



Predictors of abatacept retention over 2 years in patients with rheumatoid arthritis: results from the real-world ACTION study

Rieke Alten¹ · Xavier Mariette² · Hanns-Martin Lorenz³ · Hubert Nüßlein⁴ · Mauro Galeazzi⁵ · Federico Navarro⁶ · Melanie Chartier⁷ · Julia Heitzmann⁸ · Coralie Poncet⁹ · Christiane Rauch¹⁰ · Manuela Le Bars^{11,12}

Received: 25 October 2018 / Revised: 15 January 2019 / Accepted: 21 January 2019 / Published online: 21 February 2019
© The Author(s) 2019, corrected publication 2019

Abstract

Objectives Evaluate abatacept retention over 2 years in the AbataCepT In rOutiNe clinical practice (ACTION) study.

Method ACTION was an international, observational study of patients with moderate-to-severe rheumatoid arthritis (RA) who initiated intravenous abatacept. Crude abatacept retention rates over 2 years were estimated using Kaplan–Meier analyses in biologic-naïve and -failure patients. Clinically relevant risk factors and significant prognostic factors for retention were evaluated using a Cox proportional hazards multivariable model.

Results Overall, 2350/2364 enrolled patients were evaluable; 673 (28.6%) were biologic naïve and 1677 (71.4%) had prior biologic failure (1 biologic, 728/1677 [43.4%]; ≥ 2 biologics, 949/1677 [56.6%]). Abatacept retention rate (95% confidence interval [CI]) at 2 years was 47.9% (45.7, 50.0): 54.5% (50.4, 58.3) for biologic-naïve vs 45.2% (42.7, 47.7) for biologic-failure patients (log-rank $P < 0.001$). For patients with 1 and ≥ 2 prior biologic failures, respectively, retention rates (95% CI) were 50.2% (46.3, 53.9) vs 41.3% (38.0, 44.6; log-rank $P < 0.001$). Main reasons for discontinuation (biologic-naïve vs biologic-failure, respectively) were lack of efficacy (61.4 vs 67.7%) and safety (21.3 vs 21.2%). Rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP) double positivity versus negativity were predictive of higher retention in both biologic-naïve (hazard ratio [HR] [95% CI] 0.71 [0.53, 0.96]; $P = 0.019$) and biologic-failure patients (HR [95% CI] 0.76 [0.62, 0.94]; $P = 0.035$).

Conclusions Abatacept initiation as earlier vs later line of therapy in RA may achieve higher 2-year retention rates. RF and anti-CCP seropositivity could predict increased abatacept retention, irrespective of treatment line.

Trial registration NCT02109666

Keywords Biologic · Efficacy · Predictor · Remission · Rheumatoid arthritis

Electronic supplementary material The online version of this article (<https://doi.org/10.1007/s10067-019-04449-w>) contains supplementary material, which is available to authorized users.

✉ Rieke Alten
rieke.alten@schlosspark-klinik.de

¹ Department of Internal Medicine, Rheumatology, Clinical Immunology, and Osteology, Schlosspark-Klinik University Medicine Berlin, Heubnerweg 2, 14059 Berlin, Germany

² Department of Rheumatology, Université Paris-Sud, Paris, France

³ Department of Rheumatology, University Hospital, Heidelberg, Germany

⁴ Department of Internal Medicine and Rheumatology, University of Erlangen-Nuremberg, Nuremberg, Germany

⁵ Department of Medical Sciences, Surgery, and Neuroscience, University of Siena, Siena, Italy

⁶ Department of Rheumatology, Hospital Universitario Virgen Macarena, Seville, Spain

⁷ Marketed Product Late Stage Operation Department, Bristol-Myers Squibb, Rueil-Malmaison, France

⁸ Excelya, Boulogne-Billancourt, France

⁹ Docs International, Issy-les-Moulineaux, France

¹⁰ Department of Immunoscience, Bristol-Myers Squibb, Munich, Germany

¹¹ Speciality Development Immunology, Bristol-Myers Squibb, Rueil-Malmaison, France

¹² Present address: Janssen-Cilag European Medical Affairs Immunology-Gastroenterology, 92787 Issy-les-Moulineaux, France

Introduction

Management of patients with rheumatoid arthritis (RA) has evolved in recent years to include more personalized, strategic use of the range of therapeutic agents now available [1, 2]. Recommendations have been developed with the aim of optimizing clinical outcomes in every patient with RA through a treat-to-target approach to achieve sustained disease remission or low disease activity (LDA) [2]. In the presence of poor prognostic factors, treatment progression from a conventional synthetic (cs) disease-modifying anti-rheumatic drug (DMARD) to the inclusion of a biologic (b) DMARD such as abatacept can have unpredictable benefit [3].

Randomized controlled trials have provided evidence of the efficacy, safety and tolerability of abatacept in adults with moderate-to-severe RA [4–6]. However, a high proportion of patients with RA are unlikely to meet the stringent criteria required for participation in trials of biologics and study participants may not fully represent a clinical population [7]. Real-world data can provide valuable insights into the long-term use of biologics and the patient characteristics associated with the diverse responses observed in clinical settings [8, 9]. The determination of predictors of treatment retention and differential response will assist the development of the most appropriate, individualized treatment and has the potential to reduce unnecessary adjustments in therapy.

Abatacept is approved for the treatment of adults with moderate-to-severe RA [10, 11] and, uniquely, exerts a therapeutic effect through interaction with immune cells involved in the pathophysiology of RA by selective modulation of the C28:CD80/CD86 co-stimulation signal that is necessary for full T cell activation [12]. AbataCepT In rOutiNe clinical practice (ACTION; [ClinicalTrials.gov](https://clinicaltrials.gov) identifier: NCT02109666) was a 2-year study to provide prospective, real-world data on abatacept retention, efficacy, and safety in patients with RA. The primary objective was to evaluate the retention of abatacept prescribed to adults with RA in a routine clinical setting. Secondary objectives included the identification of predictors of abatacept retention. Here we report the final 2-year results for all patients enrolled in ACTION.

Patients and methods

Study design

ACTION was a 2-year, non-interventional, international, multicentre cohort study in patients with RA initiating intravenous (IV) abatacept in clinical practice. The study design has been reported previously [13]. Patients were enrolled across Europe (Austria, Belgium, Czech Republic, Denmark, France, Germany, Greece, Italy, Netherlands, Spain, and Switzerland) and Canada. All participating countries were

required to have regulatory approval and a reimbursement policy for abatacept to ensure availability of the drug to all eligible patients.

Rheumatologists were randomly selected for a well-balanced geographic distribution and were representative of specialists caring for patients with RA in each participating country. No product was provided to the physicians or patients by the study sponsor, and the observational design of the study did not interfere with usual clinical practice.

The final 2-year results for all patients enrolled in ACTION between May 2008 and December 2013 are reported here.

Study population

Patients eligible for inclusion were adults (aged ≥ 18 years) with moderate-to-severe RA, as defined by the American College of Rheumatology revised criteria 1987 [14], who initiated IV abatacept under the guidance of their physician and in accordance with the Summary of Product Characteristics in Europe [10] or the Product Monograph in Canada [11]. Patients were enrolled in ACTION either prospectively on initiation of abatacept or retrospectively within 3 months of initiation where authorized by the local ethics committee. Patients were recruited over three time periods that reflected the regulatory approval of abatacept in the participating countries [2]: May 2008–December 2010 (patients who were biologic naive or had prior ≥ 1 biologic failure; cohort A); September 2010–December 2013 (biologic-naive patients only; cohort B); and October 2011–December 2013 (patients with ≥ 1 prior biologic failure only; cohort C). Patients already participating in a clinical trial were excluded from ACTION.

Patients were followed up approximately every 3 months for 30 months in accordance with routine clinical practice or, if abatacept was discontinued before the end of the study, for up to 6 months after discontinuation. The ACTION study database was locked on 22 July 2016.

The study protocol and patient enrolment materials were approved by local ethics committees and regulatory agencies in each participating country (first approval received on 31 January 2008, Munich, Germany). The study was conducted in accordance with the Declaration of Helsinki [15], the International Conference on Harmonization Good Clinical Practice Guidelines [16], and the Good Epidemiological Practice Guidelines [17]. All enrolled patients provided informed consent in accordance with local laws.

