Missing Anticitrullinated Protein Antibody Does Not Affect Short-term Outcomes in Early Inflammatory Arthritis: From the Canadian Early Arthritis Cohort

Jenny Shu, Vivian P. Bykerk, Gilles Boire, Boulos Haraoui, Carol Hitchon, J. Carter Thorne, Diane Tin, Edward C. Keystone, and Janet E. Pope, for CATCH Investigators

ABSTRACT. ***Objective.*** Anticitrullinated protein antibody (ACPA) is as sensitive as, but more specific than, rheumatoid factor (RF) and is detected earlier in rheumatoid arthritis (RA). Although part of the RA classification criteria, ACPA testing is not routinely paid for/accessible in all jurisdictions. The effect of missing ACPA testing was studied to determine whether failure to perform ACPA testing could cause a care gap in early inflammatory arthritis.

Methods. Nearly 2000 patients (n = 1998) recruited to an early inflammatory arthritis cohort were allocated into 3 groups: (1) seropositive (either RF+ or ACPA+), (2) seronegative (RF– and ACPA–), and (3) missing ACPA and RF-. Analyses were adjusted for age, sex, symptom duration, and smoking status if $p < 0.1$. Disease Activity Score at 28 joints (DAS28) at 3 months was studied, because beyond then, disease activity is expected to determine ongoing treatment.

Results. More seropositive patients fulfilled the 2010 American College of Rheumatology/European League Against Rheumatism RA criteria than seronegative patients. Group 3 was slightly older and had a smaller percentage of females, as well as shorter symptom duration and less smoking. At 3 months, group 3 was treated with fewer disease-modifying antirheumatic drugs and methotrexate ($p < 0.00002$) than groups 1 and 2, but there were no significant differences in DAS28, Health Assessment Questionnaire-Disability Index (HAQ-DI), proportion receiving corticosteroids, or physician's/patient's global assessments.

Conclusion. There was no care gap in the RF-negative, unknown ACPA group because there were no significant differences in the DAS28, 3-month change in DAS28, or HAQ-DI, despite less treatment. Cost-effectiveness of ensuring ACPA testing availability in suspected RA is unknown because early outcomes did not differ, whether or not ACPA was available. (First Release September 1 2015; J Rheumatol 2015;42:2023–8; doi:10.3899/jrheum.150260)

Key Indexing Terms:
EARLY RHEUMATOID ARTHRITIS CYCLIC CITRULLINATED PEPTIDE ANTIBODIES
ANTICITRULLINATED PROTEIN ANTIBODY MISSING DATA RHEUMATOID FACTOR

Rheumatoid arthritis (RA) is the most common inflammatory polyarthritis, affecting about 1% of the population[1]. It can cause erosions and the destruction of cartilage and bone[2]. Prompt diagnosis is key in RA because earlier intervention with disease-modifying antirheumatic drugs (DMARD), which work to suppress inflammation and can prevent damage, has been associated with improved clinical outcomes and less joint damage[3].

To date, rheumatoid factor (RF) and anticitrullinated protein antibodies (ACPA) are the only 2 serum biomarkers that are widely used in the classification and prognosis of RA. RF is an autoantibody that targets the fragment crystallizable

From the Department of Medicine, Schulich School of Medicine and Dentistry, Western University, London, Ontario; Rheumatology, Mount Sinai Hospital, University of Toronto, Toronto; Rheumatology, St. Joseph's Health Care, Toronto; Southlake Regional Health Centre, Newmarket, Ontario, Canada; Rheumatology Division, Universite de Sherbrooke, Sherbrooke; Rheumatic Disease Unit, Institut de Rhumatologie, Montreal, Quebec; Arthritis Centre, University of Manitoba, Winnipeg, Manitoba, Canada; Rheumatology, Hospital for Special Surgery, Cornell University, New York, New York, USA.

The CATCH study was designed and implemented by the investigators and financially supported initially by Amgen Canada Inc. and Pfizer Canada Inc. by an unrestricted research grant since inception of CATCH. As of 2011, further support was provided by Hoffmann-La Roche Ltd., United Chemicals of Belgium Canada Inc., Bristol-Myers Squibb Canada Co., AbbVie Inc., and Janssen Biotech Inc. (a wholly owned subsidiary of Johnson & Johnson Inc.). Some funds for analysis were from the Program of Experimental Medicine, Department of Medicine, University of Western Ontario, London, Ontario, Canada.

