Association of Changes in Anticitrullinated Protein Antibody Levels With Resource Use and Disease Activity Measures in Rheumatoid Arthritis Patients a US Observational Cohort

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ABSTRACT

Purpose: Anticitrullinated protein antibody (ACPA) concentration, beyond ACPA positivity, is indicative of more aggressive radiographic progression in patients with rheumatoid arthritis (RA). However, there is limited information on the association of changes in ACPA with resource use measures and/or disease activity measures. We evaluate associations between changes in levels of ACPA and outcomes, including durable medical equipment (DME) use, hospitalizations, and disease activity, in patients with established RA.

Methods: Patients from the Brigham and Women's Hospital Rheumatoid Arthritis Sequential Study who had ACPA measurements at baseline and month 12 were included. Changes in ACPA levels from baseline to month 12 were categorized as a decrease (<−10%), no change (−10% to +10%), or increase (>+10%). DME use and hospitalizations were assessed twice yearly using patient questionnaires; disease activity was assessed annually. Binary multivariate logistic regression was used to analyze the association between changes in ACPA levels and DME use and hospitalizations; linear regression was used to assess the association with disease activity.

Findings: Of 840 patients included in the analysis, 291 (34.6%), 266 (31.7%), and 283 (33.7%) had a decrease, no change, or increase in ACPA levels, respectively. A decrease in ACPA levels was associated with a reduction in DME use (adjusted odds ratio [aOR] = 0.64; 95% CI, 0.44−0.93; $P = 0.02$) and hospitalizations (aOR = 0.62; 95% CI, 0.41−0.95; $P = 0.03$) versus no change or increase. Adjusted mean changes in disease activity score in 28 joints (C-reactive protein), total and swollen joint counts, and pain scores were significantly greater in patients with decreased ACPA levels versus those with no change or increase ($P < 0.05$).

Implications: Among patients with RA, reductions in ACPA levels of >10% were associated with reductions in DME use, hospitalizations, and disease activity. ClinicalTrials.gov identifier: NCT01793103. (*Clin Ther*. 2019;41:1057−1065) © 2019 Published by Elsevier Inc.

Key words: anticitrullinated protein autoantibodies, disease activity, health care, physical function, rheumatoid arthritis.

BACKGROUND

Anticitrullinated protein antibodies (ACPAs) are sensitive and highly specific biomarkers for the diagnosis of rheumatoid arthritis (RA) that are present years before the onset of clinical RA.[1,2] Commercial assays use a synthetic cyclic citrullinated protein (CCP) as the antigen to detect ACPAs; anti-CCP2 assays have reported high specificity and sensitivity in RA.[3,4] ACPA assessment has become standard practice in the diagnosis of RA, partly because of superior assay specificity and similar sensitivity as detection techniques for rheumatoid factor (RF).[5] ACPA positivity has been associated with more severe, erosive disease than is seen in ACPA-negative

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patients.[6,7] A high ACPA concentration, beyond ACPA positivity, is indicative of more rapid radiographic progression,[6] worse disease severity, and greater bone loss in patients with RA.[8,9]

ACPA levels fluctuate over time, with an increase observed before the onset of clinical symptoms[10] and a decrease after therapy,[11] with some patients known to seroconvert or enter immunologic remission after treatment; however, there is evidence that immunologic remission might not correlate with drug-free remission.[12,13] For example, in patients with early erosive RA treated with abatacept plus methotrexate in the Abatacept Study to Gauge Remission and Joint Damage Progression in Methotrexate-Naive Patients With Early Erosive RA (AGREE) study (clinicaltrials.gov autoantibody titers decreased, and some patients underwent conversion to ACPA and RF seronegative status.[12] Conversion to ACPA seronegative status, albeit seen more rarely than conversion to RF seronegativity,[14] was associated with a better treatment response and higher rates of remission.[12] However, the impact of these changes has not been extensively studied. There is limited information on ACPA levels in clinical trials as well as in clinical practice settings and whether an association exists between changes in ACPA levels and measures of resource use or disease activity.[15–17] The objective of this analysis was to evaluate the association between changes in ACPA levels and resource use (including durable medical equipment [DME] use and hospitalizations) and disease activity in patients with established RA.

