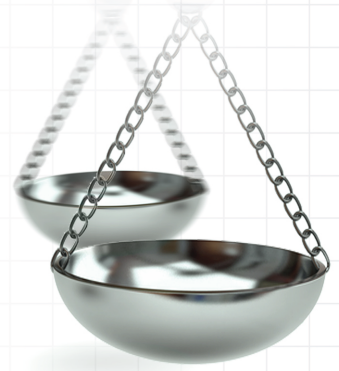




Real-world clinical outcomes and rationale for initiating abatacept as a first-line biologic for patients with anticitrullinated protein antibody- and rheumatoid factor-positive rheumatoid arthritis

Journal of **Comparative Effectiveness Research**

Alexandrina Balanean¹, Cherrishe Brown-Bickerstaff^{‡,1}, Andrew Klink¹ , Vardhaman Patel^{*,2} , Hanke Zheng² , Laetitia N'Dri², Keith Wittstock² , Bruce Feinberg¹ , Mark Chaballa², Vadim Khaychuk², Jill Kaufman¹, Prathamesh Pathak¹ & Gordon Lam³

¹ Cardinal Health, Dublin, OH 43017, USA

² Bristol Myers Squibb, Princeton, NJ 08540, USA

³ Arthritis & Osteoporosis Consultants of the Carolinas, Charlotte, NC 28207, USA

* Author for correspondence: Tel.: +1 609 302 3859; Vardhaman.Patel@bms.com

‡ At the time of analysis.

Aim: In rheumatoid arthritis (RA), seropositivity for both anticitrullinated protein antibody (ACPA) and rheumatoid factor (RF) is associated with disease severity and therapeutic response. Biologic (b) disease-modifying antirheumatic drugs (DMARDs) such as abatacept are recommended after inadequate response or contraindication to conventional synthetic DMARDs. This retrospective cohort study aimed to describe changes in Clinical Disease Activity Index (CDAI) measures over 12 months among patients with ACPA+ and RF+ RA with an inadequate response to methotrexate treated with abatacept as a first-line bDMARD. **Patients & methods:** Patient data were abstracted from medical records by treating rheumatologists. Analyses included McNemar tests for paired proportions or paired *t*-tests to assess longitudinal changes in CDAI scores, and Kaplan–Meier methods for time-to-event outcomes. Serious AEs and rationale for initiating treatment were recorded. **Results:** Overall, 296 patients were included. Mean CDAI scores improved (decreased) by 34.0, 61.0 and 74.0% (all *p* < 0.001) from baseline to 3–6 months, 6–12 months and ≥12 months after abatacept initiation, respectively. Of 279 patients not in CDAI low disease activity (LDA) or remission at baseline, 24.7% of patients achieved it within 6 months, 56.3% within 12 months and 71.0% at any point during follow-up after abatacept initiation. Median time to CDAI LDA/remission was 10.2 months. Serious AEs were reported in 2.4% of patients. Common reasons reported by rheumatologists for initiating abatacept were effectiveness/efficacy (52.7%), safety (31.4%) and patient preference (25.3%). **Conclusion:** In this analysis of patients with ACPA+ and RF+ RA treated with abatacept as a first-line bDMARD in a clinical practice setting, clinical outcomes and remission rates were improved at all time points, providing real-world evidence to further support the use of abatacept in this patient population.

First draft submitted: 14 March 2024; Accepted for publication: 15 October 2024; Published online: 18 November 2024

Keywords: abatacept • anticitrullinated protein antibody • first-line therapy • rheumatoid arthritis • rheumatoid factor

Rheumatoid arthritis (RA) is a chronic, systemic autoimmune disease characterized by inflammation and degeneration of joints and surrounding tissues that substantially reduces quality of life and can lead to early mortality [1–3]. The presence of anticitrullinated protein antibody (ACPA) and rheumatoid factor (RF) has been associated with worse prognosis, more aggressive and rapidly progressing disease, higher disease activity, lower rates of remission, higher prevalence of extra-articular manifestations and higher morbidity and mortality [4–12]. The prevalence of seropositivity, either double (ACPA+ and RF+) or single (defined as ACPA+ only, RF+ only, or undefined as

RF+ or ACPA+), among patients with RA ranges from 59 to 95%, depending on patient background, treatment status and serostatus [13–20].

RA requires early evaluation, diagnosis and treatment to prevent or minimize severe damage and functional disability [21,22]. Treatment typically involves glucocorticoids and disease-modifying antirheumatic drugs (DMARDs), initiating with a conventional synthetic (cs) DMARD [5,23]. If symptoms do not improve after 3–6 months, a different or additional csDMARD may be used; alternatively, a biologic (b) or targeted synthetic DMARD may be added to the initial treatment strategy [5,23].

The bDMARD abatacept is a selective co-stimulation modulator that disrupts the cycle of T-cell activation during the process of inflammation [24]. Abatacept has a long-established reputation of clinical efficacy and safety for the treatment of RA in a variety of patient populations [25–29], including those with ACPA+ and/or RF+ RA [8,13,15,16,30]. Several studies have demonstrated the efficacy of abatacept as a first-line bDMARD for RA [13,31,32]. For example, a large real-world analysis of patients with seropositive RA showed that first- or second-line abatacept led to improved drug survival compared with other bDMARDs [31]. Similarly, studies have demonstrated the efficacy of abatacept as a first-line bDMARD for patients with ACPA+ and/or RF+ RA [13,31,33,34]. One study found that abatacept was more effective as a first-line versus later-line bDMARD among patients with ACPA+ and RF+ RA than patients with ACPA- and RF- RA [13].

Rheumatologists' perceptions of available therapies and patient preferences are key to determining RA management strategies. Factors that may influence rheumatologist prescribing behaviors include (but are not limited to) patient characteristics and preferences, demands on consultation time, costs and funding arrangements, patient education and peer discussions [35,36]. Understanding patient needs and communicating effectively with patients may help break barriers to treatment adherence [37]. Further understanding of rationale for first-line treatment selection among US rheumatologists is needed to inform policy and guidelines related to treatment selection for patients with ACPA+ and RF+ RA.

The objectives of this study were to describe changes in Clinical Disease Activity Index (CDAI) measures over 12 months among patients with RA who were both ACPA+ and RF+ and were treated with abatacept as a first-line bDMARD, to report safety outcomes and to describe the rationale for initiating patients with ACPA+ and RF+ RA on abatacept as a first-line bDMARD.

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 after inadequate response to methotrexate (MTX). Eligible patients were identified by their treating rheumatologists in the Cardinal Health Rheumatology Provider Extended Network, which includes the Cornerstone Partners group purchasing organization (GPO) and other rheumatologists outside the GPO. In February 2021, Cornerstone represented approximately 1100 practices comprising 2300 rheumatologists across 48 US states. Purposive sampling was utilized to accumulate data for this study by treating rheumatologists at 27 practices across the USA.

An electronic case report form (eCRF) for collecting data relevant to this analysis was developed using a US Health Insurance Portability and Accountability Act-compliant eCRF, which was pre-tested by four rheumatologists. Twenty-seven rheumatologists selected a maximum of 20 consecutive patients each, starting with the earliest eligible, and completed an eCRF for each patient by abstracting relevant data from patients' electronic medical records (EMRs). 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).

Patient identification spanned from 1 January 2015 to 19 February 2020, which defined the index period for patients initiating abatacept as a first-line bDMARD (Figure 1). Data collection began on 19 February 2021 and ended on 15 April 2021. Patients were followed (but not necessarily treated) for a minimum of 1 year from the date of abatacept initiation. The end of follow-up was defined as the end of the study observation period/time of data collection, date of last visit or date of death, whichever occurred first.