J. Shu, FRCPC, Department of Medicine, Schulich School of Medicine and Dentistry, Western University; V.P. Bykerk, MD, Rheumatology, Mount Sinai Hospital, University of Toronto, and Rheumatology, Hospital for Special Surgery, Cornell University; G. Boire, MD, Rheumatology Division, Universite de Sherbrooke; B. Haraoui, MD, Rheumatic Disease Unit, Institut de Rhumatologie; C. Hitchon, MD, Arthritis Centre, University of Manitoba; J.C. Thorne, MD, Southlake Regional Health Centre; D. Tin, MD, Southlake Regional Health Centre; E.C. Keystone, MD, Rheumatology, Mount Sinai Hospital, University of Toronto; Janet E. Pope, MD, Department of Medicine, Schulich School of Medicine and Dentistry, Western University, and Rheumatology, St. Joseph's Health Care.

Address correspondence to Dr. J. Pope, 268 Grosvenor St., London, Ontario N6A 4V2, Canada. E-mail: janet.pope@sjhc.london.on.ca

Accepted for publication July 2, 2015.

portion of immunoglobulin G and was an item in the 1987 American College of Rheumatology (ACR) classification criteria for RA[4].

Antibodies that target peptides and proteins containing citrulline in patients with RA were described in 1964[5], leading to a standardized anticyclic citrullinated peptide (anti-CCP) 2 commercial test for ACPA[6]. ACPA are just as sensitive, but more specific[7], than RF and are detected earlier in RA[8]. ACPA-positive and ACPA-negative patients have been associated with different genetic and environmental risk factors[9,10], suggesting potentially different outcomes based on ACPA serology. Further, ACPA has been shown to be involved in the disease pathogenesis with the ACPA-immune response in RA starting several years before the diagnosis of the disease and even before the onset of symptoms[11], leading to its inclusion in the 2010 ACR/European League Against Rheumatism (EULAR) RA criteria with earlier identification of RA[12].

Given that ACPA testing is not uniformly covered by the public healthcare systems, such as those in Canada, our objective was to identify the effect of missing ACPA testing on the quality of care and disease outcomes of Canadians with early inflammatory arthritis in the first 3 months of treatment, because that is likely when the initial decisions regarding DMARD treatment would be made. We also suspected that, clinically, if a patient had a positive RF, the lack of known ACPA status may not be as important (even though, if missing, there would be a lower chance of fulfilling the newer 2010 classification criteria for RA). We thus assessed the effect of missing ACPA in patients with early inflammatory arthritis in terms of diagnosis and treatment opportunities to determine whether the failure to perform ACPA testing could cause a gap in care. New technology or diagnostics when introduced should be tested in real practice to determine whether there is a clinical advantage.

MATERIALS AND METHODS

The CATCH database. The CATCH (Canadian early ArThritis CoHort) study is a prospective study of patients with early inflammatory arthritis recruited at 17 sites across Canada since 2007 who are prospectively followed according to a standard protocol. The goal of the CATCH is to study both short-term and longitudinal outcomes in clinical practice. Patients referred to participating early arthritis programs across Canada were offered enrollment into the CATCH if the inclusion criteria were met. Patients recruited to the cohort provided written informed consent. Patients were followed every 3 months in Year 1. Treatment decisions were left to the discretion of the treating physician and participants received usual care, although investigators were encouraged to treat patients to achieve remission. Our study used the same inclusion criteria as the CATCH study (i.e., included all patients who had at least 3 mos of followup).

Our study was approved by the research ethics boards of all involved centers and consent was obtained according to the Declaration of Helsinki.

Patients. We included data from participants who were eligible for enrollment in the CATCH up to April 2013 (n = 2191), of whom 1998 were eligible for our study. The CATCH inclusion criteria were age > 16 years; persistent synovitis for at least 6 weeks but less than 12 months; ≥ 2 swollen joints or 1 metacarpophalangeal/proximal interphalangeal joint; ≥ 1 of positive RF, positive ACPA, morning stiffness > 45 min, response to nonsteroidal antiinflammatory drugs, or painful metatarsophalangeal squeeze test; and had a baseline and 3-month visit. Patients were excluded if they had psoriatic arthritis (PsA) or infectious, crystal-induced, or connective tissue disease. If these diagnoses were identified after their inclusion in the cohort, the patient was withdrawn. RF and ACPA values were based on positive or negative flags relative to the normal ranges of each center's laboratory and were performed at inclusion, if not performed before. The status of antibodies was stratified into 3 categories: (1) seropositive (either RF-positive or ACPA-positive), (2) seronegative (both RF-negative and ACPA-negative), or (3) missing ACPA and RF-negative. There were no restrictions as to when and what DMARD could be initiated in the first 3 months of patient treatment, so we studied the effect of missing ACPA of up to 3 months. Beyond that period, disease activity would be strongly related to treatment because diagnosis in inflammatory arthritis is most important early, and later disease course should dictate therapy. We decided that if there was a positive RF, the ACPA would be less relevant and thus divided the groups into any positive (either RF or ACPA), both negative, and missing ACPA with negative RF. Patients who had missing RF were not included in our study because RF is routinely available with minimal missing data.

