Rheumatol Ther (2022) 9:637–647
https://doi.org/10.1007/s40744-022-00427-y

ORIGINAL RESEARCH

The Role of Shared Epitope in Rheumatoid Arthritis Prognosis in Relation to Anti-Citrullinated Protein Antibody Positivity

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Received: August 13, 2021 / Accepted: January 20, 2022 / Published online: February 16, 2022

ABSTRACT

Introduction: Shared epitope (SE) is present in high proportions of anti-citrullinated protein antibody (ACPA) + patients with rheumatoid arthritis (RA) and is associated with poor prognosis. We assessed the role of SE in RA prognosis, in relation to ACPA positivity.

Methods: Patients enrolled in the Brigham and Women's RA Sequential Study were included. Changes from baseline in disease activity (Disease Activity Score in 28 joints using C-reactive protein [DAS28 (CRP)], Clinical Disease Activity Index [CDAI], Simplified Disease Activity Index [SDAI]) to 1 year were assessed. Baseline characteristics were compared by SE and ACPA status (±; chi-squared, Kruskal-Wallis). Association between number of SE alleles and ACPA status (logistic regression models), relationships between baseline characteristics and changes in disease activity (adjusted linear regression model), and effect of ACPA on the association between SE and changes in disease activity (mediation analysis) were studied.

Results: Nine hundred twenty-six patients were included. SE + versus SE − patients had significantly longer disease duration and higher disease activity scores and were more likely to have erosive disease, have higher comorbidity burden, and be RF + (all $p < 0.05$). Among patients with one or two SE alleles (vs. 0), odds of being ACPA + were 1.97 ($p = 0.0003$) and 3.82 ($p < 0.0001$), respectively. SE + versus SE − patients had worse disease activity scores as indicated by mean increases in DAS28 (CRP) of 0.22, CDAI of 2.07, and SDAI of 2.43 over 1 year (all $p < 0.05$). Direct effect of SE + accounted for 76.4–80.1% of total effect in disease activity increases.

Conclusions: SE is strongly associated with ACPA positivity and higher disease activity in patients with RA. SE was associated with greater increases in disease activity over 1 year, which was partially mediated by the presence of ACPA.

Trial Registration: ClinicalTrials.gov identifier: NCT01793103; registration date: February 15, 2013, retrospectively registered.

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PLAIN LANGUAGE SUMMARY

Patients with rheumatoid arthritis (RA) experience inflamed and damaged joints. RA is an autoimmune disease where proteins called

autoantibodies in the blood of patients with RA target the patient's own joint tissue and organs by mistake. This causes inflammation. Patients with certain autoantibodies, such as anti-citrullinated protein antibodies (ACPAs), may experience worse symptoms. There are certain genetic risk factors that may mean a person is more likely to develop RA. One example of a genetic risk factor is having the shared epitope (SE).

Our study looked at almost 1000 patients with RA in the general population. It explored the impact of having SE and ACPAs on changes in RA disease activity. Patients with SE had RA for a longer time, had more severe disease, and were more likely to have other diseases compared with patients without SE. Patients with SE were also more likely to have ACPAs. Over the course of one year, patients with SE had larger increases in RA disease activity than those patients without SE, even though they were taking the same treatments. These results suggest that patients with the genetic risk factor, SE often have RA that is harder to treat. Doctors should take this into account when selecting treatment for RA.

Keywords: Anti-citrullinated protein antibody; Registry, rheumatoid arthritis; Shared epitope

Key Summary Points

Why carry out this study?
Anti-citrullinated protein antibodies (ACPAs) are biomarkers considered predictive of a poor prognosis in rheumatoid arthritis (RA)
Many ACPA-positive patients are also positive for a genetic risk factor known as the shared epitope (SE)
The objective of this analysis of data from the Brigham and Women's RA Sequential Study was to assess the role of SE in RA prognosis in relation to ACPA positivity

What was learned from the study?
The results of this retrospective analysis of real-world data show that SE was strongly associated with ACPA positivity and higher disease activity in patients with RA
The results suggest that SE + versus SE − patients often have more severe, harder-to-treat disease, and this highlights the need for a precision medicine approach to treatment selection in clinical practice