Patient population

Eligible patients were aged ≥ 18 years with a confirmed diagnosis of RA; responded inadequately to MTX and subsequently initiated treatment with abatacept as a first-line bDMARD for RA between 1 January 2015 and 19 February 2020; were biologic- and Janus kinase inhibitor treatment-naïve; had ACPA+ and RF+ RA at or within

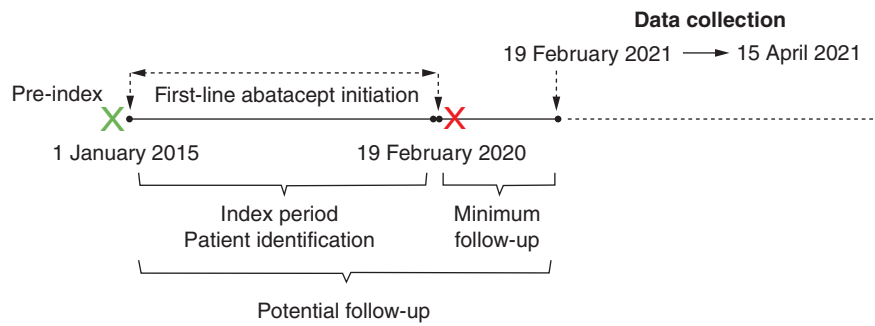


Figure 1. Abatacept as a first-line biologic disease-modifying antirheumatic drug for rheumatoid arthritis: patient identification, data collection and follow-up among treating rheumatologists.

12 months prior to initiation; and were followed (but not necessarily treated) by participating rheumatologists for ≥ 12 months after initiation of abatacept. Additionally, patients were required to have ≥ 1 CDAI score within 3 months prior to initiation (baseline) and ≥ 1 CDAI score within 3–6 months following initiation. Patients who were on abatacept for ≥ 12 months were also required to have ≥ 1 CDAI measurement between 6 and 12 months.

Patients were excluded if they had discontinued abatacept as a first-line bDMARD within 3 months of initiation; were treated with abatacept for RA in a clinical trial between 1 January 2015 and 19 February 2020; were pregnant during the study period; or had any of the following: history of cancer within 5 years prior to abatacept initiation; history of chronic hepatitis or severe chronic/recurrent bacterial or viral infection prior to initiation; diagnosis of other rheumatic disease at initiation; medical conditions contraindicated to tumor necrosis factor inhibitor agents at initiation; symptoms of severe, progressive or uncontrolled renal, hepatic, hematologic, gastrointestinal, pulmonary, cardiac, neurologic or cerebral disease; or active hepatitis, active bacterial or viral infection, active tuberculosis or risk of tuberculosis at initiation of abatacept.

Patient EMRs were not uniformly complete and data were analyzed according to the number of patients included in any particular outcome. To reduce bias, rheumatologists consecutively identified all potentially eligible patients for chart abstraction between 1 January 2015 and 19 February 2020. 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 (see Outcomes section).

Study conduct & ethical considerations

This study was conducted in accordance with accepted research practices described by the International Society for Pharmacoepidemiology [38], the Professional Society for Health Economics and Outcomes Research [39] and the Strengthening the Reporting of Observational Studies in Epidemiology guidelines [40] and maintained the ethical principles enacted by the Declaration of Helsinki [41]. Rheumatologists were required to be able to participate in research monitored by a central institutional review board (IRB; 20204039). The authors have obtained IRB approval from the Western Institutional Review Board for the research described, which consisted of protocol, eCRF and amendment review and included a waiver of patient informed consent due to the minimal amount of protected health information collected.

Outcomes

The primary outcomes were mean (standard deviation [SD] or 95% confidence interval [CI]) longitudinal change in CDAI and percent change from baseline at each study interval, percent achievement of and time to CDAI low disease activity (LDA) and/or remission (referred to hereafter as LDA/remission) and percent achievement of and time to CDAI remission alone (as defined below).

Secondary outcomes, recorded on the eCRF, were rates of serious adverse events (AEs) defined as grade 3 (serious, severe or medically significant but not immediately life-threatening, causes hospitalization or prolongation of hospitalization, disability, self-care activities of daily living limitation), grade 4 (life threatening, in need of urgent treatment) and grade 5 (death related). Additional secondary outcomes were treating rheumatologists' characteristics, reported rationale for initiating abatacept as a first-line bDMARD and for discontinuing abatacept, also reported on the eCRF.

CDAI measurements

CDAI is an overall continuous measure of disease activity using single-measure components (swollen joint count, tender joint count, physician global assessment and patient visual analog scale) [42]. Baseline CDAI scores and all subsequent CDAI measurements during abatacept therapy were recorded in the eCRF. The CDAI scores were interpreted as follows: remission, ≤ 2.8 ; LDA, > 2.8 and ≤ 10.0 ; moderate disease activity, > 10.0 to ≤ 22.0 ; and high disease activity, > 22.0 [43]. The composite outcome of LDA/remission (i.e., LDA or remission) was defined as a CDAI score of ≤ 10.0 .

Longitudinal CDAI assessment

CDAI scores were categorized into intervals for longitudinal analysis to include baseline (within 3 months prior to abatacept initiation: the baseline interval consisted of 98 days prior to abatacept initiation [up to 91 days prior plus 7-day grace period]), 3–6 months (days 85 to 182 after abatacept initiation [7-day grace period prior to day 92]), 6–12 months (days 183 to 371 after abatacept initiation [7-day grace period from day 364]) and ≥ 12 months (started at day 372) following abatacept initiation as a first-line bDMARD. The ± 7 -day grace periods accommodated variability in scheduling visits around the study intervals. Univariate and multivariable analyses were conducted using the cohort with outcomes at each study interval. A more detailed description of the CDAI measures in context of the study intervals is available in the Study Interval Context section of [Supplementary Materials](#).

Statistical analysis

Descriptive analyses of patients' demographic, clinical and treatment-related characteristics, as well as the rationale for initiating/discontinuing abatacept as a first-line bDMARD, were performed. Categorical study variables were reported using frequency counts and proportions. Continuous variables were described using measures of centrality (mean or median) and spread (minimum, maximum, SD or interquartile range [IQR], as appropriate). Median duration of abatacept use and time to LDA/remission and remission alone were assessed using the Kaplan–Meier (KM) method, accounting for right-censoring. Bivariate analyses were calculated using the McNemar test for paired proportions or paired *t*-test for paired numeric values to assess change in CDAI score across time intervals. CDAI LDA/remission and remission alone were assessed descriptively using frequency counts and proportions within 6 and 12 months of abatacept initiation as a first-line bDMARD and at any point during abatacept therapy. All analyses were conducted in SAS v9.4 (SAS Institute, USA), and 2-sided test *p*-values ≤ 0.05 were considered statistically significant.

Results**Patient population**

Overall, 296 patients were included in the study (Table 1), with a median follow-up of 21.8 months at the time of data collection. Patients had a maximum follow-up time of 73.2 months (mean [SD]: 26.5 [15.2]). Mean (SD) age at RA diagnosis was 51.7 (15.5) years and mean (SD) age at initiation of abatacept as a first-line bDMARD was 53.3 (15.6) years. Patients were predominantly female (71.3%), had commercial insurance coverage (55.1%) and most reported having never smoked (69.6%). All included patients were both ACPA+ and RF+, with ACPA levels ≥ 20 AU/ml in the 12 months prior to abatacept initiation (Table 2). During the study period a total of 58 patients discontinued treatment with abatacept, most frequently due to lack of efficacy (56.9%; $n/n = 33/58$).

