Retention rate of abatacept in rheumatoid arthritis patients in a real-life setting: results from a monocentric cohort

E. Molteni[1], C. Pirone[1], F. Ceccarelli[1], C. Castellani[1], C. Alessandri[1], M. Di Franco[1],
V. Riccieri[1], F.R. Spinelli[1], R. Priori[2,3], R. Scrivo[1], F. Conti[1]

[1]Rheumatology Unit, Department of Clinical Internal, Anesthesiological and Cardiovascular Sciences,
Sapienza University of Rome, Italy; [2]Department of Internal Medicine and Medical Specialties,
Rheumatology Clinic, Sapienza University of Rome, Italy; [3]Saint Camillus International University
of Health Science, UniCamillus, Rome, Italy

SUMMARY

Objective. Data from trials demonstrated that abatacept (ABA) has a good safety and efficacy profile in treating rheumatoid arthritis. We have studied the retention rate of ABA in a real-life cohort of patients with rheumatoid arthritis.
Methods. This is a monocentric, retrospective study including patients with rheumatoid arthritis classified by the American College of Rheumatology/European League Against Rheumatism 2010 criteria who started treatment with ABA. The Kaplan-Meier method was applied to evaluate the ABA retention rate.
Results. This analysis was conducted on 161 patients [male/female 21/140, median age 65 years, interquartile range (IQR) 18.7, median disease duration 169 months, IQR 144.0]. 111 patients (68.9%) received ABA subcutaneously. ABA was associated with methotrexate in 61.9% of patients and was the first biological disease-modifying antirheumatic drug in 41%. We observed a median ABA survival of 66 months [95% confidence interval (CI) 57.3-74.7], with a retention rate of 88% at 6 months and 50.9% at 5 years. Drug survival was significantly higher in patients treated with ABA subcutaneously and in male patients (p=0.039 and p=0.018, respectively). Adjusted for main confounders, female gender was the main predictor of withdrawal (hazard ratio 5.1, 95% CI 1.2-21.3).
Conclusions. Our study shows that better survival is associated with subcutaneous administration and male gender, confirming ABA effectiveness.

Key words: Abatacept, rheumatoid arthritis, drug therapy, intravenous injections, subcutaneous injections, retention rate.

■ INTRODUCTION

Rheumatoid arthritis (RA) is an autoimmune, rheumatic, inflammatory disease that affects approximately 0.5-1.0% of the Western population (1). It may lead to disability and increased mortality risk, which can be faced both by treating patients as early as possible and by tuning the therapeutic strategies with the available innovative drugs (2). In the wide choice of disease-modifying antirheumatic drugs (DMARDs), biologic agents (bDMARDs) play an important role in patients who do not respond to conventional synthetic DMARDs, such as methotrexate (MTX), especially when poor prognostic factors are present (3).

Nowadays, several bDMARDs have gained approval for RA treatment, including abatacept (ABA) (4). This drug binds to *CD80* and *CD86* on antigen-presenting cells, preventing these molecules from binding to *CD28* on T lymphocytes, thus blocking T cell activation (5). ABA is available in intravenous (IV) and subcutaneous (SC) formulations, both of which have been well tolerated in several randomized controlled trials (RCTs), ensuring a good safety profile in the long-term period, with a low incidence rate of serious infections and malignancies (6-8). However, populations enrolled in RCTs are known to be highly selected and controlled, urging the need to obtain clinical data in an everyday, real-world setting

Corresponding author:
Fulvia Ceccarelli, Rheumatology Unit,
Department of Clinical Internal,
Anesthesiological and Cardiovascular Sciences,
Sapienza University of Rome, Viale del
Policlinico, 155 - 00161 Rome, Italy
E-mail: fulviaceccarelli@gmail.com

(9). On this basis, we aimed to evaluate the ABA retention rate (RR) in our cohort of patients with RA.

