Association Between Baseline Anti-citrullinated Protein Antibody Status and Response to Abatacept or Non-TNF Inhibitor Therapy in Patients With RA: Results From a US National Observational Study

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Introduction

- RA is characterized by the production of autoantibodies, including anti-citrullinated protein antibodies (ACPA).[1]
- Patients with RA who are ACPA positive are more likely to develop severe, erosive disease than those who are ACPA negative.[2,3]
- Response to RA therapy may vary based on ACPA status.[4–7]
- Data from a US national observational study conducted in a clinical practice setting have shown that patients who were anti-cyclic citrullinated peptide (a surrogate for ACPA; anti-CCP) positive had a greater clinical response to treatment with abatacept, but not to a TNF inhibitor (TNFi), than those who were anti-CCP negative.[7,8]
- Real-world data comparing treatment responses to abatacept and other non-TNFi biologic or targeted synthetic (b/ts) DMARDs by ACPA status are lacking.

Objective

- To assess whether baseline anti-CCP antibody status was associated with response to treatment with abatacept or non-TNFi b/tsDMARDs in patients with RA.

Methods

Data source

- The Corrona RA registry is an independent, prospective, national, observational cohort in which treatment and outcomes data for patients with RA are collected and analyzed.
  - Patients are recruited from 180 private practices and academic sites with 769 participating rheumatologists across 42 US states.
  - As of March 2019, the Corrona RA registry included information on 51,649 patients.
  - Data on 391,242 patient visits and approximately 184,704 patient-years of follow-up observation time have been collected.
  - The mean duration of patient follow-up is 4.4 years (median 3.3 years).

Study population

- This study included adult patients (aged ⩾18 years) with RA from the Corrona registry who initiated treatment with abatacept, rituximab, tocilizumab or tofacitinib.
- There was considerable variation in the duration of follow-up for the individual b/tsDMARDs, reflecting the relevant FDA approval date for each drug. Thus, different cohorts of abatacept patients were evaluated based on the time of first availability of rituximab, tocilizumab or tofacitinib (Figure 1):
  - Overall abatacept initiators: December 1, 2005 to February 28, 2019
  - Patients initiating abatacept or rituximab: February 1, 2006 to February 28, 2019
  - Patients initiating abatacept or tocilizumab: February 1, 2010 to February 28, 2019
  - Patients initiating abatacept or tofacitinib: December 1, 2012 to February 28, 2019.
- The index date was the date of initiation of abatacept or non-TNFi b/tsDMARD.
- Eligible patients had to have anti-CCP measurements at or prior to the index date, to have never used abatacept prior to the index date and to have 6 months' follow-up after the index date.

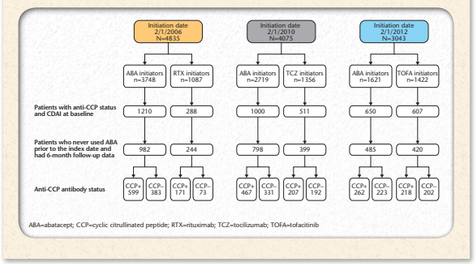
Study assessments

- Patient characteristics at index were compared by anti-CCP status (positive [+], ⩾20 U/mL; negative [–], <20 U/mL) in abatacept and non-TNFi b/tsDMARD initiators with a similar time period of initiation.
- The primary outcome was mean (SD) change in CDAI from baseline to 6 months.
- Secondary outcomes:
  - Mean (SD) change in patient global assessment (PGA) and modified HAQ (mHAQ; modification of the standard HAQ where the number of activities of daily living was reduced from 20 to 8) from baseline to 6 months
  - The proportion of patients achieving CDAI, low disease activity (LDA) or remission, a minimal clinically important difference in CDAI, or modified ACR response (20/50/70% improvement in TJC or SJC and 20/50/70% improvement in ⩾2 of: PGA, physician global assessment, patient pain and mHAQ) at 6 months.

Statistical analysis

- For patient characteristics, the anti-CCP+ and anti-CCP– group for each drug were compared separately using student *t*-tests for continuous variables and chi-square and Fisher's exact tests for categorical variables.
- Clinical responses, by anti-CCP status, were estimated separately for abatacept and for specific non-TNFi b/tsDMARDs (rituximab, tocilizumab or tofacitinib) with a similar time period of initiation (2006, 2010 or 2012, respectively).
- Predicted mean differences between the anti-CCP+ and anti-CCP– groups were estimated using mixed-effects linear regression models adjusting for baseline covariates (if $p<0.1$) with site as a random effect (to adjust for potential site differences in treatment patterns).
- For binary outcomes, odds ratios were estimated using a mixed logistic regression model with the anti-CCP– group as a reference and site as a random effect (to adjust for potential site differences in treatment patterns).