METHODS

Study Design

Details regarding the design of the Brigham and Women's Hospital Rheumatoid Arthritis Sequential Study (BRASS) registry have been reported previously.[18–20] Briefly, the BRASS registry is a single-center, prospective, observational, longitudinal cohort of 1309 adults with established or recent-onset RA who are being followed up by a hospital-based practice of 21 rheumatologists in Boston, Massachusetts. Patient demographic and clinical characteristics, disease activity, and laboratory parameters were assessed at baseline and annually thereafter. Patients followed the treatment plan provided by their rheumatologist when they enrolled in the study and throughout follow-up. Patients were eligible for the current analysis if they had documented ACPA values at baseline (first available visit at enrolment) and the month 12 follow-up visit.

This study was performed in accordance with the Declaration of Helsinki and was approved by the Partners Institutional Review Board at Brigham and Women's Hospital (agreement 2002P001762). All patients provided signed informed consent.

Measures and Data Collection

ACPA levels were measured using a validated enzyme-linked immunosorbent assay (Inova Diagnostics, San Diego, California, until discontinuation in 2011; then Euro-Diagnostica, distributed by IBL-America, Minneapolis, Minnesota). RF was measured by an immunoturbidimetric method using a Cobas Integra 700 Analyzer (Roche Diagnostics, Indianapolis, Indiana). ACPA and RF seropositivity were defined as $\geq$20 and > 15 U/mL, respectively. Total swollen joint counts (SJCs) and tender joint counts (TJCs), Disease Activity Score in 28 joints using C-reactive protein (DAS28-CRP) level, clinical disease activity index (CDAI) scores, and simplified disease activity index (SDAI) scores were assessed by investigators at each annual visit (Appendix). Pain and active arthritis on the day of assessment were assessed by the patient using a scale of 0−10, with 0 indicating not active/no pain and 10 indicating extremely active/extreme pain.[21] Follow-up postal questionnaires were completed by patients biannually to determine work productivity, use of DME (including canes, stands, walkers, wheelchairs, and commodes), hospitalizations, other resource use, and clinical and societal variables.

Study Outcomes

The main independent variable of interest was the change in ACPA levels from baseline to month 12 (categorized as decrease [<–10%], no change [–10% to +10%], or increase [> +10%]). The dependent variables evaluated included the proportion of patients using DME or being hospitalized during the 12-month follow-up and the mean change from baseline to month 12 in disease activity (DAS28-CRP, SDAI, CDAI, SJC/TJC) and pain.

Statistical Analysis

Descriptive statistics are used to describe baseline characteristics. Baseline characteristics were compared

Table I. Baseline patient characteristics by change in ACPA levels.

