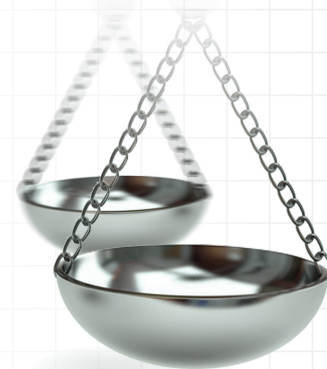




First-line tumor necrosis factor inhibitor versus abatacept treatment choice in real-world patients with anticitrullinated protein antibody- and rheumatoid factor-positive rheumatoid arthritis

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Aim: To compare characteristics of patients with anticitrullinated protein antibody-positive (ACPA+) and rheumatoid factor-positive (RF+) rheumatoid arthritis (RA) who initiated abatacept or a tumor necrosis factor inhibitor (TNFi) as a first-line biologic disease-modifying antirheumatic drug (bDMARD), and to identify factors associated with first-line bDMARD selection. **Materials & methods:** This retrospective cohort study abstracted data for patients with ACPA+/RF+ RA initiating abatacept or a TNFi as a first-line bDMARD between 1 January 2015 and 19 February 2020. Patient characteristics were compared using chi-square/Fisher exact tests (categorical variables) and Wilcoxon tests (continuous variables). Adjusted odds ratios (OR; 95% confidence interval [CI]) of initiating abatacept versus TNFi were estimated using 2-level logistic regression. **Results:** The analysis cohort included 301 patients who initiated abatacept and 203 patients who initiated a TNFi. Time from RA diagnosis to first-line initiation (>2 years vs <1 year; OR [95% CI] 2.9 [1.4–6.1]), high and moderate disease activity (versus low; 5.0 [1.8–13.9] and 4.2 [1.5–11.6], respectively), and conventional synthetic (cs) DMARD use within 12 months prior to initiation (versus no csDMARD use; 2.0 [1.1–3.6]) were associated with higher odds of initiating abatacept versus a TNFi (all $p < 0.05$). Patients with Medicare/other insurance had increased odds of initiating abatacept (versus TNFi) as age increased. Baseline ACPA >250 AU/ml was associated with lower odds of initiating abatacept over a TNFi (versus ACPA 20–250 AU/ml; 0.4 [0.2–0.8]; $p < 0.01$). **Conclusion:** In this real-world study, patients with ACPA+/RF+ RA were more likely to initiate abatacept over TNFi as a first-line bDMARD if they had delayed first-line bDMARD initiation, high/moderate disease activity, prior csDMARD use, or were of an older age. There is a need for better understanding of treatment selection and to account for these variables in future studies.

Plain language summary

What was the aim of this research? The study looked at patient or disease factors affecting doctors' choice of treatments for patients with seropositive rheumatoid arthritis (RA).

How was the research done? The analysis compared data from patient medical records for two groups of patients with RA: one group started their first targeted treatment with abatacept and the other started with a drug from a group called tumor necrosis factor inhibitors (TNFis).

What were the results? The research team studied data from the medical records of 301 patients who started abatacept and 203 patients who started a TNFi. The results showed that patients were more likely to start abatacept than a TNFi if they started treatment later after their diagnosis, had more severe disease, had used corticosteroid treatment previously, or were older. As patient age increased, they were more likely to start abatacept than a TNFi if they had Medicare or other insurance. Patients were more likely to be prescribed a TNFi than abatacept if they had higher levels of anticitrullinated protein antibody before starting treatment.

Why is this important? This study showed that many patient and disease factors may affect treatment choice for patients with seropositive RA. Further studies will be important to improve our understanding of the reasons behind treatment decisions. This research may help to ensure that patients receive the right treatment for them with the most benefit.

First draft submitted: 29 April 2025; Accepted for publication: 22 December 2025; Published online: 27 January 2026

Keywords: abatacept • anticitrullinated protein antibodies • biologic • comorbidities • disease-modifying antirheumatic drug • real-world • rheumatoid arthritis • rheumatoid factor • tumor necrosis factor inhibitor

Rheumatoid arthritis (RA) is a chronic autoimmune disease that is estimated to affect around 1.3 million adults in the US [1–4]. Autoantibodies, such as anticitrullinated protein antibodies (ACPAs) and rheumatoid factor (RF) are often indicative of a more severe and erosive form of RA and an increased risk of extra-articular manifestations/comorbidities [5–7]. For example, patients with RA who are ACPA and RF-positive have a greater risk of RA-related interstitial lung disease (RA-ILD) [8]. However, research has shown that the presence of ACPA and RF may also serve as prognostic and pharmacodynamic biomarkers to predict disease progression and treatment response, respectively, in patients with RA [9–14].