Figure 1. Patient Disposition



Results

Patient disposition and characteristics at index

- Overall, 982 patients initiating abatacept, 399 initiating tocilizumab, 244 initiating rituximab and 420 initiating tofacitinib were identified (Figure 1).
- Across treatments, those who were anti-CCP+ had a longer duration of RA and were more likely to have erosive changes on X-ray, compared with patients who were anti-CCP– (Table 1).
- Additionally, a higher percentage of anti-CCP+ patients were RF+ and more were in ACR functional class III–IV at index (Table 1).

Table 1. Baseline Characteristics at Index Date

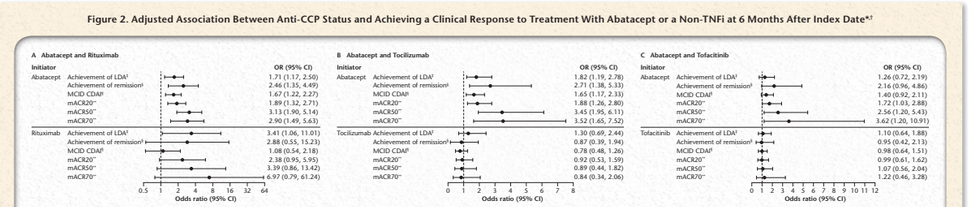
	Abatacept*			Rituximab*		
	Anti-CCP–	Anti-CCP+	p value	Anti-CCP–	Anti-CCP+	p value
n	383	599		73	171	
Age (years)	58.55 (13.62)	58.63 (12.91)	0.934	59.49 (12.55)	58.95 (12.69)	0.760
Female, n (%)	327 (85.6)	474 (79.1)	0.011	59 (80.8)	131 (76.6)	0.468
Duration of RA (years)	9.49 (9.82)	10.41 (9.77)	0.154	11.33 (10.70)	12.18 (10.14)	0.561
RF+, n (%)	136 (39.9)	425 (80.3)	<0.001	35 (54.7)	118 (79.7)	<0.001
Erosive disease, n (%)	123 (34.9)	217 (41.4)	0.054	23 (35.4)	85 (57.8)	0.003
ACR functional class III/IV, n (%)	59 (15.4)	110 (18.4)	0.226	13 (17.8)	36 (21.1)	0.562
CDAI	23.17 (13.02)	22.99 (12.69)	0.829	21.56 (14.20)	24.97 (13.23)	0.073
Patient global assessment, VAS 0–100 mm	50.45 (24.34)	49.39 (25.28)	0.517	50.75 (26.08)	52.26 (25.54)	0.675
mHAQ (0–3)	0.60 (0.49)	0.62 (0.53)	0.680	0.58 (0.54)	0.68 (0.57)	0.196
Current therapy, n (%)						
Monotherapy	113 (29.5)	156 (26.0)	0.236	11 (15.1)	32 (18.7)	0.494
Combination therapy with MTX	138 (36.0)	272 (45.4)	0.004	34 (46.6)	85 (49.7)	0.654
	Abatacept†			Tocilizumab†		
	Anti-CCP–	Anti-CCP+	p value	Anti-CCP–	Anti-CCP+	p value
n	331	467		192	207	
Age (years)	59.15 (13.65)	59.20 (12.59)	0.959	57.38 (13.82)	55.57 (12.15)	0.166
Female, n (%)	282 (85.5)	368 (78.8)	0.017	146 (76.0)	159 (76.8)	0.856
Duration of RA (years)	9.26 (9.75)	10.32 (9.32)	0.121	9.74 (9.58)	11.03 (9.56)	0.182
RF+, n (%)	119 (39.9)	326 (79.7)	<0.001	81 (47.7)	151 (80.3)	<0.001
Erosive disease, n (%)	110 (35.6)	168 (40.6)	0.173	59 (32.2)	79 (42.3)	0.047
ACR functional class III/IV, n (%)	52 (15.7)	93 (19.9)	0.129	30 (15.6)	50 (24.2)	0.033
CDAI	23.55 (12.94)	22.74 (12.74)	0.381	23.58 (14.22)	23.55 (14.49)	0.986
Patient global assessment, VAS 0–100 mm	51.34 (24.35)	49.06 (25.63)	0.205	54.17 (23.83)	50.43 (27.33)	0.148
mHAQ (0–3)	0.60 (0.49)	0.60 (0.53)	0.933	0.69 (0.53)	0.68 (0.58)	0.778
Current therapy, n (%)						
Monotherapy	100 (30.2)	132 (28.3)	0.551	61 (31.8)	52 (25.1)	0.141
Combination therapy with MTX	112 (33.8)	195 (41.8)	0.023	83 (43.2)	95 (45.9)	0.593
	Abatacept‡			Tofacitinib‡		
	Anti-CCP–	Anti-CCP+	p value	Anti-CCP–	Anti-CCP+	p value
n	223	262		202	218	
Age (years)	60.07 (13.56)	61.06 (12.62)	0.408	58.52 (12.39)	60.27 (11.48)	0.135
Female, n (%)	193 (86.6)	205 (78.2)	0.018	150 (74.6)	171 (78.4)	0.357
Duration of RA (years)	10.14 (10.45)	11.16 (10.25)	0.282	9.76 (9.53)	11.85 (9.51)	0.025
RF+, n (%)	83 (41.7)	180 (76.3)	<0.001	94 (50.8)	162 (80.2)	<0.001
Erosive disease, n (%)	65 (29.8)	87 (34.8)	0.251	44 (21.9)	72 (33.2)	<0.001
ACR functional class III/IV, n (%)	34 (15.3)	44 (16.8)	0.644	25 (12.4)	43 (19.7)	0.041
CDAI	22.41 (12.70)	21.64 (12.23)	0.496	20.74 (14.00)	20.06 (12.05)	0.596
Patient global assessment, VAS 0–100 mm	49.62 (23.99)	48.95 (25.94)	0.770	50.17 (25.26)	49.35 (27.12)	0.749
mHAQ (0–3)	0.62 (0.49)	0.62 (0.56)	0.916	0.59 (0.52)	0.58 (0.54)	0.938
Current therapy, n (%)						
Monotherapy	72 (32.3)	75 (28.6)	0.382	90 (44.6)	83 (38.1)	0.178
Combination therapy with MTX	67 (30.0)	94 (35.9)	0.174	64 (31.7)	67 (30.7)	0.834

