BRIEF REPORT

Association of Rheumatoid Factor and Anti–Citrullinated Protein Antibody Positivity With Better Effectiveness of Abatacept: Results From the Pan-European Registry Analysis

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Objective. To investigate the role of rheumatoid factor (RF) status and anti–citrullinated peptide antibody (ACPA) status as predictors of abatacept (ABA) effectiveness in patients with rheumatoid arthritis (RA).

Methods. We conducted a pooled analysis of data from 9 observational RA registries in Europe (ARTIS [Sweden], ATTRA [Czech Republic], BIOBADASER [Spain], DANBIO [Denmark], GISEA [Italy], NOR-DMARD [Norway], ORA [France], Reuma.pt [Portugal], and SCQM-RA [Switzerland]). Inclusion criteria were a diagnosis of RA, initiation of ABA treatment, and available information on RF and/or ACPA status. The primary end point was continuation of ABA treatment. Secondary end points were ABA discontinuation for ineffectiveness or adverse events and response rates at 1 year (good or moderate response according to the European League Against Rheumatism criteria with LUNDEX adjustment for treatment continuation). Hazard ratios (HRs) and 95% confidence intervals (95% CIs) for the study end points in relation to RF and ACPA status were calculated.

Results. We identified 2,942 patients with available data on RA-associated autoantibodies; data on RF status were available for 2,787 patients (77.0% of whom were RF positive), and data on ACPA status were available for 1,903 patients (71.3% of whom were ACPA positive). Even after adjustment for sociodemographic and disease- and treatment-related confounders, RF and ACPA positivity were each associated with a lower risk of ABA discontinuation for any reason (HR 0.79 [95% CI 0.69–0.90], $P < 0.001$ and HR 0.78 [95% CI 0.68–0.90], $P < 0.001$, respectively), compared to RF-negative and ACPA-negative patients. Similar associations with RF and ACPA were observed for discontinuation of ABA treatment due to ineffectiveness, with HRs of 0.72 (95% CI 0.61–0.84) and 0.74 (95% CI 0.62–0.88), respectively (both $P < 0.001$).

Conclusion. Our results strongly suggest that positivity for RF or ACPA is associated with better effectiveness of ABA therapy.

Rheumatoid factor (RF) and anti–citrullinated protein autoantibody (ACPA) (most commonly measured by anti–cyclic citrullinated peptide [anti-CCP] assay) are frequently used as diagnostic tools in clinical practice. There is evidence that the pathogenesis of rheumatoid arthritis (RA) differs between ACPA-positive and ACPA-negative disease (1–3). These autoantibodies may also be used as prognostic factors, since seropositivity for one of these antibodies is associated with worse radiographic progression (4). Furthermore, these biomarkers are associated with better response to B cell depletion therapy (5–9). Findings of a recent study suggested that response to inhibition of T cell costimulation by abatacept (ABA) may also be higher in patients with ACPA (10), and another demonstrated a higher rate of ABA continuation among ACPA-positive patients (11). We undertook the present investigation to analyze the association between RF and ACPA positivity and ABA effectiveness in a large multinational observational cohort.

PATIENTS AND METHODS

Study design. Nine European RA patient registries contributed to this collaborative observational cohort study:

ARTIS (Sweden), ATTRA (Czech Republic), BIOBADASER (Spain), DANBIO (Denmark), GISEA (Italy), NOR-DMARD (Norway), ORA (France), Reuma.pt (Portugal), and SCQM (Switzerland). The registries and their methodologies for data collection have been described in detail elsewhere (12,13). Inclusion criteria for the present analysis were a diagnosis of RA, initiation of ABA treatment, and available information on RF and/or ACPA status (positive or negative; data on levels of RF and ACPA were not available). The exposures of interest were RF positivity (yes/no) and ACPA positivity (yes/no), as reported by the treating rheumatologist. In addition, we explored "seropositive RA," i.e., being RF and/or ACPA positive, as an alternative exposure of interest. The primary end point of the study was ABA treatment continuation, a simple outcome measure reflecting a composite of effectiveness and safety. Secondary end points included ABA discontinuation due to ineffectiveness and ABA discontinuation due to adverse events, as well as rate of good or moderate response at 1 year according to the European League Against Rheumatism criteria (14), corrected for drug discontinuation using the LUNDEX formula (15), i.e., the number of patients with good EULAR response to ABA divided by the number of patients in whom the drug was initiated. We predominantly used the 28-joint Disease Activity Score (DAS28) (16) calculated using the erythrocyte sedimentation rate to assess EULAR response; when this was not available, we used the DAS28 calculated using the C-reactive protein level.

