



Subcutaneous abatacept in rheumatoid arthritis: A real-life experience



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ARTICLE INFO

Keywords:

Rheumatoid arthritis
Subcutaneous abatacept
Latin America
Real world data
Precision medicine

ABSTRACT

Objectives: To assess the effectiveness, safety, and drug survival of subcutaneous (SC) abatacept (ABA) in a cohort of rheumatoid arthritis (RA) patients in a real-world setting.

Methods: This was a retrospective cohort study from 2014 to 2018 in which patients with RA (1987 ACR criteria) were included. Patients were evaluated at a single rheumatology outpatient center in Bogotá, Colombia. The patients were classified according to their treatment background: biological-naïve (n = 65), switched from IV to SC ABA administration (125 mg-wk) (n = 32), and inadequate response to biological DMARD (n = 62). The primary endpoint was a change in DAS28-CRP and RAPID3 from baseline to 12 months. A linear mixed effect model was used to correlate repeated measures. Adverse events were assessed and recorded during each visit to the rheumatology center. Several Cox proportional hazard regression models were used to test if there were any differences in drug survival curves based on seropositivity for rheumatoid factor (RF), and anti-Cyclic Citrullinated Peptide Antibodies (anti-CCP). Statistical analysis was done using software R version 3.4.4.

Results: A total of 159 patients were included. Baseline characteristics of patients were as follows: female gender 84%, median age of 54 years (IQR 16), median disease duration 10 years (11), RF positive 96%, anti-CCP positive 89%, erosive disease 55%, median DAS28-CRP 5.0 (2), and median RAPID3 17 (10). Concomitant use of methotrexate and SC ABA monotherapy were reported at 52% and 30% respectively. Demographics and disease characteristics were similar for all groups, except for baseline DAS28-CRP, and RAPID3 in the group that switched route of administration. The interaction between time and group was significant (p = 0.0073) for RAPID3. Infections, constitutional symptoms, and headaches were the most frequent AEs. Retention rate corresponded to 60% at 48 months. The most frequent reason for drug suspension was loss of efficacy. Median time of treatment for SC ABA was 31 months (IQR 30). The only association that reached statistical significance was anti-CCP concentration [Q1–Q4] (p = 0.005). According to the Cox proportional hazard regression model, there were significant differences between survival curves for Q1 (HR 0.15; 0.03–0.64 95% CI; p = 0.0096), and Q2 (HR 0.28; 0.08–0.92 95% CI; p = 0.0363) compared to the seronegative group.

Conclusions: The results showed an improvement in RA disease activity and physical function in patients under SC ABA treatment. Patients switching from IV to SC administration of ABA had lower activity and functional impairment at baseline. SC ABA demonstrated a good safety profile consistent with previously published data. Patients with baseline levels of anti-CCP antibody concentrations had better drug survival than seronegative patients.

1. Introduction

Rheumatoid arthritis (RA) is a chronic and inflammatory systemic

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<https://doi.org/10.1016/j.jtauto.2019.100016>

Received 29 June 2019; Received in revised form 28 August 2019; Accepted 3 September 2019

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Abbreviations	
ABA	abatacept
A-BREAK	Abatacept Study to Omit Weekly Subcutaneous Injections in RA patients During Holiday BREAK
ABROAD	Abatacept Research Outcomes as a First-line Biological Agent in the Real World
ACQUIRE	Abatacept Comparison of Subcutaneous versus Intravenous in Inadequate Responders to Methotrexate
ACPA	anti-citrullinated protein autoantibody
ACR	American College of Rheumatology
ACTION	Abatacept in routine clinical practice
AE	adverse event
AIM	Abatacept in Inadequate response to Methotrexate
AMPLE	Abatacept versus Adalimumab Comparison in Biologic-Naïve RA Patients with Background Methotrexate
Anti-CCP	anti-cyclic citrullinated peptide antibodies
ATTAIN	Abatacept Trial in Treatment of Anti-tumor necrosis factor Inadequate responders
bDMARD	biologic disease modifying antirheumatic drug
BMI	body mass index
CI	confidence interval
csDMARD	conventional synthetic disease modifying antirheumatic drug
DAS28-CRP	disease activity score C-reactive protein
DMARD	disease modifying antirheumatic drug
ELISA	enzyme linked immunosorbent assay
ESR	erythrocyte sedimentation rate
EULAR	European League Against Rheumatism
IQR	interquartile range IR-bDMARD inadequate response to biologic disease modifying antirheumatic drug
IV	intravenous
LA	Latin American
LME	linear mixed effects
MTX	methotrexate
RA	rheumatoid arthritis
RAPID3	routine assessment of patient index data 3
RF	rheumatoid factor
RTC	randomized controlled trials
RWD	real-world data
SAE	serious adverse event
SC	subcutaneous
SES	socioeconomic status
TNF- α	tumor necrosis factor alpha

disease that is autoimmune in nature and is characterized by rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP) production. The disease is complex and involves environmental factors that trigger the disease in genetically susceptible individuals [1]. RA prevalence is around 1% around the world but this number changes in different ethnic populations [2]. Early therapeutic intervention with disease-modifying antirheumatic drugs (DMARDs) including methotrexate (MTX), biological treatments, and Janus Kinase inhibitors are supposed to halt inflammation, improve symptoms and signs, and preserve structural integrity of the joints in RA [3].

Different biological strategies have been used on patients with RA whose response to conventional DMARDs has been inadequate [4]. These strategies include Tumor Necrosis Factor alpha (TNF- α) agents, interleukin 6 inhibition, B-cell depletion, and T-cell targeting therapy represented by abatacept (ABA) [5]. ABA is a human fusion protein that selectively inhibits T-cell activation by binding to CD80/CD86, thus blocking CD28 on antigen-presenting cells known as the costimulatory signal (i.e., second signal) [6].

To date, several clinical trials of ABA have shown significant efficacy in terms of reducing signs and symptoms, improving function, and reducing structural damage [7–10]. Subcutaneous (SC) ABA showed similar efficacy and safety profile in the clinical trials in comparison to intravenous (IV) ABA [5]. The data also showed that patients can be switched from IV to SC ABA without a loss of efficacy, or increased adverse events (AEs) [10].

Therapeutic guidelines draw heavily on evidence from randomized controlled trials (RCTs) undertaken in well-described, highly selective populations, and managed in tightly controlled settings. As such, the therapeutic efficacy in real-life populations and routine care settings is often different from the RCTs [11]. Real-world data (RWD) refer to data collected from diversified areas of daily life that are outside the scope of highly controlled RCTs [12]. A few studies have evaluated the effectiveness, safety, and tolerability of ABA in patients with RA in routine clinical practice [13–16].

Survival time or time to discontinuation of medication is a surrogate of the long-term impact on the course of the disease in real life. It reflects the effectiveness of clinical treatment in the absence of significant AEs [17]. Treatment discontinuation can result from loss of efficacy or safety concerns, but prognostic factors for drug retention have not been explored thoroughly despite data for ABA and other biologicals being

available from national registries [18,19].