Treatment options for RA initially include conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), such as methotrexate (MTX), sulfasalazine, leflunomide and hydroxychloroquine [15,16]. Second-line treatments in cases where symptoms do not improve include switching to a different csDMARD, adding a second csDMARD, or adding a biologic DMARD (bDMARD), such as tumor necrosis factor inhibitors (TNFis), interleukin-6 inhibitors (IL-6is), or the T-cell co-stimulation modulator abatacept [15–17].

Treatment with abatacept has demonstrated favorable outcomes in adult patients with ACPA+ and/or RF+ RA and has shown benefit when used early in a subset of adults at high risk of developing RA [18–21]. Additionally, improved responses have been documented with abatacept compared with the TNFi adalimumab [22,23].

Guidelines for optimal bDMARD selection and sequencing following inadequate response to csDMARDs are not established, and there is a lack of information regarding which treatments may be suitable for specific patients. Thus, a better understanding of factors associated with first-line bDMARD selection for patients with ACPA+/RF+ RA in the real-world setting may help clinicians to optimize treatment decision-making. Therefore, this analysis aimed to compare demographic, clinical, and treatment-related characteristics of adult patients with RA who were both ACPA+ and RF+ and were treated with abatacept or a TNFi as a first-line bDMARD, as well as to identify factors associated with first-line bDMARD selection in the real-world setting.

Materials & methods

Study design & data source

This was a retrospective, observational cohort study of patients with ACPA+ and RF+ RA who initiated first-line bDMARD treatment with abatacept (intravenous [IV] or subcutaneous [SC] formulations) or a TNFi in rheumatology clinics in the US [21]. TNFis included SC adalimumab, SC certolizumab pegol, SC etanercept, IV or SC golimumab and IV infliximab. These medications were prescribed by treating rheumatologists at their own discretion as part of individualized decision-making processes. Eligible patients were identified by their treating rheumatologists in the Cardinal Health Rheumatology Provider Extended Network. As of February 2021, Cornerstone represented approximately 1100 practices comprising 2300 rheumatologists across 48 US states. Purposive sampling provided data for this analysis from 28 rheumatology practices across the US.

Data were collected as previously described [21]. In brief, Cardinal Health developed and tested an electronic case report form (eCRF), which was then utilized by 28 rheumatologists who each selected a maximum of 20 consecutive potentially eligible patients for chart abstraction, starting with the earliest eligible (to minimize selection bias and to maximize follow-up time). Patient demographic, clinical and treatment-related data were abstracted from the date of RA diagnosis through the date of last follow-up or death (if known or applicable). In an attempt to minimize unmeasured confounding bias, the collection of numerous data points of clinical relevance to the treatment patterns of patients was required.

Patient identification spanned from 1 January 2015 to 19 February 2020, which defined the index period for patients initiating abatacept or a TNFi as a first-line bDMARD [21]. All data for patients treated with abatacept as a first-line bDMARD were abstracted from patient medical records, and data collection occurred between 19

February 2021 and 15 April 2021. Data for patients treated with a TNFi were collected between 17 November 2021 and 29 November 2021.

Patient population

Eligible patients had a confirmed diagnosis of RA; were aged ≥ 18 years; were bDMARD- and Janus kinase inhibitor treatment-naïve; responded inadequately to MTX and subsequently initiated first-line abatacept or TNFi therapy on or after 1 January 2015; were ACPA+ (anticyclic citrullinated peptide 2 >20 AU/ml) and RF+ at or within 12 months prior to initiation; had one clinical disease activity index (CDAI) score [24] within 3 months prior to initiation and one CDAI score within 3–12 months following initiation; and were followed by participating rheumatologists for at least 12 months after first-line abatacept or TNFi initiation.

Patients were excluded if they had discontinued abatacept or a TNFi as a first-line bDMARD within 3 months of initiation or were treated with abatacept or a TNFi for RA in a clinical trial between 1 January 2015 and 19 February 2020 [21].

Study conduct & ethical considerations

This study was conducted in accordance with International Society for Pharmacoepidemiology Guidelines for Good Epidemiology Practices [25], the Professional Society for Health Economics and Outcomes Research [26], the Strengthening the Reporting of Observational Studies in Epidemiology guidelines [27] and the ethical principles in the Declaration of Helsinki [28]. Rheumatologists were required to be able to participate in research monitored by a central institutional review board (IRB; 20204039). The protocol, amendments, eCRF and waiver of patient informed consent (due to the minimal amount of protected health information collected) received IRB approval from the Western Institutional Review Board.