Table 1. Characteristics of the RA patients at the time of ABA treatment initiation, by RF and ACPA status*

	RF (n = 2,787; 4,377.0 patient-years)			ACPA (n = 1,357; 2,912.9 patient-years)		
	RF positive (n = 2,147)	RF negative (n = 640)	P†	ACPA positive (n = 1,357)	ACPA negative (n = 546)	P†
Age, years	57.4 ± 12.7	55.4 ± 13.7	0.001	57.2 ± 13.0	55.8 ± 13.6	0.04
Male, no. (%)	438 (20.4)	107 (16.7)	0.047	284 (20.9)	100 (18.3)	0.22
DAS28	5.1 ± 1.4	5.0 ± 1.3	0.13	5.0 ± 1.4	5.0 ± 1.4	0.45
Disease duration, years	12.0 ± 9.2	10.5 ± 8.7	<0.001	11.4 ± 8.5	10.7 ± 8.7	0.09
HAQ score	1.3 ± 0.7	1.3 ± 0.7	0.30	1.2 ± 0.7	1.3 ± 0.7	0.82
BMI, kg/m²	25.6 ± 4.9	27.0 ± 5.7	<0.001	25.8 ± 5.2	26.9 ± 5.3	0.005
CRP, mg/liter‡	23.0 ± 35.0	20.9 ± 33.4	0.002	22.1 ± 33.1	20.5 ± 30.2	0.007
ESR, mm/hour‡	33.0 ± 25.0	28.8 ± 23.7	<0.001	31.8 ± 24.5	29.0 ± 24.6	0.009
Current or past smoker, no. (%)	397 (24.0)	100 (18.6)	0.01	231 (21.9)	87 (18.7)	0.17
No. of csDMARDs taken previously, median (IQR)‡	2 (1–4)	2 (1–4)	0.61	2 (1–4)	2 (1–4)	0.54
No. of bDMARDs taken previously, median (IQR)‡	2 (1–3)	2 (1–3)	0.40	2 (1–3)	2 (1–3)	0.02
Current glucocorticoid treatment, no. (%)	1,163 (59.9)	372 (61.9)	0.42	830 (64.6)	315 (63.1)	0.60
ABA discontinuation, no. (%)	1,038 (48.3)	349 (54.5)	0.007	660 (48.6)	306 (56.0)	0.004
Reason for discontinuation, no. (%)			0.007			0.01
Adverse event	214 (20.6)	46 (13.2)		125 (18.9)	38 (12.4)	
Remission	13 (0.1)	3 (0.1)		11 (1.7)	2 (0.1)	
Other reasons§	194 (18.7)	43 (12.3)		122 (18.5)	50 (16.3)	
Ineffectiveness	617 (59.4)	257 (73.6)		402 (60.9)	216 (70.6)	