■ MATERIALS AND METHODS

Study design
This monocentric, retrospective, longitudinal, observational study was conducted on consecutive adult RA patients starting treatment with IV or SC ABA according to the standard of care at the Rheumatology Unit, Sapienza University of Rome, Italy, from June 2007 to December 2020.

Source population
All the patients fulfilled the 2010 American College of Rheumatology/European League Against Rheumatism (EULAR) classification criteria for RA (10). ABA was administered at the recommended therapeutic dose of 125 mg weekly for the SC route and 500-1000 mg per month according to patients' weight for the IV route (6). For each patient, we collected demographic, clinical, and laboratory parameters.

The study was approved by the local ethics committee and was performed according to the Declaration of Helsinki. All patients provided written informed consent for future research studies at the time of enrollment.

Aim of the study
As the main objective of the study, we evaluated the RR of ABA, defined as the proportion of patients who persist on treatment (consecutive time of treatment) in both IV and SC formulations. Treatment initiation was defined as the date of the first ABA dose, and the date of discontinuation as the date of the first missed dose for interruptions of at least 3 months or the date of the switch to SC administration for IV patients. Furthermore, at baseline (T0), after 4 (T4) and 12 months (T12), the Disease Activity Score using 28 joint counts (DAS28) with C reactive protein (DAS28-CRP) (11), and response to the treatment by using EULAR response criteria (6) were calculated. The reasons for withdrawal of treatment were registered and classified as lack of efficacy (LaE), loss of efficacy (LoE), switch to SC administration, or adverse events (AEs).

Statistical analysis
We expressed demographic, clinical, and laboratory characteristics as absolute frequencies and percentages for categorical variables, and as medians with interquartile range (IQR) for continuous ones. The Kaplan-Meier method was applied to evaluate the RR of ABA. Cox proportional hazard model was calculated to identify the role of baseline factors as predictors of ABA discontinuation. Results are reported as a hazard ratio (HR) with 95% confidence intervals (CI). Univariate analysis of nominal variables was performed using the χ^2 test or Fisher test. For the univariate analysis of the continuous variables, the Mann-Whitney U or Wilcoxon tests were performed. Statistical analysis was elaborated using Statistical Package for Social Sciences 25.0 (IBM SPSS, Armonk, NY, USA). A 2-tailed $p<0.05$ was considered statistically significant.

■ RESULTS

Baseline characteristics
The baseline characteristics of the patients are reported in Table 1. We included 161 patients treated with ABA (male/female 21/140; median age 65 years, IQR 18.7; median disease duration 169 months, IQR 144.0). Rheumatoid factor was positive in 70.3% of patients, and anti-citrullinated protein antibodies (ACPA) in 66.4%.

ABA was prescribed as a first-line bD-MARD in 66 patients (41%), who showed a significantly shorter disease duration in comparison with patients previously treated with other bDMARDs (109 months, IQR 119.5 *versus* 190.5 months, IQR 152.5, respectively; p<0.0001). ABA was administered by SC injections in 111 patients (68.9%) and IV in the remaining 50 (31.1%). Patients receiving SC ABA were more often bio-naïve (p=0.006) and ACPA positive (p=0.002) than IV patients. No significant difference was found between these two groups of patients in terms of age and disease duration. Furthermore, ABA was administered in association with MTX in 96 patients (61.9%); this combination therapy was more common in patients

Table I - Baseline demographics, clinical, and laboratory features according to the line of treatment and administration route.

	Overall (n=161)	First-line (n=66)	SC (n=111)	IV (n=50)	p value
Demographic and disease characteristics					
Median age, years (IQR)	65 (18.75)	64.5 (20.75)	64.0 (21.0)	68.0 (14.5)	NS
Female, n (%)	140 (87.0)	57 (86.4)	95 (85.6)	45 (90.0)	NS
Median disease duration, months (IQR)	169 (144.0)	109 (119.5)	157 (132.0)	188 (188.0)	NS
Treatment					
Concomitant MTX, n (%)	96 (61.9)	40 (61.5)	58 (54.7)	38 (76.0)	*0.01*
Concomitant GCs, n (%)	51 (31.7)	23 (34.8)	36 (32.4)	15 (30.0)	NS
ABA first-line, n (%)	66 (41.0)	66 (100)	54 (48.6)	12 (24.0)	*0.006*
ABA second-line, n (%)	95 (59.0)	0 (0)	57 (51.4)	38 (76.0)	*0.006*
Laboratory features					
RF positive, n (%)	83 (70.3)	27 (64.3)	57 (75.0)	26 (61.9)	NS
ACPA positive, n (%)	77 (66.4)	30 (61.2)	60 (73.2)	17 (50.0)	*0.02*