Study outcomes

The primary endpoint was crude abatacept retention rate over 2 years. Retention was defined as consecutive time on treatment. Biologic-failure patients were those in whom a previous biologic was ineffective or had caused safety or tolerability concerns, patients in clinical remission or in whom there was a

major improvement of symptoms following a previous biologic, or patients who had discontinued a previous biologic for any reason [18]. The first date of abatacept discontinuation and the reasons for discontinuation were recorded by the physician at follow-up, irrespective of whether the patient subsequently switched to subcutaneous (SC) abatacept or resumed treatment with IV abatacept. Exposure to abatacept was defined as the time between the dates of the first and last infusion of abatacept, plus 30 days.

Clinical response to abatacept at 2 years was assessed using European League Against Rheumatism (EULAR) response rates based on the 28-joint Disease Activity Score (DAS28) (erythrocyte sedimentation rate [ESR] or C-reactive protein [CRP]) and classified as good/moderate or no response [19]. Other assessments included clinical remission defined by DAS28 (ESR or CRP; <2.6), Clinical Disease Activity Index (CDAI; ≤ 2.8), Simplified Disease Activity Index (SDAI; ≤ 3.3), and Boolean criteria [20].

Potential predictors of abatacept retention, including demographics, disease characteristics, co-morbidities at abatacept initiation, and previous and current treatments at baseline, were assessed in biologic-naive patients and in patients with prior biologic failure. Between-country effects were explored in patients from countries that recruited more than 10 patients, with Germany (highest number of enrolments) as the reference country.

Safety was monitored and evaluated in accordance with local regulations. The drug manufacturer's pharmacovigilance department was notified of any adverse events (AEs) or serious adverse events (SAEs) assessed by the treating physician as related to abatacept or any other Bristol-Myers Squibb drug. An SAE was defined as an AE that was fatal or life-threatening, required or extended hospitalization, led to persistent or significant disability or incapacity, induced a birth defect, or was considered an important medical event. Deaths from any cause were reported. Safety is presented for the overall population, irrespective of treatment line.

Statistical analyses

Baseline characteristics and demographics were reported using descriptive statistics including sample size, mean, median and standard deviation (SD) for continuous variables, and frequency and percentage for categorical variables, and were compared using Fisher's exact tests. Crude abatacept retention rates over 2 years with corresponding 95% confidence intervals (CIs) were estimated using Kaplan–Meier analyses for patients stratified by previous biologic exposure (biologic naive, 1 previous biologic, and ≥ 2 previous biologics) and compared by treatment line using a log-rank test.

Clinical outcomes at 2 years were assessed in patients with relevant baseline data collected no later than 8 days after the

first abatacept infusion and were compared by treatment line using Fisher's exact tests.

Clinically relevant known risk factors and predictors of abatacept discontinuation with significance ($P \leq 0.20$) in univariable analyses and no collinearity were entered into multivariable Cox proportional hazards regression models (as shown in Supplementary Table S1 [see Online Resource 1]). Factors with a significance of $P \leq 0.10$ after backward selection were retained in the final multivariable models. Results are presented as hazard ratios (HRs) with corresponding 95% CIs and P values. The HRs were statistically significant when the 95% CIs did not cross 1.

Results

Patients

Between May 2008 and December 2013, 2364 patients were enrolled in ACTION across Europe and Canada (cohort A, 1137 patients from 9 countries; cohort B, 555 patients from 8 countries; cohort C, 672 patients from 8 countries; Supplementary Fig. S1 [see Online Resource 2]). A total of 2350 patients were evaluable; 673 (28.6%) were biologic naive and 1677 (71.4%) had failed biologic treatment (1 biologic, 728/1677 [43.4% patients]; ≥ 2 biologics, 949/1677 [56.6% patients]) (Fig. 1). One patient erroneously classified as biologic naive for the 1-year analysis of ACTION was reclassified as a biologic-failure patient for this analysis [18]. For biologic-failure patients, 816/1677 (48.7%) had failed 1 tumor necrosis factor inhibitor (TNFi) and 805/1677 (48.0%) had failed ≥ 2 TNFis; 56/1677 (3.3%) had failed a non-TNFi biologic only.

Overall, baseline demographics were similar in all patients irrespective of treatment line (Table 1); however, in those who were biologic naive vs those with previous biologic failure at abatacept initiation, a higher proportion of patients had mean disease duration of ≤ 2 years (35.7 vs 9.0%; $P < 0.001$), mean CRP was lower (1.7 vs 2.1 mg/dL; $P = 0.01$), and a smaller proportion of patients had radiographic erosions (58.2 vs 71.5%; $P < 0.001$). Hypertension was the most common co-morbidity overall (38.2% and 39.1% of biologic-naive and biologic-failure patients, respectively). At abatacept initiation, over 90% of all patients had received prior methotrexate (Table 1); however, a greater proportion of biologic-failure vs biologic-naive patients had previous exposure to > 3 csDMARDs (6.9 vs 1.2%; $P < 0.001$), initiated abatacept as monotherapy (25.5 vs 16.6%; $P < 0.001$), and initiated abatacept with corticosteroids at a dose of > 5 mg/day (54.9 vs 47.3%; $P < 0.01$). The bDMARDs most commonly used previously by biologic-failure patients were etanercept and adalimumab (60.2% and 57.7% patients, respectively; Table 1).

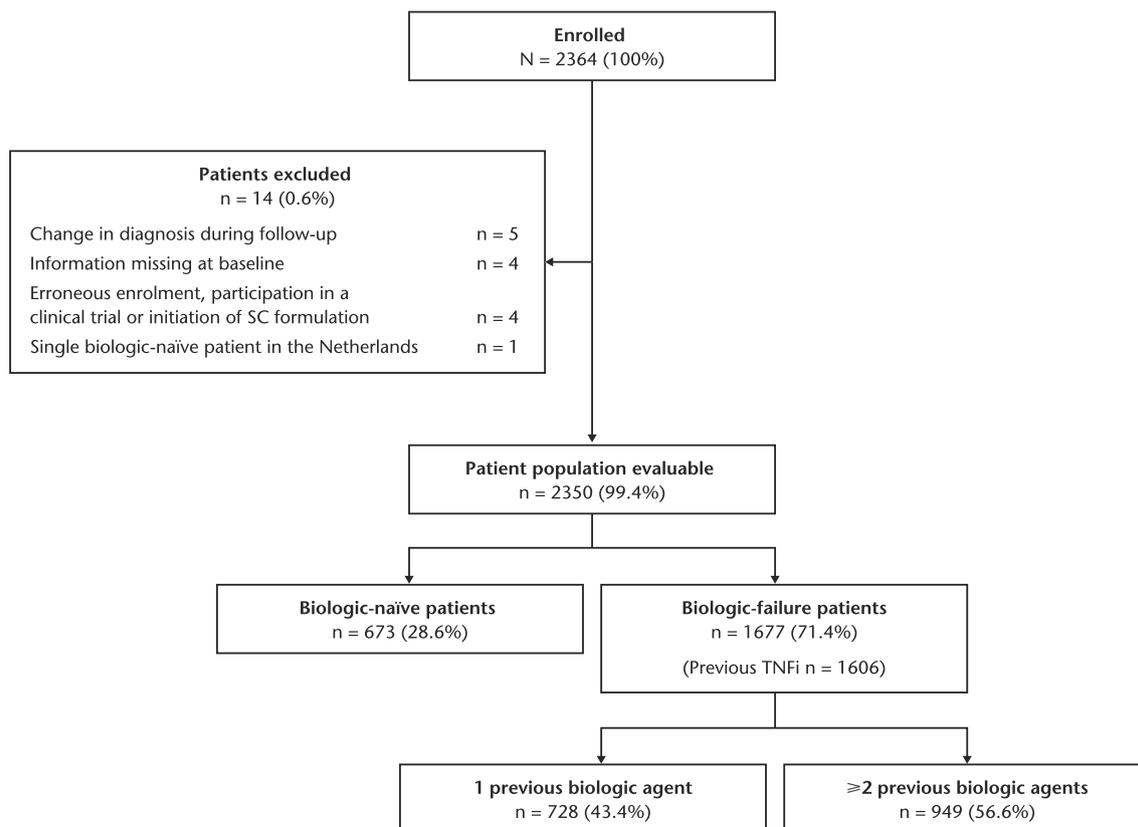


Fig. 1 Patient disposition

Retention

A total of 2350 of the 2364 patients enrolled were evaluable at 2 years. The overall crude retention rate (95% CI) at 2 years for the evaluable patients was 47.9% (45.7, 50.0). Retention rates (95% CI) at 2 years were significantly higher in biologic-naïve vs biologic-failure patients (54.5% [50.5, 58.3] vs 45.2% [42.7, 47.7], respectively; $P < 0.001$). Crude retention rates at 2 years decreased with increasing number of previous biologics: 50.2% (46.3, 53.9) vs 41.3% (38.0, 44.6); log-rank test: $P < 0.001$ for 1 vs ≥ 2 previous biologics, respectively. The difference in retention rates between each line of treatment was statistically significant (log-rank test, $P < 0.001$; Fig. 2). Over 2 years, the most common reasons for discontinuation of abatacept in biologic-naïve and biologic-failure patients, respectively, were inefficacy (61.4% and 67.7%) and safety (21.3% and 21.2%).