Disease variables and outcomes. The demographic information included age, sex, and current smoking status and symptom duration. Clinical outcomes were regularly recorded at all centers and joints were assessed by a rheumatologist. The baseline and 3-month measurements assessed included the 28-joint Disease Activity Score (DAS28), the Health Assessment Questionnaire-Disability Index (HAQ-DI), proportion meeting the 2010 ACR/EULAR RA classification criteria (baseline only), proportion receiving methotrexate (MTX), proportion receiving corticosteroid, number of DMARD, proportion in DAS28 remission, change in DAS28 over 3 months, physician's global assessment (PGA), and patient's global assessment (PtGA). Disease remission was defined as DAS28 < 2.6 and the change in DAS28 from baseline to 3 months was calculated. Followup antibody measurements were conducted at the same time as disease outcome measures.

Statistical analysis. Descriptive statistics (proportions, means, standard errors of the mean, ranges) were used to summarize patients' baseline data. Associations between antibody status and categorical early RA (ERA) outcomes were studied using Pearson chi-square analyses while continuous variables were studied using 1-way ANOVA analyses. Spearman correlations were used to further characterize relationships between antibody status and disease outcomes. To generate OR, continuous variables were divided into less than or equal to their mean and greater than their mean. Binary logistic regression was used to determine the effect of serology status on clinical outcomes. Covariates (such as age, sex, symptom duration, and smoking status) were used in the regression models if p were < 0.1 in univariate analyses comparing antibody status groups. A statistical significance of $p < 0.05$ was considered significant in the regression models. All statistical analyses were performed using SPSS 21.0 software. OR compared groups that were seropositive to double seronegative and missing ACPA with negative RF.

RESULTS

Cohort baseline characteristics. At baseline, there were 2191 patients enrolled in the CATCH with 1998 eligible for our study. Mean age of participants was 53 years old, with 72.6% women (n = 1445), mean symptom duration at presentation of 6 months, and 18.3% current smokers (n = 363; Table 1). Patients were allocated into 3 groups: (1) 58.2% seropositive (n = 1276, either RF+ or ACPA+), (2) 22.7% seronegative (n = 497, RF– and ACPA–), and (3) 10.3% missing ACPA (n = 225, RF–1). There were 42.0% RF+ patients, 33.6% ACPA+, 33.0% ACPA–, and 33.4% missing ACPA. There were 151 patients (8.7%) with missing RF and missing ACPA

Table 1. Characteristics of the 3 groups at baseline and 3 months based on RF and ACPA status (DAS28 ≤ 2.6 = remission). One-way ANOVA analysis and Pearson chi-square analyses were used. Negative values represent a decrease in the value compared with the baseline. Participants are seropositive if either RF-positive or ACPA-positive; they are seronegative if RF-negative and ACPA-negative. Values are mean ± SEM unless otherwise specified.

