Evaluation of Anti-cyclic Citrullinated Peptide Autoantibody Levels in Clinical Practice and its Association With Disease Activity

E Alemao,[1] C Iannaccone,[2] M Frits,[2] JS Coblyn,[2] N Shadick,[2] ME Weinblatt[2]

[1]Bristol-Myers Squibb, Princeton, NJ, USA; [2]Brigham and Women's Hospital, Boston, MA, USA

Abstract

Background/Purpose: Testing for anti-citrullinated peptide antibodies (ACPA) is included in the 2010 ACR classification criteria for RA. ACPA concentration, beyond ACPA positivity, is indicative of more aggressive radiographic progression. However, there is limited information on ACPA levels in clinical practice settings and its association with disease activity measures.

Methods: Data were analyzed from patients (pts) enrolled in a large, US RA registry established in 2003. The registry mostly comprises patients with established RA who were evaluated semi-annually for multiple clinical PROs and resource utilization parameters. The current analysis is based on patients enrolled in the registry with ACPA values at the time of baseline visit. Baseline and follow-up ACPA levels were based on a well-documented and validated ELISA from Inova Diagnostics until its discontinuation in 2011; the Euro-Diagnostica assay (distributed by IBL-America, Minneapolis, MN), which supplied the 'capture' antibody for the original Inova Diagnostics ELISA, has been used since. In assessments, the correlation between the two assays was 0.984. Mean changes from baseline over the first 5 years (yrs) of enrolling into the registry were calculated. Four categories of ACPA change from baseline were created based on quartiles of the distribution of ACPA change to Yr 1. Multivariate regression analyses controlling for baseline covariates were conducted to evaluate associations between ACPA change from baseline quartiles and disease activity measures defined by CDAI, SDAI, DAS28 (CRP) and joint counts.

Results: Overall, 1309 (97%) registry pts were included in the current analysis. The mean (SD) age of the cohort was 56.01 (14.04) yrs and 83.2% were females. Figure 2 represents the mean of ACPA levels up to Yr 5. The mean (SD) change in ACPA+ pts was –0.5 (71.3) U/mL, 50.8 (93.9) U/ml, 33.1 (123.1) U/mL, 33.9 (132.0) U/mL, 40.6 (122.4) for Yr 1 through Yr 5, respectively. The ACPA mean change to Yr 1 quartiles had the following cut-off values: Q1 >–488.1 to ≤–13.6 U/mL; Q2 >–13.6 to ≤0.0 U/mL; Q3 >0 to ≤8.8 U/mL; Q4 >8.8 U/mL. The mean reductions in disease activity based on CDAI, SDAI and joint counts were greatest for Q1 (Figure 3). Similar patterns of change in disease activity were observed after controlling for baseline covariates in multivariate analysis.

Conclusion: We observed that ACPA titers change over time and ACPA increase is primarily observed in ACPA+ pts with higher ACPA values at baseline. Pts with reduction in ACPA show a numerically greater reduction in disease activity levels.

Introduction

- Anti-cyclic citrullinated peptide autoantibody (ACPA) positivity is included in the 2010 ACR/EULAR classification criteria for RA.
- Detection of ACPA levels has become standard, partly due to improved assay specificity (with similar sensitivity) compared with detection techniques for antibodies against RF.[1]
- ACPA concentration, beyond ACPA positivity, is indicative of more aggressive radiographic progression and worse disease severity.[2,3]
- However, there are limited data on ACPA levels in clinical practice settings, their change over time and the association of changes in ACPA levels with disease activity measures.

Objective

- To evaluate ACPA levels in clinical practice settings and their change over time.
- To evaluate the association of changes in ACPA levels with clinical outcomes.

Methods

Patient population

- Patients enrolled in the Brigham and Women's Hospital Rheumatoid Arthritis Sequential Study (BRASS) registry who were ACPA positive at the time of baseline visit were included in this analysis.
- BRASS was initiated in 2003–2004. Details concerning the study design have been reported elsewhere[4–6] (see http://www.brassstudy.org).
  - The BRASS registry is a single-center, prospective, observational, longitudinal cohort of >1200 adults with established or recent-onset RA who are being followed by a hospital-based practice of 21 rheumatologists in Boston, US.
  - Physicians assessed patient demographics and clinical characteristics, disease activity and laboratory parameters at baseline and annually thereafter. Follow-up questionnaires to assess patient-reported outcomes were also mailed to patients every 6 months (Figure 1).