In an exploratory analysis to include the patients who discontinued IV abatacept but either switched to SC abatacept or restarted IV abatacept within 6 months (77/186 [41.4%] biologic-naïve and 186/526 [35.4%] biologic-failure patients), the overall retention rate (95% CI) at 2 years was 61.2% (59.1%, 63.2%) and remained higher for biologic-naïve than for biologic-failure patients (68.9% [65.1%, 72.4%] vs 58.1% [55.6%, 60.5%], respectively).

Predictors of retention

Overall, 1603 of 2350 (68.2%) evaluable patients were included in the analysis of predictors of abatacept retention. Patients with data missing for any variables tested in the model were excluded.

Biologic-naïve patients

In total, four of the 27 variables tested in the univariable analysis were entered into an initial multivariable Cox proportional hazard regression model: diabetes mellitus, country, rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP) serostatus, and patient's sex. After backward selection, only three variables were retained in the final multivariable model according to statistical significance (diabetes mellitus, country, and RF and anti-CCP serostatus; Fig. 3a). Biologic-naïve patients were less likely to have discontinued abatacept at 2 years if they were RF and anti-CCP double positive vs double negative at baseline (HR: 0.71; 95% CI: 0.53, 0.96; $P = 0.019$); single-positive vs double-negative status at baseline was not associated with a lower likelihood of abatacept discontinuation. Biologic-naïve patients with diabetes mellitus were less likely than those without this comorbidity to have discontinued abatacept (HR, 0.61; 95% CI 0.38, 0.99; $P = 0.043$). Abatacept retention at 2 years varied

Table 1 Baseline patient characteristics

| | Biologic naive (<i>n</i> = 673) | Biologic failure (<i>n</i> = 1677) |
|---|----------------------------------|-------------------------------------|
| Age, years | 59.9 (12.7) | 57.0 (12.5) |
| Female, <i>n</i> (%) | 496 (73.7) | 1379 (82.2) |
| BMI, kg/m ² | 27.0 (5.4); <i>n</i> = 644 | 27.1 (5.6); <i>n</i> = 1597 |
| BMI, <i>n</i> (%) | | |
| < 25 kg/m ² | 265 (41.1) | 649 (40.6) |
| 25–< 30 kg/m ² | 224 (34.8) | 543 (34.0) |
| ≥ 30–< 35 kg/m ² | 104 (16.1) | 266 (16.7) |
| ≥ 35 kg/m ² | 51 (7.9) | 139 (8.7) |
| RA duration, years | 7.2 (8.2); <i>n</i> = 669 | 12.1 (9.1); <i>n</i> = 1669 |
| RA duration, <i>n</i> (%) | | |
| ≤ 2 years | 239/669 (35.7)* | 151/1669 (9.0) |
| 3–5 years | 155/669 (23.2) | 320/1669 (19.2) |
| 6–10 years | 122/699 (18.2) | 421/1669 (25.2) |
| > 10 years | 153/699 (22.9) | 777/1669 (46.6) |
| TJC28 | 9.0 (6.5); <i>n</i> = 633 | 10.4 (7.2); <i>n</i> = 1599 |
| SJC28 | 6.6 (5.0); <i>n</i> = 641 | 7.0 (5.6); <i>n</i> = 1607 |
| DAS28 (ESR) ^a | 5.3 (1.2); <i>n</i> = 582 | 5.5 (1.3); <i>n</i> = 1422 |
| DAS28 (CRP) ^a | 4.8 (1.1); <i>n</i> = 568 | 5.0 (1.1); <i>n</i> = 1411 |
| CDAI ^a | 27.5 (11.5); <i>n</i> = 565 | 30.0 (12.9); <i>n</i> = 1388 |
| SDAI ^a | 29.1 (12.0); <i>n</i> = 526 | 31.8 (13.6); <i>n</i> = 1279 |
| HAQ-DI | 1.4 (0.7); <i>n</i> = 579 | 1.5 (0.7); <i>n</i> = 1471 |
| PtGA, 100 mm VAS | 62.0 (20.3); <i>n</i> = 620 | 65.4 (19.9); <i>n</i> = 1539 |
| CRP, mg/dL | 1.7 (2.6); <i>n</i> = 590 | 2.1 (3.5); <i>n</i> = 1474** |
| ESR, mm/h | 33.1 (23.7); <i>n</i> = 605 | 33.7 (23.7); <i>n</i> = 1491 |
| RF positive, n/N (%) | 415/578 (71.8) | 987/1385 (71.3) |
| Anti-CCP positive, n/N (%) | 368/556 (66.2) | 884/1309 (67.5) |
| RF and anti-CCP antibody status, n/N (%) | | |
| Double positive | 311/513 (60.6) | 717/1166 (61.5) |
| Single positive | 77/513 (15.0) | 182/1166 (15.6) |
| Double negative | 125/513 (24.4) | 267/1166 (22.9) |
| Radiographic erosion, n/N (%) | 353/607 (58.2) | 1034/1446 (71.5)* |
| ≥ 1 Co-morbidity, <i>n</i> (%) | 518 (77.0) | 1226 (73.1) |
| Diabetes mellitus | 85 (12.6) | 207 (12.3) |
| COPD | 69 (10.3) | 128 (7.6) |
| Cardiac disorders | 62 (9.2) | 124 (7.4) |
| Neoplasms ^b | 36 (5.3) | 42 (2.5)* |
| Number of previous csDMARDs ^c , <i>n</i> (%) | | |
| ≤ 3 | 655 (98.8) | 1561 (93.1) |
| > 3 | 8 (1.2) | 116 (6.9)* |
| Previous MTX, <i>n</i> (%) | 621 (92.3) | 1552 (92.5) |
| Previous other csDMARDs, <i>n</i> (%) | | |
| Leflunomide | 278 (41.3) | 951 (56.7)* |
| Hydroxychloroquine/chloroquine | 229 (34.0) | 681 (40.6)** |
| Sulfasalazine | 148 (22.0) | 578 (34.5)* |
| Previous corticosteroids, <i>n</i> (%) | 533 (79.2) | 1386 (82.6) |
| Previous other biologics, <i>n</i> (%) | | |
| Adalimumab | – | 967 (57.7) |
| Anakinra | – | 69 (4.1) |
| Canakinumab | – | 1 (0.1) |