Characteristic	Change in ACPA level			*P* value[a]	Total included (n = 840)	Total BRASS cohort[b] (n = 1350)	*P* value[c]
	Decrease (<−10%) (n = 291)	No change (−10% to +10%) (n = 266)	Increase (>+10%) (n = 283)				
Age, mean (SD), y	56.6 (13.1)	57.4 (13.1)	55.8 (14.3)	0.452	56.6 (13.5)	56.5 (14.1)	0.898
Sex, No. (%)							
Female	240 (82.5)	217 (81.6)	239 (84.5)	0.656	696 (82.9)	1112 (82.4)	0.547
Male	51 (17.5)	49 (18.4)	44 (15.5)		144 (17.1)	238 (17.6)	
Race, No. (%)							
White	272 (93.5)	245 (92.1)	261 (92.2)	0.719	778 (92.6)	1238 (91.7)	0.163
Other	17 (5.8)	20 (7.5)	20 (7.1)		57 (6.8)	102 (7.6)	
BMI, kg/m^2							
No.	278	256	273	0.411	807	1275	0.710
Mean (SD)	26.9 (5.3)	26.8 (5.7)	26.3 (5.2)		26.7 (5.4)	26.8 (5.7)	
Duration of RA, mean (SD), y	12.9 (12.1)	14.1 (11.7)	13.3 (12.4)	0.257	13.4 (12.1)	12.9 (12.0)[d]	0.009
No. of comorbidities, mean (SD)	1.9 (1.5)	1.9 (1.4)	1.9 (1.4)	0.595	1.9 (1.4)	1.9 (1.5)	0.999
Biologic DMARD, No. (%)							
Yes	139 (47.8)	118 (44.4)	119 (42.0)	0.383	376 (44.8)	608 (45.0)	0.794
No	152 (52.2)	148 (55.6)	164 (58.0)		464 (55.2)	742 (55.0)	
DAS28-CRP, mean (SD)	3.9 (1.6)	4.0 (1.5)	3.8 (1.6)	0.193	3.9 (1.6)	3.7 (1.6)[e]	<0.001
SDAI							
No.	273	245	260	0.316	778	1187	<0.001
Mean (SD)	23.7 (18.2)	23.7 (16.4)	22.1 (17.5)		23.2 (17.4)	22.0 (17.3)	
CDAI							
No.	273	245	260	0.347	778	1205	<0.001
Mean (SD)	22.8 (17.5)	22.8 (16.1)	21.1 (16.5)		22.2 (16.7)	21.1 (16.7)	
SJC/TJC							
Mean (SD)	15.8 (14.8)	16.0 (13.6)	14.5 (13.7)	0.305	15.4 (14.1)	14.3 (14.1)[d]	<0.001
Active arthritis (0−10 scale)							
No.	279	247	260	0.517	786	1219	0.843
Mean (SD)	3.7 (2.8)	3.5 (2.8)	3.4 (2.7)		3.5 (2.8)	3.6 (2.8)	

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Table I. (*Continued*)

Characteristic	Change in ACPA level			*P* value[a]	Total included (n = 840)	Total BRASS cohort[b] (n = 1350)	*P* value[c]
	Decrease (<−10%) (n = 291)	No change (−10% to +10%) (n = 266)	Increase (>+10%) (n = 283)				
Pain (0–10 scale)							
No.	279	248	260	0.476	787	1220	0.725
Mean (SD)	3.5 (2.7)	3.3 (2.7)	3.2 (2.7)		3.3 (2.7)	3.3 (2.8)	

ACPA = anti–citrullinated protein antibody; BMI = body mass index; BRASS = Brigham and Women's Hospital Rheumatoid Arthritis Sequential Study; CDAI = clinical disease activity index; DAS28-CRP = Disease Activity Score in 28 joints using C-reactive protein; DMARD disease-modifying antirheumatic drug; RA = rheumatoid arthritis; SDAI = simplified disease activity index; SJC/TJC = swollen and tender joint count.

[a] Including patients who did not have ACPA measurement at baseline and month 12.

[b] Overall difference among the 3 ACPA groups.

[c] Included versus not included.

[d] n = 1349.

[e] n = 1328.

using the χ^2 test for categorical variables and the Wilcoxon sum rank test for continuous variables. $P < 0.05$ (2-sided) was considered statistically significant. Multivariate logistic regression analyses were used to determine the association between change in ACPA levels and binary outcome variables (ie, DME use and hospitalizations), and linear regression analyses were used to investigate the association between change in ACPA levels and disease activity measures, controlling for baseline covariates (age, sex, race, body mass index [BMI], RA duration, number of comorbidities, baseline disease activity, and previous biologic disease-modifying antirheumatic drug [DMARD] treatment). All odds ratios (ORs) and mean changes from baseline were adjusted for baseline covariates. All statistical analyses were performed using SAS software, version 9.4 (SAS institute Inc, Cary, North Carolina).