INTRODUCTION

The pathology of rheumatoid arthritis (RA) is driven by a persistent autoimmune response. RA is characterized by the production of pathogenic autoantibodies and pro-inflammatory cytokines [1, 2], which lead to synovitis, structural damage, and functional impairment [3]. The presence of autoantigens drives the ongoing immune response in autoimmune rheumatic diseases; it is hypothesized that hypercitrullination and generation of neo-citrullinated proteins may occur in RA target tissues (e.g., the joints) and drive the immune response [4]. Anti-citrullinated protein antibodies (ACPAs) are highly specific serological biomarkers for RA that can be present before clinical RA symptoms [5] and are considered predictive of a poor prognosis [6]. ACPAs stimulate pro-inflammatory cytokine production, induce osteoclastogenesis, and promote autoantigen release from neutrophils, thereby contributing to the development and perpetuation of RA [7].

Certain risk alleles such as the shared epitope (SE) are associated with RA and can also be predictive of poor disease prognosis [8, 9]. SE is a term that describes the consensus amino acid sequences in the peptide-binding groove of major histocompatibility complex Class II receptors on antigen-presenting cells; it is characterized by common sequences at amino acids 70–74 (e.g., QKRAA) in the third hypervariable region of the β-chain of the HLA-DR

molecule [10, 11]. Up to 80% of ACPA + patients with RA are SE + [9, 12–16]. SE positivity is strongly associated with earlier onset of RA [17], greater severity of erosions [16, 18], and higher mortality [19]. SE increases the likelihood of autoreactive T-cell activation via increasing the binding of citrullinated self-proteins to HLA on antigen-presenting cells [20]. The interrelationship among the SE, ACPA positivity, and disease outcomes is yet to be fully elucidated. The objective of this retrospective analysis was to assess the role of the SE in RA prognosis in relation to ACPA positivity.

METHODS

Study Design and Data Source

This analysis included patients with known SE and ACPA status who enrolled in the Brigham and Women's Rheumatoid Arthritis Sequential Study (BRASS; NCT01793103) Registry between March 2003 and June 2019. Details regarding the design of the registry, which was a cohort of patients with a diagnosis of RA (1987 American College of Rheumatology criteria [21] or based on the opinion of their rheumatologist), have been reported previously [22–24]. *HLA-DRB1* SE status was determined by allele-specific polymerase chain reaction and DNA sequencing for most patients and by a genome-wide association study-based imputation for the remainder. Anti-cyclic citrullinated peptide 2 (anti-CCP2) antibody (a surrogate for ACPA) levels were measured using a validated enzyme-linked immunosorbent assay (Inova Diagnostics, San Diego, CA, USA, until its discontinuation in 2011, thereafter, Euro-Diagnostica [distributed by IBL-America, Minneapolis, MN, USA]).

Patients with all of the following information available at baseline were eligible for inclusion in the analysis: SE status, Disease Activity Score in 28 joints using C-reactive protein (DAS28 [CRP]) score, ACPA titer, age, sex, RA duration, body mass index (BMI), number of painful joints, and number of swollen joints.

Endpoints and Assessments

Baseline demographics and disease characteristics were examined by SE status (+ , 1 or 2 SE alleles; − , 0 alleles) and by ACPA status (+ , anti-CCP2 $\geq$ 20 U/ml; − , anti-CCP2 $<$ 20 U/ml). Records collected on or within 12 months prior to the index date (date of first valid ACPA record with all available information) were used as baseline information. Changes from baseline in DAS28 (CRP), Clinical Disease Activity Index (CDAI), and Simplified Disease Activity Index (SDAI) to 1 year were measured (with 6-month window for collection of outcomes; i.e., 6–-18 months after index date for CDAI and SDAI).