Table 1 (continued)

| | Biologic naive (<i>n</i> = 673) | Biologic failure (<i>n</i> = 1677) |
|---|----------------------------------|-------------------------------------|
| Certolizumab | – | 52 (3.1) |
| Etanercept | – | 1010 (60.2) |
| Golimumab | – | 22 (1.3) |
| Infliximab | – | 512 (30.5) |
| Ocrelizumab | – | 3 (0.2) |
| Rituximab | – | 239 (14.3) |
| Tocilizumab | – | 181 (10.8) |
| Number of previous biologics, <i>n</i> (%) | | |
| 1 | – | 728 (43.4) |
| ≥ 2 | – | 949 (56.6) |
| Number of previous TNFi, <i>n</i> (%) | | |
| 1 | – | 872 (52.0) |
| ≥ 2 | – | 805 (48.0) |
| Treatment pattern at initiation, <i>n</i> (%) | | |
| Abatacept monotherapy | <i>112 (16.6)</i> | <i>427 (25.5)*</i> |
| MTX (± other csDMARDs) | 436 (77.7) | 947 (75.7) |
| MTX alone | 358 (63.8) | 829 (66.3) |
| MTX + other csDMARD | 78 (13.9) | 118 (9.4) |
| Other csDMARDs | 125 (22.3) | 303 (24.3) |
| Corticosteroids | 455 (67.6) | 1190 (71.0) |
| > 5 mg/day | <i>208/440 (47.3)</i> | <i>625/1138 (54.9)**</i> |
| ≤ 5 mg/day | 232/440 (52.7) | 513/1138 (45.1) |
| Median dose, mg/day | <i>5.0; n = 440</i> | <i>7.5; n = 1138**</i> |

Data are mean (SD) unless indicated otherwise

^a Calculated

^b Benign, malignant, and unspecified (neoplasms not classified as either benign or malignant). Information on malignancies at baseline was not routinely collected

^c MTX and corticosteroids not taken into account

Data in italics indicate a significant difference between biologic-naive and biologic-failure groups ($P < 0.05$)

* $P < 0.001$; ** $P < 0.01$

anti-CCP, anti-cyclic citrullinated peptide; *BMI*, body mass index; *CDAI*, Clinical Disease Activity Index; *COPD*, chronic obstructive pulmonary disease; *CRP*, C-reactive protein; *csDMARD*, conventional synthetic DMARD; *DAS28*, 28-joint Disease Activity Score; *ESR*, erythrocyte sedimentation rate; *HAQ-DI*, Health Assessment Questionnaire–Disability Index; *MTX*, methotrexate; *PtGA*, Patient Global Assessment of disease activity; *RA*, rheumatoid arthritis; *RF*, rheumatoid factor; *SD*, standard deviation; *SDAI*, Simplified Disease Activity Index; *SJC28*, swollen joint count in 28 joints; *TJC28*, Tender joint count in 28 joints; *VAS* visual analogue scale

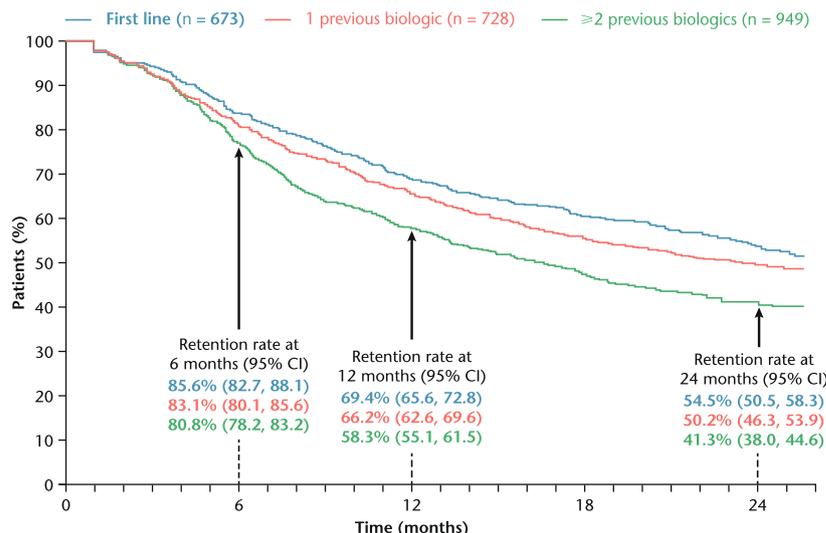
by country, with patients in Canada, Greece, and Italy less likely to have discontinued than those in Germany ($P < 0.001$). Patient's sex was not identified as a predictor of retention at 2 years.

Patients with previous biologic failure

In total, six of the 31 baseline variables tested in the univariable analyses were entered into the initial multivariable model: main reason for stopping the last biologic, abatacept monotherapy vs combination therapy, country, Patient Global Assessment of disease activity (PtGA), RF and anti-CCP serostatus, and bronchospasm and obstruction co-morbidity.

After backward selection, four variables were retained in the final multivariable model according to statistical significance (main reason for stopping the last biologic, abatacept monotherapy vs combination therapy, PtGA, and RF and anti-CCP serostatus; Fig. 3b). Biologic-failure patients were less likely to have discontinued abatacept at 2 years if they were RF and anti-CCP double positive vs double negative at baseline (HR, 0.76; 95% CI 0.62, 0.94; $P = 0.035$). Primary efficacy failure (± secondary efficacy failure, remission, or other reasons) was associated with a trend towards a higher likelihood of abatacept discontinuation at 2 years (HR, 1.28; 95% CI 1.00, 1.63; $P = 0.014$). Initiation of abatacept in combination with methotrexate (± other DMARDs) was less likely than

Fig. 2 Crude abatacept retention rates over 2 years by treatment line



| Patients at risk (n) | Baseline | 6 months | 12 months | 24 months |
|-----------------------|----------|----------|-----------|-----------|
| Biologic-naïve | 673 | 551 | 433 | 239 |
| 1 previous biologic | 728 | 584 | 449 | 224 |
| ≥2 previous biologics | 949 | 735 | 504 | 223 |

initiation as monotherapy to be associated with discontinuation at 2 years (HR, 0.68; 95% CI 0.55, 0.83; $P < 0.001$). Biologic-failure patients with a PtGA score of ≥ 70 vs < 70 mm on a visual analogue scale (VAS) of 0–100 mm at baseline were more likely to have discontinued abatacept at 2 years (HR, 1.26; 95% CI 1.05, 1.52; $P = 0.040$). The country in which abatacept was initiated or a baseline co-morbidity of bronchospasm and obstruction were not identified as predictors of abatacept retention at 2 years.

Clinical outcomes

Good/moderate EULAR response rates based on DAS28 (ESR, otherwise CRP) increased over 2 years of abatacept treatment in both biologic-naïve and biologic-failure patients. Of the 605 patients with data available for the evaluation of EULAR response at 2 years, the proportion of patients with a good/moderate response was higher in biologic-naïve patients than in those with previous biologic failure (Fig. 4). A good or moderate EULAR response (95% CI) was attained at 2 years by 90.7% (86.8, 94.6) of patients who were biologic naïve and 81.6% (77.7, 85.4) of patients with previous biologic failure (1 previous biologic failure, 81.7% [76.2, 87.2]; ≥ 2 previous biologic failures, 81.5% [76.1, 86.9]) (Fisher’s exact test, $P = 0.005$; Fig. 4). Overall, RF/anti-CCP positivity vs double negativity was associated with a higher good/moderate EULAR response rate at 2 years: 87.7%, 83.4%, and 75.6% in double RF/anti-CCP-positive, single RF- or anti-CCP-positive, and double RF/anti-CCP-negative patients, respectively; Fisher’s exact test $P = 0.007$.

At 2 years, clinical remission rates were numerically higher in biologic-naïve vs biologic-failure patients: DAS28 (ESR)

($n = 591$): 49.5 vs 35.1%; DAS28 (CRP) ($n = 579$): 57.1 vs 49.3%; CDAI ($n = 201$): 31.5 vs 27.4%; SDAI ($n = 151$): 32.7 vs 25.6%; and Boolean ($n = 579$): 28.9 vs 20.2%. In the exploratory analysis, which included the patients who had discontinued abatacept and had either switched to SC abatacept or restarted IV abatacept within 6 months, clinical remission rates at the last follow-up before discontinuation in the biologic-naïve vs biologic-failure patients were DAS28 (ESR) ($n = 71$): 36.4 vs 18.4%; DAS28 (CRP) ($n = 75$): 26.1 vs 26.9%; CDAI ($n = 85$): 4.3 vs 4.8%; SDAI ($n = 72$): 13.6 vs 6.0%, and Boolean ($n = 75$): 4.3 vs 5.8%. Remission rates at the first follow-up after abatacept was restarted were DAS28 (ESR) ($n = 189$): 21.0 vs 15.0%; DAS28 (CRP) ($n = 191$): 35.1 vs 17.9%; CDAI ($n = 219$): 17.5 vs 6.4%; SDAI ($n = 172$): 21.6 vs 5.0%; and Boolean ($n = 191$): 19.3 vs 3.0%.