Characteristics	Total	Seropositive	Seronegative	Missing ACPA, RF–	p	p Adjusted for Covariates
Baseline						
No. patients, n (%)	1998	1276 (58.2)	497 (22.7)	225 (10.3)	N/A	
Age, yrs, range	16–92	17–88	17–88	17–88	N/A	
Age	53.04 ± 0.34	51.63 ± 0.44	54.04 ± 0.67	55.58 ± 0.80	0.000009*	
RF serology, n (%)		1110 (50.7)	813 (37.1)	268 (12.2)	N/A	
ACPA serology, n (%)		736 (33.6)	724 (33.0)	731 (33.4)	N/A	
Female, n (%)	1445 (72.6)	958 (75.5)	336 (67.6)	151 (67.4)	0.0007*	
Symptom duration, mos	6.04 ± 0.08	6.24 ± 0.11	5.89 ± 0.18	5.26 ± 0.21	0.0008*	
Smoking status, n (%)					0.003*	
Current smoker	363 (18.3)	256 (20.2)	82 (16.7)	25 (11.2)		
Ex-smoker	736 (37.1)	480 (37.8)	172 (35.0)	84 (37.7)		
Never	885 (44.6)	533 (42.0)	238 (48.4)	114 (51.1)		
ESR	26.85 ± 0.53	28.07 ± 0.66	24.85 ±1.08	26.57 ± 1.46	0.01*	0.002*
CRP	14.04 ± 0.41	14.20 ± 0.52	13.67 ± 0.83	13.98 ± 1.19	0.86	0.35
SJC28	7.23 ± 0.14	7.05 ± 0.17	7.44 ± 0.30	7.74 ± 0.38	0.19	0.29
DAS28	4.89 ± 0.04	4.92 ± 0.05	4.81 ± 0.07	4.90 ± 0.10	0.45	0.63
HAQ-DI	1.00 ± 0.02	1.01 ± 0.02	0.98 ± 0.03	0.97 ± 0.05	0.57	0.69
Meets 2010 ACR/EULAR classification criteria for RA, n (%)	1569 (78.8)	1138 (89.7)	293 (59.0)	138 (61.6)	0.000001*	0.000001*
MTX, n (%)	1296 (64.9)	889 (69.7)	283 (56.9)	124 (55.1)	0.000001*	0.000001*
No. DMARD	1.31 ± 0.02	1.41 ± 0.02	1.17 ± 0.04	1.05 ± 0.05	0.000001*	0.000001*
No. DMARD, range	0–4	0–4	0–4	0–4	N/A	
Corticosteroid, n (%)	966 (48.3)	614 (48.1)	234 (47.1)	118 (52.4)	0.40	0.34
PGA	5.71 ± 0.07	5.73 ± 0.09	5.77 ± 0.13	5.48 ± 0.19	0.46	0.0009*
PtGA	4.63 ± 0.06	4.77 ± 0.07	4.35 ± 0.11	4.51 ± 0.17	0.004*	0.66
3 mos						
No. patients, n (%)	1743	1062 (60.9)	359 (20.6)	171 (9.8)	N/A	
ESR	18.70 ± 0.48	19.65 ± 0.60	16.63 ± 0.91	18.54 ± 0.15	0.03*	0.086
CRP	7.09 ± 0.33	6.98 ± 0.41	7.65 ± 0.73	6.60 ± 0.74	0.54	0.42
SJC28	3.46 ± 0.11	3.44 ± 0.14	3.51 ± 0.21	3.42 ± 0.25	0.95	0.33
DAS28	3.55 ± 0.04	3.51 ± 0.05	3.60 ± 0.09	3.70 ± 0.13	0.33	0.32
Change in DAS28	–1.35 ± 0.05	–1.38 ± 0.05	–1.21 ± 0.10	–1.41 ± 0.15	0.29	0.07
Proportion in DAS28, n (%)	343 (28.2)	248 (29.8)	62 (24.3)	33 (25.2)	0.17	0.06
HAQ-DI	0.63 ± 0.16	0.61 ± 0.02	0.69 ± 0.04	0.67 ± 0.05	0.12	0.02*
MTX, n (%)	1194 (75.0)	830 (78.2)	250 (69.6)	114 (66.7)	0.0002*	0.0002*
No. DMARD	1.60 ± 0.02	1.67 ± 0.03	1.51 ± 0.05	1.36 ± 0.06	0.00002*	0.0009*
Corticosteroid, n (%)	559 (35.1)	370 (34.8)	133 (37.0)	56 (32.7)	0.59	0.45
PGA	2.56 ± 0.06	2.57 ± 0.07	2.50 ± 0.12	2.59 ± 0.18	0.87	0.96
PtGA	3.71 ± 0.07	3.56 ± 0.09	4.07 ± 0.15	3.84 ± 0.22	0.01*	0.005*

* $p < 0.05$. RF: rheumatoid factor; ACPA: anticitrullinated protein antibodies; DAS28: 28-joint Disease Activity Score; SEM: standard error of the mean; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; SJC28: swollen joint count at 28 joints; ACR: American College of Rheumatology; HAQ-DI: Health Assessment Questionnaire-Disability Index; EULAR: European League Against Rheumatism; MTX: methotrexate; DMARD: disease-modifying antirheumatic drugs; PGA: physician's global assessment; PtGA: patient's global assessment; N/A: not applicable.

who were excluded from the analyses. There were no statistically significant differences between the DAS28 and HAQ-DI at baseline (Table 1). Adjusted results mostly did not affect the results except in PtGA and PGA.