The median (IQR) time from RA diagnosis to abatacept initiation was 8.1 (4.0–24.0) months. The majority of patients (56.4%) required prior insurance authorization to receive abatacept, which was administered intravenously in 59.5% of patients. At the time of data collection, 80.4% of patients were still receiving abatacept as a first-line bDMARD; as such, the KM median duration of abatacept was not reached (estimated survival probability for discontinuation did not fall below 50%).

CDAI assessments*Longitudinal CDAI assessment*

Compared with baseline, there were statistically significant decreases in CDAI scores across all study intervals assessed after initiation of abatacept as a first-line bDMARD (Table 3). From baseline to 3–6 months, the mean (SD) CDAI score improved (decreased) from 27.5 (12.8) to 17.8 (11.4) ($p < 0.001$), reflecting a mean (95% CI) decrease of 34.0% (-38.0 to -30.0). From baseline to 6–12 months, mean (SD) CDAI score improved from

Table 1. Cohort demographic overview.

Characteristic	n = 296
Age in years, mean (SD)	
At RA diagnosis	51.7 (15.5)
At first-line abatacept initiation	53.3 (15.6)
Race, n (%)	
White	204 (68.9)
Black/African-American	50 (16.9)
Asian	26 (8.8)
Native Hawaiian or other Pacific Islander	6 (2.0)
American Indian or Alaska Native	4 (1.4)
Unknown	6 (2.0)
Ethnicity, n (%)	
Non-Hispanic/non-Latino/non-Latina	240 (81.1)
Hispanic/Latino/Latina	55 (18.6)
Sex at birth, n (%)	
Female	211 (71.3)
Male	84 (28.4)
Unknown	1 (0.3)
BMI at abatacept initiation, mean (SD), kg/m ²	27.2 (5.7)
Smoking status at abatacept initiation, n (%)	
Never smoked	206 (69.6)
Former smoker	56 (18.9)
Current smoker	34 (11.5)
Payer [†] , n (%)	
Commercial	163 (55.1)
Medicare	110 (37.2)
Medicaid	21 (7.1)
Military	5 (1.7)
Self-pay	2 (0.7)
Other	1 (0.3)
Duration of follow-up (from initiation of abatacept as a first-line bDMARD), months	
Median (IQR)	21.8 (14.3–33.1)

[†]Not mutually exclusive.

bDMARD: Biologic disease-modifying antirheumatic drug; IQR: Interquartile range; RA: Rheumatoid arthritis; SD: Standard deviation.

27.5 (12.8) to 10.6 (8.3) ($p < 0.001$), reflecting a decrease (95% CI) of 61.0% (-64.6 to -57.4). From baseline to ≥ 12 months, mean (SD) CDAI score improved from 27.5 (12.8) to 7.2 (7.6) ($p < 0.001$), corresponding to a decrease (95% CI) of 74.0% (-77.9 to -70.1).

CDAI LDA/remission

Of the 279 patients not in LDA/remission at baseline, 69 (24.7%) and 157 (56.3%) achieved the composite outcome of LDA/remission within 6 and 12 months of initiating abatacept as a first-line bDMARD, respectively (Table 4 & Figure 2). Additionally, 198 patients (71.0%) achieved CDAI LDA/remission at any time during abatacept therapy. The KM median (95% CI) time to CDAI LDA/remission was 10.2 (9.0–11.1) months. Supplementary Figure 1 shows the proportion of patients with CDAI remission alone over time during abatacept therapy as a first-line bDMARD.

Serious AEs reported during treatment with abatacept as a first-line bDMARD

Overall, 7 patients (2.4%) reported grade 3 serious AEs and no patients reported grade 4 or 5 serious AEs (Table 2).

Table 2. Cohort clinical and treatment overview.

Diagnostic characteristics	n = 296
ACPA+ and RF+ within 12 months prior to initiating abatacept as a first-line bDMARD, n (%) [†]	296 (100.0)
ACPA level within the 12 months prior to initiating abatacept as a first-line bDMARD ^{†,‡}	
≥20 AU/ml	296 (100.0)
>60 AU/ml	225 (76.0)
>250 AU/ml	78 (26.4)
Serum biomarker levels within 3 months prior to initiating abatacept as a first-line bDMARD, mean (SD) [‡]	
CRP, mg/dl (n = 215 [72.6%])	14.3 (14.9)
ESR, mm/hour (n = 207 [69.9%])	54.1 (24.3)
Clinical characteristics and comorbidities at initiation of abatacept as a first-line bDMARD, [‡] n (%)	
Extra-articular manifestations (within 1 month prior to or at initiation)	141 (47.6)
Type 2 diabetes [§]	39 (13.2)
Chronic obstructive pulmonary disease [§]	9 (3.0)
Congestive heart failure [§]	7 (2.4)
Type 1 diabetes [§]	4 (1.4)
Time to treatment	
Months from RA diagnosis to first-line abatacept initiation, median (IQR)	8.1 (4.0–24.0)
Medication use at baseline (within 12 months prior to/at initiation of abatacept as a first-line bDMARD), n (%) ^{†,¶}	
NSAIDs	172 (58.1)
csDMARDs [#]	134 (45.3)
Opioid/narcotic analgesics	31 (10.5)
Corticosteroids	
No	233 (78.7)
Yes	49 (16.6)
Unknown	14 (4.7)
During first-line abatacept therapy, n (%) ^{††}	
Concomitant use of MTX	194 (65.5)
Prior authorization required for initiation of abatacept as a first-line bDMARD, n (%)	167 (56.4)
Abatacept route of administration, n (%) [‡]	
Intravenous infusion	176 (59.5)
Subcutaneous (auto-injector)	98 (33.1)
Subcutaneous (prefilled syringe)	28 (9.5)
Serious AEs reported during routine clinical practice captured in study period, n (%) [‡]	
Grade 3	7 (2.4)
Grade 4	0 (0.0)
Grade 5	0 (0.0)
Patient status at final follow-up, n (%) ^{‡‡}	
In active therapy with first-line abatacept	238 (80.4)
In active therapy with bDMARD, JAK inhibitor or IL-6 inhibitor	45 (15.2)
Alive with RA, receiving supportive care only or not in active therapy	9 (3.0)
Unknown, lost to follow-up	3 (1.0)
Other (on rituximab)	1 (0.3)

[†] ACPA and RF measured within 12-month study interval prior to or at initiation of abatacept as a first-line bDMARD, and mean value of each closest to initiation is reported (if more than 1 was entered); RF/ACPA if measured within 3 months of abatacept initiation.

[‡] Not mutually exclusive.

[§] Comprehensive of the CCI and additionally reports diabetes mellitus by type, hemiplegia and obesity.

[¶] Use reported at time of initiation of abatacept as a first-line bDMARD or anytime during the 12-month study interval prior to initiation.

[#] Other than MTX; patients may have reported more than 1 csDMARD at baseline: 134 patients reported 159 instances of csDMARD use.

^{††} Patients may have been followed (but not necessarily treated) by participating rheumatologist for ≥12 months after initiating abatacept as a first-line bDMARD.

^{‡‡} Patients may have been followed (but not necessarily treated) by participating rheumatologist for ≥12 months after initiating abatacept as a first-line bDMARD.