Treatment pattern

Changes from baseline concomitant DMARD medication over 2 years were assessed in 286 biologic-naïve patients and in 564 patients with previous biologic failure. At 2 years, the pattern of abatacept co-treatment was unchanged in 89.5% of biologic-naïve patients (42/47 patients who had initiated abatacept as monotherapy and 214/239 patients who had initiated abatacept as combination therapy). At the same time point, the pattern of co-treatment was unchanged in 88.3% of biologic-failure patients (100/120 patients who had initiated abatacept as monotherapy and 398/444 patients who had initiated abatacept as combination therapy). The proportions of patients co-prescribed corticosteroids with abatacept were smaller at 2 years vs baseline: 141/286 (49.3%) vs 455/673 (67.6%) biologic-naïve patients, and 319/564 (56.6%) vs

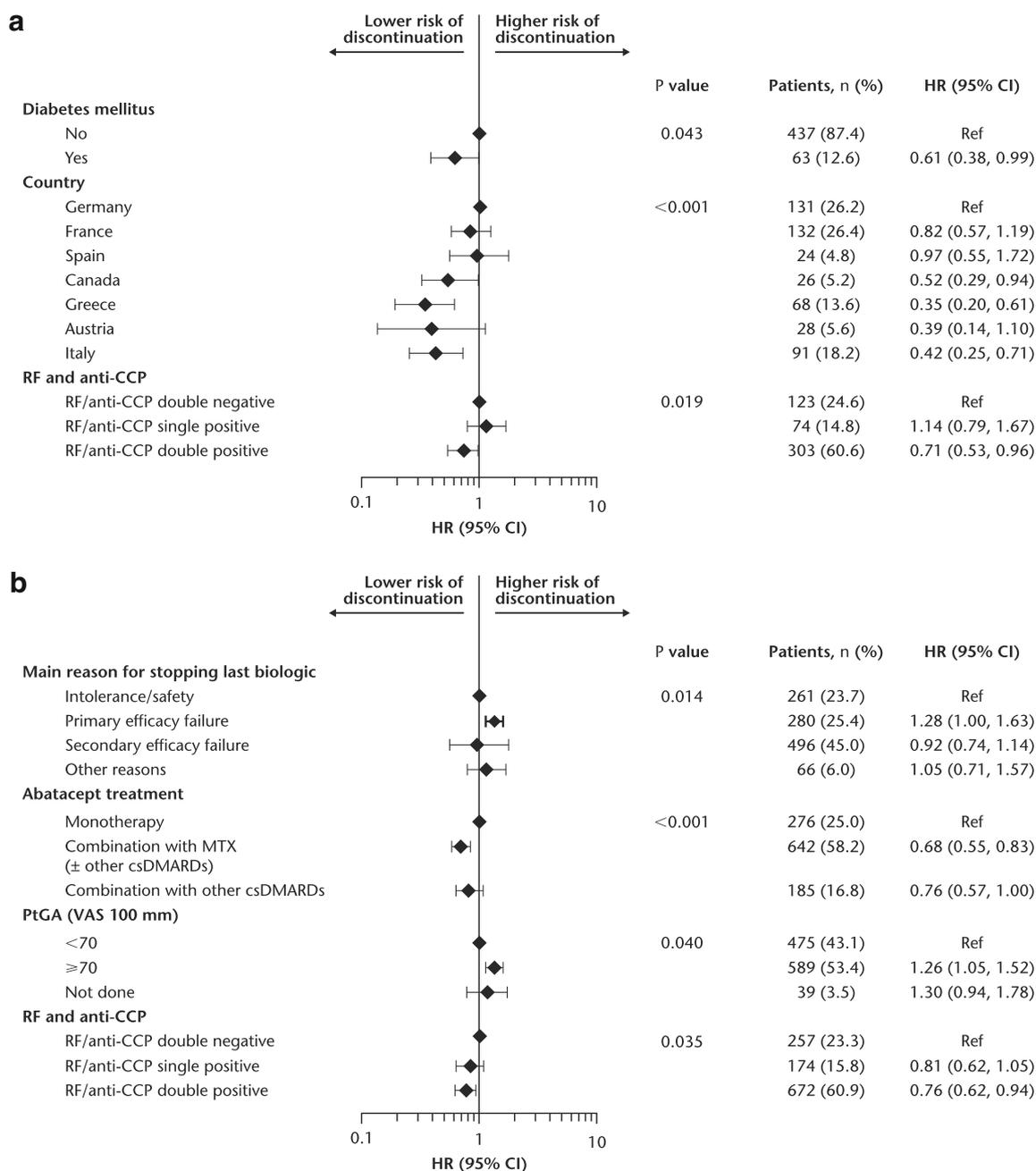


Fig. 3 Multivariable model of abatacept retention in: **a** biologic-naive patients; **b** patients with previous biologic failure

1190/1677 (71.0%) biologic-failure patients. The median dose of corticosteroid co-prescribed at 2 years was unchanged from baseline in biologic-naive patients (5 mg) and decreased from 7.5 mg to 6.0 mg in biologic-failure patients.

The proportions of patients who switched between the IV and SC formulations of abatacept over 2 years were similar in both biologic-naive and biologic-failure groups (13.1% and 13.4%, respectively). Patient choice was the most common reason for switching from the IV to SC formulation in both groups (biologic-naive, 54.9% patients; biologic-failure 62.0% patients).

Safety

A total of 381 SAEs were reported in 193/2364 (8.2%) patients; 94 SAEs led to abatacept discontinuation. There were 27 deaths, 2 of which were due to opportunistic infections (*Pneumocystis jirovecii*; candida). Serious infections were reported in 76 patients: most were upper respiratory tract infections; others included 4 opportunistic infections (4 cases: *Pneumocystis jirovecii* [2 cases], cytomegalovirus [1 case], candida [1 case]), and herpes (8 cases). Malignancies were reported in 24 patients (acute myeloid leukemia [1 patient],

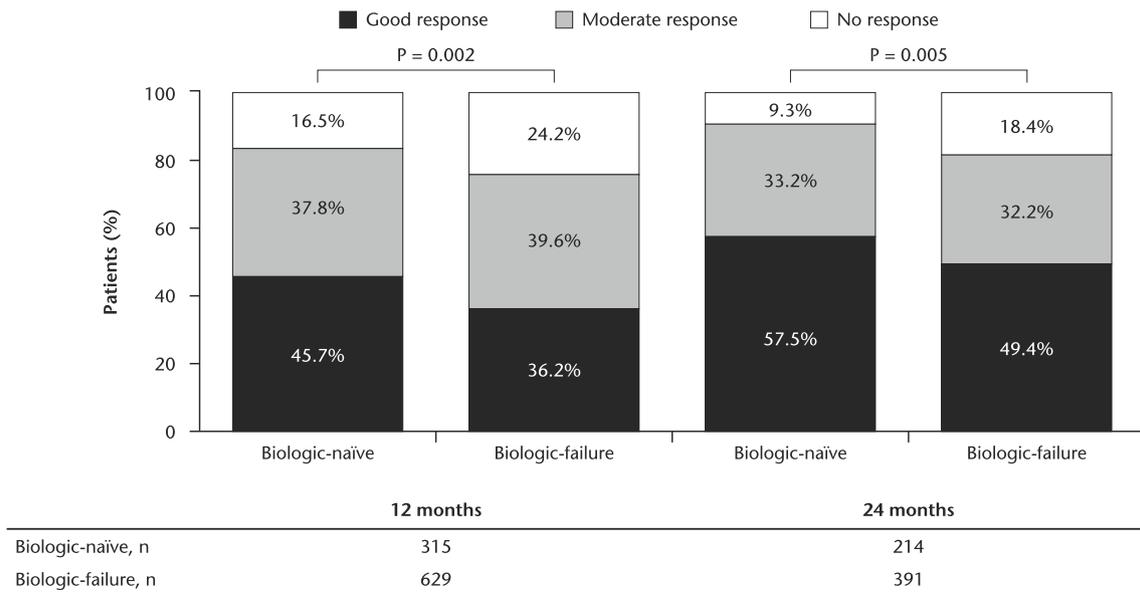


Fig. 4 EULAR response over 2 years by treatment line

basal cell carcinoma [5 patients], bladder neoplasm [1 patient], benign breast neoplasm [1 patient], Bowen’s disease [3 patients], brain neoplasm [1 patient], breast cancer [2 patients], melanoma [2 patients], neoplasm [1 patient], non-Hodgkin’s lymphoma [2 patients], ovarian adenoma [1 patient], pelvic mass [1 patient], and squamous cell carcinoma of the skin [1 patient]); two patients had pre-existing malignancies at baseline (brain tumor, Bowen’s disease). Serious cardiac disorders were reported in 17 patients, serious vascular disorders occurred in 15 patients and serious immune system disorders were reported in 20 patients.