Statistical Analyses

Baseline characteristics were compared by SE and ACPA status using chi-squared tests for categorical variables and Kruskal-Wallis tests for continuous variables. Logistic regression models were used to examine the association between the number of SE alleles and ACPA status. Baseline ACPA status was considered as the dependent variable, and SE status, age, sex, biologic use, Charlson Comorbidity Index (CCI) score, disease activity, and smoking status were considered as independent variables (all at baseline). These variables were selected as they are risk factors for RA or measures or surrogates of disease activity. The relationships between baseline characteristics and changes in disease activity were analyzed using a separate linear regression model. Change in disease activity was considered the dependent variable and SE status, age, sex, biologic use, CCI score, disease activity, and smoking status the independent variables (all at baseline). The contribution of ACPA on the association between SE and the changes in disease activity was assessed using a mediation analysis.

Compliance with Ethics Guidelines

The BRASS Registry has been conducted in accordance with International Society for Pharmacoepidemiology Guidelines for Good Pharmacoepidemiology Practices [25],

Table 1 Baseline characteristics by SE and ACPA status

Parameter	SE +				SE −				*p* value (SE + vs SE−)
	Overall (*n* = 603)	ACPA + (*n* = 456)	ACPA− (*n* = 147)	*p* value (ACPA + vs ACPA−)	Overall (*n* = 323)	ACPA + (*n* = 167)	ACPA − (*n* = 156)	*p* value (ACPA + vs ACPA−)	
Age, years	57.3 (13.8)	57.5 (13.6)	56.6 (14.5)	0.6000	57.4 (14.2)	59.7 (13.7)	55.0 (14.4)	**0.0060**	0.9857
Female, *n* (%)	493 (81.8)	369 (80.9)	124 (84.4)	0.3487	271 (83.9)	145 (86.8)	126 (80.8)	0.1388	0.4133
Disease duration, years	15.5 (12.4)	16.6 (12.4)	12.1 (11.7)	< **0.0001**	12.1 (11.5)	15.0 (12.1)	8.9 (9.8)	< **0.0001**	< **0.0001**
Erosive disease, *n* (%)	360 (59.7)	298 (65.4)	62 (42.2)	< **0.0001**	153 (47.4)	102 (61.1)	51 (32.7)	< **0.0001**	**0.0062**
RF + , *n* (%)	433 (71.8)	395 (86.6)	38 (25.9)	< **0.0001**	168 (52.0)	145 (86.8)	23 (14.7)	< **0.0001**	< **0.0001**
BMI, kg/m^2	26.6 (5.7)	26.5 (5.7)	26.8 (5.8)	0.6713	27.2 (5.6)	27.5 (6.0)	26.8 (5.1)	0.4076	0.0604
Smoking status, yes, *n* (%)	283 (46.9)	225 (49.3)	58 (39.5)	**0.0499**	147 (45.5)	79 (47.3)	68 (43.6)	0.3820	0.7548
Presence of cardiovascular disease, *n* (%)	32 (5.3)	28 (6.1)	4 (2.7)	0.1078	10 (3.1)	9 (5.4)	1 (0.6)	**0.0203**	0.1233
Presence of osteoporosis, *n* (%)	83 (13.8)	65 (14.3)	18 (12.2)	0.5386	33 (10.2)	22 (13.2)	11 (7.1)	0.0695	0.1201
CCI score	1.5 (0.9)	1.5 (0.9)	1.4 (0.8)	0.1290	1.3 (0.8)	1.4 (0.9)	1.3 (0.6)	0.1195	**0.0347**
Current medications, *n* (%)									
TNFis	261 (43.3)	216 (47.4)	45 (30.6)	**0.0004**	99 (30.7)	62 (37.1)	37 (23.7)	**0.0090**	**0.0002**
Non-TNFi biologics	6 (1.0)	5 (1.1)	1 (0.7)	1.0000	4 (1.2)	1 (0.6)	3 (1.9)	0.3564	0.746