ACPA: Anticitrullinated protein antibody; AE: Adverse event; bDMARD: Biologic disease-modifying antirheumatic drug; CCI: Charlson Comorbidity Index; CRP: C-reactive protein; csDMARD: Conventional synthetic disease-modifying antirheumatic drug; ESR: Erythrocyte sedimentation rate; IL: Interleukin; IQR: Interquartile range; JAK: Janus kinase; MTX: Methotrexate; NSAID: Nonsteroidal anti-inflammatory drug; RA: Rheumatoid arthritis; RF: Rheumatoid factor; SD: Standard deviation.

Table 3. Mean CDAI scores and changes from baseline at 3–6, 6–12 and ≥ 12 months of initiating abatacept as a first-line bDMARD (n = 296).

Patients with CDAI value, n	Baseline (n = 296)	3–6 months after abatacept initiation (n = 243)	6–12 months after abatacept initiation (n = 227)	≥ 12 months after abatacept initiation (n = 142)
CDAI, mean (SD)	27.5 (12.8)	17.8 (11.4)	10.6 (8.3)	7.2 (7.6)
Absolute change from baseline, mean (95% CI)	-	-10.5 (-12.0 to -9.0)	-17.9 (-19.5 to -16.3)	-21.3 (-22.9 to -19.7)
Percent change from baseline, mean (95% CI) [†]	-	-34.0 (-38.0 to -30.0)	-61.0 (-64.6 to -57.4)	-74.0 (-77.9 to -70.1)

p < 0.001 for all timepoints. p-values were calculated for each time interval vs baseline: p-value calculated using McNemar test for paired proportions or paired t-test for paired numeric values.

[†] A negative percent change from baseline (i.e., a decrease) indicates improvement.

CDAI: Clinical Disease Activity Index; CI: Confidence interval; SD: Standard deviation.

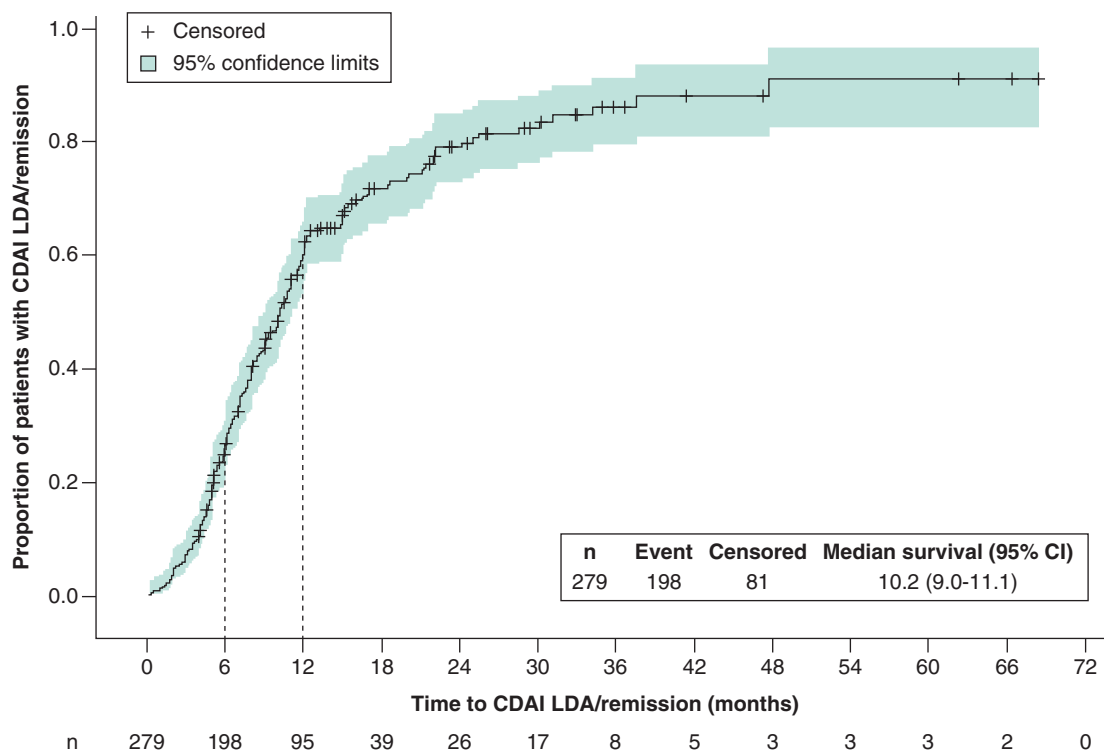
Table 4. Rates of and time to CDAI LDA or remission (LDA/remission) during treatment with abatacept as a first-line bDMARD.

CDAI LDA or remission rate, n (%)	n = 296
Patients not in LDA/remission at baseline (total)	279 (94.3)
Achieving LDA/remission within 6 months of initiation [†]	69 (24.7)
Achieving LDA/remission within 12 months of initiation [†]	157 (56.3)
Achieving LDA/remission any time during abatacept therapy as a first-line bDMARD [†]	198 (71.0)
Time to CDAI LDA or remission	
Months to LDA/remission, median (95% CI)	10.2 (9.0–11.1)

CDAI is calculated from single-measure components (swollen joint count, total joint count, physician global assessment and patient visual analog scale) into overall continuous measure of disease activity. CDAI LDA and/or remission: CDAI ≤ 10 .

[†] Presented as a proportion of the patients not in LDA and/or remission at baseline (n = 279).

CDAI: Clinical Disease Activity Index; CI: Confidence interval; LDA: Low disease activity.

**Figure 2. Time to Clinical Disease Activity Index low disease activity and/or remission (low disease activity/remission) during treatment with abatacept as a first-line biologic disease-modifying antirheumatic drug.**

CDAI LDA/remission: CDAI ≤ 10 . n = 279 (patients not in LDA and/or remission at baseline).

CDAI: Clinical Disease Activity Index; CI: Confidence interval; LDA: Low disease activity.

Table 5. Rationale for initiating abatacept as a first-line bDMARD versus other RA therapy.

Reason(s) reported by treating rheumatologists for initiating abatacept as a first-line bDMARD vs TNF, JAK or IL-6 inhibitor therapy, n (%) [†]	n = 296
Effectiveness/efficacy based on prior experience/research studies	156 (52.7)
Safety profile	93 (31.4)
Patient preference	75 (25.3)
Insurance	68 (23.0)
Infusion schedule/dosing	58 (19.6)
Contraindications of other medications	20 (6.8)
Comorbidities for which abatacept may be amenable (e.g., seropositive RA and psoriatic arthritis overlap)	18 (6.1)
Practice/hospital protocol	4 (1.4)
Other (total) [‡]	13 (4.4)

[†]Not mutually exclusive.

[‡]Other reasons included: n = 3 ACPA/RF positivity; n = 2 Sjögren syndrome (anti-TNF contraindication); n = 1 for each of remote history of histoplasmosis treatment, episode of congestive heart failure, brain lesions, RA and myositis, no box warning, wanted to discontinue methotrexate and optic neuritis (anti-TNF contraindication).

ACPA: Anticitrullinated protein antibody; bDMARD: Biologic disease-modifying antirheumatic drug; IL: Interleukin; JAK: Janus kinase; RA: Rheumatoid arthritis; RF: Rheumatoid factor; TNF: Tumor necrosis factor.

Table 6. Rationale for discontinuing abatacept initiated as a first-line bDMARD.

Reason(s) reported for discontinuing abatacept therapy [†]	n = 58
Lack of effectiveness	33 (56.9)
Patient preference	12 (20.7)
Insurance/financial issues	9 (15.5)
Adverse event/toxicity	8 (13.8)
Other (lost to follow-up)	1 (1.7)

[†]Not mutually exclusive.