* Except where indicated otherwise, values are the mean ± SD. RA = rheumatoid arthritis; ABA = abatacept; RF = rheumatoid factor; ACPA = anti−citrullinated protein antibody; DAS28 = 28-joint Disease Activity Score; HAQ = Health Assessment Questionnaire; BMI = body mass index; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; csDMARDs = conventional synthetic disease-modifying antirheumatic drugs; IQR = interquartile range; bDMARDs = biologic DMARDs.
† By chi-square test for categorical variables and by t-test for continuous variables test unless otherwise noted.
‡ Characteristic was compared using Wilcoxon's rank sum test, due to non-normal distribution.
§ Other reasons include pregnancy, surgery, or reason not recorded.
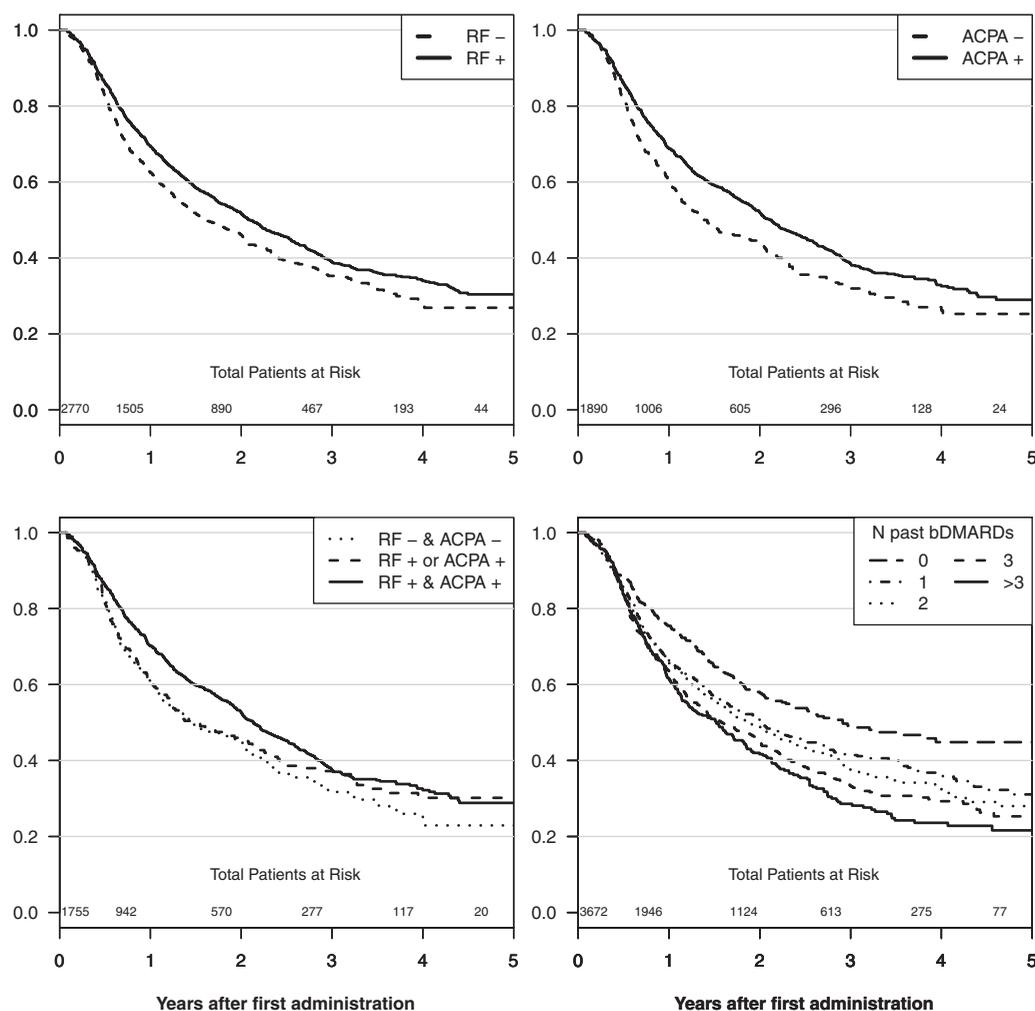
Figure 1. Kaplan-Meier curves for rheumatoid arthritis patient discontinuation of abatacept treatment for any reason, stratified by rheumatoid factor (RF) status ($P = 0.006$ by log rank test), by anti−citrullinated protein antibody (ACPA) status ($P < 0.001$ by log rank test), by type of autoantibody seropositivity (RF, ACPA, or both) ($P = 0.007$ by log rank test), and by number of past biologic disease-modifying antirheumatic drugs (bDMARDs) received ($P < 0.001$ by log rank test).

Statistical analysis. Patients and disease characteristics at the time of ABA initiation were analyzed using standard descriptive statistics. Data are presented as the mean ± SD or median and interquartile range (IQR), depending on their distribution. ABA treatment continuation was analyzed by the Kaplan-Meier method. The impact of RF and ACPA on discontinuation of ABA was assessed using Cox proportional hazard models with adjustment for potential confounders. Potential confounders assessed in a multivariate analysis included patient demographic characteristics (age, sex), disease characteristics (DAS28 at baseline, disease duration), and treatment characteristics (number of synthetic and biologic disease-modifying antirheumatic drugs [DMARDs] received previously, date of ABA initiation [categorized as before 2008, 2008–2009, or 2010 or after]). Time to discontinuation was defined as the time between drug initiation and last administration plus 1 dispensation interval. Data on patients lost to follow-up were censored at the last registered visit. When data

on covariates were sporadically missing, we used random regression imputation techniques (17). Given the inherent differences between registries, we tested for effect modification by registry using an interaction term between seropositivity and national registry.