SC, subcutaneous route of administration; IV, intravenous route of administration; IQR, interquartile range; MTX, methotrexate; GCs, glucocorticoids; ABA, abatacept; RF, rheumatoid factor; ACPA, anti-citrullinated peptide antibodies; NS, not significant.

treated with IV ABA than in those treated with SC ABA (p=0.01). Glucocorticoids (GCs) were assumed by 31.7% of the patients with a median dosage of 2 mg/day (IQR 4) of prednisone equivalent; no significant difference was found in any group of patients receiving ABA in association with GCs, as reported in Table I.

### Patients' disposition and drug retention rate

Among the 161 patients enrolled, survival analysis was run in 160; effectiveness and safety analysis at 4 and 12 months (T4 and T12) was conducted in 106 (65.8%) and 62 (38.5%) patients, respectively. We observed an overall median ABA survival of 66 months (95% CI 57.3-74.7), with a RR of 88% at 6 months, 75% at 12 months, and 50.9% at 5 years of follow-up, as shown in Figure 1.

Drug survival was significantly higher in patients treated with SC ABA and in male patients (p=0.039 and p=0.018, respectively). When adjusted for main confounders (including age, disease duration, concomitant treatment, and positivity of ACPA), female gender was the main predictor for ABA withdrawal (HR 5.1, 95% CI 1.2-21.3). Conversely, SC administration was a protective factor for maintaining ABA treatment (HR 5.1, 95% CI 1.2-21.3 and HR 0.5, 95% CI 0.3-0.9, for males and females, respectively), confirming the opposite role of gender in predicting treatment survival. ABA withdrawal was reported in 72 patients, including 56% of those treated with IV ABA and 39.6% of patients treated with SC ABA. The main reasons for discontinuation were LaE and LoE (23.6%), followed by AE (18.0%); 18 patients (11.1%) switched from IV to SC administration, mainly to take advantage of the shorter time of administration process.