Rheumatologist characteristics

Of the 27 treating rheumatologists, the largest proportion (37.0%) worked in large private community practice settings of ≥10 physicians, 22.2% worked in small private community practice settings of two to five physicians and 22.2% were solo practitioners (Supplementary Table 1). Participating rheumatologists had a mean (SD) of 15.0 (6.8) years in practice. Most of the 296 patients (94.3%) had been managed solely by the participating rheumatologists. Further details of the rheumatologists included in this analysis can be found in the Supplementary Results.

Rationale for initiating abatacept as a first-line bDMARD & patient discontinuations

The most common reason reported by the treating rheumatologists for initiating abatacept, instead of another therapy, as a first-line bDMARD was effectiveness/efficacy based on prior experience/research studies (52.7%; Table 5). Other common reasons included safety profile (31.4%) and patient preference (25.3%).

Of the 58 patients who discontinued first-line abatacept, lack of effectiveness (56.9%), patient preference (20.7%) and insurance/financial issues (15.5%) were among the reasons reported (Table 6).

Discussion

In this retrospective cohort study, a statistically significant and clinically meaningful decrease in CDAI disease activity was observed over 12 months in patients with ACPA+ and RF+ RA who were treated with abatacept as a first-line bDMARD after an inadequate response to MTX. A high proportion of patients (71%) who were not in CDAI LDA/remission at baseline achieved this status during the study period. The rate of serious AE occurrence reported during the study was low, which may have contributed to the low abatacept discontinuation rate. Patients with poor prognostic factors, such as ACPA and/or RF seropositivity, require early treatment to help minimize joint inflammation and damage, functional disability and disease progression [5,21,23]. The findings from the present study demonstrate that rheumatologists were primarily concerned with effectiveness and safety when making treatment decisions, and indicate that abatacept has therapeutic benefit and an acceptable safety profile in patients with ACPA+ and RF+ RA. The favorable outcomes (reduction in CDAI from baseline and achievement

of LDA and/or remission) for patients with ACPA+ and RF+ RA treated with abatacept as a first-line bDMARD reported in the present study concur with and strengthen the previous literature on this topic [8,13,15,32,44,45].

One important aspect of RA management is supporting patients so they remain on treatment. The many factors requiring consideration when selecting an appropriate treatment for individual patients can be problematic. However, initiating the right treatment at the right time can prevent discontinuation and treatment swapping, which in turn can improve outcomes and patient quality of life. Our analysis has demonstrated a high rate of patients with ACPA+ and RF+ RA remaining on abatacept (80%) at the time of data collection (minimum treatment period of 1 year). This is supported by previous studies that have shown high retention rates of abatacept as a first-line bDMARD, ranging from 52% to 75% [13,15,31,32,46,47].

The majority of patients who switch to an alternative treatment do so due to inefficacy, side effects or contraindications with other drugs/patient circumstances (for example, pregnancy) [5,23,48]. Serostatus is one factor that may affect treatment retention. Although our study did not compare clinical outcomes among patients with seropositive RA versus those with seronegative RA, we have shown that clinical outcomes (CDAI scores and proportions of patients in LDA/remission) were significantly improved over time, up to 12 months from baseline, with first-line abatacept in patients with ACPA+ and RF+ RA. Previous studies that have compared different serostatuses and abatacept treatment status have shown patients with ACPA and/or RF seropositive RA to have significantly improved outcomes versus patients with seronegative RA [13,16,49,50]. Of particular note is the large pan-European analysis of 9 observational registries across Europe, encompassing almost 3000 patients with ACPA+ and/or RF+ RA treated with abatacept. The multi-registry analysis showed that the presence of ACPA and RF were each individually associated with a lower risk of abatacept discontinuation and may be associated with better effectiveness of abatacept for RA outcomes [51]. Additionally, several studies have shown significantly improved outcomes when abatacept was administered as a first-line treatment [13,32,44,47]. A multicenter, observational study of >200 patients with RA demonstrated that patients experienced reduced disease activity irrespective of bDMARD received [32]. The study also demonstrated the movement of patients through different lines of therapy. Patients who received first-line bDMARDs such as etanercept, adalimumab or rituximab were more likely to switch to a further line of treatment than patients who received first-line abatacept [32]. Furthermore, patients who received abatacept as a first-line therapy spent significantly longer on treatment compared with patients who received other bDMARDs [32]. A large (n >8000), real-world cohort study of patients with seropositive RA showed that treatment with tocilizumab, tofacitinib or abatacept as first- or second-line therapy may have better drug retention versus treatment with other bDMARDs (including TNFis) [31]. An exploratory analysis of the Abatacept versus Adalimumab Comparison in Biologic-Naive RA Subjects with Background Methotrexate (AMPLE) phase IIIb randomized trial demonstrated that both abatacept and adalimumab were more effective in patients who were positive for anti-cyclic citrullinated peptide-2 (anti-CCP2, the diagnostic test for assessing ACPA levels) at baseline than those who were anti-CCP2-negative at baseline [8]. Recently, Michaud *et al.* conducted an analysis on pooled data from the AMPLE, Abatacept study to Gauge Remission and joint damage progression in methotrexate-naïve patients with Early Erosive RA (AGREE), Assessing Very Early Rheumatoid arthritis Treatment (AVERT) and AVERT-2 clinical trials. The authors demonstrated the differential effect of abatacept (versus MTX or adalimumab) among patients with ACPA and RF seropositive, early and active RA and concluded that ACPA and RF seropositivity has potential utility to guide treatment selection [52].

Pathways for future research may include further investigation into the mechanism of action of abatacept in patients with ACPA+ and RF+ RA to support current literature on the processes involved with ACPA and RF protein binding [53–59]. Additionally, further investigation into the longitudinal assessment of ACPA levels in patients with ACPA+ and RF+ RA to identify ACPA level variations and possible correlations with RF levels in disease response during first and later lines of therapy may provide additional information for clinicians [14,60]. Additionally, comparison of abatacept as a first-line bDMARD with other bDMARDs will be investigated in future analyses.

Due to the heterogeneity of RA in disease presentation, progression and response, the American College of Rheumatology and the European Alliance of Associations for Rheumatology recognize that varying treatment approaches may be required and modified throughout the therapeutic course [5,23]. Curating high-quality, real-world data and making them accessible to researchers and clinicians will inform better hypotheses, study designs, drug discovery and development, clinical practice and post-marketing surveillance for the treat-to-target approach in managing RA. The present study shows that rheumatologists consider effectiveness/efficacy, prior experience,

research studies, safety and patient preference when determining treatment options for patients with ACPA+ and RF+ RA.

There are several strengths to this analysis. These data were collected from patients treated by rheumatologists that represent >1000 practices across 48 US states. Chart review studies leveraging EMR data are well suited for describing outcomes of treatment sequencing (e.g., using abatacept in the first-line as opposed to the second-line or later setting). These clinical parameters are important for elucidating patient journeys, especially in targeted and precision medicine. Additionally, the rheumatologists participating in this study benefited from access to data contained in unstructured fields of patients' EMRs (e.g., disease activity/response reporting and clinical notes from interdisciplinary care teams). To avoid biases that may have arisen from single-site or single-source data sets, our study data were gathered from unique sites and providers irrespective of EMR platform, health system or GPO. Finally, the data were abstracted by the patients' rheumatologists, enabling collection of high-quality data independent of third-party abstractors' assumptions.