Table 1 continued

Parameter	SE +				SE −				*p* value (SE + vs SE−)
	Overall (*n* = 603)	ACPA + (*n* = 456)	ACPA− (*n* = 147)	*p* value (ACPA + vs ACPA−)	Overall (*n* = 323)	ACPA + (*n* = 167)	ACPA − (*n* = 156)	*p* value (ACPA + vs ACPA−)	
csDMARDs	416 (69.0)	308 (67.5)	108 (73.5)	0.1768	221 (68.4)	120 (71.9)	101 (64.7)	0.1694	0.8591
Baseline disease activity scores									
DAS28 (CRP)	4.0 (1.6)	4.1 (1.7)	3.6 (1.5)	**0.0004**	3.8 (1.6)	3.9 (1.6)	3.6 (1.6)	0.0896	**0.0251**
CDAI	23.1 (17.3)	24.6 (17.8)	18.3 (14.9)	**0.0003**	20.6 (16.9)	22.1 (17.4)	18.9 (16.2)	0.0858	**0.0248**
SDAI	24.1 (18.1)	25.7 (18.6)	19.3 (15.4)	**0.0003**	21.4 (17.3)	22.9 (17.7)	19.7 (16.8)	0.0794	**0.0220**

Data are presented as mean (SD) unless otherwise specified. Bold text indicates significant *p* values ($p < 0.05$)

ACPA anti-citrullinated protein antibody, *BMI* body mass index, *CCI* Charlson Comorbidity Index, *CDAI* Clinical Disease Activity Index, *csDMARD* conventional synthetic disease-modifying antirheumatic drug, *DAS28 (CRP)* Disease Activity Score in 28 joints using C-reactive protein), *RF* rheumatoid factor, *SD* standard deviation, *SDAI* Simplified Disease Activity Index, *SE* shared epitope, *TNFi* tumour necrosis factor inhibitor

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applicable regulatory requirements, and ethical tenets originating Helsinki Declaration of 1964 and its later amendments. All patients provided written informed consent before participating in the BRASS Registry, which was approved by the Partners Institutional Review Board at Brigham and Women's Hospital.

RESULTS

Patient Disposition and Baseline Characteristics

A total of 926 patients were included in the analysis. Overall, 65.1% (603/926) of patients were SE + , of whom 75.6% (456/603) were ACPA + and 71.8% (433/603) were RF + . In comparison, 51.7% (167/323) of SE − patients were ACPA + and 52.0% (168/323) were RF + . Among both SE + and SE − patients, 87% of ACPA + patients were also RF + . SE + versus SE − patients were similar in terms of age, sex, BMI, and smoking status (Table 1) [26]. However, SE + versus SE − patients had a significantly longer disease duration and were more likely to have erosive disease and a higher comorbidity burden (as measured by CCI) and be RF + (all $p < 0.05$). Other than comorbidity burden, these characteristics were also more prevalent in ACPA + versus ACPA − patients in both SE + and SE − patients.

A similar proportion of SE + and SE − patients was receiving treatment with non-tumour necrosis factor inhibitor (TNFi) biologics or conventional synthetic disease-modifying antirheumatic drugs (DMARDs) at baseline; however, a greater proportion of SE + patients was receiving TNFi therapies compared with SE − patients. Baseline DAS28 (CRP), CDAI, and SDAI scores were significantly higher among SE + versus SE − patients ($p < 0.05$). Among SE + patients, ACPA + versus ACPA − patients had significantly higher disease activity scores at baseline (all $p < 0.001$); there was no significant difference in SE − patients. After adjusting for differences at baseline, the odds of being ACPA + were 1.97 (95% confidence interval [CI]: 1.36, 2.84; $p = 0.0003$) for patients with 1 SE allele compared with 3.82 (95% CI: 2.44, 5.98; $p < 0.0001$) for patients with two SE alleles (both vs. 0 SE alleles). For patients with two SE alleles (vs. 1 allele), the odds of being ACPA + were 1.98 (95% CI: 1.27, 3.08; $p = 0.003$).