Discussion

Final results from this prospective, international study of abatacept showed that, in real-world clinical practice, around 48% of patients remained on abatacept treatment at 2 years, irrespective of treatment line. In this first real-world study to include a cohort of biologic-naïve patients treated with abatacept, higher abatacept retention rates at 2 years were associated with lower previous exposure to biologics: biologic-naïve patients showed a retention rate of 55% compared with a rate of 45% in patients with previous biologic failure. This was consistent with findings from independent registry studies for abatacept [21, 22] and other biologics [23–26]. Predictors of abatacept retention were identified using multivariable analysis. Abatacept treatment achieved continued clinical improvement over 2 years and was well tolerated; the safety profile was consistent with that previously reported in clinical trials and the real-world setting [27–29] with no new safety signals identified. In general, the current findings confirm earlier observations from interim analyses of

the ACTION study [30–32, 18] and provide clinically applicable data on various parameters of disease activity in both biologic-naïve patients and in those with previous biologic failure.

ACTION was a long-term, observational study of adult patients with moderate-to-severe RA who initiated IV abatacept in routine clinical practice from May 2008 to December 2013. In this first analysis of ACTION to include the full study cohort, the overall retention of abatacept at 2 years was 47.9%, lower than the 54.4% reported in a previous interim analysis which included the patients enrolled from May 2008 to December 2010 only [32]. A later year of prescription has been associated with a higher risk of discontinuation of other biologics, possibly due to an increased likelihood of a change in therapy with the availability of more treatment options [33]. The SC formulation of abatacept gained European and Canadian approval for use in moderate-to-severe RA in 2012 and 2013, respectively [10, 11]. In our exploratory analysis to include patients who, following discontinuation of IV abatacept, either switched to the SC formulation or restarted IV abatacept, overall retention at 2 years was higher than in the main analysis in which these patients were excluded.

Double positivity for both RF and anti-CCP was associated with a greater likelihood of abatacept retention than either single positivity or double negativity, irrespective of treatment line. Real-world evidence from a pooled analysis of European RA registries has previously shown that RF and anti-CCP positivity were each strongly associated with improved retention of abatacept [34]. A positive association has also been demonstrated between abatacept retention and anti-CCP positivity in patients in clinical trials [35, 36] and a registry study [37]. In contrast, evidence of an association between

seropositivity and improved retention of other biologics is lacking. A good/moderate EULAR response to abatacept at 2 years was significantly associated with an RF/anti-CCP positive versus double-negative serostatus and could suggest an increased clinical response to abatacept in more severe disease. Positivity for RF and anti-CCP was reported to be similarly predictive of more successful long-term treatment of biologic-failure patients with rituximab in a registry study [23]. The underlying reasons for improved response and retention rates in patients with seropositivity are not yet fully understood; however, a recent study demonstrated that abatacept inhibits autoantibody-mediated production of inflammatory cytokines by monocytes via the induction of indoleamine 2,3-dioxygenase [38]. These inhibitory effects may explain the rapid anti-inflammatory effects of abatacept and its preferential efficacy in anti-CCP-positive patients [38].

The presence of co-morbidities is an important aspect of the therapeutic management of RA [39]; patient comorbidity has been shown to be predictive of the discontinuation of TNFis in RA [40]. In this final 2-year analysis of ACTION, biologic-naïve patients with diabetes mellitus were at a lower risk of abatacept discontinuation than those without this co-morbidity. This finding could reflect a clinician preference for abatacept in patients with RA and diabetes mellitus; however, this would require confirmation in further study. Data from healthcare claims databases suggest that abatacept is associated with a reduced risk of cardiovascular outcomes compared with TNFis in patients with RA and diabetes mellitus [41].

Although there were no local reimbursement restrictions, differences in abatacept retention by country were observed within the biologic-naïve patient group in the multivariable analysis, and these were independent of patient characteristics. These differences in retention may reflect national differences in prescribing guidelines; for example, although abatacept monotherapy is approved in Europe and Canada [10, 11], clinical guidelines in Germany permit abatacept monotherapy only in patients who are intolerant of methotrexate. Differences in abatacept retention have been observed previously across countries in a pooled analysis of data from European registries and were indicative of a lack of uniformity in access to biologics [22]. Irrespective of regional variations, real-world studies continue to provide valuable data on abatacept for clinicians.

The current analysis also identified a higher baseline PtGA (≥ 70 mm on a VAS scale of 0–100 mm) and the initiation of abatacept as monotherapy vs in combination with a csDMARD as predictors of lower retention in biologic-failure patients. Patient sex was not found to be a significant predictor of abatacept retention in biologic-naïve patients, consistent with the findings for retention in a population-based, observational study of patients with RA receiving biologic therapy for the first time [42].

Several interim analyses of ACTION have investigated potential predictors of clinical response in specific patient populations [31, 32, 43, 44]. Identification of predictors in heterogeneous patient populations in a clinical setting may assist the prediction of clinical response with increased accuracy and improve the ability to attain treatment targets for the optimal management of RA [2]. Although multivariable analyses to investigate predictors of response were not performed in the current analysis, double RF/anti-CCP positivity was associated with better EULAR response vs double negativity, consistent with previous real-world evidence of an association between seropositivity and improved clinical outcomes with abatacept [37, 45]. The rates for good/moderate EULAR response based on DAS28 (ESR, otherwise CRP) and DAS28 (ESR or CRP) remission at 2 years were higher in biologic-naïve than in biologic-failure patients, suggesting a greater benefit with earlier treatment, and reflecting changes in the management of RA over the study period and the earlier selection of bDMARDs for patients with poor prognostic factors [2].

ACTION was an observational study of abatacept in routine practice. The study methodology did not interfere with the usual clinical care of patients with RA, very few patients were lost to follow-up, and the results generated were representative and relevant to each participating country. Inherent limitations of observational, real-world studies include referral and channeling bias, the absence of an active comparator, and loss of patients to follow-up. Moreover, as there was no requirement for the investigator to perform follow-up visits or clinical assessments consistent with other registry studies worldwide, the data generated could be incomplete. To evaluate the impact of missing data in this real-world study, the same multivariable model was performed both with and without imputation; the predictors of retention identified were consistent with the assumptions tested (data not shown).

In conclusion, abatacept retention and EULAR response rates were higher in patients who received abatacept as an earlier line of treatment and in those who were seropositive for both RF and anti-CCP; additional predictors of abatacept retention were observed by treatment line. These findings have the potential to inform the development of an individualized treatment plan for the optimal management of patients with moderate-to-severe RA.

Acknowledgments Professional medical writing and editorial assistance was provided by Linda Brown and Mary Tetlow at Caudex and funded by Bristol-Myers Squibb.

Funding This work was supported by Bristol-Myers Squibb.