Effect of ACPA and RF on clinical outcomes. A higher proportion of group 1 met the 2010 ACR/EULAR RA criteria relative to both group 2 (OR 6.43, 95% CI 4.95–8.36, $p < 0.001$) and group 3 (OR 5.91, 95% CI 4.24–8.24, $p < 0.001$; Table 2). In comparison with group 3 at baseline, both groups 1 and 2 had higher mean number of DMARD (OR 2.33, 95% CI 1.67–3.24 for group 1 and OR 1.78, 95% CI 1.24–2.56 for group 2, both $p < 0.001$; Table 2). At 3 months there were also fewer mean number of DMARD in group 3. An OR of 2.33 meant that the odds of group 3 relative to group 1 of having a greater change in the mean DAS28 over 3 months was 2.33 (which is higher than group 3). In general, seropositive patients were more likely to meet the ACR/EULAR RA criteria and to be treated with more DMARD, including MTX, at baseline and 3 months compared with the other groups (as measured by significant OR).

Table 2. Influence of RF and ACPA status on outcome measures at baseline and 3 months. Analyses used binomial logistic regression adjusted for age, sex, symptom duration, and smoking status. Comparisons for statistical significance are made among groups as listed at top of each column. Values are OR (95% CI), followed by p value.

Variables	Group 1 Relative to Group 3	Group 2 Relative to Group 3	Group 1 Relative to Group 2
Baseline			
Meets the 2010 ACR/EULAR classification criteria for RA	5.91 (4.24–8.24) 0.000001*	0.94 (0.68–1.30) 0.69	6.43 (4.95–8.36) 0.000001*
Mean no. DMARD	2.33 (1.67–3.24) 0.000001*	1.78 (1.24–2.56) 0.002*	1.31 (1.05–1.62) 0.02*
Proportion taking corticosteroid	0.96 (0.72–1.29) 0.81	0.83 (0.60–1.15) 0.26	1.18 (0.95–1.46) 0.14
Proportion on MTX	1.98 (1.47–2.67) 0.000006*	1.09 (0.79–1.50) 0.60	1.83 (1.47–2.28) 0.000001*
HAQ-DI score	1.14 (0.84–1.54) 0.41	1.08 (0.77–1.51) 0.67	1.07 (0.85–1.34) 0.57
DAS28 score	1.05 (0.78–1.42) 0.73	0.94 (0.68–1.31) 0.73	1.13 (0.90–1.42) 0.28
PtGA	1.10 (0.82–1.49) 0.52	1.17 (0.84–1.64) 0.36	0.93 (0.74–1.17) 0.55
PGA	1.23 (0.91–1.66) 0.17	0.80 (0.57–1.12) 0.20	1.55 (1.24–1.95) 0.0002*
3 mos			
Mean no. DMARD	1.90 (1.36–2.66) 0.0002*	1.81 (1.24–2.64) 0.002*	1.05 (0.82–1.34) 0.70
Proportion on corticosteroid	1.22 (0.86–1.74) 0.26	1.28 (0.86–1.89) 0.22	0.95 (0.74–1.23) 0.69
Proportion on MTX	1.82 (1.27–2.59) 0.001*	1.16 (0.79–1.72) 0.45	1.57 (1.19–2.06) 0.001*
HAQ-DI score	0.77 (0.54–1.11) 0.14	1.10 (0.74–1.65) 0.63	0.69 (0.53–0.91) 0.008*
Proportion in DAS28 remission	1.34 (0.87–2.06) 0.19	0.93 (0.57–1.53) 0.78	1.43 (1.02–1.99) 0.04*
DAS28 score	0.75 (0.52–1.09) 0.13	0.79 (0.52–1.22) 0.29	0.95 (0.71–1.27) 0.73
Change in DAS28	1.18 (0.81–1.73) 0.39	0.84 (0.54–1.30) 0.44	1.40 (1.04–1.89) 0.02*
PtGA	0.78 (0.56–1.10) 0.15	1.18 (0.81–1.71) 0.40	0.67 (0.52–0.86) 0.002*
PGA	0.96 (0.68–1.37) 0.84	1.0 (0.67–1.48) 0.98	0.97 (0.74–1.26) 0.82

* $p < 0.05$, indicating significance. RF: rheumatoid factor; ACPA: anticitrullinated protein antibodies; Group 1: seropositive (RF+ and/or ACPA+); Group 2: seronegative (RF–/ACPA–); Group 3: missing ACPA and RF–; ACR: American College of Rheumatology; EULAR: European League Against Rheumatism; DMARD: disease-modifying antirheumatic drugs; MTX: methotrexate; HAQ-DI: Health Assessment Questionnaire-Disability Index; DAS28: 28-joint Disease Activity Score; PtGA: patient's global assessment; PGA: physician's global assessment.