Data are mean (SD) unless stated otherwise
*Patients who initiated abatacept or rituximab from February 1, 2006 to February 28, 2019; †Patients who initiated abatacept or tocilizumab from February 1, 2010 to February 28, 2019; ‡Patients who initiated abatacept or tofacitinib from December 1, 2012 to February 28, 2019
Data on RF status, erosive disease in all treatment groups in all cohorts, and sex among abatacept-treated patients in the two earlier cohorts, were only available for a reduced set of RA patients
Anti-CCP+=anti-CCP positive, ⩾20 U/mL; anti-CCP–=anti-CCP negative, <20 U/mL; CCP=cyclic citrullinated peptide; mHAQ=modified HAQ; VAS=visual analog scale

Patient outcomes by anti-CCP status at 6 months

- For patients initiating abatacept, during most time periods of treatment initiation, the adjusted mean changes in CDAI, PGA and mHAQ at 6 months following the index date were significantly higher for anti-CCP+ versus anti-CCP– patients (Table 2).

Figure 2. Adjusted Association Between Anti-CCP Status and Achieving a Clinical Response to Treatment With Abatacept or a Non-TNFi at 6 Months After Index Date*,†



Data are presented as odds ratio (95% CI), logarithmic scale
*Adjusted for baseline covariates that differed by baseline CCP status ($p<0.1$), not including factors that reduced the sample size by >10% or were correlated with CDAI: adjusted variables for each cohort are listed in the footnote of Table 2
†Refer to Methods and Table 1 for time period of initiation for each drug
‡CDAI <10 (among those with moderate or higher disease activity); §CDAI <2.8 (among those with LDA or higher); ¶drop of 2 if LDA, drop of 6 if moderate disease activity, drop of 11 if high disease activity; **mACR based on 2 out of 4 measures (not using ESR or CRP)
CCP=cyclic citrullinated peptide; mACR20/50/70=20/50/70% improvement in modified ACR criteria; MCID=minimal clinically important difference

- In addition, for abatacept-treated patients, for the majority of secondary outcomes, the odds of achieving any one outcome were significantly higher for anti-CCP+ versus anti-CCP– patients (Figure 2).
- For patients initiating rituximab, the adjusted mean change in CDAI and PGA (Table 2) and the odds of achieving CDAI LDA were significantly higher (Figure 2) among anti-CCP+ versus anti-CCP– patients; differences in other secondary outcomes were observed but were not statistically significant.
- No significant differences in outcomes by anti-CCP status were observed in tocilizumab- or tofacitinib-treated patients.