This analysis is not without limitations. Firstly, the purposive sampling methodology used in this study was intended to select rheumatologists and patients based on prespecified criteria; as such, our findings may not represent all patients with ACPA+ and RF+ RA or all rheumatologists. The current analysis did not include any comparison with other treatment strategies, therefore the relative effectiveness of abatacept could not be assessed – this will be the focus of a future study. One of the inclusion criteria was that patients were required to have been followed by participating rheumatologists for ≥ 12 months after initiation of abatacept; it is possible that had patients not been followed for ≥ 12 months they may have had a lower response rate compared with those that had been followed for ≥ 12 months. Moreover, selection bias (unequal probability of patient selection from all eligible patients), bias associated with missing or incomplete data, and unmeasured confounding cannot fully be accounted for in statistical analysis, due to not being able to include all patient characteristics with potentially prognostic significance or those that may influence physician prescribing behavior and treatment decisions. Selection bias was mitigated by rheumatologists selecting all potentially eligible patients for chart abstraction consecutively, and unmeasured confounding was minimized by the collection of numerous data points that were of clinical relevance to patient treatment patterns. Additional outcomes such as physical functioning and radiographic progression, which could provide further important data regarding the course of RA disease over time, are not routinely collected in this patient population and therefore were not feasible to include in this retrospective cohort study. 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 EMRs. Data relating to AEs should be interpreted with caution due to patients who discontinued abatacept within 3 months of initiation being excluded from the analysis. Additionally, as AEs often occur outside of the clinical practice setting, they may be underreported compared with clinical trials or prospective observational studies (particularly those of grade 2 or lower if medical intervention is not required). The AEs assessed in this study were reported as part of routine clinical practice and were grade 3 or higher; because these AEs were more likely to result in a clinic or emergency visit than less serious AEs, higher-grade AEs were more likely to be captured in the EMR.

Conclusion

Real-world effectiveness and safety data from this study further support the efficacy and safety of abatacept, with a high overall rate of CDAI LDA/remission observed. Findings suggest that patients with ACPA+ and RF+ RA may benefit from treatment with abatacept as a first-line bDMARD in routine clinical practice. Our work contributes to a more comprehensive understanding of the patient journey and decision-making in patients with ACPA+ and RF+ RA treated with abatacept and may illuminate pathways for decisions to optimize patient care and outcomes.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: <https://bpl-prod.literatumonline.com/doi/10.57264/cer-2023-0144>

Author contributions

A Balanean, A Klink, V Patel, H Zheng, K Wittstock, B Feinberg, V Khaychuk and G Lam were responsible for study conception and design and drafting and revision of the manuscript. J Kaufman was responsible for data acquisition. A Balanean, C Brown-Bickerstaff, A Klink and P Pathak were responsible for data analysis. A Balanean, C Brown-Bickerstaff, A Klink, V Patel, H Zheng, L N'Dri, B Feinberg, M Chaballa, J Kaufman, P Pathak and G Lam 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.

Financial disclosure

This study was funded by Bristol Myers Squibb. A Balanean is an employee of Cardinal Health. C Brown-Bickerstaff was an employee of Cardinal Health at the time of the analysis and is currently employed at Ontada, TX, USA. 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. H Zheng is a pre-doctoral fellow at Bristol Myers Squibb. G Lam received speaking and consulting fees from Cardinal Health, Bristol Myers Squibb, AbbVie, Janssen, UCB, Pfizer and Sanofi Genzyme. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Competing interests disclosure

The authors have no competing interests or relevant affiliations with any organization or entity with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Writing disclosure

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

Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations.

Data sharing statement

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

Open access

This work is licensed under the Attribution-NonCommercial-NoDerivatives 4.0 Unported License. To view a copy of this license, visit <https://creativecommons.org/licenses/by-nc-nd/4.0/>

Summary points

- Seropositivity for rheumatoid factor (RF) and anticitrullinated protein antibody (ACPA) in patients with rheumatoid arthritis (RA) has been associated with worse prognosis, more aggressive and rapidly progressing disease, higher disease activity, lower remission rates, higher prevalence of extra-articular manifestations and higher mortality.
- This analysis aimed to record changes in Clinical Disease Activity Index (CDAI) measures over time among patients with ACPA+ and RF+ RA treated with abatacept as a first-line biologic disease-modifying antirheumatic drug (bDMARD), and to report rates of serious adverse events, rheumatologists' treatment rationale for initiating abatacept as a first-line bDMARD and reasons for discontinuation.
- In this real-world analysis of 296 patients with ACPA+ and RF+ RA treated with abatacept as a first-line bDMARD, there were statistically significant improvements in mean CDAI scores over time: 34% decrease at 3–6 months, 61% decrease at 6–12 months and 74% decrease at ≥ 12 months after initiation of abatacept (all $p < 0.001$).
- Approximately 25% and 56% of patients achieved a combined outcome of LDA and/or remission within 6 and 12 months, respectively, of initiating abatacept as a first-line bDMARD; 71% achieved this at any point during therapy.
- The safety profile of abatacept aligned with previous studies, with no new safety signals identified.
- Rheumatologists' most common reasons for initiating patients on abatacept as a first-line bDMARD were effectiveness/efficacy, safety and patient preference; lack of effectiveness was the most common reason for abatacept discontinuation.
- The improvement in clinical outcomes found in this group of patients with ACPA+ and RF+ RA treated with abatacept as a first-line bDMARD provides real-world effectiveness data to support the clinical trial efficacy of abatacept and its use in clinical practice.

References

Papers of special note have been highlighted as: ● of interest; ●● of considerable interest