Effectiveness

Clinical outcome results are shown in Figures 2 and 3. At T4, we lost 55 patients (N=106), and at T12, an additional 99 patients (N=62). In the whole RA cohort, we observed a significant decrease of DAS28-CRP at both T4 (p<0.0001) and T12 (p<0.0001). The improvement was confirmed when stratifying patients according to the route of ABA administration (Figure 2). The proportion of patients achieving an EULAR response (good or moderate) was 51% at T4 and 67.7% at T12 (Figure 3). Moreover, at T4, we noticed a significant association of improvement in EULAR response (good or moderate) with male gender and SC administration (p=0.01 and p=0.01, respectively).
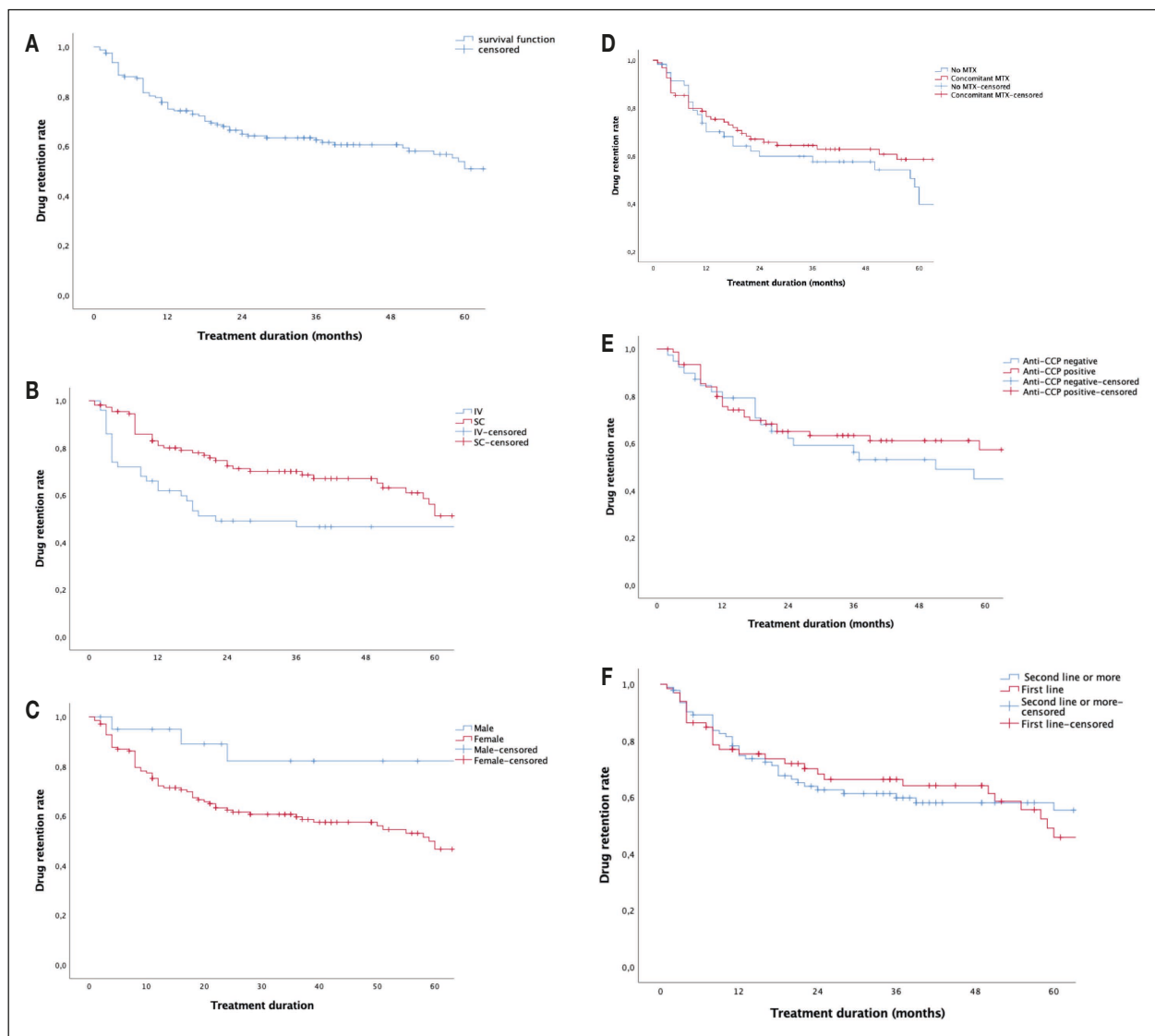
Figure 1 - Retention rate of the overall cohort (A), and according to the administration route (B), gender (C), concomitant methotrexate (D), and anti-citrullinated protein antibodies positivity (E), first-line *versus* second-line (F). In detail, we analyzed 160 patients at baseline, 116 patients at 12 months, 87 patients at 24 months, 71 patients at 36 months, 52 at 48 months, and 37 at 60 months.
Significant values in the comparison reported in the figure: subcutaneous *versus* intravenous abatacept p=0.039 (B); male *versus* female patients p=0.018 (C); methotrexate yes or no p=0.42 (D); anti-citrullinated protein antibodies positive *versus* anti-citrullinated protein antibodies negative p=0.82 (E); first-line *versus* second-line p=0.08 (F). SC, subcutaneous; IV, intravenous; MTX, methotrexate; CCP, cyclic citrullinated peptides.