RESULTS

Baseline Patient Characteristics by Change in ACPA Levels

A total of 840 of 1350 patients (62%) in the BRASS registry had baseline and month 12 ACPA values and were included in the analysis (Table I). Overall, 291 patients (34.6%), 266 patients (31.7%), and 283 patients (33.7%) in the present study had a decrease, no change, or increase in ACPA levels, respectively. The mean (SD) change in ACPA levels was −35.4 (19.3), −0.5 (4.9), and 196.8 (1368.8) U/mL for the patients with a decrease, no change, and increase in ACPA levels, respectively ($P < 0.001$). At baseline, there was no significant difference in mean age, sex, BMI, duration of RA, number of comorbidities, prior use of biologic DMARDs, or disease activity scores among the change in ACPA level groups. The proportion of patients who were ACPA positive at baseline was, however, significantly different across the 3 ACPA groups (decrease, 69.4%; no change, 62.8%; increase, 59.4%; $P = 0.039$).

Those patients excluded (n = 510) from the full BRASS cohort (n = 1350) for this analysis had a shorter mean duration of RA (11.9 years) than those patients included (13.4 years; $P = 0.009$). In addition, the baseline mean DAS28-CRP score of the excluded patients was significantly lower (3.5) than that of the patients included in this study (3.9; $P < 0.001$).