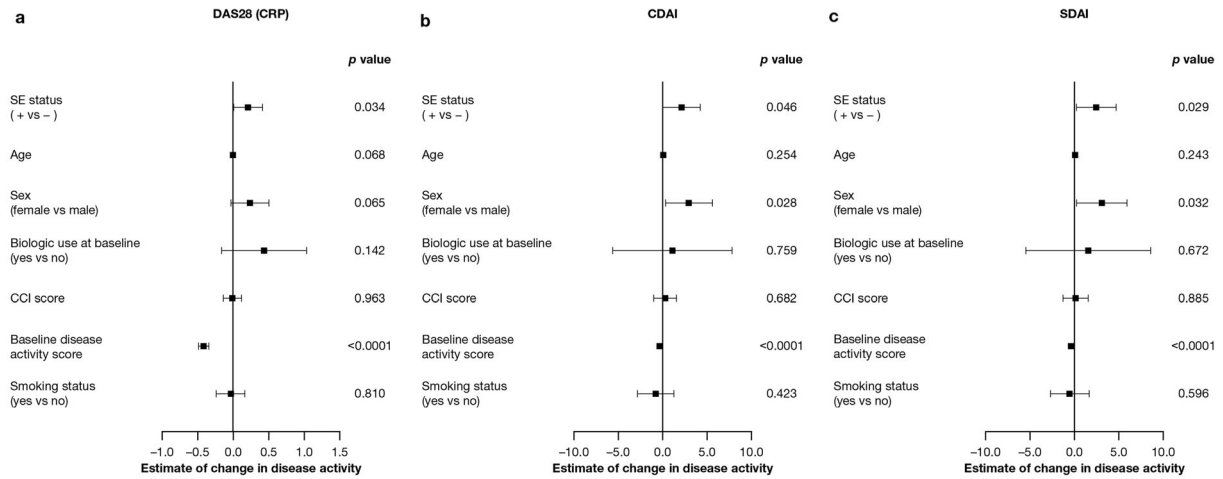

Fig. 1 Linear regression model of the association between baseline characteristics and change in disease activity [26]. **a** Change in DAS28 (CRP), **b** change in CDAI, and **c** change in SDAI. *BL* baseline, *CCI* Charlson comorbidity index, *CDAI* Clinical Disease Activity Index, *DAS28 (CRP)* Disease Activity Score in 28 joints using C-reactive protein, *SDAI* Simple Disease Activity Index, *SE* shared epitope Figure reproduced from Zhuo J, et al. *Ann Rheum Dis.* 2020;79 (suppl 1):963 (abstract SAT0061)

Table 2 Mediation analysis for SE and ACPA association with change in disease activity

Parameter	Change in DAS28 (CRP) score (n = 666)		Change in CDAI score (n = 653)		Change in SDAI score (n = 629)	
	Estimate	p value	Estimate	p value	Estimate	p value
Total effect of SE on disease activity change	0.2162	**0.0346**	2.0493	**0.0471**	2.404	**0.0306**
Direct effect of SE on disease activity change excluding mediation of ACPA	0.1731	0.1013	1.5652	0.1404	1.8923	0.098
Indirect effect of SE on disease activity change due to ACPA mediation and interaction	0.0431	0.1834	0.4841	0.1333	0.5117	0.1431

The model has been adjusted with additional covariates: age, sex, Charlson Comorbidity Index score; baseline biologic use (yes vs. no), smoking status (yes vs. no), baseline disease activity score, and interaction term (ACPA*SE). Bold text indicates significant p values ($p < 0.05$)

ACPA anti-citrullinated protein antibody, *CDAI* Clinical Disease Activity Index, *DAS28 (CRP)* Disease Activity Score in 28 joints using C-reactive protein, *SDAI* Simplified Disease Activity Index, *SE* shared epitope

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Association Between Baseline Characteristics and Change in Disease Activity

At 1 year, 666 (71.9%), 653 (70.5%), and 629 (67.9%) patients had disease activity and all covariate data available and, as such, were included in the DAS28 (CRP), CDAI, and SDAI analyses, respectively. Patients with missing data were distributed proportionally between SE + and SE − groups; 65.2–65.8% of included patients were SE + across disease measures. Patients who were SE + versus SE − had significantly greater (mean [95% CI]) increases in DAS28 (CRP) (0.22 [0.02, 0.42]; $p = 0.034$), CDAI (2.07 [0.04, 4.09]; $p = 0.046$), and SDAI (2.43 [0.25, 4.61]; $p = 0.029$) scores over 1 year (Fig. 1) [26]. Disease activity scores at baseline were also significantly ($p < 0.0001$ for all outcomes) associated with mean (95% CI) changes in DAS28 (CRP) (− 0.40 [− 0.47 − 0.34]), CDAI (− 0.42 [− 0.47, − 0.36]), and SDAI (− 0.43 [− 0.49, − 0.37]) scores at 1 year.