RWD regarding ABA in the Latin American (LA) population are scarce [20,21]. The intention of this study was to assess SC ABA effectiveness and safety in a cohort of Colombian patients with moderate-to-severe RA in a real-life setting. It was also to determine whether baseline anti-CCP/RF antibody concentration, treatment background, and erosive disease related to SC ABA survival (incomplete sentence).

2. Material and methods

2.1. Study population

Colombian patients with RA seen at the Dermatology and Rheumatology Center FUNINDERMA (Bogotá, Colombia) were included. Inclusion criteria were as follows: 1) patients who voluntarily agreed to participate, read, and signed an informed consent; 2) Colombian patients (born and resident); 3) onset of arthritis at an age equal to or greater than 16 years; 4) fulfillment of 1987 American College of Rheumatology classification criteria for RA; 5) patients with moderate to severe disease for whom SC ABA had been prescribed as part of the Rheumatologist criterion. Exclusion criteria corresponded to withdrawal of informed consent at any time during the study.

2.2. Study design

This was a non-interventional, observational, and retrospective cohort study. A non-probability (convenience) sampling was done. Patients included were followed from around April 2014 to April 2018. Each patient was evaluated by the same rheumatologist. The frequency of visits in the center was defined by the usual clinical practice of following a treat to target approach. The information on patient socio-demographic and cumulative clinical and laboratory data were obtained by interview, physical examination, and chart review. The data collected from each individual were stored in an electronic and secure database. The database was audited by three independent reviewers from the research group.

Information related to SC ABA treatment was collected at each visit to the center. This information included the number of applications per month, reasons for skipping one or more doses, reasons for temporary or definitive suspension, Routine Assessment of Patient Index Data 3 (RAPID3), and systemic and local AEs. For patients with all data available

for the appointment including C-reactive protein (CRP), Disease Activity Score 28 (DAS28) was calculated for each visit. A telephone contact (handled by nurse, epidemiologist or rheumatologist) was made at the end of every month in order to complete information for those patients who had not seen the doctor that month.

2.3. Outcome definition

Several clinical and laboratory variables were assessed including DAS28, RAPID3, treatment background, erosive subphenotype, and seropositivity status. A DAS28 based on CRP instead of ESR was preferred for estimating disease activity. RAPID3 is an index found within a multi-dimensional health assessment questionnaire for routine clinical care composed of only 3 self-report scores for physical function, pain, and patient global estimate. Each of these is scored on a 0–10 scale, for a total of 0–30. All patients were classified based on their treatment background: biologic-naïve, switched from IV to SC ABA administration (125 mg/week), and inadequate response to biological DMARD (IR-bDMARD). Erosive disease was determined by EULAR definition [22].

Values of CRP, anti-CCP and RF were recorded at the time of inclusion. In the case of several determinations prior to the inclusion, the highest value was recorded. Autoantibodies were coded as qualitative and/or quantitative variables. In most cases, baseline anti-CCP antibody status (positive/negative) and concentration were determined using an anti-CCP3 IgG ELISA (INOVA Diagnostics). Patients with a baseline anti-CCP IgG concentration of ≥ 20 UI/mL were considered to be positive and were further divided into equal quartiles based on concentration [Q1–Q4 (highest concentration)]. A similar process was followed for RF. The Immunoturbidimetry was the most frequently technique used for RF measurement.

Systemic injection reactions were defined as nonlocal AE that occurred during the first 24 h after SC ABA injection and included constitutional symptoms (e.g., fatigue, sleepiness, general malaise, chills), gastrointestinal symptoms (e.g., nausea, diarrhea, vomiting, abdominal pain), sicca symptoms (e.g., xerostomia, xerophthalmia, xerosis), respiratory symptoms (e.g., cough, rhinorrhea, rhinitis), and others such as headaches, arthralgia, dizziness, and skin rash. Local injection-site reactions (defined as AE that occurred at the site of SC ABA injection) were prespecified, and included pain, hematoma, edema, erythema, pruritus, papule, burning, and irritation.

2.4. Statistical analysis

Categorical variables were analyzed by frequencies. Quantitative continuous variables are described as the median and interquartile range (IQR). In order to establish the comparability between treatment background subgroups, a statistical hypothesis test was done of quantitative continuous and categorical variables with the Kruskal-Wallis and Chi-square tests respectively.

A linear mixed effects (LME) model was used for correlation of repeated measures (i.e., change in DAS28 and RAPID3 from baseline to follow-up regarding treatment background) [23]. Interaction between the time of measurement follow-up and treatment group was considered in the modeling in order to assess if evolution of DAS28 or RAPID3 differed between the three groups. Data was processed in order to collect treatment duration for each patient as well as to establish whether they continued the treatment at the end of the follow-up. Patients who did not have information related to the start date of treatment were excluded from the survival analysis. Several Cox proportional hazard regression models were used to test whether there were any differences in drug survival curves based on treatment background, erosive disease, seropositivity for RF/anti-CCP (antibody status and concentration [Q1–Q4]). Statistical analysis was done in the software R version 3.4.4 [24].

2.5. Ethical considerations

This study was done in compliance with Act 008430/1993 by *Ministry of Health of the Republic of Colombia*, which classified it as minimal-risk research. The institutional review board of the *Universidad del Rosario* approved the study design within the “Common mechanisms of autoimmune diseases” macro-observational project.

3. Results

3.1. Baseline characteristics

A total of 159 patients were included. Distribution regarding subgroups is depicted in [Table 1](#). The profile of the majority of patients included corresponded to: female gender (84%), median age of 54 years (IQR 16), high educational level (greater than or equal to 9 years), high socioeconomic level (44%), and private healthcare insurance coverage (54%). An important part of the population had multimorbidity with hypertension (34%), and osteoporosis (25%) being the most frequent causes described. Prevalence of malignancy was 5% with solid organ cancer being the most frequent (e.g., breast and thyroid). The proportion of patients with obesity and current smoking were 9% and 5% respectively. The most prevalent infections were latent tuberculosis (22%), urinary tract infection (18%), skin and soft-tissue infections (8.8%), herpes zoster (8.1%), and upper respiratory tract infections (7%).

Regarding RA-related characteristics, the duration median for RA corresponded to long-standing disease (10 years). RF was positive in 96% of the patients and anti-CCP in 89%. Data for anti-CCP antibodies was only available from 73% of patients. Fifty five percent of the patients had erosive disease. The proportion of patients with extra-articular manifestations was 35% with rheumatoid nodulosis being the leading form of presentation (18%). Autoimmune diseases co-occurring within patients (i.e., polyautoimmunity) [25] was described in 12% of the population at baseline. Autoimmune thyroid disease was the most frequent association. The groups had similar demographics and disease characteristics, including a proportion of SC ABA monotherapy, except for educational level ($p = 0.0191$), private insurance ($p = 0.0006$), and duration of RA ($p < 0.0001$).

3.2. Effectiveness

As was expected, there were differences in the basal scores among groups ([Table 2](#)). The analysis shows that biological-naïve and IR-bDMARD groups presented higher DAS28 and RAPID3 scores than switch from IV to SC ABA group. After 6 months of SC ABA administration, the DAS28-CRP scores for all patients went from 5.0 (IQR 2) to 3.4 (2), and after 12 months, they changed to 3.2 (2). Correspondingly, RAPID3 score changed from 17 (10) to 12 (10), and after 12 months, they went to 12.3 (10).