RESULTS

Patient characteristics. We identified a total of 3,905 patients (ARTIS 1,018, ATTRA 215, BIOBADASER 297, DANBIO 286, GISEA 370, NOR-DMARD 52, ORA 1,011, Reuma.pt 33, SCQM 623) in whom ABA treatment had been initiated, representing 6,110.9 patient-years of follow-up (median 1.6 years per patient [IQR 0.5–2.4]). A total of 2,942 patients had available data on RF and/or ACPA status (data on RF for 2,787

Table 2. Multivariable (including RF status) Cox models for discontinuation of ABA treatment for any reason, due to ineffectiveness, and due to adverse event*

Variable	Discontinued for any reason		Discontinued due to ineffectiveness		Discontinued due to adverse event	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
RF positive	0.79 (0.69–0.90)	<0.001	0.72 (0.61–0.84)	<0.001	1.45 (1.01–2.09)	0.045
Age (years)	1.00 (0.99–1.00)	0.44	0.99 (0.99–1.00)	0.02	1.02 (1.00–1.03)	0.01
Sex (referent: male)	0.98 (0.84–1.14)	0.79	0.81 (0.68–0.98)	0.03	1.14 (0.78–1.66)	0.49
Disease duration at baseline (years)	1.00 (0.99–1.00)	0.89	1.00 (0.99–1.01)	0.98	1.00 (0.99–1.02)	0.80
DAS28	1.06 (1.01–1.11)	0.01	1.09 (1.03–1.15)	0.005	0.89 (0.80–1.00)	0.04
No. of csDMARDs taken previously (referent: none)						
1	1.13 (0.89–1.44)	0.32	1.30 (0.95–1.79)	0.11	0.78 (0.42–1.47)	0.45
2	1.11 (0.87–1.42)	0.42	1.00 (0.72–1.38)	0.99	1.13 (0.63–2.04)	0.68
3	0.98 (0.76–1.27)	0.90	1.14 (0.81–1.60)	0.45	1.49 (0.81–2.74)	0.20
4+	1.10 (0.86–1.41)	0.44	1.35 (0.98–1.86)	0.06	1.01 (0.60–1.97)	0.79
No. of bDMARDs taken previously (referent: none)						
1	1.07 (0.88–1.31)	0.50	0.88 (0.67–1.14)	0.33	1.54 (0.90–2.66)	0.12
2	1.27 (1.04–1.56)	0.02	0.89 (0.68–1.17)	0.40	0.49 (0.86–2.58)	0.16
3	1.21 (0.97–1.51)	0.09	0.96 (0.72–1.27)	0.77	0.86 (0.45–1.64)	0.65
4+	1.42 (1.11–1.81)	0.005	1.00 (0.74–1.37)	0.98	1.25 (0.64–2.45)	0.51
Date of ABA initiation (referent: before 2008)						
2008–2009	0.90 (0.75–1.07)	0.24	1.19 (0.96–1.47)	0.12	1.25 (0.82–1.92)	0.30
2010 and after	0.99 (0.81–1.21)	0.93	1.81 (1.40–2.33)	<0.001	1.65 (1.00–2.73)	0.052

* HR = hazard ratio; 95% CI = 95% confidence interval (see Table 1 for other definitions).

patients and data on ACPA for 1,903). A total of 2,147 patients were RF positive (77.0% of those with available data), and 1,357 were ACPA positive (71.3% of those with available data). A total of 1,408 patients were seropositive for at least 1 autoantibody, 1,121 patients were seropositive for both RF and ACPA, and 360 patients were seronegative for both RF and ACPA (missing data for either RF or ACPA in 53 patients). Before pooling

Table 3. Multivariable (including ACPA status) Cox models for discontinuation of ABA treatment for any reason, due to ineffectiveness, and due to adverse event*