Outcomes

This analysis aimed to identify demographic and clinical characteristics associated with first-line bDMARD selection among US patients with ACPA+/RF+ RA in a real-world setting.

Statistical analysis

Demographic and clinical characteristics were summarized using descriptive statistics. Unadjusted comparisons of demographic, clinical and treatment characteristics across the abatacept and TNFi treatment cohorts were conducted using chi-square tests (or Fisher exact tests where $n < 5$) for categorical variables and Wilcoxon rank-sum tests for continuous variables. Adjusted odds ratios (ORs) of receiving abatacept versus TNFi as a first-line bDMARD were calculated using logistic regression. Given that patient data provided from the same provider may have high intra-class correlation at the provider level, 2-level logistic regression was utilized to adjust for the clustering effect. Analyses were adjusted for numerous demographic and disease characteristics.

All independent variables that had a $p < 0.2$ in univariate modeling were included in the initial multivariable model. Independent variables with the highest p-values were dropped from subsequent multivariable model iterations until all variables included in the model were significant. All analyses were conducted in SAS v9.4 (SAS Institute, NC, USA) and 2-sided test $p \leq 0.05$ were considered statistically significant.

Results

Study population

In total, 504 patients identified by 28 rheumatologists were included in this analysis: 301 patients initiated abatacept (IV, $n = 178$; SC, $n = 125$ [not mutually exclusive]) and 203 patients initiated a TNFi (adalimumab, $n = 69$; certolizumab pegol, $n = 41$; etanercept, $n = 38$; infliximab, $n = 34$; golimumab, $n = 21$) as a first-line bDMARD. The rheumatologists had a median of 13.5 years in practice, with 71.4% practicing in the community setting and 53.6% being in urban locations. Participating rheumatologists had a broad geographic distribution across the US, with 32.1% in the Northeast, 28.6% in the South, 25.0% in the West and 14.3% in the Midwest.

Demographic, clinical & treatment-related characteristics at initiation of abatacept or TNFi as a first-line bDMARD

Patients who initiated abatacept as a first-line bDMARD were older at initiation, a greater proportion were >2 years post RA diagnosis, and a greater proportion had Medicare coverage compared with patients who initiated a TNFi (all $p < 0.001$; Table 1). A greater proportion of patients who initiated a TNFi had commercial insurance, compared with patients who initiated abatacept ($p < 0.001$).

A numerically higher proportion of patients who initiated abatacept had a Charlson Comorbidity Index (CCI) of 1 or 2 compared with patients who initiated a TNFi. The three most commonly reported comorbidities in the overall study population were reported in higher proportions among patients who initiated abatacept than a TNFi: Type 2 diabetes: 13.3 versus 8.9% ($p = 0.127$); mild liver disease 4.3 versus 3.9% ($p = 0.835$); and obesity (BMI ≥ 30) 7.0 versus 5.9% ($p = 0.655$). A higher proportion of patients who initiated abatacept had extra-articular manifestations and congestive heart failure compared with patients who initiated a TNFi ($p = 0.004$ and $p = 0.045$, respectively). A higher number of patients who initiated abatacept had chronic obstructive pulmonary disease at first-line bDMARD initiation, compared with patients who initiated a TNFi (3.0 vs 0.5%; $p = 0.055$).

Baseline CDAI differed between patients who initiated abatacept as a first-line bDMARD and those who initiated a TNFi. In the abatacept group, more patients had high disease activity (CDAI >22) than in the TNFi group, whereas in the TNFi group, more patients had remission/low disease activity (CDAI ≤ 10) than in the abatacept group. A greater proportion of patients who initiated abatacept (versus a TNFi) received the first-line bDMARD intravenously ($p < 0.001$) and used corticosteroids and csDMARDs within 12 months prior to first-line bDMARD initiation ($p = 0.011$ and $p < 0.001$, respectively).

At first-line bDMARD initiation, a lower proportion of patients who received abatacept had baseline ACPA levels >250 AU/ml than those who received a TNFi ($p < 0.001$).

Multivariate analysis: factors associated with first-line bDMARD selection

Patients with >2 years from the time of RA diagnosis to first-line bDMARD initiation had greater adjusted odds of initiating abatacept than a TNFi versus patients who initiated first-line <1 year from RA diagnosis (OR [95% CI]: 2.92 [1.39–6.13]; $p = 0.005$; Figure 1).