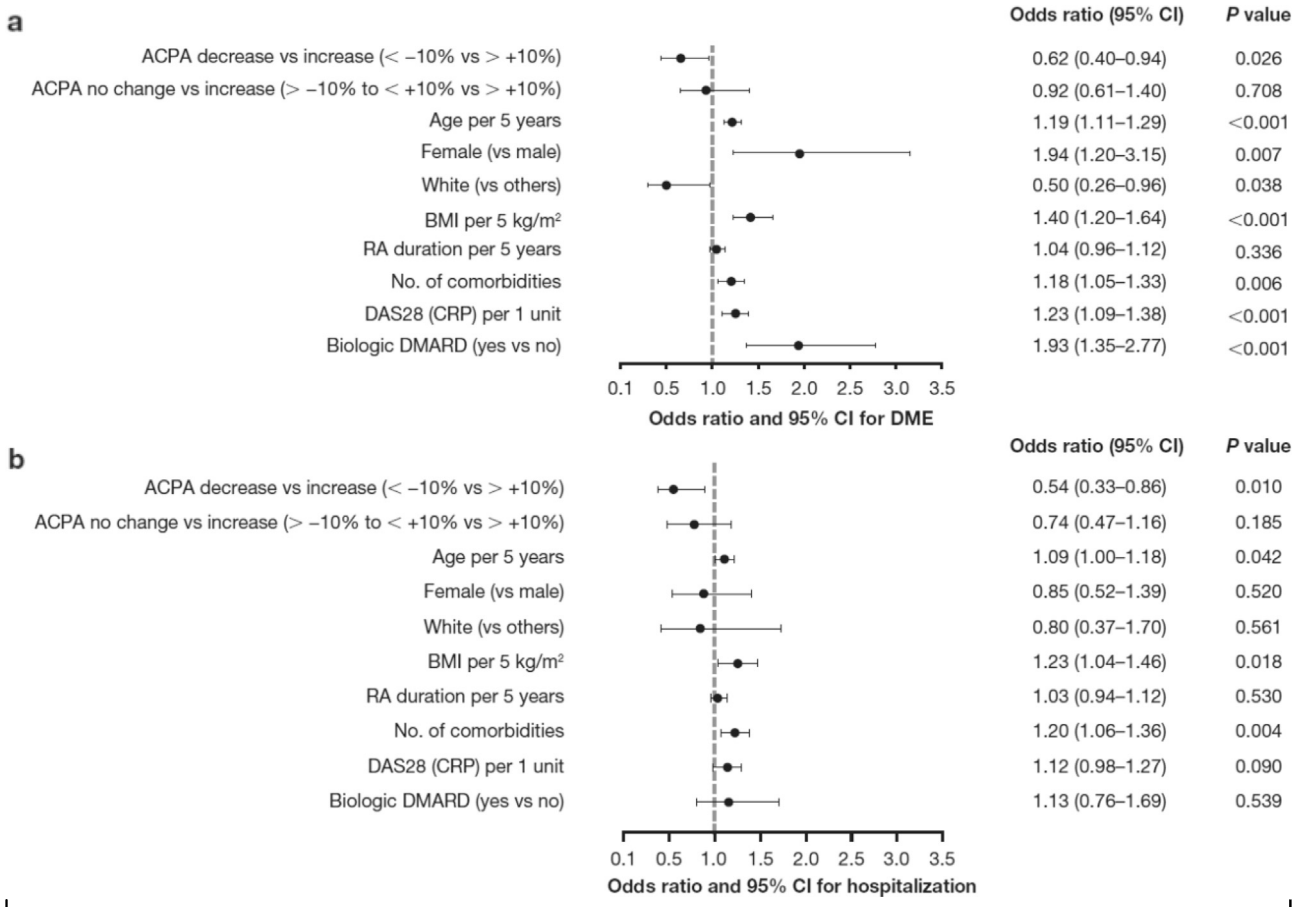

Fig. 1. Odds ratios for durable medical equipment (DME) use (A) and hospitalization (B) by anti−citrullinated protein antibody (ACPA) change from baseline to 12 months and by baseline characteristics. BMI = body mass index; DAS28-CRP = Disease Activity Score in 28 joints using C-reactive protein; DMARD disease-modifying antirheumatic drug; RA = rheumatoid arthritis.

Association Between Resource Use and Change in ACPA Levels

During the 12-month follow-up, DME use was 23.4%, 30.1%, and 28.6% and the hospitalization rate was 13.4%, 16.5%, and 20.1% in patients with a decrease, no change, or increase in ACPA levels, respectively. Multivariate analysis revealed that a decrease in ACPA levels was associated with a reduction in DME use (adjusted OR [aOR] = 0.62; 95% CI, 0.40−0.94; $P = 0.026$) and hospitalizations (aOR = 0.54; 95% CI, 0.33−0.86; $P = 0.010$) compared with an increase in ACPA levels (Fig. 1); there was no significant difference in DME use (aOR = 0.92; 95% CI, 0.61−1.40; $P = 0.708$) or hospitalizations (aOR = 0.74; 95% CI, 0.47−1.16; $P = 0.185$) between no change and an increase in ACPA levels (Fig. 1). The aORs associated with a decrease versus no change or an increase in ACPA levels were 0.64 (95% CI, 0.44−0.93; $P = 0.019$) for DME use and 0.62 (95% CI, 0.41−0.95; $P = 0.029$) for hospitalizations. Further controlling for ACPA positivity at baseline, the aORs associated with a decrease versus no change or an increase in ACPA levels were 0.66 (95% CI, 0.45−0.96; $P = 0.028$) for DME use and 0.63 (95% CI, 0.41−0.96; $P = 0.032$) for hospitalizations. Changes in RF levels were associated with DME use (aOR = 0.62; 95% CI, 0.39−0.99; $P = 0.044$) but not with hospitalizations (aOR = 0.79; 95% CI, 0.47−1.34; $P = 0.383$).