Variable	Discontinued for any reason		Discontinued due to ineffectiveness		Discontinued due to adverse event	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
ACPA positive	0.78 (0.68–0.90)	<0.001	0.74 (0.62–0.88)	<0.001	1.49 (1.00–2.24)	0.053
Age (years)	1.00 (0.99–1.00)	0.52	0.99 (0.99–1.00)	0.07	1.01 (1.00–1.02)	0.14
Sex (referent: male)	1.01 (0.85–1.20)	0.88	0.86 (0.70–1.07)	0.17	1.07 (0.70–1.65)	0.74
Disease duration at baseline (years)	1.00 (0.99–1.01)	0.63	0.99 (0.98–1.01)	0.30	1.00 (0.98–1.02)	0.89
DAS28	1.10 (1.05–1.16)	<0.001	1.09 (1.02–1.17)	0.007	0.93 (0.82–1.06)	0.28
No. of csDMARDs taken previously (referent: none)						
1	1.19 (0.91–1.55)	0.21	1.27 (0.90–1.80)	0.17	0.87 (0.43–1.76)	0.71
2	1.12 (0.85–1.48)	0.41	0.97 (0.68–1.38)	0.87	1.17 (0.60–2.28)	0.64
3	0.96 (0.72–1.28)	0.79	1.04 (0.72–1.50)	0.84	1.46 (0.73–2.90)	0.29
4+	1.07 (0.75–1.31)	0.95	1.27 (0.89–1.81)	0.18	1.16 (0.58–2.32)	0.68
No. of bDMARDs taken previously (referent: none)						
1	1.07 (0.84–1.36)	0.58	1.05 (0.76–1.45)	0.77	1.33 (0.71–2.49)	0.37
2	1.19 (0.94–1.51)	0.16	1.01 (0.73–1.40)	0.97	1.35 (0.72–2.52)	0.35
3	1.10 (0.85–1.43)	0.48	1.03 (0.73–1.45)	0.87	0.65 (0.31–1.37)	0.26
4+	1.38 (1.04–1.83)	0.03	1.19 (0.82–1.72)	0.36	1.03 (0.48–2.21)	0.95
Date of ABA initiation (referent: before 2008)						
2008–2009	0.93 (0.76–1.13)	0.45	1.10 (0.87–1.39)	0.42	1.44 (0.85–2.43)	0.18
2010 and after	0.97 (0.77–1.23)	0.81	1.55 (1.16–2.07)	0.003	2.09 (1.14–3.86)	0.02

* HR = hazard ratio; 95% CI = 95% confidence interval (see Table 1 for other definitions).

data from the registries, we explored the association between RF/ACPA and ABA treatment continuation in the different registries to test for a possible effect modification. No significant interaction between the country of the registry and the effect of seropositivity on drug continuation was observed ($P = 0.46$). Baseline characteristics of seropositive versus seronegative patients are reported in Table 1.

Overall continuation of ABA treatment (primary outcome measure). RF positivity and ACPA positivity were each associated with a decreased overall risk of ABA discontinuation, with a crude median length of treatment of 1.6 years and 2.1 years among RF-negative and RF-positive patients, respectively ($P = 0.006$ by log rank test) and 1.4 years and 2.1 years among ACPA-negative and ACPA-positive patients, respectively ($P < 0.001$ by log rank test). Double seropositivity (for both RF and ACPA) and single seropositivity for either RF or ACPA were also associated with a significantly lower risk of ABA discontinuation ($P = 0.007$ by log rank test) (Figure 1).

Due to colinearity between RF and ACPA we performed a separate multivariate analysis for each, with adjustment for potential confounding factors. RF positivity was associated with a significantly lower risk of ABA discontinuation for any reason after adjustment for age, sex, disease activity, number of past synthetic and biologic DMARDs taken, and year of ABA initiation, with a hazard ratio (HR) of discontinuation of 0.79 (95% confidence interval [95% CI] 0.69–0.90) ($P < 0.001$) (Table 2). ACPA positivity was also associated with a significantly reduced risk of ABA discontinuation for any reason in multivariate analysis (HR 0.78 [95% CI 0.68–0.90], $P < 0.001$) (Table 3). Other statistically significant predictors of ABA treatment continuation were DAS28 and number of biologic agents taken previously (Tables 2 and 3 and Figure 1).