Results of the LME model for DAS28 and RAPID3 are depicted in [Fig. 1](#) and [Table 2](#). The interaction between time and group was not significant ($p = 0.2442$) for DAS28, therefore, this measure is the same for each group. In contrast, RAPID3 interaction between time and group was significant ($p = 0.0073$). Nevertheless, as time goes on, the three groups evolve and achieve very similar scores (around 11.8), thus making them indistinguishable in terms of the average score.

3.3. Security profile

A total of 6 (3.8%) patients had an SAE, which is the most commonly described infection. Serious infections (community acquired pneumonia) were found in 4 (3.1%) patients. One opportunistic infection (esophageal candidiasis) was reported. Four new cases of malignancies were reported in 3 patients: cutaneous T cell lymphoma (mycosis fungoides) and metastatic prostate cancer in 1 patient each. Squamous cell skin carcinoma and melanoma were described in the same patient. A total of 3 patients

Table 1
Baseline clinical and laboratory characteristics of 159 patients with RA.

Group	TOTAL (N = 159)	Biologic naïve (n = 65)	Switch ABA IV→SC (n = 32)	IR-bDMARD (n = 62)
Variable	n/N (%), Median (IQR)	n/N (%), Median (IQR)	n/N (%), Median (IQR)	n/N (%), Median (IQR)
Sociodemographic characteristics				
Female	134/159 (84.2)	51 (78.5)	27 (84.4)	56 (90.3)
Age (years)	54 (16)	53 (15)	56 (15)	54.5 (19)
Educational level (years)	15 (5)	12 (6)	16 (3)	16 (5)
High SES	44/99 (44.4)	14/44 (31.8)	13/18 (72.2)	17/37 (45.9)
Private insurance	87/159 (54.7)	26 (40)	26 (81.3)	35 (56.5)
Comorbidity				
Cardiovascular disease	66/142 (46.5)	26/58 (44.8)	15/31 (48.4)	25/53 (47.2)
Osteoporosis	49/143 (34.3)	9/58 (15.5)	14/30 (46.7)	26/55 (47.3)
Diabetes mellitus type 2	16/146 (11)	8/61 (13.1)	4/30 (13.3)	4/55 (7.3)
Malignancy	10/146 (6.8)	3/61 (4.9)	5/30 (16.7)	2/55 (3.6)
Latent tuberculosis infection	37/152 (24.3)	23/64 (35.9)	4/29 (13.8)	10/59 (16.9)
RA characteristics				
Age of onset of disease (years)	41 (24)	42.5 (24)	38 (20)	38.5 (22)
Duration of RA (years)	10 (11)	7 (7)	16.5 (11)	11 (11)
Acute phase reactants				
CRP, positive	141/154 (91.5)	58 (89.2)	27/29 (93.1)	56/60 (93.3)
CRP (mg/L)	20.1 (38)	12 (24)	32.6 (68)	24.5 (40)
ESR, positive	101/153 (66)	37/64 (57.8)	22/29 (75.9)	42/60 (70)
ESR (mm/h)	37.5 (30)	37 (40)	37 (26)	39 (27)
Auto-antibodies				
RF, positive	145/151 (96)	60/64 (93.8)	28/30 (93.3)	57/57 (100)
RF, titer	138.5 (267)	124 (167)	220.5 (308)	143 (290)
Anti-CCP, positive	105/117 (89.7)	40/43 (93)	22/26 (84.6)	43/48 (89.6)
Anti-CCP, titer (UI/ mL)	235.9 (332)	232.4 (387)	220 (300)	241.8 (283)
Erosions	61/159 (38.4)	18 (27.7)	16 (50)	27 (43.5)
Rheumatoid nodulosis	33/159 (20.8)	9 (13.8)	10 (31.3)	14 (22.6)
Polyautoimmunity	19/159 (11.9)	10 (15.3)	1 (3.1)	8 (12.9)
Concomitant treatment				
Steroids	52/159 (32.7)	27 (41.5)	6 (18.8)	19 (30.6)
ABA + MTX	84/159 (52.8)	39 (60)	14 (43.8)	31 (50)
ABA + other csDMARD	27/159 (17)	17 (26.1)	1 (3.1)	9 (14.5)
ABA monotherapy	48/159 (30.2)	9 (13.8)	17 (53.1)	22 (35.5)

ABA: abatacept; anti-CCP: anti-Cyclic Citrullinated Peptide; CRP: C-reactive protein; csDMARD: conventional synthetic Disease-Modifying AntiRheumatic Drug; ESR: Erythrocyte Sedimentation Rate; IQR: InterQuartile Range; IR-bDMARD: Inadequate Response to biologic Disease-Modifying AntiRheumatic Drug; IV: intravenous; MTX: methotrexate; RA: rheumatoid arthritis; RF: rheumatoid factor; SC: subcutaneous; SES: socioeconomic status.

Table 2
Baseline and follow-up DAS28/RAPID3 scores based on group.

Variable	TOTAL (N = 159)	Biologic naïve (n = 65)	Switch ABA IV→SC (n = 32)	IR-bDMARD (n = 62)
DAS28-CRP				
Baseline	5.1 (2)		2.4 (2)	5.4 (2)
6 months	3.9 (2)		2.8 (0)	3.2 (2)
12 months	3.7 (3)		2.7 (2)	3.0 (2)
RAPID3				
Baseline	18.8 (8)		12.7 (13)	17.6 (8)
6 months	11.7 (10)		11.9 (12)	12 (10)
12 months	12.3 (10)		12.3 (11)	10.9 (10)
Linear mixed effect model				
DAS28-CRP	Estimate; 95% CI	Estimate; 95% CI	Estimate; 95% CI	Estimate; 95% CI
Baseline	4.97; 4.60–5.34	3.93; 3.25–4.61	4.85; 4.44–5.26	
6 months	3.64; 3.24–4.03	2.59; 1.91–3.28	3.52; 3.07–3.96	
12 months	3.67; 3.21–4.13	2.63; 1.95–3.31	3.55; 3.06–4.05	
RAPID3				
Baseline	17.9; 16.22–19.62	13.4; 10.99–15.85	17.0;	15.26–18.76
6 months	11.3; 9.58–13.06	12.3; 9.82–14.93	12.1;	10.28–14.07
12 months	12.0; 10.22–13.78	11.6; 9.06–14.24	11.6;	9.59–13.62

Linear mixed effect model represents the average scores for DAS28 and RAPID3 based on time and group. Confidence intervals (CI) calculated with 95% confidence. ABA: abatacept; CRP: C-reactive protein; DAS28: Disease Activity Score; IQR: InterQuartile Range; IR-bDMARD: Inadequate Response to biological Disease-Modifying AntiRheumatic Drug; IV: intravenous; RAPID3: Routine Assessment of Patient Index Data 3; SC: subcutaneous; SES: socioeconomic status.