Patients with a high CDAI score at initiation of first-line bDMARD were more likely to initiate abatacept than a TNFi versus patients with low disease activity (OR [95% CI]: 5.04 [1.83–13.88]; $p = 0.002$). Similarly, patients with a moderate CDAI score were more likely to initiate abatacept than a TNFi versus patients with low disease activity (OR [95% CI]: 4.18 [1.50–11.64]; $p = 0.006$). Patients who used csDMARDs (other than MTX) within the 12 months prior to first-line bDMARD initiation were more likely to initiate abatacept than a TNFi versus patients who did not use csDMARDs (OR [95% CI]: 2.00 [1.11–3.62]; $p = 0.021$).

Additionally, patients with Medicare and other insurance (as opposed to commercial coverage) were more likely to initiate abatacept than a TNFi as a first-line bDMARD as age increased. For example, patients at 70 years of age with Medicare insurance were more likely to initiate abatacept than a TNFi (OR [95% CI]: 3.61 [1.44–9.07]; $p = 0.006$).

Patients with baseline ACPA levels >250 AU/ml had lower adjusted odds than patients with baseline ACPA levels 20–250 AU/ml of initiating abatacept than a TNFi as a first-line bDMARD (OR [95% CI]: 0.41 [0.22–0.78]; $p = 0.006$).

Discussion

In this large, real-world study of patients with ACPA+/RF+ RA, factors potentially associated with greater odds of initiating abatacept as a first-line bDMARD over a TNFi included longer time (>2 years) from diagnosis to first-line bDMARD initiation, prior csDMARD use, and moderate/high baseline CDAI. Additionally, older patients and those who had Medicare/other noncommercial insurance were also more likely to receive abatacept than a TNFi.

Patient characteristics at the time of diagnosis have been explored for predicting response to treatment and for aiding treatment decisions [29–32]. In general, patients with RA who present with poor prognostic factors (such as seropositivity, either ACPA and/or RF; highly active disease, presence of erosions, presence of extra-articular manifestations and/or comorbidities) are at an increased risk of disease progression [6,33]. As such, it has been noted that poor prognostic factors were considered in the development of the most recent ACR guidelines for the treatment of RA. These factors may influence physicians and patients when deciding upon an appropriate treatment

Table 1. Demographic, clinical and treatment-related characteristics.

Characteristic	First-line bDMARD		p-value
	Abatacept (n = 301)	TNFi (n = 203)	
Age at first-line bDMARD initiation, mean (SD), years	53.3 (15.5)	48.2 (14.2)	<0.001
Female, n (%)	214 (71.1)	136 (67.0)	0.416
Race, n (%)			0.141
White	208 (69.1)	147 (72.4)	
Black/African-American	50 (16.6)	28 (13.8)	
Asian	27 (9.0)	25 (12.3)	
Native Hawaiian or other Pacific Islander	6 (2.0)	1 (0.5)	
American Indian or Alaska Native	4 (1.3)	2 (1.0)	
Other	6 (2.0)	0 (0.0)	
Ethnicity, n (%)			0.834
Non-Hispanic/Non-Latino/Non-Latina	245 (81.4)	169 (83.3)	
Hispanic/Latino/Latina	55 (18.3)	34 (16.7)	
Unknown	1 (0.3)	0 (0.0)	
Health insurance status at first-line bDMARD initiation, n (%)			<0.001
Commercial	165 (54.8)	138 (68.0)	
Medicare	110 (36.5)	37 (18.2)	
Other†	26 (8.5)	28 (13.8)	
BMI at first-line bDMARD initiation, mean (SD)	27.2 (5.7)	27.4 (5.1)	0.422
Smoking status at first-line bDMARD initiation, n (%)			0.492
Never smoked	208 (69.1)	135 (66.5)	
Current smoker	35 (11.6)	31 (15.3)	
History of smoking	58 (19.3)	37 (18.2)	
Presence of extra-articular manifestations at first-line bDMARD initiation, n (%)	144 (47.8)	71 (35.0)	0.004
Charlson Comorbidity Index at first-line bDMARD initiation, n (%)			0.060
0	227 (75.4)	168 (82.8)	
1	59 (19.6)	31 (15.3)	
2	13 (4.3)	2 (1.0)	
3+	2 (0.7)	2 (1.0)	
Presence of congestive heart failure at first-line bDMARD initiation, n (%)	7 (2.3)	0 (0.0)	0.045
Presence of chronic obstructive pulmonary disease at first-line bDMARD initiation, n (%)	9 (3.0)	1 (0.5)	0.055
Baseline ACPA‡ >250 AU/ml, n (%)	78 (25.9)	90 (44.3)	<0.001
Baseline CDAI§, n (%)			0.026
Remission/low disease activity (≤10)	18 (6.0)	26 (12.8)	
Moderate disease activity (>10 and ≤22)	112 (37.2)	74 (36.5)	
High disease activity (>22)	171 (56.8)	103 (50.7)	
Time from RA diagnosis to first-line bDMARD initiation, n (%)			<0.001
<1 year	179 (59.5)	147 (72.4)	
1–2 years	47 (15.6)	33 (16.3)	
>2 years	75 (24.9)	23 (11.3)	
First-line bDMARD route of administration, n (%)			<0.001
Intravenous	178 (59.1)	46 (22.7)	
Subcutaneous	125 (41.5)	157 (77.3)	<0.001
Corticosteroid use within the 12 months prior to first-line bDMARD initiation, n (%)			0.011
Yes	49 (16.3)	21 (10.3)	
No	237 (78.7)	166 (81.8)	
Unknown	15 (5.0)	16 (7.9)	
Use of csDMARDs within the 12 months prior to first-line bDMARD initiation, n (%)	135 (44.9)	57 (28.1)	<0.001
Use of NSAIDs within the 12 months prior to first-line bDMARD initiation, n (%)	174 (57.8)	129 (63.5)	0.197
Use of opioid/narcotic analgesics within the 12 months prior to first-line bDMARD initiation, n (%)	31 (10.3)	11 (5.4)	0.052

