
	8	RF	46	**23**	**20**	**13**	Systemic sclerosis	MTX
	9	RF	41	**12**	**5**	**4**	Seropositive RA	No
	10	RF	27	**2**	1	**3**	UA	No
	11	ACPA	37	**19**	—	**11**	Seronegative RA	MTX
	12	ACPA	33	26	—	**23**	UA	No
	13	ACPA	29	**17**	**12**	**17**		No
	14	ACPA	27	**2**	**2**	**2**	Seronegative RA	MTX/SSZ

DMARD: disease-modifying antirheumatic drug; RA: rheumatoid arthritis; UA: undifferentiated arthritis; ReA: reactive arthritis; MTX: methotrexate; SSZ: sulfasalazine; ACPA: anti-citrullinated protein antibody; RF: rheumatoid factor.

Table 4. Baseline values* and 1 year changes in antibody levels (U/ml) in patients with samples available from the 1 year followup visit.

	Mean Baseline Level (95% CI)	Median Baseline Level (25; 75 percentile)	Mean Change (95% CI)	Median Change (25; 75 percentile)	p†
ACPA overall (n = 206)	27.7 (18.2, 37.2)	3.0 (2.0; 6.0)	0.1 (–2.9, 3.1)	0.0 (–1.0; 1.0)	0.15
ACPA-positive (n = 31)	165.8 (130.5, 201.1)	206.0 (48.0; 251.0)	–6.5 (–18.9, 5.8)	0.0 (–25.0; 0.0)	0.31
ACPA-negative (n = 175)	3.3 (2.8, 3.7)	2.0 (0.0; 4.0)	1.3 (–1.4, 4.0)	0.0 (–2.0; 1.0)	0.42
IgM RF overall (n = 205)	16.9 (10.7, 23.1)	3.0 (1.0; 9.0)	–2.8 (–6.3, 0.7)	0.0 (2.0; 1.0)	0.10
IgM RF-positive (n = 29)	92.7 (59.3, 126.2)	55.0 (37.5; 93.5)	–24.6 (–47.9, –1.2)	–22.0 (–33.5; 5.5)	0.02
IgM RF-negative (n = 176)	4.4 (3.8, 5.0)	3.0 (1.0; 7.0)	0.8 (–0.2, 1.7)	0.0 (–2.0; 1.0)	0.57

* ACPA levels were reported in units from 2 to 250, and IgM RF levels were reported in units from 2 to 300. Levels less than 2 were reported as < 2 and analyzed as 1. Any level greater than 250/300 was reported as > 250/>300 and analyzed as 251/301, respectively. † Wilcoxon signed-rank test. ACPA: anti-citrullinated protein antibody; RF: rheumatoid factor.

Table 5. Antibody levels (U/ml) during followup in 2 patients switching from "low-positive" (25-74 U/ml) to "high-positive" (≥ 75 U/ml) antibody category according to the 2010 classification criteria for rheumatoid arthritis. Values representing a new status are shown in bold.

Patient	Antibody	Baseline	3 Months	6 Months	12 Months	24 Months
A	ACPA/RF	74/9	51/5	54/1	45/2	**77**/29
B	ACPA/RF	4/56	2/60	2/58	2/**114**	—/—*

* Missing values. ACPA: anti-citrullinated protein antibody; RF: rheumatoid factor.

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