Effect of ACPA on the Association Between SE and Change in Disease Activity

Using a mediation analysis, the direct effect of SE + accounted for 76.4–80.1% of the total effect in the increases in DAS28 (CRP), CDAI, and SDAI scores, and the indirect effect of SE + mediated by ACPA accounted for 19.9–23.6% (Table 2) [26]; neither the direct nor the indirect effects were significant. Mediation analysis of the effect of ACPA on the change in disease activity was not performed for SE − patients.

DISCUSSION

The results of this retrospective analysis of real-world data show that SE was strongly associated with ACPA positivity and greater disease activity in patients with RA. SE was associated with greater increases in disease activity over the course of 1 year, despite patients receiving standard treatments including biologic DMARDs. The increases in disease activity were partially mediated by the presence of ACPA.

In the present study, 65.1% of patients with RA were SE +; a higher proportion of ACPA + (73.2%; 456/623) versus ACPA − (48.5%; 147/303) patients were SE +. These findings are in line with previous research, which has shown that up to 80% of ACPA + patients with RA are SE + [13–15] and 49% of ACPA − patients are SE + [14], indicating that the patients included

in this study are representative of the general RA population.

While a number of studies have highlighted the link between SE, ACPA, and disease activity [9, 14–16], our study shows that, to some extent, SE has a direct negative effect on disease activity, regardless of the presence of ACPAs. In a meta-analysis of patients with RA, a greater number of copies of the SE was associated with a higher odds ratio for erosive disease [27]. A subsequent study demonstrated that the number of copies of the SE allele was associated with the presence of erosive disease among ACPA + patients with RA ($p < 0.02$), but not among ACPA – patients with RA [14]. Studies of the effects of SE on disease activity, regardless of the presence of ACPAs, are lacking.

Despite treatment, a worsening of disease activity throughout the study was seen for SE + versus SE − patients. This may possibly be explained, in part, by the fact that in the present study, < 50% of patients received treatment with biologics; most of whom were treated with a TNFi at baseline. Biological therapy has improved the prognoses of patients with RA; however, 30–40% of patients have an inadequate response to TNFis [28]. Bogas et al. recently observed that after TNFi failure, regardless of whether primary or secondary inefficacy, a 24-month EULAR response was more frequently achieved after using a non-TNFi versus using a second TNFi [29]. A recent study on the role of SE in the effectiveness of TNFi treatment for patients with RA participating in the BRASS registry concluded that similar efficacy responses with TNFi therapies are seen regardless of SE status [30]. There is evidence to suggest that abatacept, a non-TNFi biologic, shows differential efficacy compared with TNFis in ACPA + patients. For example, in a US-based clinical practice setting, greater efficacy was seen with abatacept, but not TNFis, in ACPA + versus ACPA − patients with RA [31]. Similarly, in a meta-analysis of 19 studies, ACPA positivity was associated with better European League Against Rheumatism responses in patients with RA receiving abatacept but not a TNFi [32]. In addition, in a retrospective observational study of 72 patients, the clinical efficacy of abatacept was significantly higher in SE + versus SE − patients with RA [33]. Hence, the differential efficacy of abatacept vs. TNFis seen in ACPA + patients may also translate to SE + patients.