Data availability Bristol-Myers Squibb policy on data sharing may be found at <https://www.bms.com/researchers-and-partners/independent-research/data-sharing-request-process.html>

Compliance with ethical standards

Conflict of interest RA: grant/research support: Bristol-Myers Squibb; speakers bureau: Bristol-Myers Squibb. XM: grant/research support: Biogen, Pfizer, UCB; speakers bureau: Bristol-Myers Squibb, LFB, GSK, Pfizer, UCB. H-ML: consulting fees: AbbVie, Bristol-Myers Squibb, Roche-Chugai, UCB, MSD, GSK, Sobi, Medac, Novartis, Janssen-Cilag, AstraZeneca, Pfizer, Actelion. HN: consulting fees: AbbVie, Bristol-Myers Squibb, Celgene, Janssen, Lilly, MSD, Novartis, Pfizer, Roche, UCB. MG: none declared. FN: grant/research support: Pfizer, MSD, AbbVie, Bristol-Myers Squibb, Roche; speakers bureau: Pfizer, MSD, Roche, UCB, AbbVie, Bristol-Myers Squibb; consultant: Pfizer, MSD, Roche, UCB, AbbVie, Bristol-Myers Squibb, Janssen, Lilly. MC: employee: Bristol-Myers Squibb. JH: consultant: Bristol-Myers Squibb. CP: consultant: Bristol-Myers Squibb. CR: shareholder and employee: Bristol-Myers Squibb. MLB: shareholder and employee: Bristol-Myers Squibb (at time of study).

Ethical approval The study was conducted in accordance with the Declaration of Helsinki, the International Conference on Harmonization Good Clinical Practice Guidelines, and the Good Epidemiological Practice Guidelines. All enrolled patients provided informed consent in accordance with local laws.

Open Access This article is distributed under the terms of the Creative Commons Attribution 4.0 International License (<http://creativecommons.org/licenses/by/4.0/>), which permits unrestricted use, distribution, and reproduction in any medium, provided you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made.

References

- Singh JA, Saag KG, Bridges SLJ, Akl EA, Bannuru RR, Sullivan MC, Vaysbrot E, McNaughton C, Osani M, Shmerling RH, Curtis JR, Furst DE, Parks D, Kavanaugh A, O'Dell J, King C, Leong A, Matteson EL, Schousboe JT, Drevlow B, Ginsberg S, Grober J, St Clair EW, Tindall E, Miller AS, McAlindon T (2016) 2015 American College of Rheumatology guideline for the treatment of rheumatoid arthritis. *Arthritis Care Res (Hoboken)* 68:1–25
- Smolen JS, Landewé R, Bijlsma J, Burmester G, Chatzidionysiou K, Dougados M, Nam J, Ramiro S, Voshaar M, van Vollenhoven R, Aletaha D, Aringer M, Boers M, Buckley CD, Buttgerit F, Bykerk V, Cardiel M, Combe B, Cutolo M, van Eijk-Hustings Y, Emery P, Finckh A, Gabay C, Gomez-Reino J, Gossec L, Gottenberg JE, Hazes JM, Huizinga T, Jani M, Karateev D, Kouloumas M, Kvien T, Li Z, Mariette X, McInnes I, Mysler E, Nash P, Pavelka K, Poor G, Richez C, van Riel P, Rubbert-Roth A, Saag K, da Silva J, Stamm T, Takeuchi T, Westhovens R, de Wit M, van der Heijde D (2017) EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update. *Ann Rheum Dis* 76:960–977. <https://doi.org/10.1136/annrheumdis-2016-210715>
- Kiely PD (2016) Biologic efficacy optimization—a step towards personalized medicine. *Rheumatology (Oxford)* 55:780–788
- Genovese MC, Schiff M, Luggen M, Becker JC, Aranda R, Teng J, Li T, Schmidely N, Le BM, Dougados M (2008) 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* 67:547–554
- Kremer JM, Genant HK, Moreland LW, Russell AS, Emery P, Abud-Mendoza C, Szechinski J, Li T, Teng J, Becker JC, Westhovens R (2008) Results of a two-year follow up study of patients with rheumatoid arthritis who received a combination of abatacept and methotrexate. *Arthritis Rheum* 58:953–963
- Westhovens R, Kremer J, Emery P, Russell A, Alten R, Barre E, Dougados M (2014) 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
- Yoshida K, Radner H, Kavanaugh A, Sung YK, Bae SC, Kishimoto M, Matsui K, Okada M, Tohma S, Weinblatt ME, Solomon DH (2013) Use of data from multiple registries in studying biologic discontinuation: challenges and opportunities. *Clin Exp Rheumatol* 31:S28–S32
- Curtis JR, Jain A, Askling J, Bridges SL Jr, Carmona L, Dixon W, Finckh A, Hyrich K, Greenberg JD, Kremer J, Listing J, Michaud K, Mikuls T, Shadick N, Solomon DH, Weinblatt ME, Wolfe F, Zink A (2010) A comparison of patient characteristics and outcomes in selected European and US rheumatoid arthritis registries. *Semin Arthritis Rheum* 40:2–14
- Vashisht P, Sayles H, Cannella AC, Mikuls TR, Michaud K (2016) Generalizability of patients with rheumatoid arthritis in biologic agent clinical trials. *Arthritis Care Res (Hoboken)* 68:1478–1488
- Orencia 250 mg powder for concentrate for solution for infusion. (2017). <http://www.medicines.org.uk/emc/medicine/19714/SPC/>. Accessed May 21, 2018
- Product monograph: Orencia (abatacept). (2015). http://www.bmscanada.ca/static/products/en/pm_pdf/ORENCIA_EN_PM.pdf. Accessed October 10, 2018
- Cutolo M, Sulli A, Paolino S, Pizzorni C (2016) CTLA-4 blockade in the treatment of rheumatoid arthritis: an update. *Expert Rev Clin Immunol* 12:417–425
- Nüßlein H, Alten R, Galeazzi M, Lorenz HM, Boumpas D, Nurmohamed MT, Bensen WG, Burmester GR, Peter HH, Rainer F, Pavelka K, Chartier M, Poncet C, Rauch C, Le Bars M (2014) Real-world effectiveness of abatacept for rheumatoid arthritis treatment in European and Canadian populations: a 6-month interim analysis of the 2-year, observational, prospective ACTION study. *BMC Musculoskelet Disord* 15(14)
- Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, Healey LA, Kaplan SR, Liang MH, Luthra HS (1988) The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheumatol* 31:315–324
- World Medical Association Declaration of Helsinki. Recommendations guiding physicians in biomedical research involving human subjects (1997) *JAMA* 277:925–926
- ICH Harmonised Tripartite Guideline Guideline for good clinical practice (2001). *J Postgrad Med* 47:199–203
- Olsen J (2007) Good Epidemiological Practice (GEP): IEA Guidelines for Proper Conduct in Epidemiological Research
- Alten R, Mariette X, Lorenz HM, Galeazzi M, Cantagrel A, Nusslein HG, Chartier M, Elbez Y, Rauch C, Le Bars M (2017) Real-world predictors of 12-month intravenous abatacept retention in patients with rheumatoid arthritis in the ACTION observational study. *RMD Open* 3:e000538. <https://doi.org/10.1136/rmdopen-2017-000538>
- Fransen J, van Riel PL (2009) The disease activity score and the EULAR response criteria. *Rheum Dis Clin N Am* 35:745–757
- Felson DT, Smolen JS, Wells G, Zhang B, van Tuyl LH, Funovits J, Aletaha D, Allaart CF, Bathon J, Bombardieri S, Brooks P, Brown A, Matucci-Cerinic M, Choi H, Combe B, de Wit M, Dougados M, Emery P, Furst D, Gomez-Reino J, Hawker G, Keystone E, Khanna D, Kirwan J, Kvien TK, Landewé R, Listing J, Michaud K, Martin-Mola E, Montie P, Pincus T, Richards P, Siegel JN, Simon LS, Sokka T, Strand V, Tugwell P, Tyndall A, van der Heijde D, Verstappen S, White B, Wolfe F, Zink A, Boers M (2011) American College of Rheumatology/European league against rheumatism provisional definition of remission in rheumatoid arthritis for clinical trials. *Ann Rheum Dis* 70:404–413