At baseline (and at 3 months), group 1 also had a higher proportion of patients receiving MTX than group 3 (OR 1.98, 95% CI 1.47–2.67, $p < 0.001$), but groups 2 and 3 were not statistically different from each other ($p = 0.60$; Table 2). It is of note that at 3 months, group 3 was not statistically different from the other 2 groups with respect to mean DAS28, HAQ-DI, 3-month change in DAS28, proportion in DAS28 remission, PtGA, and PGA (Table 2). There were also no statistically significant differences among the groups at baseline or at 3 months for corticosteroid use (Table 1 and Table 2). Relative to group 2, group 1 had a lower HAQ-DI by 3 months (OR 0.69, 95% CI 0.53–0.91, $p = 0.0084$) and greater 3-month change in DAS28 (OR 1.40, 95% CI 1.04–1.89, $p = 0.024$; Table 2).

DISCUSSION

We demonstrated that there were no significant differences in outcomes at 3 months among patients with RA who had ACPA testing compared with RF-negative patients who did not have ACPA testing. We did not determine whether these results would persist in the longterm. Others have concluded that diagnostic testing such as RF and ACPA serology could potentially improve patient outcomes by providing information that can be used to increase confidence in the clinical diagnosis and prognosis for physicians and patients (thus increasing certainty), as well as identifying patients with RA who may benefit from downstream management actions (such as more aggressive DMARD treatment)[13]. Thus, there is potential for the results of the ACPA test to influence treatment, but this is contrary to our results in ERA. Analogous to other chronic conditions such as malignancy, in which confidence and certainty in the diagnosis carries great weight in the management and decision making, results of serological tests likely lead to appropriate management even if they do not have a statistically significant effect on early outcome measures. The patients included in the CATCH have suspected or confirmed RA, so we have a starting point where there is a high pretest probability of RA prior to initiating therapy.

There have been many studies comparing treatment response with DMARD and biologics between ACPA-positive versus ACPA-negative patients[14,15,16,17,18]. However, examining the effect of missing ACPA where ACPA testing is not funded in several Canadian provinces was warranted. The pattern of missing ACPA was likely without bias (i.e., the test is not covered at many laboratories and thus not performed or missing in one-third of patients)[19].

The 3 groups we stratified our cohort into were based on the premises that physicians were likely to treat either RF-positive or ACPA-positive as a single entity (seropositive RA) and that it would be more effective to study the RF-negative group with missing ACPA versus known negative group for both RF and ACPA and known positive group (either RF-positive or ACPA-positive, including if

missing ACPA but RF-positive)[12]. Given that the CATCH has many patients with early and still undifferentiated inflammatory arthritis, it is possible that fulfilling the RA criteria and seropositive status may influence physicians to treat the patients more aggressively, but this cohort enrolls suspected and confirmed ERA (i.e., excludes those with crystal arthritis, erosive osteoarthritis, PsA, and connective tissue disease). In the CATCH at 3 months, the group with missing ACPA was prescribed fewer DMARD and less MTX in comparison with both the seropositive and seronegative groups, which were not treated differently from each other. We do not know why this group received different treatment because they had similar DAS28, change in DAS28, and HAQ-DI at 3 months. However, longer term effects on clinical outcomes such as DAS28 and HAQ-DI may not manifest in the first 3 months. Specifically, a previous study found that ACPA status did not affect the clinical presentation in the first 3 months from inflammatory arthritis symptom onset[20]. However, we focused on the data in the first 3 months for the CATCH because ACPA status should have the most effect on clinical decisions for initiating treatment in the first 2 visits. The CATCH rheumatologists treat to a target of remission (without a standardized protocol), so at 3 months there would often be a change in therapy if remission was not achieved; therefore, it is expected that the rheumatologists would alter treatment at 3 months irrespective of serology if this target was not reached. We have already published that the PGA at 3 months was the most predictive of 1-year remission and not baseline data, including serology[21].