(1.8%) died during follow-up. The events leading to death were severe soft-tissue infection and sepsis in a patient with a history of complicated total hip replacement, and metastatic prostate cancer. The cause of death of the third patient could not be known due to loss of contact. In all deceased patients, SC ABA had previously been suspended.

One hundred and forty-six (91.8%) patients had an AE which, in most cases, was mild and moderate in severity. A significant proportion of patients presented more than one AE during the follow-up. Infections were described in 118 (74.2%) patients with upper respiratory tract (64%) and urinary tract infection (11%) being reported the most frequently.

Systemic injection reactions were reported in 102 (64.6%) patients. The most frequent reactions described were constitutional symptoms, headaches, and gastrointestinal symptoms. Local injection-site reactions were reported in 50 (31.4%) patients and were mostly mild in intensity. No new cases of anaphylaxis nor autoimmune disorders were reported. For details see [Table 3](#).

3.4. Subcutaneous abatacept adherence

Retention rate corresponded to 60% at 48 months. The most frequent reasons for drug suspension were loss of efficacy, insurance-related problems (i.e., access to medication/specialist), and adverse drug reactions. Other causes included lack of efficacy, surgery (i.e., articular replacement), patient preference, and pregnancy. Twenty-three patients (14%) were changed to another bDMARD (TNF-α inhibitors 10, Tocilizumab 7, and Rituximab 6), and 19 (12%) to Janus Kinase inhibitors (Tofacitinib).

3.5. Survival analysis

Median time of treatment for SC ABA was 31 months (IQR 30). The only association that reached statistical significance was anti-CCP concentration [Q1–Q4] (p = 0.005). A median titer of anti-CCP was 235.9 UI/mL (IQR 332), and the number of patients in each quartile group was

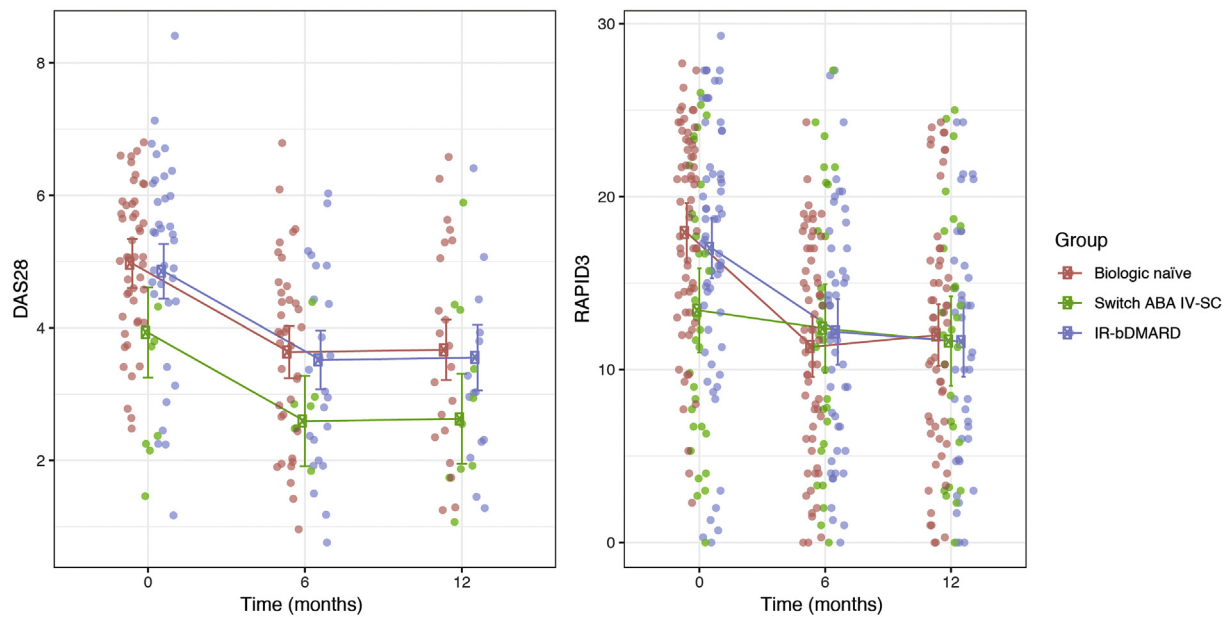


Fig. 1. Linear mixed effect model for DAS28/RAPID3 scores based on time and group. A linear mixed effects model was used for correlation among repeated measures (i.e., change in DAS28 and RAPID3 from baseline to follow-up regarding treatment background). The interaction between time and group was significant ($p = 0.0073$) for RAPID3. ABA: abatacept; DAS28: Disease Activity Score; IR-bDMARD: Inadequate Response to biological Disease-Modifying AntiRheumatic Drug; IV: intravenous; RAPID3: Routine Assessment of Patient Index Data 3; SC: subcutaneous.

Table 3
Subcutaneous abatacept security profile.

Adverse events	n (%)
Infections	
Common cold	102 (64.1)
Urinary tract infection	18 (11.3)
Soft tissue infection	15 (9.4)
Bronchitis	14 (8.8)
Pharyngitis	13 (8.2)
Gastroenteritis	11 (6.9)
Herpes zoster	9 (5.6)
Systemic injection reactions	
Constitutional symptoms	65 (40.9)
Gastrointestinal symptoms	40 (25.6)
Sicca symptoms	35 (22)
Respiratory symptoms	19 (11.9)
Others	
Headache	64 (40.3)
Arthralgia	28 (17.6)
Dizziness	23 (14.5)
Skin rash	18 (11.3)
Local injection-site reactions	
Pain	20 (12.6)
Hematoma	17 (10.7)
Edema	8 (5)
Erythema	7 (4.4)
Pruritus	7 (4.4)
Papule	5 (3.1)
Burning	5 (3.1)
Irritation	3 (1.9)

Q1 (22–136 = 25), Q2 (139.6–255 = 26), Q3 (258–451.6 = 25), Q4 (455–1544 = 26), and Negative (<20 = 12). According to the Cox proportional hazard regression model, there were significant differences between survival curves for Q1 (HR 0.15; 0.03–0.64 95% CI; $p = 0.0096$), and Q2 (HR 0.28; 0.08–0.92 95% CI; $p = 0.0363$), compared to the negative group (Fig. 2). These results show a higher drug retention of SC ABA for these subsets of patients.

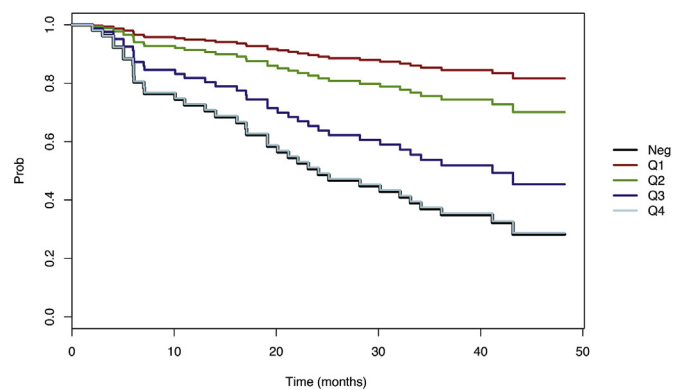


Fig. 2. Subcutaneous abatacept survival by anti-CCP antibody concentration. Cox proportional hazard regression model for SC ABA treatment survival as a function of anti-CCP concentration for 48 months. Antibody-positive patients were divided into equal quartiles (Q1–Q4), representing increasing antibody concentrations. Based on this model, there were significant differences between survival curves for Q1 (HR 0.15; 0.03–0.64 95% CI; $p = 0.0096$), and Q2 (HR 0.28; 0.08–0.92 95% CI; $p = 0.0363$), compared to the negative group.