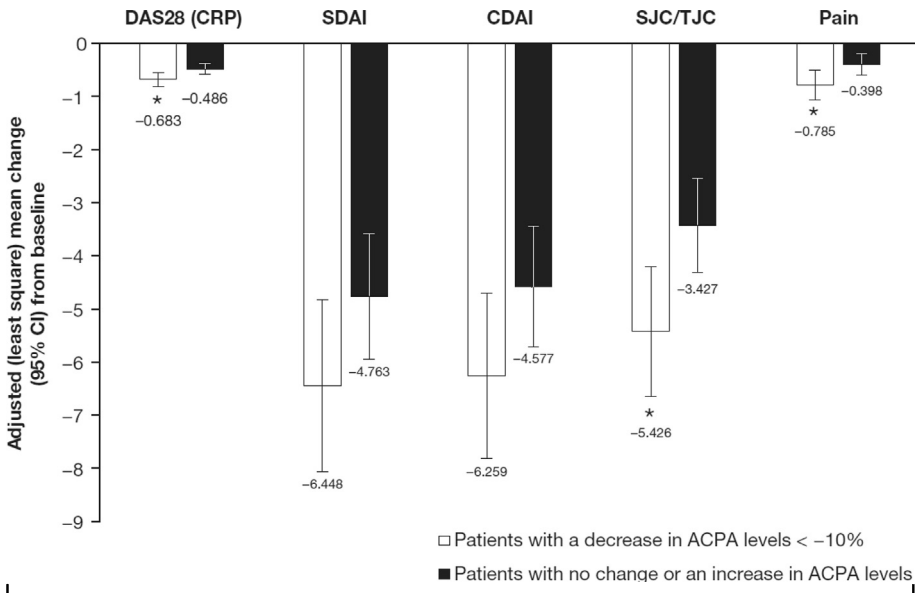

Fig. 2. **Disease activity and pain in patients with a decrease versus no change or increase in anti−citrullinated protein antibody (ACPA) levels. Data are adjusted mean (95% CI) change from baseline. Disease activity and pain were measured on a visual analog scale of 0−100 mm. Asterisk indicates $P < 0.05$ for the difference between patients with a decrease in ACPA levels versus no change or an increase in ACPA. CDAI = clinical disease activity index; DAS28-CRP = Disease Activity Score in 28 joints using C-reactive protein; RA = rheumatoid arthritis; SDAI = simplified disease activity index; SJC/TJC = swollen and tender joint count.**

Association Between Disease Activity and Change in ACPA Levels

The r^2 values for DAS28-CRP, CDAI, SJC/TJC, SDAI, and pain were 0.27, 0.31, 0.30, 0.32, and 0.34, respectively, indicating a good fit for the multivariate regression models. The adjusted mean changes from baseline in DAS28-CRP, SJC/TJC, and pain in patients with a decrease in ACPA levels (<–10%) were significantly greater than in those patients with an increase (>+10%) or no change in ACPA ($P < 0.05$) (Fig. 2). A similar trend was observed for SDAI and CDAI, where there were greater adjusted mean changes from baseline to month 12 in patients with a decrease in ACPA levels compared with those with an increase or no change in ACPA (SDAI: –6.448 vs –4.763, $P = 0.099$; CDAI: –6.259 vs –4.577, $P = 0.087$) (Fig. 2). Multivariate analysis also found that changes in DAS28-CRP, SDAI, CDAI, SJC/TJC, and pain scores were all significantly associated with their respective baseline score (all $P < 0.001$), RA duration (all $P < 0.001$ except for pain, $P = 0.042$), and prior use of biologic DMARDs (all $P < 0.05$). None of the disease activity outcomes was significantly associated with age or race; SDAI was significantly associated with comorbidities ($P = 0.032$), SJC/TJC with sex ($P = 0.035$), and pain with BMI ($P < 0.001$).

DISCUSSION

This study found that among patients with RA decreases in ACPA levels were associated with reductions in DME use, hospitalizations, and disease activity (assessed using a range of standard composite measures). Current clinical emphasis on ACPA testing is primarily for diagnostic purposes because ACPA levels are mostly measured only as part of the diagnostic workup for RA. The ACPA tests are very specific for RA and can improve the diagnosis of patients with early disease; however,

use in early RA is still inconclusive.[4] The overall ACPA testing rates in the United States vary from 63.5% (95% CI, 62.5−64.4) in Optum Clinformatics Data Mart Medicare to 70.6% (95% CI, 70.3−70.9) in IMS PharMetrics Plus.[22] In addition to being a diagnostic marker, ACPA is being considered as a marker of poor disease prognosis because evidence indicates ACPA is a good prognostic indicator of joint damage and bone loss.[7−9,23] The prognostic value of ACPA is further supported by results from US claims database indicating that ACPA-positive patients (compared with ACPA-negative patients) were more likely to be managed by disease-modifying agents (conventional DMARDs [71.2% vs 49.6%; $P < 0.001$] or biologic DMARDs [20.3% vs 11.8%; $P < 0.001$]), have more physician visits (5.58 vs 3.91 times per year; $P < 0.001$), and have higher annual disease-associated total expenditures ($7941 vs $5243).[15]