■ **DISCUSSION**

In this study, we evaluated the response to ABA in patients with RA through RR, which is considered a good predictor of effectiveness and safety in real-life scenarios. This issue has been evaluated in other studies, which are summarized in Table II (12-17).

We observed a good RR, which was 75% at 12 months of follow-up. Moreover, male gender and SC administration resulted positive predictive factors for ABA RR. On the other hand, in our study, ACPA positivity and the concomitant assumption of MTX were associated with a slightly higher RR at 60 months, even if not statistically signifi-
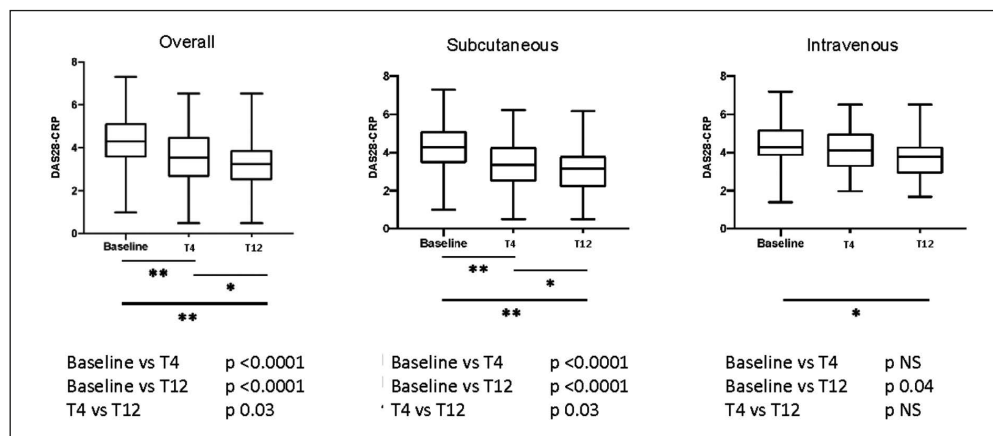
Figure 2 - Disease Activity Score using 28 joint counts with C reactive protein change during follow-up in the overall population and according to the administration route. T4, after 4 months; T12, after 12 months; NS, not significant.

cant (Figure 1D, E), likely due to the limited sample size. This data is in accordance with the results of other studies (12-15).
The majority of studies focusing on ABA survival provide data on 12-month endpoints, including the ACTION study and the French-Ric Network study (13, 14). The 12-month RR derived from the studies published so far ranges from 55% to 77% (12-16). Thus, our 12-month RR equal to 75% stands in the upper limit of this range. However, we also provide data on a longer follow-up period, reaching 60 months, where the RR was 50.9%. This result agrees with the study published by Westhovens et al., reporting a 51% RR at 60 months (11). In a large number of studies (12-19), drug survival was mainly related to ACPA positivity and ABA given as a first-line drug.
RR is generally considered a surrogate of drug effectiveness in a real-life setting (18). Comparing ABA's RR with that of other bDMARDs (adalimumab, rituximab, and tocilizumab), similar effectiveness at different endpoints has been reported, together with a lower risk of infection in patients treated with ABA (20-22).
In our cohort, the improvement in DAS28-CRP was more evident in the SC administration than in IV, partially in contrast with data from the literature (22, 23). A possible explanation for this observation may reside in the characteristics of the popula-
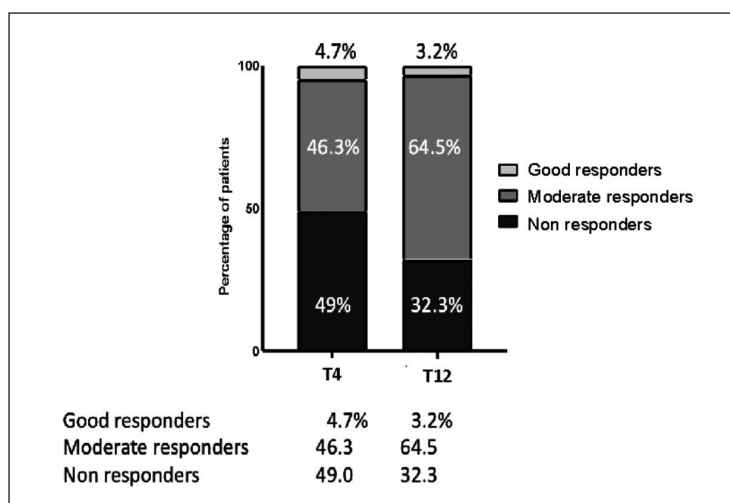
Figure 3 - Proportions of patients achieving a good or moderate European League Against Rheumatism response during follow-up. T4, after 4 months; T12, after 12 months.