4. Discussion

To our knowledge, this is the first retrospective cohort that includes LA patients exposed to SC ABA in routine clinical practice. The main strength of this study is the monthly monitoring of each patient for 48 months, which allowed the consolidation of accumulated information related to the effectiveness and safety of SC ABA.

A preliminary analysis of our population [26] showed that RAPID3 had a substantial partial correlation with DAS28 in biological-naïve (0.7511; $p < 0.0001$), and IR-bDMARD (0.7756, $p < 0.0001$) patients under SC ABA treatment. As described elsewhere, RAPID3 was designed for simple scoring in a busy clinical setting to facilitate quantitative assessment of patient status [27]. A RAPID3 ‘patient-only’ index, without a joint count or any measurement from a health professional or laboratory, distinguished standard treatment from control group in two ABA

clinical trials: AIM (Abatacept in Inadequate response to Methotrexate) [28], and ATTAIN (Abatacept Trial in Treatment of Anti-tumor necrosis factor Inadequate responders) [29], at levels similar to DAS28.

There are different ways by which a RA patient is initiated to SC ABA. Based on the studies, the patients could be bio-naïve or inadequate responders to other biologicals. There are few studies based on RWD that compare the results of efficacy and safety in different subgroups including those that switched from IV to SC administrations as in the present study. Several patients prefer the autonomy that they get by having the possibility of self-injecting subcutaneously versus the need to go to a hospital or IV unit for a day. There are also a number of doctors who prefer the SC method to IV administration given the same clinical profile because it offers fewer organizational complexities [30].

Using a self-administered questionnaire, Desplats et al. [31] analyzed the reasons for choosing to continue IV infusions or to switch to SC injections of ABA or tocilizumab in RA patients. Concerns about repeated hospital care (72%), greater autonomy with SC injections (38.7%), and economic considerations (21.5%) were reasons behind the decision to switch to SC administration. However, there is conflicting information in some LA countries. For example, Brazil's Health Ministry did not approve the use of SC ABA for the treatment of moderate to severe RA after the therapeutic failure of two synthetic DMARDs. This decision was based on independent research, cost analysis, and a popular opinion survey. They concluded that SC ABA could not be approved since, in their protocol for RA treatment, TNF inhibitors do not fall under the same line of treatment as biological therapies that use other mechanisms of action [32].

Treatment with SC ABA over an extended period after switching from IV to SC has been associated with high patient retention. Thus selection bias due to patient attrition was reduced. Overall, the efficacy and safety profile of SC ABA has been consistent throughout the global population [7,8,10,33]. Furthermore, some results have been shown for the switch in the opposite direction, from SC to IV presentation based on the requirement to cover a 4-week interval needed for vacations in the A-BREAK open trial. The authors showed that switching from weekly SC to IV ABA and back after 4 weeks is an effective and safe way to bridge vacations in RA patients with low disease activity or remission [34]. In the present study, only 5 patients needed to return to IV administration, but these cases were mainly due to subjective preferences.

In some researchers' experience [35], the transition from IV to SC ABA in clinical practice was accepted by more than half of the patients treated using IV, but, in about one-third of the cases, it was necessary to return to administration by IV because of the onset of an arthritic flare. This case series (51 patients treated) does not allow for definitive conclusions. Monti et al. [36] showed opposite results based on a similar population (21 patients included). That group did not experience any significant loss of efficacy that would require a return to monthly IV infusions. Possible explanations may be found in the study group characteristics given that its population had a relatively shorter period of IV treatment preceding the switch to SC ABA. Our results did not show a loss of efficacy in the group that switched. Nevertheless, there is a significant proportion of missing data with respect to the duration of the previous IV ABA.

Although authors [35] who argue that there is a clinical failure in the switch from IV to SC postulate a possible influence of Body Mass Index (BMI) on the therapeutic concentrations of ABA, other authors, using stringent criteria, showed that those concentrations and clinical remission rates were similar across BMI groups and administration routes [37].

RWD originate from a variety of sources associated with, or used in, routine clinical settings, including patient/disease registries [38]. One of the strengths of these registries is that their time frame is longer than RCTs. In the present study, the duration of follow-up is superior to most pivotal ABA studies, which could make it possible to identify late-onset AEs.

An integrated analysis of safety data from the double-blind and open-label periods of 5 clinical trials including a total of 1879 RA refractory patients with 4214.6 patient-years of exposure, showed that treatment

with SC ABA was associated with a low incidence of serious infections, malignancies, autoimmune events, and injection-site reactions [39]. Our data regarding the safety profile of SC ABA are similar to the 5-year extension period of the ACQUIRE study [40], and RWD from the ACTION study [13]. In addition, similar results have been found in Argentine patients with respect to the security profile when exposed to IV ABA administration [20].

Clinical response to biologicals varies widely among individuals with RA. To date, there are few, and in some cases, conflicting results in the personalized approach to patients with RA treated with ABA. Recently, our group (unpublished data) did a systematic literature review of articles including factors associated with the response to ABA in RA [41]. Selected articles included a total of 1944 patients and assessed biomarkers (decreased circulating CD28-negative T cells) [42,43], seropositivity (RF/anti-CCP2 antibodies) [17,44,45], RA disease duration (early versus long-standing) [46], and multi-target therapy (concomitant use of tacrolimus) [47]. Only the seropositive subphenotype was validated in several groups, which included a real-life registry [44], and a non-inferiority trial [45].

Our data provide evidence that seropositive anti-CCP patients have better retention rates for SC ABA compared to seronegative patients. Among seropositive patients, those with anti-CCP antibody concentrations between 22 and 255 UI/mL [Q1–Q2] had better drug survival. It is noteworthy that the behavior of those patients who are highly seropositive (i.e., antibody concentrations between 455 and 1544 UI/mL [Q4]) is very similar to seronegative patients.

Drug retention in observational studies can be considered a composite measure and index of effectiveness, safety, and tolerability [48]. Retention rate corresponded to 60% at 48 months in our study. In the German cohort of the ACTION study (intravenous ABA) [13], ABA retention rates at 2 years were similar in the biologic-naïve and biologic-failure cohorts (~40%), and were both lower than in the biologic-naïve cohort of patients from other participating countries (59%). Variations in ABA retention rates by country were also reported in an analysis of nine European registries [49]. Geographical differences in retention and response are likely due to numerous factors, including genetic variation and differences in health-care systems.