The literature is limited on sequential testing of ACPA over time.[24,25] Recent studies have highlighted that the biologic DMARDs might differentially affect ACPA levels as measured via anti-CCP2 titers.[24] However, the clinical significance of these reductions is ACPA levels was not fully elucidated in these studies. The present study is the first to highlight the association between economic and clinical outcomes and changes in ACPA levels. Although we noticed a greater reduction in DME use, hospitalizations, and disease activity in patients with reductions in ACPA levels, ACPA reduction was not a necessary criterion to observe these outcomes. There were patients who did not experience ACPA reductions and had favorable outcomes. Our findings are aligned with those of a recent publication that found that patients with moderate and good European League Against Rheumatism (EULAR) responses at 4 and 12 months tended to also have a higher median percentage of ACPA reductions.[26]

Data from clinical trials indicate that RA therapies, such as abatacept and rituximab, can decrease the levels of anti−cyclic citrullinated peptide in patients with RA.[11,27] In addition, abatacept and adalimumab have superior efficacy in patients with RA who are seropositive for anti−cyclic citrullinated peptide compared with those who are seronegative.[28] In a prospective analysis of a phase 3 trial evaluating therapy reduction in patients with RA in ongoing remission, relapse after treatment reduction or withdrawal was associated with ACPA positivity.[29] Hence, the measurement of ACPA levels throughout disease progression could potentially be used to determine how a patient will respond to a particular treatment, thus helping physicians make more informed treatment decisions.

The 2016 update to the EULAR guidelines recommends the addition of a biologic DMARD or JAK inhibitor for patients with an inadequate response to methotrexate and who have poor prognostic factors (ie, RF/ACPA positivity [particularly those with high levels], high disease activity, early joint damage, or failure of at least 2 conventional synthetic DMARDs),[30] indicating the increasing importance of ACPA in treatment decision making. However, there is currently no guidance on which biologic DMARD should be given to patients with poor prognostic factors, including ACPAs. Further investigations are necessary to better understand the changes in ACPA levels during RA progression and treatment.

The current data are from an observational cohort of patients with RA; such studies allow large numbers of patients to be observed for longer durations compared with randomized controlled trials. In addition, data collected from observational studies are more reflective of real-world clinical practice than those derived from clinical trials. A further strength of this study is that it was conducted at a single site that involved a single laboratory to conduct the ACAP assay overtime. This strength should be balanced by the limitation in generalizability of these findings. This observational study reports the analysis of outcomes based on a limited follow-up of 12 months postbaseline data, which is associated with a number of limitations, including the lack of longer-term outcomes as well as assessing the effects of comorbidities. The associations between ACPA levels and DME use and hospitalizations were expressed as categorical (rather than continuous) variables and therefore could lead to an underestimation of the effect. In addition, confounding by unmeasured variables should also be considered when evaluating these results. Other limitations of this study include the self-reporting of DME use and hospitalizations, which introduces the possibility of recall bias, and the lack of adjustment for specific biologic treatments, preventing explorations of treatment effect.

CONCLUSIONS

The results of the present study indicate that reductions in ACPA levels are associated with increased clinical benefit and decreased health care resource use in a real-world setting. Similar associations were seen between RF levels and DME use but not hospitalizations. Different therapies impact ACPA levels, thus these results could help inform physicians regarding treatment decisions, specifically when selecting treatments for patients with higher ACPA levels. Further research is necessary to evaluate the significance of sequential ACPA testing in clinical practice.