21. Finckh A, Gomez-Reino J, Iannone F, Lie E, Canhao H, Pavelka K, Turesson C, Mariette X, Gottenberg JE, Hetland M, ABA oboP-E-Ro (2014) The impact of DMARD co-therapy on abatacept effectiveness in rheumatoid arthritis patients. A pan-European analysis of RA registries. *Ann Rheum Dis* 73(Suppl2):FR10298. <https://doi.org/10.1136/annrheumdis-2014-eular.3004>
22. Finckh A, Neto D, Iannone F, Loza E, Lie E, van Riel P, Hetland ML, Pavelka K, Gottenberg JE, Canhão H, Mariette X, Turesson C (2015) The impact of patient heterogeneity and socio-economic factors on abatacept retention in rheumatoid arthritis across nine European countries. *RMD Open* 1:e000040
23. De Keyser F, Hoffman I, Durez P, Kaiser MJ, Westhovens R (2014) Longterm followup of rituximab therapy in patients with rheumatoid arthritis: results from the Belgian MabThera in Rheumatoid Arthritis registry. *J Rheumatol* 41:1761–1765
24. Forsblad-d'Elia H, Bengtsson K, Kristensen LE, Jacobsson LTH (2012) Drug survival, efficacy and predictors for survival on tocilizumab in real-life patients with rheumatoid arthritis; results from the Swedish Biologics Register. *Arthritis Rheumatol* 64:S201
25. Greenberg JD, Reed G, Decktor D, Harrold L, Furst D, Gibofsky A, Dehoratius R, Kishimoto M, Kremer JM (2012) A comparative effectiveness study of adalimumab, etanercept and infliximab in biologically naive and switched rheumatoid arthritis patients: results from the US CORRONA registry. *Ann Rheum Dis* 71:1134–1142
26. Rotar Z, Hocesvar A, Rebolj KA, Praprotnik S, Tomsic M (2015) Retention of the second-line biologic disease-modifying antirheumatic drugs in patients with rheumatoid arthritis failing one tumor necrosis factor alpha inhibitor: data from the BioRx.si registry. *Clin Rheumatol* 34:1787–1793
27. Maxwell LJ, Singh JA (2010) Abatacept for rheumatoid arthritis: a Cochrane systematic review. *J Rheumatol* 37:234–245
28. Schiff M, Poncet C, Le BM (2010) Efficacy and safety of abatacept therapy for rheumatoid arthritis in routine clinical practice. *Int J Clin Rheumatol* 5:581–591
29. Weinblatt ME, Moreland LW, Westhovens R, Cohen RB, Kelly SM, Khan N, Pappu R, Delaet I, Luo A, Gujrathi S, Hochberg MC (2013) Safety of abatacept administered intravenously in treatment of rheumatoid arthritis: integrated analyses of up to 8 years of treatment from the abatacept clinical trial program. *J Rheumatol* 40:787–797
30. Alten R, Nüßlein H, Galeazzi M, Lorenz HM, Mariette X, Cantagrel A, Chartier M, Elbez Y, Rauch C, Le Bars M (2016) Do predictors of IV abatacept retention depend on the line of rheumatoid arthritis treatment: 12-month interim analysis of the observational, prospective ACTION study. *Ann Rheum Dis* 75:202
31. Nüßlein HG, Alten R, Galeazzi M, Lorenz HM, Nurmohamed MT, Bensen WG, Burmester GR, Peter HH, Pavelka K, Chartier M, Poncet C, Rauch C, Le Bars M (2015) Prognostic factors for abatacept retention in patients who received at least one prior biologic agent: an interim analysis from the observational, prospective ACTION study. *BMC Musculoskelet Disord* 16:176. <https://doi.org/10.1186/s12891-015-0636-9>
32. Nüßlein HG, Alten R, Galeazzi M, Lorenz HM, Nurmohamed MT, Bensen WG, Burmester GR, Peter HH, Peichl P, Pavelka K, Chartier M, Poncet C, Rauch C, Le BM (2016) Efficacy and prognostic factors of treatment retention with intravenous abatacept for rheumatoid arthritis: 24-month results from an international, prospective, real-world study. *Clin Exp Rheumatol* 34:489–499
33. Gabay CRM, Scherer A, Finckh A (2015) Effectiveness of biologic DMARDs in monotherapy versus in combination with synthetic DMARDs in rheumatoid arthritis: data from the Swiss Clinical Quality Management Registry. *Rheumatology (Oxford)* 54:1664–1672. <https://doi.org/10.1093/rheumatology/kev019>
34. Gottenberg JE, Courvoisier DS, Hernandez MV, Iannone F, Lie E, Canhao H, Pavelka K, Hetland ML, Turesson C, Mariette X, Finckh A (2016) 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* 68:1346–1352
35. Huizinga TWJ, Connolly SE, Johnsen A, Zhu J, Furst DE, Bykerk VP, Burmester GR, Combe BG, Wong DA, Trouw LA, Toes REM, Emery P (2015) Effect of anti-cyclic citrullinated peptide 2 immunoglobulin M serostatus on efficacy outcomes following treatment with abatacept plus methotrexate in the AVERT trial. *Ann Rheum Dis* 74(Suppl 2):234–235
36. Sokolove J, Schiff M, Fleischmann R, Weinblatt ME, Connolly SE, Johnsen A, Zhu J, Maldonado MA, Patel S, Robinson WH (2016) 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* 75:709–714
37. Harrold LR, Litman HJ, Connolly SE, Kelly S, Hua W, Alemao E, Rosenblatt L, Rebello S, Kremer JM (2018) Effect of anticitrullinated protein antibody status on response to abatacept or antitumor necrosis factor-alpha therapy in patients with rheumatoid arthritis: a US National Observational Study. *J Rheumatol* 45:32–39. <https://doi.org/10.3899/jrheum.170007>
38. Bozec A, Luo Y, Ngdahl C et al. (2018) Abatacept blocks anti-citrullinated protein antibody and rheumatoid factor mediated cytokine production in human macrophages in IDO-dependent manner. *Arthritis Res Ther* 20. <https://doi.org/10.1093/rheumatology/kyt224>
39. Ranganath VK, Maranian P, Elashoff DA, Woodworth T, Khanna D, Hahn T, Sarkisian C, Kremer JM, Furst DE, Paulus HE (2013) Comorbidities are associated with poorer outcomes in community patients with rheumatoid arthritis. *Rheumatology (Oxford)* 52:1809–1817
40. McWilliams DF, Walsh DA (2016) Factors predicting pain and early discontinuation of tumour necrosis factor-a-inhibitors in people with rheumatoid arthritis: results from the British society for rheumatology biologics register. *BMC Musculoskeletal Disorders*. <https://doi.org/10.1186/s12891-12016-11192-12897> doi:27515300
41. Kang EH, Yin Zhu J, Brill G, Lewey J, Patomo E, Desai RJ, Kim SC (2018) Comparative cardiovascular risk of abatacept and tumor necrosis factor inhibitors in patients with rheumatoid arthritis with and without diabetes mellitus: a multidatabase cohort study. *J Am Heart Assoc* 7:e007393. <https://doi.org/10.1161/JAHA.117.007393>
42. Lee J, Mason R, Martin L, Barnabe C (2014) Biologic therapy response and drug survival for females compared to males with rheumatoid arthritis: a cohort study. *Rheumatol Int* 34:1449–1453
43. Alten R, Nüßlein H, Galeazzi M, Lorenz H-M, Mariette X, Cantagrel A, Chartier M, Desachy G, Poncet C, Rauch C, Le Bars M (2015) Body mass index does not influence the efficacy of abatacept in patients with RA who are biologic naive: 6-month results from a real-world, international prospective study. *Arthritis Rheumatol* 67(suppl 10):abstract 553. <https://acrabstracts.org/abstract/body-mass-index-does-not-influence-the-efficacy-of-abatacept-in-patients-with-ra-who-are-biologic-naive-6-month-results-from-a-real-world-international-prospective-study/>
44. Alten R, Nusslein HG, Mariette X, Galeazzi M, Lorenz HM, Cantagrel A, Chartier M, Poncet C, Rauch C, Le Bars M (2017) Baseline autoantibodies preferentially impact abatacept efficacy in patients with rheumatoid arthritis who are biologic naive: 6-month results from a real-world, international, prospective study. *RMD Open* 3:e000345. <https://doi.org/10.1136/rmdopen-2016-000345>
45. Harigai M, Ishiguro N, Inokuma S, Mimori T, Ryu J, Takei S, Tanaka Y, Takasaki Y, Yamanaka H, Watanabe M, Tamada H, Koike T (2016) Postmarketing surveillance of the safety and effectiveness of abatacept in Japanese patients with rheumatoid arthritis. *Mod Rheumatol* 8:1–8

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.