Data regarding SC ABA retention based on anti-CCP antibody titers are scarce. The closest evidence corresponds to a post-hoc analysis of the AMPLE trial. In this study, patients with the highest baseline anti-CCP2 antibody concentrations had a better clinical response (i.e., change from baseline in disease activity and disability) to ABA than patients with lower concentrations [45]. Our data probably defines a subset of patients with greater severity of the disease and, therefore, a lower retention of the drug.

A pooled analysis of data from 9 observational RA registries in Europe (Pan-European Registry, including 2942 patients) shows that even after adjustment for sociodemographic and disease- and treatment-related confounders, RF and anti-citrullinated protein autoantibody (ACPA) positivity were each associated with a lower rate of ABA discontinuation for any reason, compared to RF-negative and ACPA-negative patients [49]. In addition, in a US-based clinical practice setting (The Corona RA registry), anti-CCP positive ABA initiators were associated with a significantly greater Clinical Disease Activity Index response versus anti-CCP negative ABA initiators [50]. This differential treatment response was not described for TNF inhibitors. The ABROAD study has demonstrated that ACPA positivity was significantly associated with sustained clinical remission in elderly patients treated with IV ABA [51]. These results suggest that positivity for RF or ACPA is associated with the better effectiveness of ABA therapy.

Currently, the response to biologicals is not universal for any of the treatment options available, and selection of an effective therapy is currently based on a trial-and-error approach [52]. Therefore, the study and description of our population will make it possible to identify the prognostic factors that could help to improve decision making and optimize outcomes in patients with RA.

5. Study limitations

Several limitations have been described for RWDs in the literature [53]. A limitation that must be considered in our study is that of lost data, especially for DAS28, due to the lack of recent acute phase reactants and/or limited time for the evaluation of these patients in a real-world clinical scenario. Moreover, there is no standard, universally accepted anti-CCP assay, and so findings may have differed with an alternative assay.

6. Final remarks and conclusions

Our results suggest that the patient subgroup that switched from IV to SC ABA had lower activity and functional impairment at baseline. RA physical function demonstrates a dependent relationship as a function of time and treatment background. RAPID3, an index without formal joint counts, appears attractive for evaluation of disease activity in RA patients in a real-life setting. Long-term safety of SC ABA is less well-known compared to IV administration. SC administration of 125 mg/week of ABA demonstrates a safety profile consistent with previously published data. Drug survival of SC ABA is similar regardless of treatment background, erosive disease, and RF status. Patients with the lowest baseline anti-CCP antibody concentrations had better drug survival than patients with higher concentrations. More RWD are required to analyze the association of anti-CCP status with the biological treatment effect. The identification of predictors of response to treatment is a necessary step towards personalized medicine in RA. These results highlight the importance of identifying factors associated with the response to biologicals in order to optimize treatment and reduce costs.

Funding

This work was supported by Bristol-Myers Squibb [grant number IM101-708]. The sponsor did not participate in the study design, collection, analysis, interpretation of data, writing of the manuscript, or decision to submit this article for publication.

Conflict of interest

RDM has received speaker grants, research grants or participate in advisory boards from Pfizer, Roche, Abbott, AbbVie, Bristol-Myers Squibb, Biopas, and Novartis.

ARV has received honoraria for participation on speakers' bureaus for AbbVie, Amgen, Biopas, BMS, and Pfizer, as well as participation on Advisory Board from GSK.

Acknowledgments

The authors are grateful to all members of the Center of Dermatology and Rheumatology (FUNINDERMA) for their contribution to this work, especially Dr. Iván Enrique Rodríguez-Mantilla, Dra. Adriana Díaz-Esteba, and Liliana Velandia. They would also like to express their gratitude to Elizabeth Cruz for the design of the graphics, and Cristhian Ramírez for support in the revision and editing of the text.