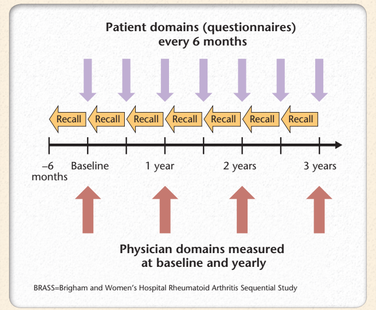
Study outcomes

- Primary endpoint: changes from baseline in ACPA levels over time (1–5 years) in ACPA-positive patients.
- Secondary endpoints: mean changes from baseline to Year 1 in CDAI, DAS28 (CRP) and SDAI.

Statistical analyses

- Descriptive statistics were used for patients included in the analysis.
- Mean ACPA values were evaluated for each year of follow-up within BRASS. In addition, changes in mean ACPA values by baseline ACPA quartiles were also assessed.

Figure 1. BRASS Study Design



BRASS=Brigham and Women's Hospital Rheumatoid Arthritis Sequential Study

- Patients were grouped into quartiles (Q1–Q4) based on the change in ACPA levels from baseline to Year 1.
- Univariate and multivariate regression analyses controlling for baseline covariates were conducted to evaluate associations between changes from baseline in ACPA levels (based on quartiles; categorical independent variable) and changes from baseline in efficacy parameters (in CDAI, DAS28 [CRP] and SDAI; continuous dependent variables).

Results

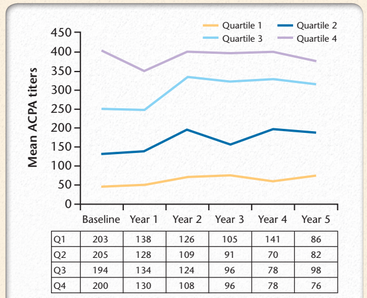
- The characteristics of patients included in the analysis are reflective of patients with established RA seen in clinical practice. The average age (SD) of patients in the analysis sample was 56.66 (13.81) years, with a mean disease duration of 14.95 (12.28) years. Mean DAS28 (CRP) was 3.97 (1.72), with an average SJC plus TJC of 16.12 (14.73). The baseline characteristics were similar across baseline ACPA quartiles and no trends were observed (Table 1).
- Overall, mean ACPA levels were stable between baseline and Year 1 for the overall population as well as for those in baseline ACPA quartiles Q1–Q3, while a reduction in mean ACPA levels was observed in baseline Q4. There was an increase in mean ACPA levels in baseline Q2–Q4 from Year 1 to Year 2 (Figure 2).

Table 1. Baseline Characteristics Overall and by ACPA Quartiles

	ACPA Q1* Mean (SD) n=203	ACPA Q2* Mean (SD) n=205	ACPA Q3* Mean (SD) n=194	ACPA Q4* Mean (SD) n=200	All Patients Mean (SD) N=802
Age, years	56.30 (13.50)	55.57 (14.15)	57.11 (14.54)	57.73 (13.03)	56.66 (13.81)
BMI, kg/m²	26.81 (5.62)	26.72 (6.77)	26.62 (5.17)	27.04 (5.54)	26.80 (5.81)
Disease duration, years	14.76 (12.42)	15.10 (12.18)	15.45 (11.96)	14.51 (12.62)	14.95 (12.28)
DAS28 (CRP)	3.84 (1.64)	4.00 (1.77)	3.95 (1.63)	4.09 (1.82)	3.97 (1.72)
CDAI	21.43 (16.30)	24.51 (18.25)	22.40 (16.68)	23.84 (18.24)	23.06 (17.40)
SDAI	22.34 (16.91)	25.58 (19.25)	23.19 (17.09)	24.99 (18.99)	24.04 (18.11)
Physician global	32.04 (21.27)	33.41 (22.07)	32.13 (20.75)	34.82 (23.23)	33.10 (21.84)
Total joint counts	14.75 (14.05)	16.89 (15.36)	15.89 (14.36)	16.93 (15.20)	16.12 (14.73)
MHAQ	0.41 (0.44)	0.43 (0.49)	0.41 (0.47)	0.46 (0.49)	0.43 (0.47)
Anti-CCP	46.82 (18.72)	132.16 (31.97)	248.32 (28.99)	399.16 (130.82)	205.24 (149.56)

*Q1 cutoffs 20.0 U/ml to <=82.8 U/ml; Q2 cutoffs 82.8 to <194.1 U/ml; Q3 cutoffs 194.1 to <=293.1; Q4 cutoffs >=293.1
ACPA=Anti-cyclic citrullinated peptide autoantibody; Anti-CCP=anti-cyclic citrullinated peptide