tions, since in our study, patients receiving SC ABA were more often ACPA-positive, more frequently received combination therapy with MTX, and usually, ABA was taken as first-line treatment. Indeed, seropositivity, combination therapy, and first-line strategy are well-known predictors of a good response to therapy with ABA (12). In contrast, the population receiving IV ABA was characterized by higher age and a significantly higher rate of first-line bDMARD failures.

Table II - Studies assessing abatacept retention rate in patients with rheumatoid arthritis.

Article	Study design	Population (n)	Administration route (IV/SC, %)	RR at 6 months (%)	RR at 12 months (%)	Predictors of discontinuation
Cagnotto et al., 2020 (12)	Observational, nation-wide register-based, longitudinal, prospective	2716	50/50	75	55	Male gender (HR 0.85, CI 0.74-0.98), elevated VAS pain and MTX at baseline had significant independent effects on ABA discontinuation
Westhovens et al., 2020 (13)	Non-interventional, observational, longitudinal, retrospective	135	100/0	Not available	76	None
Nüßlein et al., 2014 (17)	Non-interventional, multicenter, prospective, observational	1114	100/0	88.6	Not available	None
Salmon et al., 2020 (14)	Ambispective, multicentric, observational	517	Not specified	83	68	Not available
pope et al., 2015 (16)	Observational, register-based, transversal	1771	100/0	Not available	66	none
ogawa et al., 2019 (15)	Multicenter, observational, prospective	109	100/0	Not available	77	not available

ABA, abatacept; RR, retention rate; SC, subcutaneous route of administration; IV, intravenous route of administration; HR, hazard ratio; CI, confidence interval; VAS, visual analog scale; MTX methotrexate.

We observed a significant decrease in DAS28-CRP values from baseline at all time points, with the achievement of a moderate/good EULAR response in 67.7% of patients after 12 months of both IV and SC therapy. This result is in accordance with other data available in the literature (12, 13).

Again, we noticed a significant association between the achievement of an EULAR response (good or moderate) at T4, the male gender, and SC administration. An association between the male gender and good response to ABA treatment has already been documented in a large retrospective nationwide register, where female gender was a major predictor of treatment discontinuation, with an HR of 0.85 (95% CI 0.75-0.96) (17). Indeed, male gender was associated with a better clinical response and a lower risk of discontinuation with tumor necrosis factor inhibitors (17).

Certainly, the lack of information about the patients' comorbidities could be a limitation of our study. Furthermore, the observation design did not allow to specify the type of all AEs.

■ CONCLUSIONS

In conclusion, the analysis of our monocentric RA cohort demonstrates a high RR for ABA at both 4 and 12 months of treatment, confirming the good profile of this drug in terms of effectiveness and safety. In addition, we noticed that male patients receiving SC ABA had a better response after 4 months of treatment.

Contributions
All the authors made a substantial intellectual contribution, read and approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

Conflict of interest
The authors declare that they do not have

any potential conflict of interest and any financial or personal relationships that may pose conflicts of interest.

Ethics approval and consent to participate

The study was approved by the local ethics committee and was performed according to the Declaration of Helsinki.

Informed consent

All patients provided written informed consent for future research studies at the time of enrollment.

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Availability of data and materials

Data and materials are available from the corresponding author upon request.

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