Values of p were determined by unadjusted Wilcoxon test, chi-square test or Fisher's exact test, as appropriate, and show TNFi vs abatacept.

Data from this table were previously presented at ACR Convergence 2022; 10–14 November 2022; Philadelphia, PA, USA (poster 1417).

†Includes patients with Medicaid, military coverage (e.g., Tricare/Veterans Affairs) and self-pay patients.

‡ACPA measured within 12-month period prior to/at initiation of first-line bDMARD, and value closest to initiation is reported (if more than one entered).

§Baseline CDAI [24] assessed within 3 months prior to/at initiation of first-line bDMARD.

ACPA: Anticitrullinated protein antibody; bDMARD: Biologic disease-modifying antirheumatic drug; CDAI: Clinical Disease Activity Index; csDMARD: Conventional synthetic disease-modifying antirheumatic drug; NSAID: Non-steroidal anti-inflammatory drug; RA: Rheumatoid arthritis; SD: Standard deviation; TNFi: Tumor necrosis factor inhibitor.

OR (95% CI, p-value)

1 year increase in age at first-line bDMARD initiation

Patients with commercial insurance	1.01 (0.98–1.04, p = 0.521)
Patients with Medicare	1.03 (0.98–1.08, p = 0.196)
Patients with other insurance [†]	1.11 (1.03–1.19, p = 0.005)

Insurance (reference: commercial)

Medicare at age 40	1.91 (0.47–7.80, p = 0.368)
Medicare at age 50	2.36 (0.86–6.49, p = 0.096)
Medicare at age 60	2.92 (1.31–6.51, p = 0.009)
Medicare at age 70	3.61 (1.44–9.07, p = 0.006)
Other insurance [†] at age 40	0.63 (0.26–1.53, p = 0.305)
Other insurance [†] at age 50	1.56 (0.59–4.12, p = 0.370)
Other insurance [†] at age 60	3.87 (0.87–17.20, p = 0.075)
Other insurance [†] at age 70	9.63 (1.12–82.75, p = 0.039)

Time from RA diagnosis to first-line bDMARD initiation (reference: within 1 year)

Within 1 and 2 years	0.94 (0.48–1.83, p = 0.855)
≥ 2 years	2.92 (1.39–6.13, p = 0.005)

Baseline CDAI[‡] (reference: remission/low disease activity)

High disease activity	5.04 (1.83–13.88, p = 0.002)
Moderate disease activity	4.18 (1.50–11.64, p = 0.006)

csDMARD use within 12 months prior to first-line bDMARD initiation (reference: no)

Yes	2.00 (1.11–3.62, p = 0.021)
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Baseline ACPA[§] (reference: 20–250 AU/mL)