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APPENDIX A

Table. Date Collection Schedule.

Patient Domains	Questionnaire Time Points (months)																				
	0	6	12	18	24	30	36	42	48	54	60	66	72	78	84	90	96	102	108	114	120
Demographics																					
Age	✓		✓		✓		✓		✓		✓		✓		✓		✓		✓		✓
Marital Status	✓		✓				✓		✓				✓		✓		✓		✓		✓
Education	✓																				
# of children	✓												✓								
# of siblings	✓																				
Birth order			✓																		
Family Hx	✓	✓					✓						✓								
Ethnicity	✓																				
Race	✓																				
Social Support	✓		✓										✓								
Smoking	✓		✓		✓		✓		✓		✓		✓		✓		✓		✓		✓
Beverages	✓																				
Alcohol only			✓		✓		✓		✓		✓		✓				✓				✓
General Health																					
Symptoms		✓	✓	✓		✓		✓		✓		✓		✓		✓		✓		✓	
Co-morbidities	✓		✓		✓		✓		✓		✓		✓		✓		✓		✓		✓
New conditions		✓		✓		✓		✓		✓		✓		✓		✓		✓		✓	
Surgeries	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Dyspnoea Q.	✓		✓		✓		✓		✓		✓		✓				✓				✓
Cognitive fxn	✓		✓		✓		✓		✓		✓		✓				✓				✓
Menopause		✓					✓		✓		✓		✓		✓		✓		✓		✓
Pregnancy			✓		✓		✓		✓		✓		✓		✓		✓		✓		✓
Oral Contraceptives							✓								✓						
Menstruation hx							✓														
Use of antibiotics	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Vaccinations			✓																		

Table. (*Continued*)

Daycare/Teacher/ Healthcare			✓																		
Teeth and Gums							✓						✓								
Morning stiffness	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Current Medications	**0**	**6**	**12**	**18**	**24**	**30**	**36**	**42**	**48**	**54**	**60**	**66**	**72**	**78**	**84**	**90**	**96**	**102**	**108**	**114**	**120**
Arthritis	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Pain	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Corticosteroid	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
CAM			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Vitamins	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Non-Arthritis Meds	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Alternative providers	✓		✓		✓		✓		✓		✓		✓		✓		✓		✓		✓
Exercise	✓		✓		✓		✓		✓		✓		✓		✓		✓		✓		✓
Past Medications																					
All arthritis	✓		✓		✓		✓		✓		✓		✓		✓		✓		✓		✓
Methotrexate		✓		✓		✓		✓		✓		✓		✓		✓		✓		✓	
Validated Scales																					
MDHAQ	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
SF-12					✓		✓		✓		✓		✓		✓		✓		✓		✓
MHI-5	✓		✓		✓						✓		✓		✓		✓		✓		✓
PHQ-9			✓								✓		✓								
EuroQol(EQ-5D)		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
RADAI	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Arthritis Self-Efficacy	✓		✓								✓		✓								
Flare Question	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓		✓	
RA Concerns			✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓		✓		✓	
Quality of Life Scale							✓														
MOS Sleep Scale							✓		✓		✓				✓		✓		✓		✓
Employ/Disab/incom	✓		✓		✓		✓		✓		✓		✓		✓		✓		✓		✓
Health Ins					✓								✓		✓		✓				
Health Care Utiliz		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Widespread Pain Index	✓		✓		✓		✓		✓		✓		✓		✓		✓		✓		✓

Physician Domains	Baseline	Annual
Inclusion Criteria	✓	
Health & Symptoms		
Morning Stiffness	✓	✓
VAS	✓	✓
Infection/Opportunistic Infections	✓	✓
Extra-Articular Manifestations	✓	✓
Co-morbidities/drug toxicities	✓	✓
28 Joint Count	✓	✓
Medication Changes		
Start	✓	✓
Stop/reason	✓	✓
Change/reason	✓	✓