Figure 2. Mean ACPA Titer by Quartile Over Time

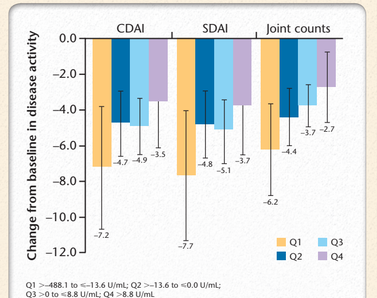


	Baseline	Year 1	Year 2	Year 3	Year 4	Year 5
Q1	203	138	126	105	141	86
Q2	205	128	109	91	70	82
Q3	194	134	124	96	78	98
Q4	200	130	108	96	78	76

ACPA=Anti-cyclic citrullinated peptide autoantibody

- Patients in Q1 had a change in ACPA levels from baseline ranging from >–488 to ≤–13.6 U/mL, patients in Q2 from >–13.6 to ≤0.0 U/mL, patients in Q3 from >0.0 to ≤8.8 U/mL and patients in Q4 had an increase in ACPA levels of >8.8 U/mL.
- There was an association between changes in ACPA levels and disease activity measures as well as joint counts. Patients having the largest reductions in ACPA levels (i.e. Q1) had the highest reduction in disease activity measures (Figure 3).

Figure 3. Association Between Change From Baseline in ACPA Levels and Change in Disease Activity Levels



Q1 >–488.1 to <=–13.6 U/mL; Q2 >–13.6 to <=0.0 U/mL; Q3 >0 to <=8.8 U/mL; Q4 >8.8 U/mL
ACPA=Anti-cyclic citrullinated peptide autoantibody

- After controlling for baseline covariates, patients with the greatest reduction in ACPA levels (from –488 to ≤–13.6 U/mL, Q1) had on average a 4.18-fold greater reduction in SDAI compared with those with the largest increase in ACPA levels (>8.8 U/mL, Q4). The degree of reduction in disease activity decreased when Q1 was compared with Q3 (mean difference in SDAI of –2.74) and Q1 was compared with Q2 (mean difference in SDAI of –2.744). Similar trends were also noticed with CDAI and joint counts (Table 2).

Table 2. Association of Change in ACPA and Disease Activity Measures/Joint Counts – Multivariate*

	ACPA quartiles compared	Mean difference in outcome	95% CI
SDAI	Q1 vs Q4	–4.182	–9.655, 1.292
	Q1 vs Q3	–2.800	–7.520, 1.919
	Q1 vs Q2	–2.744	–7.597, 2.108
CDAI	Q1 vs Q4	–3.935	–9.149, 1.279
	Q1 vs Q3	–2.504	–6.998, 1.989
	Q1 vs Q2	–2.337	–6.960, 2.286
Joint counts	Q 1 vs Q4	–3.471	–7.786, 0.846
	Q1 vs Q3	–2.335	–6.048, 1.378
	Q1 vs Q2	–1.871	–5.683, 1.941

*covariates in the model were baseline TNF treatment, baseline nonbio DMARD, RA duration, age, gender, BMI, mHAQ

Conclusions

- We observed that ACPA titers change over time and an increase in ACPA levels is primarily observed in ACPA-positive patients with higher ACPA levels at baseline.
  - The clinical relevance of these changes needs to be further investigated.
- Patients with a reduction in ACPA levels show a numerically greater reduction in disease activity levels.

References

1. Whiting PF, et al. *Annals of Internal Medicine* 2010;**152**:456–64; W155–466.
2. Mjaavatten MD, et al. *Arthritis Res Ther* 2010;**12**:R76.
3. *Ann Rheum Dis* January 2015 Vol **74** No 1
4. Bykerk VP et al. *J Rheumatol* 2014;**41**:227–34.
5. Iannaccone CK et al. *Rheumatology* (Oxford) 2011;**50**:40–6.
6. Iannaccone CK *Arthritis Care Res (Hoboken)* 2013;**65**:1183–9

Acknowledgments

The authors would like to thank KK Gandhi, formerly of Bristol-Myers Squibb, for his contribution to this work. The BRASS Registry is supported by Bristol-Myers Squibb, Amgen, Crescendo Bioscience and UCB. Editorial assistance was provided by Jasmin Schulz, PhD, at Caudex and funded by Bristol-Myers Squibb.

Disclosures

EA: employee and shareholder: Bristol-Myers Squibb; CI: none; MF: none; JC: none; NS: research grants: Amgen, Questcor, Crescendo Biosciences, UCB, Bristol-Myers Squibb; MW: research grants: Bristol-Myers Squibb, Myriad Genetics, UCB; consulting fees/remuneration: Amgen, AbbVie, Bristol-Myers Squibb, Lilly, Novartis, Merck, Pfizer, Roche, Crescendo Biosciences, Myriad Genetics, UCB.