Table 2. Adjusted Mean Improvement From Baseline in Disease and Disability Outcomes at 6 Months After Index Date, by Anti-CCP Status, for Abatacept or Non-TNFi Initiators

Adjusted outcome*	Abatacept†			Rituximab†		
	Anti-CCP–	Anti-CCP+	p value	Anti-CCP–	Anti-CCP+	p value
n	383	599		73	171	
Primary outcome: Δ CDAI	4.12 (0.14)	7.82 (0.12)	0.001	0.87 (0.42)	7.51 (0.26)	0.002
Δ patient global assessment	2.84 (0.27)	10.03 (0.22)	<0.001	0.63 (1.01)	11.84 (0.51)	0.006
Δ mHAQ	0.00 (0.01)	0.09 (0.00)	<0.001	0.07 (0.02)	0.16 (0.01)	0.076
	Abatacept†			Tocilizumab†		
	Anti-CCP–	Anti-CCP+	p value	Anti-CCP–	Anti-CCP+	p value
n	331	467		192	207	
Primary outcome: Δ CDAI	3.99 (0.21)	7.85 (0.19)	0.001	5.81 (0.36)	6.26 (0.32)	0.705
Δ patient global assessment	2.50 (0.34)	9.94 (0.29)	<0.001	8.14 (0.66)	5.68 (0.64)	0.109
Δ mHAQ	0.00 (0.01)	0.09 (0.01)	<0.001	0.05 (0.01)	0.07 (0.01)	0.969
	Abatacept†			Tofacitinib†		
	Anti-CCP–	Anti-CCP+	p value	Anti-CCP–	Anti-CCP+	p value
n	223	262		202	218	
Primary outcome: Δ CDAI	3.46 (0.16)	5.98 (0.15)	0.103	3.96 (0.15)	4.85 (0.17)	0.912
Δ patient global assessment	0.94 (0.33)	6.74 (0.26)	0.012	5.64 (0.45)	8.70 (0.47)	0.560
Δ mHAQ	0.01 (0.01)	0.06 (0.01)	0.245	0.02 (0.01)	0.06 (0.01)	0.348

Data are presented as mean (standard error)
*Adjusted for baseline covariates that differed by CCP status ($p<0.1$), not including factors that reduced the sample size by >10% or were correlated with CDAI. Only the main variable category is listed below, however some variables were further broken down within each category:
- ***Adjusted variables for the 2006–2019 cohort included:*** for both drugs–BMI, marital status, smoking status, work status, initiation year; for abatacept only–gender, race-ethnicity, insurance, college, duration of RA, ACR functional class, history of malignancies, history of serious infections, prior csDMARD, prior non-TNFi use, current therapy, prednisone use, morning stiffness; for rituximab only–history of COPD, prior TNFi use
- ***Adjusted variables for the 2010–2019 cohort included:*** for both drugs–race-ethnicity, insurance, work status, duration of RA, ACR functional class, initiation year; for abatacept only–gender, BMI, college, marital status, history of malignancies, history of serious infections, prior csDMARD, prior non-TNFi use, current combination therapy, morning stiffness; for tocilizumab only–smoking status, prior TNFi use, prior biologics/tsDMARDs, prednisone use
- ***Adjusted variables for the 2012–2019 cohort included:*** for both drugs–race-ethnicity, BMI, work status, duration of RA, initiation year; for abatacept only–gender, marital status, morning stiffness; for tofacitinib only–ACR functional class, prior csDMARD, prior TNFi use, current therapy

†Refer to Methods and Table 1 for time period of initiation for each drug
Δ=change; anti-CCP+=anti-CCP positive, ⩾20 U/mL; anti-CCP–=anti-CCP negative, <20 U/mL; b=biologic; CCP=cyclic citrullinated peptide; COPD=chronic obstructive pulmonary disorder; cs=conventional synthetic; mHAQ=modified HAQ; TNFi=TNF inhibitor; ts=targeted synthetic

Limitations

- The sample size was relatively small, particularly for rituximab-treated patients, and the duration of follow-up (6 months) was relatively short for all treatments.
- Additionally, this study was not designed to compare differences in outcomes between abatacept and other b/tsDMARDs.

Conclusions

- After 6 months of therapy, the improvement in outcomes among anti-CCP+ patients treated with abatacept or rituximab was significantly better than outcomes among the respective anti-CCP– patients.
- No significant difference in clinical response was observed between anti-CCP+ and anti-CCP– patients treated with tocilizumab or tofacitinib.
- An analysis comparing the effectiveness of abatacept versus other non-TNFi b/tsDMARDs by ACPA status is planned.

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