> 250 AU/mL	0.41 (0.22–0.78, p = 0.006)
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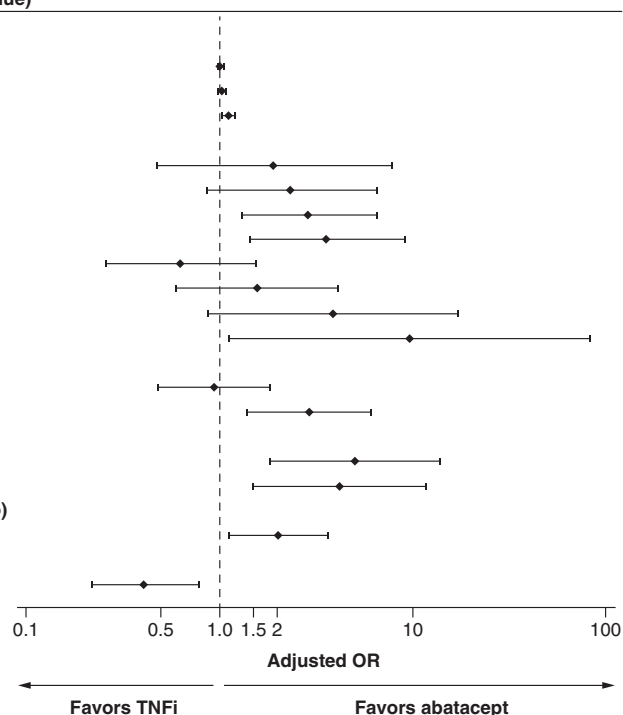


Figure 1. Odds ratios of receiving abatacept versus a tumor necrosis factor inhibitor as a first-line biologic disease-modifying antirheumatic drug.

The multivariate analysis adjusted for age at RA diagnosis, age at 1L initiation, sex, race, ethnicity, insurance, provider practice setting, provider regional location, time from RA diagnosis to 1L initiation, BMI, CCI, smoking, extra-articular manifestations, presence of congestive heart failure, presence of chronic obstructive pulmonary disease, corticosteroid use, baseline ACPA, baseline CDAI, baseline swollen joint count, baseline tender joint count, baseline evaluator global assessment, baseline Physician Global Assessment, csDMARD use within 12 months prior to first-line initiation, use of nonsteroidal anti-inflammatory drugs within 12 months prior to first-line initiation, use of opioids within the 12 months prior to first-line initiation, and route of administration. The reported OR and final model adjusted for the interaction of age and insurance (continuous) and age and insurance (categorical), time to diagnosis to 1L treatment, baseline ACPA (categorical), baseline CDAI (categorical) and csDMARD use within 12 months prior to first-line treatment.

[†]Includes patients with Medicaid, military coverage (e.g., Tricare/Veterans Affairs) and self-pay patients.

[‡]Baseline CDAI assessed within 3 months prior to/at initiation of first-line bDMARD, where remission/low disease activity is ≤ 10 , moderate disease activity is > 10 and ≤ 22 and high disease activity is > 22 [24].

[§]ACPA measured within 12-month period prior to/at initiation of first-line bDMARD, and value closest to initiation is reported (if more than one entered).

ACPA: Anticitrullinated protein antibody; bDMARD: Biologic disease-modifying antirheumatic drug; CDAI: Clinical disease activity index; CI: Confidence interval; csDMARD: Conventional synthetic disease-modifying antirheumatic drug; OR: Odds ratio; RA: Rheumatoid arthritis; TNFi: Tumor necrosis factor inhibitor.

Data from this figure were previously presented at ACR Convergence 2022; 10–14 November 2022; PA, USA (poster 1417).

course [15,29,32]. However, clinical practice guidelines also refer to bDMARDs as a class and provide minimal guidance on the optimal selection, sequence or combinations of treatments for different patient populations.

Clinical trial and real-world evidence suggest that abatacept demonstrates greater improvements in clinical response compared with TNFis in patients with poor prognostic features, including dual seropositivity, high baseline ACPA titer and moderate-to-high disease activity [22,23,34–39]. TNFis, in contrast, are more commonly selected as the first-line bDMARD and may be a suitable option for patients with lower disease activity, those with negative or unknown biomarkers or patients with fewer medical comorbidities [40]. In the present analysis, influence of prognostic factors on treatment selection revealed mixed results. There was greater likelihood of initiating abatacept over a TNFi among patients with poorer prognostic factors, including moderate/high disease activity and delayed treatment initiation, and patients who initiated abatacept as a first-line bDMARD were more likely to have extra-articular manifestations and comorbidities/chronic conditions. However, patients with ACPA+/RF+ RA and baseline ACPA levels > 250 AU/ml (versus 20–250 AU/ml) were less likely to initiate abatacept than a TNFi as a first-line bDMARD.