The limitations of this study should be considered. BRASS is a single-center registry and, although patients were enrolled over a long period of time, for the purpose of these analyses, they were studied over a relatively short time period and a large window for the 1-year outcomes was provided (6–18 months after index date) to maximize the number of patients eligible for inclusion. In addition, due to the observational nature of this study, there was an absence of randomization and blinding, leading to potential bias. The logistic regression models included risk factors for RA and measures/surrogates of disease activity including biologic use, but it should be noted that there were significant differences in characteristics such as disease duration, which was longer in SE + patients, and TNFi use at baseline between comparison groups, which may have impacted disease activity and outcome. These differences and other characteristics, for example, prior treatments, total Sharp score, and treatment duration, were not included in the regression analysis. Although this less controlled setting results in a more heterogeneous population with concomitant medications and comorbidities, which may influence the results, the real-world nature of the study makes the findings generalizable to clinical practice. The availability and inclusion of information on ACPA titers and specific risk alleles would have been useful in further confirming the gene-dose effects of SE.

CONCLUSIONS

The results of this retrospective, real-world study indicate that SE is strongly associated with ACPA positivity and higher disease activity in patients with RA. Among patients receiving standard treatments, including biologics, SE positivity was associated with greater increases in disease activity over 1 year, which were partially mediated by ACPA. These results suggest that SE + versus SE − patients often have more

severe, harder-to-treat disease, demonstrating the need for a precision medicine approach in treatment selection.

ACKNOWLEDGEMENTS

Funding. Sponsorship for this study and the journal's Rapid Service Fee were funded by Bristol Myers Squibb.

Authorship. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Authors' 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. Joe Zhuo: Conception, design, acquisition, analysis, and interpretation of the data for the manuscript. Qian Xia: Acquisition, analysis, and interpretation of the data for the manuscript. Niyati Sharma: Acquisition, analysis, and interpretation of the data for the manuscript. Sheng Gao: Analysis and interpretation of the data for the manuscript. Sonie Lama: Analysis and interpretation of the data for the manuscript. Jing Cui: Acquisition of the data for the manuscript. Vivi Feathers: Acquisition of the data for the manuscript. Nancy Shadick: Analysis and interpretation of the data for the manuscript. Michael E. Weinblatt: Acquisition, analysis, and interpretation of the data for the manuscript.

Medical Writing, Editorial, and Other Assistance. The authors are grateful to Evo Alemao for his valuable contributions. Professional medical writing and editorial assistance was provided by Lola Parfitt, MRes, at Caudex and was funded by Bristol Myers Squibb.

Prior Presentation. This manuscript is based on work that has been previously presented in a poster at EULAR 2020 (Zhuo J, et al. *Ann Rheum Dis*. 2020;79[suppl 1]:963 [abstract SAT0061]).

Disclosures. Joe Zhuo, Qian Xia, Sonie Lama: employees and shareholders: Bristol Myers Squibb. Niyati Sharma: consultant: Bristol Myers Squibb; employee: Flipkart; former employee: Mu-Sigma. Sheng Gao: employee: Janssen; shareholder and former employee: Bristol Myers Squibb. Jing Cui and Vivi Feathers have nothing to disclose. Nancy Shadick: grant/research support: Amgen, Bristol Myers Squibb, Crescendo Biosciences, Lilly, Mallinckrodt, and Sanofi-Regeneron; consultant: Bristol Myers Squibb. Michael E. Weinblatt: grant/research support: Amgen, Bristol Myers Squibb, Crescendo, Lilly, and Sanofi; consultant: AbbVie, Amgen, Arena, Bristol Myers Squibb, Can-Fite, Corrona, Crescendo, GlaxoSmithKline, Gilead, Horizon Therapeutics, Johnson and Johnson, Lilly, Pfizer, Roche, Scipher, Set Point, and Tremeau.

Compliance with Ethics Guidelines. The BRASS Registry has been conducted in accordance with International Society for Pharmacoepidemiology Guidelines for Good Pharmacoepidemiology Practices, applicable regulatory requirements, and ethical tenets originating in the Helsinki Declaration of 1964, and its later amendments. All patients provided written informed consent before participating in the BRASS Registry, which was approved by the Partners Institutional Review Board at Brigham and Women's Hospital.

Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request. Bristol Myers Squibb policy on data sharing may be found at https://www.bms.com/researchers-and-partners/independent-research/data-sharing-request-process.html.

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