Secondary outcome measures. In multivariate analysis, the HR for drug discontinuation due to ineffectiveness was 0.72 (95% CI 0.61–0.84) ($P < 0.001$) for RF-positive versus RF-negative patients and 0.74 (95% CI 0.62–0.88) ($P < 0.001$) for ACPA-positive versus ACPA-negative patients (Tables 2 and 3). In contrast, RF positivity was associated with a higher risk of ABA discontinuation due to adverse events (HR 1.45 [95% CI 1.01–2.09], $P = 0.045$) (Table 2).

Among patients still receiving ABA treatment at 1 year, the rate of EULAR good/moderate response tended to be slightly higher in RF-positive than in RF-negative patients (84.1% versus 80.5%; $P = 0.059$) but not in ACPA-positive versus ACPA-negative patients

(82.4% versus 79.7%; $P = 0.225$). The LUNDEX-corrected rate of EULAR good/moderate response, taking into account rates of drug continuation at 1 year, was significantly higher in RF-positive patients (60.6%, versus 52.6% in RF-negative patients; $P < 0.001$) but not in ACPA-positive patients (57.0%, versus 52.3% in ACPA-negative patients; $P = 0.09$).

DISCUSSION

This study explored the association between RF and ACPA positivity and ABA effectiveness in a cohort of patients from European countries. Patients who were positive for RF or ACPA had lower discontinuation rates, due to fewer interruptions of ABA treatment for ineffectiveness. Furthermore, rates of good/moderate response as assessed by the EULAR criteria were higher among seropositive patients.

Superior effectiveness in RA patients who are seropositive has also been reported for rituximab (5–9). It is unclear whether such an association also exists for anti−tumor necrosis factor (anti-TNF) therapy; a recent meta-analysis did not demonstrate an association between autoantibody status and response to treatment with anti-TNF (18).

It is difficult to investigate association between RA patients' autoantibody status and response to ABA in controlled studies, since in most such studies the majority of patients enrolled are RF/ACPA positive. Anti-CCP positivity was associated with EULAR response and ABA treatment continuation at 6 months in an intermediate analysis of 558 patients from the ORA registry (10), who were also included in the present study. In a sensitivity analysis in which patients from the ORA registry were excluded, the results remained unchanged (data not shown). ABA treatment continuation was superior among patients who were double-positive for both RF and ACPA compared to patients who were positive for either RF or ACPA. Such an additive effect of autoantibodies on response to therapy has been reported previously only for rituximab (8).

The underlying reasons for the association between autoantibody status and response to ABA remain to be elucidated, and the association may not be causal. It could be speculated that autoantibody-positive RA patients represent a more homogeneous RA population, and are thus more prone to respond to drugs targeting the pathogenesis of the disease. Of note, the effect of ABA on T cell subset modulation is more marked in ACPA-positive patients (19). Likewise, we cannot totally rule out the possibility of some misclassification, e.g., that some of the patients classified as having

seronegative RA might actually have spondyloarthritis, which does not respond well to costimulation inhibition. Additionally, since B lymphocytes express CD80 and CD86, which bind CTLA-4, ABA treatment could result in the inhibition of presentation of peptides to T cells by ACPA- and RF-producing B cells. Interestingly, ABA causes decreases in synovial B cells (20), circulating post-switch memory B cells (21), and serum levels of immunoglobulins and free light chains of immunoglobulins and autoantibodies. Finally, in mice, ABA decreases the differentiation of follicular helper T cells (22), which play a major role in B cell activation. This may result in better effectiveness in patients for whom the contribution of B cells in RA pathogenesis is more pronounced. Double-positivity for RF and ACPA may help identify patients with this phenotype.

The limitations of this study are related to the observational nature of registries. Information on RF or ACPA was missing for 15% and 35% of patients, respectively, which reduced the statistical power, in particular in analyses of the effect of these autoantibodies on EULAR response. We believe it is fair to assume that the missing data on RF and ACPA were missing at random, though, and thus the results should not be biased by this. Possible selection biases and unmeasured confounding factors cannot be excluded. Although there were some differences between registries contributing to the present database, the association between autoantibodies and treatment continuation was consistent across European registries. RF and ACPA positivity remained strongly predictive of better drug continuation in multivariate analyses, even after adjustment for baseline DAS28.

In conclusion, positivity for RF and positivity for ACPA were consistently associated with better effectiveness of ABA across 9 European registries. RF and ACPA could represent helpful prognostic biomarkers for selection of biologic agents to use in a personalized medicine approach to the treatment of RA.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Gottenberg had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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