These data suggest that factors beyond patient characteristics and anticipated efficacy and safety – such as provider familiarity, insurance coverage and treatment adherence – have an influence on bDMARD selection. One of the most influential determinants of treatment choice, particularly for elderly patients, is insurance coverage. This can be a key deciding factor in the shared decision-making process [41]. In the US, persons aged ≥ 65 become eligible for one or more of four parts (A–D) of Medicare federal health insurance [42–44]. Because each Medicare part covers different services (inpatient versus outpatient services, drugs taken at home versus those received in clinic), the accessibility of abatacept versus TNFi to Medicare patients can depend on the type of Medicare coverage. In addition, insurance policies such as prior authorization and step therapy (or ‘fail first’) requirements in Medicare plans are prevalent, and these can also influence whether a TNFi or abatacept will be reimbursed as a first-line therapy [45]. Similarly, the joint US federal and state Medicaid insurance program for low-income individuals has prior authorization and ‘fail first’ step therapy requirements that influence the accessibility of abatacept versus TNFi [46]. Thus, societal factors (e.g., socioeconomic status) can play a key role in treatment choice. In patients with Medicare or Medicaid insurance, it may be that these requirements play a role in the prevalent access to TNFi as first-line biologic therapy (e.g., earlier in the course of disease) [47,48]. This aligns with the results of our analysis, which show that as patients increase in age, disease severity and treatment experience, abatacept becomes the first-line biologic of choice. Additional research is needed to understand the weight of these factors, for both patients and clinicians, in shared decision-making.

Limitations of this study include common inherent limitations of observational research studies and the potential introduction (by not accounting for all patient characteristics that may influence physician prescribing decisions) of unmeasured and residual confounding that cannot be accounted for in descriptive, univariate, multivariate, or subgroup analyses. The selection procedures for participating rheumatologists and patients potentially restrict the external generalizability of the results (data are not available to describe nonparticipating providers or nonselected patients). While this analysis included >500 patients across 28 rheumatology clinics, the purposive sampling used in this analysis meant that rheumatologists and patients were recruited based on prespecified criteria and therefore may not be representative of all patients with ACPA+/RF+ RA or of all rheumatologists, particularly outside of the US. As a medical chart review study, the accuracy and completeness of the data collected were limited by the quality of the data in the patient electronic medical records, and treatment adherence was not recorded. Selection bias (unequal probability of patient selection from all eligible charts), missing/incomplete data may also have occurred; however, selection bias was mitigated by advising rheumatologists to select all potentially eligible patients consecutively for chart abstraction. These data, while informative, reiterate the need to account for differences in patient demographic, clinical and treatment-related characteristics observed across treatment cohorts when assessing relative effectiveness of bDMARDs.

Strengths of this analysis include the retrospective medical chart review design, which provides in-depth data describing outcomes of treatment sequencing, including patient demographic and disease characteristics by using an efficient, reliable and verifiable method. The chart review approach allowed access to data contained in unstructured files in the patient electronic medical record (e.g., disease activity/response, clinical notes, radiologic assessments) and potentially, to contemporaneous data collection (as abstraction may occur using the patient’s most recent visit). Multiple clinically relevant data points were collected by treating rheumatologists. The data were abstracted by the patients’ treating rheumatologists, ensuring collection of high-quality data independent of assumptions by third-party abstractors.

Conclusion

In this real-world study of patients with ACPA+/RF+ RA, potential factors associated with greater odds of initiating abatacept as first-line bDMARD over a TNFi were identified. Patients with longer time (>2 years) from RA diagnosis, a higher burden of extra-articular manifestations and comorbidities, prescription of csDMARDs within 12 months, or moderate/high disease activity were more likely to initiate abatacept than a TNFi as a first-line bDMARD. An association between insurance status and increasing age was also observed. This analysis revealed a disconnect between evidence demonstrating increased benefit of abatacept treatment for patients with high ACPA levels at diagnosis and the observed lower likelihood of its use as first-line bDMARD. Results of this study underscore the need to understand better other potential drivers (e.g., tolerability, response and accessibility) behind associations observed between patient characteristics and first-line bDMARD treatment selection.