References

- J.S. Smolen, D. Aletaha, A. Barton, G.R. Burmester, P. Emery, G.S. Firestein, et al., Rheumatoid arthritis, *Nat Rev Dis Prim* 4 (2018) 18001, <https://doi.org/10.1038/nrdp.2018.1>.
- L.A. Ramírez, C. Rodríguez, M.H. Cardiel, Burden of illness of rheumatoid arthritis in Latin America: a regional perspective, *Clin. Rheumatol.* 34 (Suppl 1) (2015) S9–S15, <https://doi.org/10.1007/s10067-015-3012-0>.
- P. Rein, R.B. Mueller, Treatment with biologicals in rheumatoid arthritis: an overview, *Rheumatol Ther* 4 (2017) 247–261, <https://doi.org/10.1007/s40744-017-0073-3>.
- J.L. Nam, S. Ramiro, C. Gaujoux-Viala, K. Takase, M. Leon-Garcia, P. Emery, et al., Efficacy of biological disease-modifying antirheumatic drugs: a systematic literature review informing the 2013 update of the EULAR recommendations for the management of rheumatoid arthritis, *Ann. Rheum. Dis.* 73 (2014) 516–528, <https://doi.org/10.1136/annrheumdis-2013-204577>.
- E. Keystone, A. Alkhalaf, M. Makkaw, Subcutaneous abatacept in rheumatoid arthritis: current update, *Expert Opin. Biol. Ther.* 15 (2015) 1221–1230, <https://doi.org/10.1517/14712598.2015.1065248>.
- J.L. Greene, G.M. Leytze, J. Emswiler, R. Peach, J. Bajorath, W. Cosand, et al., Covalent dimerization of CD28/CTLA-4 and oligomerization of CD80/CD86 regulate T cell costimulatory interactions, *J. Biol. Chem.* 271 (1996) 26762–26771, <https://doi.org/10.1074/jbc.271.43.26762>.
- M.C. Genovese, A. Covarrubias, G. Leon, E. Mysler, M. Keiserman, R. Valente, et al., Subcutaneous abatacept versus intravenous abatacept: a phase IIIb noninferiority study in patients with an inadequate response to methotrexate, *Arthritis Rheum.* 63 (2011) 2854–2864, <https://doi.org/10.1002/art.30463>.
- P. Nash, S. Nayiager, M.C. Genovese, A.J. Kivitz, K. Oelke, C. Ludivico, et al., Immunogenicity, safety, and efficacy of abatacept administered subcutaneously with or without background methotrexate in patients with rheumatoid arthritis: results from a phase III, international, multicenter, parallel-arm, open-label study, *Arthritis Care Res.* 65 (2013) 718–728, <https://doi.org/10.1002/acr.21876>.
- J. Kaine, G. Gladstein, I. Strusberg, M. Robles, I. Louw, S. Gujrathi, et al., Evaluation of abatacept administered subcutaneously in adults with active rheumatoid arthritis: impact of withdrawal and reintroduction on immunogenicity, efficacy and safety (phase IIb ALLOW study), *Ann. Rheum. Dis.* 71 (2012) 38–44, <https://doi.org/10.1136/annrheumdis-2011-200344>.
- E.C. Keystone, J.M. Kremer, A. Russell, J. Box, C. Abud-Mendoza, M.G. Elizondo, et al., Abatacept in subjects who switch from intravenous to subcutaneous therapy: results from the phase IIIb ATTUNE study, *Ann. Rheum. Dis.* 71 (2012) 857–861, <https://doi.org/10.1136/annrheumdis-2011-200355>.
- J.C. Sarmiento-Monroy, C. Villota-Eraso, M.J. Mantilla-Ribero, N. Molano-González, M. Rodríguez-Jiménez, A. Rojas-Villarraga, et al., AB0354 Subcutaneous abatacept in patients with rheumatoid arthritis: a real-life experience, *Ann Rheum Dis* 75 (2) (2016) 1024, <https://doi.org/10.1136/annrheumdis-2016-eular.5165>.
- Garrison LP, Neumann PJ, Erickson P, Marshall D, Mullins CD. Using real-world data for coverage and payment decisions: the ISPOR Real-World Data Task Force report. *Value Health n.d.*;10:326–335. doi:10.1111/j.1524-4733.2007.00186.x.
- H.G. Nüßlein, R. Alten, M. Galeazzi, H.-M. Lorenz, D. Boumpas, M.T. Nurmohamed, et al., 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 (2014) 14, <https://doi.org/10.1186/1471-2474-15-14>.
- K. Murakami, M. Sekiguchi, S. Hirata, T. Fujii, K. Matsui, S. Morita, et al., Predictive factors for structural remission using abatacept: results from the ABROAD study, *Mod. Rheumatol.* (2018) 1–7, <https://doi.org/10.1080/14397595.2018.1482609>.
- K. Takabayashi, F. Ando, T. Suzuki, Comparing the effectiveness of biological disease-modifying antirheumatic drugs using real-world data, *Mod. Rheumatol.* (2018) 1–11, <https://doi.org/10.1080/14397595.2018.1447264>.
- N. Takahashi, T. Kojima, A. Kaneko, D. Kida, Y. Hirano, T. Fujibayashi, et al., Longterm efficacy and safety of abatacept in patients with rheumatoid arthritis treated in routine clinical practice: effect of concomitant methotrexate after 24 weeks, *J. Rheumatol.* 42 (2015) 786–793, <https://doi.org/10.3899/jrheum.141288>.
- H.G. Nüßlein, R. Alten, M. Galeazzi, H.-M. Lorenz, M.T. Nurmohamed, W.G. Bensen, et al., 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 (2015) 176, <https://doi.org/10.1186/s12891-015-0636-9>.
- M.-E. Truchetet, N. Poursac, T. Barnetche, E. Shipley, J.-E. Gottenberg, B. Bannwarth, et al., Abatacept monotherapy compared with abatacept plus disease-modifying anti-rheumatic drugs in rheumatoid arthritis patients: data from the ORA registry, *Arthritis Res. Ther.* 18 (2016) 72, <https://doi.org/10.1186/s13075-016-0956-7>.
- A. Finckh, D. Neto, F. Iannone, E. Loza, E. Lie, P. van Riel, et al., The impact of patient heterogeneity and socioeconomic factors on abatacept retention in rheumatoid arthritis across nine European countries, *RMD Open* 1 (2015), e000040, <https://doi.org/10.1136/rmdopen-2014-4-000040>.
- F. Dal Pra, M.N. Tamborena, E. Mysler, J. Velasco, A. Berman, A. Spindler, et al., Seguridad de abatacept en pacientes con artritis reumatoidea, *Rev. Argent. Reumatol.* 23 (2012) 30–36.
- F. Becerra Rojas, C. Benites Chacaltana, E. Aiello, C. Zingoni, G. Bergman, P. Drost, et al., Costo efectividad de Abatacept en comparación con otras terapias biológicas para el tratamiento de la artritis reumatoide moderada a severamente activa en pacientes que han fallado al tratamiento con metotrexato en EsSalud para el año 2010, *Acta Med.* 28 (2011) 200–210, <https://doi.org/10.22201/facmed.14058871p.2018.2.63555>.
- D. van der Heijde, A.H.M. van der Helm-van Mil, D. Aletaha, C.O. Bingham, G.R. Burmester, M. Dougados, et al., EULAR definition of erosive disease in light of the 2010 ACR/EULAR rheumatoid arthritis classification criteria, *Ann. Rheum. Dis.* 72 (2013) 479–481, <https://doi.org/10.1136/annrheumdis-2012-202779>.
- J. Pinheiro, D. Bates, S. DebRoy, D. Sarkar, R Core Team, Linear and nonlinear mixed effects models. R package version 3.1-137. <https://cran.r-project.org/package=nlme>, 2018.
- R Core Team, A Language and Environment for Statistical Computing, R Foundation for Statistical Computing, Vienna, Austria, 2017, p. 201.
- A. Rojas-Villarraga, J. Amaya-Amaya, A. Rodríguez-Rodríguez, R.D. Mantilla, J.-M. Anaya, Introducing polyautoimmunity: secondary autoimmune diseases No