There may be unmeasured confounding factors contributing to the differences between the groups such as location and access to ACPA testing among sites. Further, a central laboratory was not used for the RF and ACPA measurements, which could lead to variability in measurements across sites, but within sites, the antibodies that were available were standardized. As with any study, loss to followup could cause bias, but the dropout rate over the first 3 months of the CATCH was less than 10%. With respect to treatment, all traditional DMARD were reimbursed for those qualifying for provincial drug plans. We did not divide the RF-positive stratum into further groups (positive for RF and ACPA, positive for RF and negative for ACPA, positive for ACPA and negative for RF, and positive for RF and missing ACPA) because that would have yielded groups with insufficient power to perform adjusted analyses, and *a priori* we assumed that any seropositive patient would likely be treated similarly even though those with both antibodies being positive could have a worse prognosis.

The scope of our study cannot determine whether ACPA testing should be reimbursed only in RF-negative patients or in all patients with early suspected RA. It is important to note that the sensitivity of ACPA for RA is at best 75% to 78%[22], and its use in those who are RF-positive is uncertain. Additionally, when the test is missing in our early inflammatory arthritis cohort, treatment was slightly different, but the outcomes in early disease were not different at a time where the value of knowing the diagnosis was important. The seronegative RF patients who had missing ACPA received less MTX treatment and this is concordant with the seronegative patients in the development of the RA classification criteria where the gold standard of RA was a patient with early inflammatory arthritis who received MTX[12]. One could debate whether ACPA testing, such as the use of anti-CCP, is necessary in early suspected RA despite its inclusion in the RA criteria. The results are difficult to interpret because the outcomes were similar, even though DMARD treatment was different (such as the use of DMARD; MTX). When planning our study, we did not know whether the absence of an ACPA result yielded treatment similar to the result being negative. However, we assumed that in the RF-positive patients, the result of the ACPA would not be important for guidance in early treatment (which may not be true), but that the RF-positive patients had the opportunity to meet the RA classification criteria. There was potential circular reasoning because these patients were thought to have ERA or they would not have been enrolled in the CATCH. In patients with early inflammatory arthritis who were RF-negative, rheumatologists treated patients with missing ACPA similarly to those who had negative ACPA results. The costs of new tests are often not studied until there is wide adoption and at that point, often the testing is established as standard of care. Our study suggests that in ERA, the absence of ACPA test results does not seem to matter. We did compare seropositive results with seronegative or missing ACPA and negative RF because RF testing is widely available and reimbursed.

Patients with missing ACPA were less likely to fulfill RA criteria and were treated differently with fewer DMARD and less MTX, but no difference in corticosteroids. If the RF was negative, the missing ACPA and negative ACPA groups had comparable treatment. There may be a care gap in the unknown ACPA group that was RF–negative (because there was less treatment with MTX), but there were no significant differences in outcomes such as DAS28, 3-month change in DAS28, or HAQ-DI despite less treatment, so there may not be a care gap depending on the perspective chosen (treatment or early outcome). Further study with longterm outcomes is needed regarding the incremental cost effectiveness for classifying RA with respect to performing ACPA testing for patients with new onset inflammatory arthritis, including all patients, just RF-negative patients, and patients not having ACPA testing available. Perhaps in ERA, ACPA does not add value with respect to early outcomes. If other studies confirm these findings, then ACPA testing may not yield added value.

List of study collaborators. CATCH investigators: Vandana Ahluwalia, Pooneh Akhavan, Hector Arbillaga, Murray Baron, Mary Bell, William Bensen, Gilles Boire, Vivian P. Bykerk, Alf Cividino, Ines Colmegna, Paul Haraoui, Carol Hitchon, Shahin Jamal, Edward C. Keystone, Alice Kinkhoff, Majed Kraishi, Maggie Larche, Chris Lyddell, Henri Menard, Dianne

Mosher, Bindu Nair, Erin Norris, Chris Penney, Janet E. Pope, Laurence Rubin, Emily Shaw, Evelyn Sutton, J. Carter Thorne, Michel Zummer.