Summary points

- Rheumatoid arthritis (RA) is a chronic autoimmune disease that affects an estimated 1.3 million adults in the US and can be complicated by the presence of poor prognostic factors such as anticitrullinated protein antibodies (ACPA), rheumatoid factor (RF), extra-articular manifestations and comorbidities.
- Although treatment guidelines are available for RA, there is little guidance for the sequence of biologic disease-modifying antirheumatic drugs (bDMARDs) following conventional synthetic (cs) DMARD failure.
- This analysis aimed to compare demographic and clinical characteristics of patients with RA who were both ACPA+ and RF+ and initiated abatacept (n = 301) or a tumor necrosis factor inhibitor (TNFi) (n = 203) as a first-line bDMARD, and to identify factors associated with first-line bDMARD selection in the real-world setting.
- Analysis showed that initiation of abatacept as a first-line bDMARD (versus a TNFi) was significantly associated with older age at bDMARD initiation, having Medicare insurance coverage, being >2 years since RA diagnosis (all $p < 0.001$), and the presence of extra-articular manifestations and congestive heart failure ($p < 0.05$ for each).
- Additionally, a higher proportion of patients who initiated abatacept (versus a TNFi) had specific comorbidities: chronic obstructive pulmonary disease, Type 2 diabetes, mild liver disease and obesity.
- The odds of initiating abatacept (versus a TNFi) were greater among patients with >2 years from RA diagnosis (odds ratio [OR] 2.9), patients with a high clinical disease activity index (CDAI) score (OR 5.0), patients with a moderate CDAI score (OR 4.2) and patients who used csDMARDs within the 12 months prior to bDMARD initiation (OR 2.0).
- An association was also observed between insurance status and increasing age.
- These data underscore the need for consideration of many different prognostic factors by clinicians when discussing and deciding on a treatment pathway with their patients.
- Further analysis is required to understand potential drivers behind first-line bDMARD treatment selection for patients with ACPA+/RF+ RA fully.

Author contributions

G Lam, H Zheng, A Klink, V Patel, L N'Dri, K Wittstock, C Brown-Bickerstaff, V Khaychuk and B Feinberg were responsible for study conception and design of the analysis. P Asgarisabet, E Bland, C Brown-Bickerstaff, B Feinberg and A Klink were responsible for data acquisition. E Bland and P Asgarisabet were responsible for data analysis. G Lam, H Zheng, A Klink, V Patel, E Bland, L N'Dri, P Asgarisabet, C Brown-Bickerstaff, M Chaballa and B Feinberg were responsible for data interpretation. All authors were responsible for drafting the work or reviewing it critically for important intellectual content and final approval of the version to be published.

Acknowledgments

The authors thank the Cardinal Health Research Operations team for assistance with data acquisition and William John of Cardinal Health for assistance with early drafts of the manuscript.

Financial disclosure

This study was funded by Bristol Myers Squibb.

Competing interests disclosure

G Lam has received speaking and consulting fees from AbbVie, Bristol Myers Squibb, Cardinal Health, Janssen, Pfizer, Sanofi Genzyme, and UCB. H Zheng is a pre-doctoral fellow at Bristol Myers Squibb. A Klink is an employee of and owns equity stock in Cardinal Health. V Patel, L N'Dri, K Wittstock, M Chaballa and V Khaychuk are employees of and own equity stock in Bristol Myers Squibb. E Bland and P Asgarisabet are employees of Cardinal Health. C Brown-Bickerstaff was an employee of Cardinal Health at the time of the analysis and is currently employed at Ontada, Irving, TX, USA. B Feinberg has nothing to disclose. The authors have no other competing interests or relevant affiliations with any organization or entity with the subject matter or materials discussed in the manuscript apart from those disclosed.

Writing disclosure

Professional medical writing and editorial assistance was provided by Rachel Rankin at Caudex, a division of IPG Health Medical Communications, and was funded by Bristol Myers Squibb.

Ethical conduct of research

This study was conducted in accordance with International Society for Pharmacoepidemiology Guidelines for Good Epidemiology Practices, the Professional Society for Health Economics and Outcomes Research and the Strengthening the Reporting of Observa-

tional Studies in Epidemiology guidelines and the ethical principles in the Declaration of Helsinki. Rheumatologists were required to be able to participate in research monitored by a central institutional review board (IRB; 20204039). The protocol, amendments, eCRF and waiver of patient informed consent (due to the minimal amount of protected health information collected) received IRB approval from the Western Institutional Review Board.

Data sharing statement

All datasets on which the conclusions of the manuscript report are available on request.

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