- longer exist, *Autoimmune Dis.* 254319 (2012) 1–9, [dx.doi.org/10.1155/2012/254319](https://doi.org/10.1155/2012/254319).
- [26] J. Sarmiento-Monroy, E. Rodríguez-Mantilla, N. Molano-González, M. Rodríguez-Jiménez, R.D. Mantilla, A. Rojas-Villarraga, Correlation between routine assessment of patient index data 3 (RAPID3) and disease activity score 28 (DAS28) in patients with rheumatoid arthritis treated with subcutaneous abatacept, in: 4th Int. Congr. Controv. Rheumatol. Autoimmun. CORA 2017, 2017. Bologna, Italy.
- [27] T. Pincus, C.J. Swearingen, M. Bergman, Y. Yazici, RAPID3 (Routine Assessment of Patient Index Data 3), a rheumatoid arthritis index without formal joint counts for routine care: proposed severity categories compared to disease activity score and clinical disease activity index categories, *J. Rheumatol.* 35 (2008) 2136–2147, <https://doi.org/10.3899/jrheum.080182>.
- [28] J.M. Kremer, H.K. Genant, L.W. Moreland, A.S. Russell, P. Emery, C. Abud-Mendoza, et al., Effects of abatacept in patients with methotrexate-resistant active rheumatoid arthritis: a randomized trial, *Ann. Intern. Med.* 144 (2006) 865–876.
- [29] M.C. Genovese, J.-C. Becker, M. Schiff, M. Luggen, Y. Sherrer, J. Kremer, et al., Abatacept for rheumatoid arthritis refractory to tumor necrosis factor alpha inhibition, *N. Engl. J. Med.* 353 (2005) 1114–1123, <https://doi.org/10.1056/NEJMoa050524>.
- [30] Mola EM, Balsa A, Martínez Taboada V, Marengo JL, Navarro Sarabia F, Gómez-Reino J, et al. Practice guidelines for the use of subcutaneous abatacept. *Reumatol Clin n.d.*;10:218–226. doi:10.1016/j.reuma.2013.11.006.
- [31] M. Desplats, T. Pascart, G. Jelin, L. Norberciak, P. Philippe, E. Houvenagel, et al., Are abatacept and tocilizumab intravenous users willing to switch for the subcutaneous route of administration? A questionnaire-based study, *Clin. Rheumatol.* 36 (2017) 1395–1400, <https://doi.org/10.1007/s10067-017-3587-8>.
- [32] Conitec, *Abatacepte para o tratamento da Artrite Reumatoide Moderada a Grave.* Brazil, Secretaria de Ciência, Tecnologia e Insumos Estratégicos, 2016.
- [33] K. Amano, T. Matsubara, T. Tanaka, H. Inoue, M. Iwahashi, T. Kanamono, et al., Long-term safety and efficacy of treatment with subcutaneous abatacept in Japanese patients with rheumatoid arthritis who are methotrexate inadequate responders, *Mod. Rheumatol.* 25 (2015) 665–671, <https://doi.org/10.3109/14397595.2015.1012786>.
- [34] R.B. Mueller, M. Gengenbacher, S. Richter, J. Dudler, B. Moller, J. von Kempis, Change from subcutaneous to intravenous abatacept and back in patients with rheumatoid arthritis as simulation of a vacation: a prospective phase IV, open-label trial (A-BREAK), *Arthritis Res. Ther.* 18 (2016) 88, <https://doi.org/10.1186/s13075-016-0985-2>.
- [35] R. Reggia, F. Franceschini, A. Tincani, I. Cavazzana, Switching from intravenous to subcutaneous formulation of abatacept: a single-center Italian experience on efficacy and safety, *J. Rheumatol.* 42 (2015) 193–195, <https://doi.org/10.3899/jrheum.141042>.
- [36] S. Monti, S. Breda, V. Grosso, M. Todoerti, C. Montecucco, R. Caporali, Switching from intravenous to subcutaneous formulation of abatacept: different results in a series of 21 patients, *J. Rheumatol.* 42 (2015) 1993–1994, <https://doi.org/10.3899/jrheum.150230>.
- [37] M.-A. D'Agostino, R. Alten, E. Mysler, M. Le Bars, J. Ye, B. Murthy, et al., Body mass index and clinical response to intravenous or subcutaneous abatacept in patients with rheumatoid arthritis, *Clin. Rheumatol.* 36 (2017) 2655–2665, <https://doi.org/10.1007/s10067-017-3788-1>.
- [38] V.B. Katkade, K.N. Sanders, K.H. Zou, Real world data: an opportunity to supplement existing evidence for the use of long-established medicines in health care decision making, *J. Multidiscip. Healthc.* 11 (2018) 295–304, <https://doi.org/10.2147/JMDH.S160029>.
- [39] R. Alten, J. Kaine, E. Keystone, P. Nash, I. Delaet, M.C. Genovese, Long-term safety of subcutaneous abatacept in rheumatoid arthritis: integrated analysis of clinical trial data representing more than four years of treatment, *Arthritis Rheum.* 66 (2014) 1987–1997, <https://doi.org/10.1002/art.38687>.
- [40] M.C. Genovese, C. Pacheco-Tena, A. Covarrubias, G. Leon, E. Mysler, M. Keiserman, et al., Longterm safety and efficacy of subcutaneous abatacept in patients with rheumatoid arthritis: 5-year results from a phase IIIb trial, *J. Rheumatol.* 45 (2018) 1085–1092, <https://doi.org/10.3899/jrheum.170344>.
- [41] J.-C. Sarmiento-Monroy, C. Villota-Eraso, R.D. Mantilla-Hernández, Factors associated with response to abatacept in rheumatoid arthritis: a systematic literature review, in: 10th Int. Congr. Autoimmun., 2016. Leipzig.
- [42] M. Scarsi, T. Ziglioli, P. Airo, Decreased circulating CD28-negative T cells in patients with rheumatoid arthritis treated with abatacept are correlated with clinical response, *J. Rheumatol.* 37 (2010) 911–916, <https://doi.org/10.3899/jrheum.091176>.
- [43] M. Scarsi, T. Ziglioli, P. Airo, Baseline numbers of circulating CD28-negative T cells may predict clinical response to abatacept in patients with rheumatoid arthritis, *J. Rheumatol.* 38 (2011) 2105–2111, <https://doi.org/10.3899/jrheum.110386>.
- [44] J.E. Gottenberg, P. Ravaut, A. Cantagrel, B. Combe, R.M. Flipo, T. Schaefferbeke, 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 (2012) 1815–1819, <https://doi.org/10.1136/annrheumdis-2011-201109>.
- [45] J. Sokolove, M. Schiff, R. Fleischmann, M.E. Weinblatt, S.E. Connolly, A. Johnsen, 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 (2016) 709–714, <https://doi.org/10.1136/annrheumdis-2015-207942>.
- [46] Y. Yazici, D. Moniz Reed, C. Klem, L. Rosenblatt, G. Wu, J.M. Kremer, Greater remission rates in patients with early versus long-standing disease in biologic-naive rheumatoid arthritis patients treated with abatacept: a post hoc analysis of randomized clinical trial data, *Clin. Exp. Rheumatol.* 29 (2011) 494–499.
- [47] N. Takahashi, T. Fujibayashi, D. Kida, Y. Hirano, T. Kato, D. Kato, et al., Concomitant methotrexate and tacrolimus augment the clinical response to abatacept in patients with rheumatoid arthritis with a prior history of biological DMARD use, *Rheumatol. Int.* 35 (2015) 1707–1716, <https://doi.org/10.1007/s00296-015-3283-4>.
- [48] K. Ebina, M. Hashimoto, W. Yamamoto, A. Ohnishi, D. Kabata, T. Hirano, et al., Drug retention and discontinuation reasons between seven biologics in patients with rheumatoid arthritis -The ANSWER cohort study, *PLoS One* 13 (2018), e0194130, <https://doi.org/10.1371/journal.pone.0194130>.
- [49] J.E. Gottenberg, D.S. Courvoisier, M.V. Hernandez, F. Iannone, E. Lie, H. Canhao, 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 Rheum.* 68 (2016) 1346–1352, <https://doi.org/10.1002/art.39595>.
- [50] L.R. Harrold, H.J. Litman, S.E. Connolly, S. Kelly, W. Hua, E. Alemao, et al., 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 (2018) 32–39, <https://doi.org/10.3899/jrheum.170007>.
- [51] M. Sekiguchi, T. Fujii, K. Matsui, K. Murakami, S. Morita, K. Ohmura, et al., Differences in predictive factors for sustained clinical remission with abatacept between younger and elderly patients with biologic-naive rheumatoid arthritis: results from the ABROAD study, *J. Rheumatol.* 43 (2016) 1974–1983, <https://doi.org/10.3899/jrheum.160051>.
- [52] J. Bluett, A. Barton, Precision medicine in rheumatoid arthritis, *Rheum. Dis. Clin. N. Am.* 43 (2017) 377–387, <https://doi.org/10.1016/j.rdc.2017.04.008>.
- [53] H.-S. Kim, S. Lee, J.H. Kim, Real-world evidence versus randomized controlled trial: clinical research based on electronic medical records, *J. Korean Med. Sci.* 33 (2018) e213, <https://doi.org/10.3346/jkms.2018.33.e213>.