1. Kay J, Upchurch KS. ACR/EULAR 2010 rheumatoid arthritis classification criteria. *Rheumatology* 51(Suppl. 6), vi5–vi9 (2012).
2. Ding Q, Hu W, Wang R et al. Signaling pathways in rheumatoid arthritis: implications for targeted therapy. *Signal Transduct. Target. Ther.* 8(1), 68 (2023).
3. Dadoun S, Zeboulon-Ktorza N, Combescure C et al. Mortality in rheumatoid arthritis over the last fifty years: systematic review and meta-analysis. *Joint Bone Spine* 80(1), 29–33 (2013).
4. Aletaha D, Neogi T, Silman AJ et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Arthritis Rheum.* 62(9), 2569–2581 (2010).
5. Smolen JS, Landewe RBM, Bijlsma JWJ et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update. *Ann. Rheum. Dis.* 79(6), 685–699 (2020).
6. Van Der Helm-Van Mil AHM, Verpoort KN, Breedveld FC, Toes RE, Huizinga TW. Antibodies to citrullinated proteins and differences in clinical progression of rheumatoid arthritis. *Arthritis Res. Ther.* 7(5), R949–958 (2005).
7. Hecht C, Englbrecht M, Rech J et al. Additive effect of anti-citrullinated protein antibodies and rheumatoid factor on bone erosions in patients with RA. *Ann. Rheum. Dis.* 74(12), 2151–2156 (2015).
8. Sokolove J, Schiff M, Fleischmann R et al. Impact of baseline anti-cyclic citrullinated peptide-2 antibody concentration on efficacy outcomes following treatment with subcutaneous abatacept or adalimumab: 2-year results from the AMPLE trial. *Ann. Rheum. Dis.* 75(4), 709–714 (2016).
9. Katchamart W, Koolvisoot A, Aromdee E, Chiowchanwesawakit P, Muengchan C. Associations of rheumatoid factor and anti-citrullinated peptide antibody with disease progression and treatment outcomes in patients with rheumatoid arthritis. *Rheumatol. Int.* 35(10), 1693–1699 (2015).
10. Humphreys JH, Van Nies JaB, Chipping J et al. Rheumatoid factor and anti-citrullinated protein antibody positivity, but not level, are associated with increased mortality in patients with rheumatoid arthritis: results from two large independent cohorts. *Arthritis Res. Ther.* 16(6), 483 (2014).
- **Compared with single-positive or seronegative status, seropositivity for both anticitrullinated protein antibody (ACPA) and rheumatoid factor (RF) – but not their level – has been associated with increased mortality in early inflammatory rheumatoid arthritis (RA).**
11. Ajeganova S, Humphreys JH, Verheul MK et al. Anticitrullinated protein antibodies and rheumatoid factor are associated with increased mortality but with different causes of death in patients with rheumatoid arthritis: a longitudinal study in three European cohorts. *Ann. Rheum. Dis.* 75(11), 1924–1932 (2016).
12. Bonfiglioli KR, De Medeiros Ribeiro AC, Carneletto AP et al. Extra-articular manifestations of rheumatoid arthritis remain a major challenge: data from a large, multi-centric cohort. *Adv. Rheumatol.* 63(1), 34 (2023).
13. Alten R, Mariette X, Flipo RM et al. Retention of subcutaneous abatacept for the treatment of rheumatoid arthritis: real-world results from the ASCORE study: an international 2-year observational study. *Clin. Rheumatol.* 41(8), 2361–2373 (2022).
14. Harrold LR, Bryson J, Lehman T et al. Association between baseline anti-cyclic citrullinated peptide antibodies and 6-month clinical response following abatacept or TNF inhibitor treatment: a real-world analysis of biologic-experienced patients with RA. *Rheumatol. Ther.* 8(2), 937–953 (2021).
15. Alten R, Mariette X, Lorenz HM et al. Predictors of abatacept retention over 2 years in patients with rheumatoid arthritis: results from the real-world ACTION study. *Clin. Rheumatol.* doi:10.1007/s10067-019-04449-w (2019).
16. Harrold LR, Litman HJ, Connolly SE et al. Effect of anticitrullinated protein antibody status on response to abatacept or antitumor necrosis factor- α therapy in patients with rheumatoid arthritis: a US national observational study. *J. Rheumatol.* 45(1), 32–39 (2018).
17. Tymms K, Butcher B, Smith T, Littlejohn G. Impact of anti-citrullinated protein antibody on tumor necrosis factor inhibitor or abatacept response in patients with rheumatoid arthritis. *Eur. J. Rheumatol.* 8(2), 67–72 (2020).
18. Courvoisier DS, Chatzidionysiou K, Mongin D et al. The impact of seropositivity on the effectiveness of biologic anti-rheumatic agents: results from a collaboration of 16 registries. *Rheumatology (Oxford)* 60(2), 820–828 (2021).
19. Emery P, Gottenberg JE, Rubbert-Roth A et al. Rituximab versus an alternative TNF inhibitor in patients with rheumatoid arthritis who failed to respond to a single previous TNF inhibitor: SWITCH-RA, a global, observational, comparative effectiveness study. *Ann. Rheum. Dis.* 74(6), 979–984 (2015).
20. Kekow J, Mueller-Ladner U, Schulze-Koops H. Rituximab is more effective than second anti-TNF therapy in rheumatoid arthritis patients and previous TNF α blocker failure. *Biologics* 6, 191–199 (2012).
21. Burgers LE, Raza K, Van Der Helm-Van Mil AH. Window of opportunity in rheumatoid arthritis - definitions and supporting evidence: from old to new perspectives. *RMD Open* 5(1), e000870 (2019).
22. Combe B, Landewe R, Daien CI et al. 2016 update of the EULAR recommendations for the management of early arthritis. *Ann. Rheum. Dis.* 76(6), 948–959 (2016).

23. Fraenkel L, Bathon JM, England BR *et al.* 2021 American College of Rheumatology guideline for the treatment of rheumatoid arthritis. *Arthritis Rheumatol.* 73(7), 1108–1123 (2021).
24. Malmstrom V, Catrina AI, Klareskog L. The immunopathogenesis of seropositive rheumatoid arthritis: from triggering to targeting. *Nat. Rev. Immunol.* 17(1), 60–75 (2017).
25. Schiff M, Weinblatt ME, Valente R *et al.* Head-to-head comparison of subcutaneous abatacept versus adalimumab for rheumatoid arthritis: two-year efficacy and safety findings from AMPLE trial. *Ann. Rheum. Dis.* 73(1), 86–94 (2014).
26. Schiff M, Keiserman M, Coddling C *et al.* Efficacy and safety of abatacept or infliximab vs placebo in ATTEST: a phase III, multi-centre, randomised, double-blind, placebo-controlled study in patients with rheumatoid arthritis and an inadequate response to methotrexate. *Ann. Rheum. Dis.* 67(8), 1096–1103 (2008).
27. Genovese MC, Covarrubias A, Leon G *et al.* Subcutaneous abatacept versus intravenous abatacept: a phase IIIb noninferiority study in patients with an inadequate response to methotrexate. *Arthritis Rheumatol.* 63(10), 2854–2864 (2011).
28. Genovese MC, Schiff M, Luggen M *et al.* Efficacy and safety of the selective co-stimulation modulator abatacept following 2 years of treatment in patients with rheumatoid arthritis and an inadequate response to anti-tumour necrosis factor therapy. *Ann. Rheum. Dis.* 67(4), 547–554 (2008).
29. Westhovens R, Kremer J, Emery P *et al.* Long-term safety and efficacy of abatacept in patients with rheumatoid arthritis and an inadequate response to methotrexate: a 7-year extended study. *Clin. Exp. Rheumatol.* 32, 553–562 (2014).
- **In methotrexate methotrexate (MTX)-naïve patients with high-risk early RA, combination therapy with MTX and abatacept had higher clinical and radiographic efficacy compared with MTX alone and had a comparably favorable safety profile.**
30. Emery P, Burmester GR, Bykerk VP *et al.* Evaluating drug-free remission with abatacept in early rheumatoid arthritis: results from the phase 3b, multicentre, randomised, active-controlled AVERT study of 24 months, with a 12-month, double-blind treatment period. *Ann. Rheum. Dis.* 74(1), 19–26 (2015).
31. Choi S, Ghang B, Jeong S *et al.* Association of first, second, and third-line bDMARDs and tsDMARD with drug survival among seropositive rheumatoid arthritis patients: cohort study in A real world setting. *Semin. Arthritis Rheum.* 51(4), 685–691 (2021).
- **Patients with seropositive RA who received tocilizumab, tofacitinib, or abatacept as first- or second-line therapies had lower risk of drug failure risk compared with other DMARDs.**
32. Choy E, Groves L, Sugrue D *et al.* Outcomes in rheumatoid arthritis patients treated with abatacept: a UK multi-centre observational study. *BMC Rheumatol.* 5(1), 3 (2021).
- **Patients treated with biologic disease-modifying antirheumatic drugs (bDMARDs) including abatacept had decreased disease activity, and those treated with abatacept in the first- or second-line setting remained on treatment significantly longer versus those receiving other bDMARDs.**
33. Jansen DTSL, Emery P, Smolen JS *et al.* Conversion to seronegative status after abatacept treatment in patients with early and poor prognostic rheumatoid arthritis is associated with better radiographic outcomes and sustained remission: *post hoc* analysis of the AGREE study. *RMD Open* 4(1), e000564 (2018).
34. Han X, Lobo F, Broder MS *et al.* Persistence with early-line abatacept versus tumor necrosis factor-inhibitors for rheumatoid arthritis complicated by poor prognostic factors. *J. Health Econ. Outcomes Res.* 8(1), 71–78 (2021).
35. Lalor AF, Brooker JE, Rozbroj T *et al.* Factors influencing clinician prescribing of disease-modifying anti-rheumatic drugs for inflammatory arthritis: a systematic review and thematic synthesis of qualitative studies. *Semin. Arthritis Rheum.* 55, 151988 (2022).
36. Roodenrijs NMT, Van Der Goes MC, Welsing PMJ *et al.* Non-adherence in difficult-to-treat rheumatoid arthritis from the perspectives of patients and rheumatologists: a concept mapping study. *Rheumatology (Oxford)* 60(11), 5105–5116 (2021).
37. Voshaar MJH, Van Den Bemt BJF, Van De Laar M, Van Dulmen AM, Vriezekolk JE. Healthcare professionals' perceptions on barriers and facilitators to DMARD use in rheumatoid arthritis. *BMC Health Serv. Res.* 22(1), 62 (2022).
38. International Society for Pharmacoepidemiology. Guidelines for Good Pharmacoepidemiology Practices (GPP). *Pharmacoepidemiol. Drug Saf.* 25(1), 2–10 (2016).
39. Berger ML, Sox H, Willke RJ *et al.* Good practices for real-world data studies of treatment and/or comparative effectiveness: recommendations from the Joint ISPOR–ISPE Special Task Force on Real-World Evidence in Health Care Decision Making. *Value Health* 20(8), 1003–1008 (2017).
40. Von Elm E, Altman DG, Egger M *et al.* The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *PLoS Med.* 4(10), e296 (2007).
41. World Medical Association Declaration of Helsinki. Recommendations guiding physicians in biomedical research involving human subjects. *JAMA* 277(11), 925–926 (1997).
42. Salaffi F, Di Carlo M, Farah S, Marotto D, Atzeni F, Sarzi-Putini P. Rheumatoid arthritis disease activity assessment in routine care: performance of the most widely used composite disease activity indices and patient-reported outcome measures. *Acta Biomed.* 92(4), e2021238 (2021).
43. Aletaha D, Smolen J. The Simplified Disease Activity Index (SDAI) and the Clinical Disease Activity Index (CDAI): a review of their usefulness and validity in rheumatoid arthritis. *Clin. Exp. Rheumatol.* 23(Suppl 39, 5), S100–S108 (2005).