REFERENCES

1. Rindfleisch JA, Muller D. Diagnosis and management of rheumatoid arthritis. Am Fam Physician 2005;72:1037-47.
2. Wiik AS, van Venrooij WJ, Pruijn GJ. All you wanted to know about anti-CCP but were afraid to ask. Autoimmun Rev 2010; 10:90-3.
3. Lard LR, Visser H, Speyer I, vander Horst-Bruinsma IE, Zwinderman AH, Breedveld FC, et al. Early versus delayed treatment in patients with recent-onset rheumatoid arthritis: comparison of two cohorts who received different treatment strategies. Am J Med 2001;111:446-51.
4. 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.
5. Nienhuis RL, Mandema E. A new serum factor in patients with rheumatoid arthritis; the antiperinuclear factor. Ann Rheum Dis 1964;23:302–5.
6. Pruijn GJ, Wiik A, van Venrooij WJ. The use of citrullinated peptides and proteins for the diagnosis of rheumatoid arthritis. Arthritis Res Ther 2010;12:203.
7. Whiting PF, Smidt N, Sterne JA, Harbord R, Burton A, Burke M, et al. Systematic review: accuracy of anti-citrullinated peptide antibodies for diagnosing rheumatoid arthritis. Ann Intern Med 2010;152:456-64.
8. Rantapää-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.
9. Huizinga TW, Amos CI, van der Helm-van Mil AH, Chen W, van Gaalen FA, Jawaheer D, et al. Refining the complex rheumatoid arthritis phenotype based on specificity of the HLA-DRB1 shared epitope for antibodies to citrullinated proteins. Arthritis Rheum 2005;52:3433-8.
10. Klareskog L, Stolt P, Lundberg K, Källberg H, Bengtsson C, Grunewald J, et al. A new model for an etiology of rheumatoid arthritis: smoking may trigger HLA-DR (shared epitope)-restricted immune reactions to autoantigens modified by citrullination. Arthritis Rheum 2006;54:38-46.
11. van de Stadt LA, de Koning MH, van de Stadt RJ, Wolbink G, Dijkmans BA, Hamann D, et al. Development of the anti-citrullinated protein antibody repertoire prior to the onset of rheumatoid arthritis. Arthritis Rheum 2011;63:3226-33.
12. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO 3rd, et al. 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum 2010; 62:2569-81.
13. Bossuyt PM, Reitsma JB, Linnet K, Moons KG. Beyond diagnostic accuracy: the clinical utility of diagnostic tests. Clin Chem 2012;58:1636-43.
14. Willemze A, Böhringer S, Knevel R, Levarht EW, Stoeken-Rijsbergen G, Houwing-Duistermaat JJ, et al. The ACPA recognition profile and subgrouping of ACPA-positive RA patients. Ann Rheum Dis 2012;71:268-74.
15. van Dongen H, van Aken J, Lard LR, Visser K, Ronday HK, Hulsmans HM, et al. Efficacy of methotrexate treatment in patients with probable rheumatoid arthritis: a double-blind, randomized, placebo-controlled trial. Arthritis Rheum 2007;56:1424-32.
16. Sellam J, Hendel-Chavez H, Rouanet S, Abbed K, Combe B, Le Loët X, et al. B cell activation biomarkers as predictive factors for the response to rituximab in rheumatoid arthritis: a six-month, national, multicenter, open-label study. Arthritis Rheum 2011;63:933-8.
17. de Vries-Bouwstra JK, Goekoop-Ruiterman YP, Verpoort KN, Schreuder GM, Ewals JA, Terwiel JP, et al. Progression of joint damage in early rheumatoid arthritis: association with HLA-DRB1, rheumatoid factor, and anti-citrullinated protein antibodies in relation to different treatment strategies. Arthritis Rheum 2008;58:1293-8.
18. Machold KP, Stamm TA, Nell VP, Pflugbeil S, Aletaha D, Steiner G, et al. Very recent onset rheumatoid arthritis: clinical and serological patient characteristics associated with radiographic progression over the first years of disease. Rheumatology 2007;46:342-9.
19. Donders AR, van der Heijden GJ, Stijnen T, Moons KG. Review: a gentle introduction to imputation of missing values. J Clin Epidemiol 2006;59:1087-91.
20. Cader MZ, Filer AD, Buckley CD, Raza K. The relationship between the presence of anti-cyclic citrullinated peptide antibodies and clinical phenotype in very early rheumatoid arthritis. BMC Musculoskelet Disord 2010;11:187.
21. Pyne L, Bykerk VP, Boire G, Haraoui B, Hitchon C, Thorne JC; CATCH Investigators. Increasing treatment in early rheumatoid arthritis is not determined by the disease activity score but by physician global assessment: results from the CATCH study. J Rheumatol 2012;39:2081-7.
22. Aggarwal R, Liao K, Nair R, Ringold S, Costenbader KH. Anti-citrullinated peptide antibody (ACPA) assays and their role in the diagnosis of rheumatoid arthritis. Arthritis Rheum 2009;61:1472-83.