44. Alten R, Tony HP, Bannert B *et al.* Subcutaneous abatacept for the treatment of rheumatoid arthritis in routine clinical practice in Germany, Austria, and Switzerland: 2-year retention and efficacy by treatment line and serostatus. *Clin. Rheumatol.* 42(9), 2321–2334 (2023).
45. Gottenberg JE, Courvoisier DS, Hernandez MV *et al.* Brief report: association of rheumatoid factor and anti-citrullinated protein antibody positivity with better effectiveness of abatacept: results from the pan-European registry analysis. *Arthritis Rheumatol.* 68(6), 1346–1352 (2016).
46. Azuma T, Misaki K, Kusaoi M *et al.* Influence of concomitant methotrexate use on the clinical effectiveness, retention, and safety of abatacept in biologic-naïve patients with rheumatoid arthritis: post-hoc subgroup analysis of the ORIGAMI study. *Mod. Rheumatol.* 33(2), 271–278 (2023).
47. Tamura N, Azuma T, Misaki K *et al.* Effectiveness and safety of subcutaneous abatacept in biologic-naïve RA patients at Week 52: a Japanese multicentre investigational study (ORIGAMI study). *Mod. Rheumatol.* 32(5), 846–856 (2022).
48. Götestam Skorpen C, Hoeltzenbein M, Tincani A *et al.* The EULAR points to consider for use of antirheumatic drugs before pregnancy, and during pregnancy and lactation. *Ann. Rheum. Dis.* 75(5), 795–810 (2016).
49. Gottenberg JE, Ravaud P, Cantagrel A *et al.* Positivity for anti-cyclic citrullinated peptide is associated with a better response to abatacept: data from the ‘Orencia and Rheumatoid Arthritis’ registry. *Ann. Rheum. Dis.* 71(11), 1815–1819 (2012).
50. Harrold LR, Connolly SE, Wittstock K *et al.* Baseline anti-citrullinated protein antibody status and response to abatacept or non-TNFi biologic/targeted-synthetic DMARDs: US observational study of patients with RA. *Rheumatol. Ther.* 9(2), 465–480 (2022).
51. Gottenberg JE, Courvoisier DS, Hernandez MV *et al.* Brief report: association of rheumatoid factor and anti-citrullinated protein antibody positivity with better effectiveness of abatacept: results from the pan-European registry analysis. *Arthritis Rheumatol.* 68(6), 1346–1352 (2016).
52. Michaud K, Conaghan PG, Park SH *et al.* Benefits of autoantibody enrichment in early rheumatoid arthritis: analysis of efficacy outcomes in four pooled abatacept trials. *Rheumatol. Ther.* 10(4), 951–967 (2023).
53. Poulsen TBG, Damgaard D, Jørgensen MM *et al.* Identification of potential autoantigens in anti-CCP-positive and anti-CCP-negative rheumatoid arthritis using citrulline-specific protein arrays. *Sci. Rep.* 11(1), 17300 (2021).
- **Patterns of ACPA-recognized proteins may have diagnostic utility for further RA subtyping.**
54. Rigby W, Buckner JH, Louis Bridges S *et al.* HLA-DRB1 risk alleles for RA are associated with differential clinical responsiveness to abatacept and adalimumab: data from a head-to-head, randomized, single-blind study in autoantibody-positive early RA. *Arthritis Res. Ther.* 23(1), 245 (2021).
55. Kurowska W, Kuca-Warnawin EH, Radzikowska A, Maslinski W. The role of anti-citrullinated protein antibodies (ACPA) in the pathogenesis of rheumatoid arthritis. *Cent. Eur. J. Immunol.* 42(4), 390–398 (2017).
56. Trela M, Perera S, Sheeran T, Rylance P, Nelson PN, Attridge K. Citrullination facilitates cross-reactivity of rheumatoid factor with non-IgG1 Fc epitopes in rheumatoid arthritis. *Sci. Rep.* 9(1), 12068 (2019).
57. Aripova N, Kremer JM, Pappas DA *et al.* Anti-citrullinated protein antibody profiles predict changes in disease activity in patients with rheumatoid arthritis initiating biologics. *Rheumatology (Oxford)* doi:10.1093/rheumatology/kead260 (2023).
58. Hirose W, Harigai M, Amano K *et al.* Impact of the HLA-DRB1 shared epitope on responses to treatment with tofacitinib or abatacept in patients with rheumatoid arthritis. *Arthritis Res. Ther.* 23(1), 228 (2021).
59. Fernandes-Cerqueira C, Ossipova E, Gunasekera S *et al.* Targeting of anti-citrullinated protein/peptide antibodies in rheumatoid arthritis using peptides mimicking endogenously citrullinated fibrinogen antigens. *Arthritis Res. Ther.* 17(1), 155 (2015).
- **Two kinds of chains originating from fibrinogen α can prevent pathogenic binding of ACPA with CCP, and targeting ACPAs may reduce bone destruction and alleviate clinical RA symptoms.**
60. Wunderlich C, Oliveira I, Figueiredo CP, Rech J, Schett G. Effects of DMARDs on citrullinated peptide autoantibody levels in RA patients – a longitudinal analysis. *Semin. Arthritis Rheum.* 46(6), 709–714 (2017).