Subcutaneous abatacept in rheumatoid arthritis: A real-life experience

Juan Camilo Sarmiento-Monroy a,*, Luisa Parada-Arias b, Milena Rodríguez-López b, Mónica Rodríguez-Jiménez c, Nicolás Molano-González c, Adriana Rojas-Villarraga d, Rubén Darío Mantilla a

a Center of Dermatology and Rheumatology FUNINDERMA, Av. Carrera 20 No. 82-31, Bogotá, Colombia
b Universidad El Bosque, Av. Carrera 9 No. 131A-2, Bogotá, Colombia
c Center for Autoimmune Diseases Research (CREA), School of Medicine and Health Sciences, Universidad Del Rosario, Carrera 26 No. 63B-51, 111221, Bogotá, Colombia
d Titular Research Professor, Research Institute, Fundación Universitaria de Ciencias de La Salud- FUCS, Carrera 19 No. 8A-32, Bogotá, Colombia

A R T I C L E   I N F O

Keywords:
- Rheumatoid arthritis
- Subcutaneous abatacept
- Latin America
- Real world data
- Precision medicine

A B S T R A C T

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-week) (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 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.

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
similar efficacy in real-life populations and routine care settings is 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 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 (IBDMDARD). 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. 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, hematoema, 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 IBDMARD 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
Baseline and follow-up DAS28/RAPID3 scores based on group.

| Group                         | TOTAL (n = 159) | Biologic naive (n = 65) | Switch ABA IV→SC (n = 32) | IR-bDMARD (n = 62) |
|-------------------------------|-----------------|-------------------------|---------------------------|-------------------|
| **Baseline**                  |                 |                         |                           |                   |
| DAS28-CRP                     | Estimate        | 95% CI                  | Estimate                  | 95% CI            |
| 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 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.

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).

**3.4. 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).
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.

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) |

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.

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
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.

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]. The registries were derived from a variety of repurposing studies, 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 AE.

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 Argentinian 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 subtypephenotype 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 AMPLEx 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 (ACP) 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 Corrona 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 SC ABA had lower activity and functional impairment at baseline. RA

anti-CCP antibody concentrations had better drug survival than patients

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. Strubberg, 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, doi:10.1136/annrheumdis-2011-200344.

E.C. Keystone, J.M. Kremer, A. Russell, J. Box, C. Abud-Mendoza, M.G. Ellizondo, et al., Abatacept in subjects who switch from intravenous to subcutaneous therapy: results from the phase IIb 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-Gonzalez, A. Rojas-Villarraga, et al., Ankylosing spondylitis in patients with rheumatoid arthritis: a real-life experience, Ann Rheum Dis 75 (2016) 1024, https://doi.org/10.1136/annrheumdis-2016-eular.5165.

Garriston 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.:326-335. doi:10.1111/j.1524-4733.2007.00186.x.

H.G. Nülein, R. Alten, M. Galeazzi, H.-M. Lorenz, D. Boumpas, M.T. Nurmontohamed, et al., Real-world effectiveness of abatacept for rheumatoid arthritis treatment in European and Canadian populations: a 6-month interim analysis of the 2010 ACR/EULAR rheumatoid arthritis classification criteria, Ann. Rheum. Dis. 73 (2014) 516-528, https://doi.org/10.1136/annrheumdis-2013-204577.

Research review information 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. Alkhafaf, M. Makkawy, Subcutaneous abatacept in rheumatoid arthritis: current update, Expert Opin. Biol. Ther. 15 (2015) 1221-1230, https://doi.org/10.1517/14712598.2015.1063245.

J.L. Greene, G.M. Leyte, J. Emweller, R. Peach, J. Bajorath, W. Cosand, et al., Covalent dimerization of C228/C214A-LA oligomerization of CD86/CD80 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. Mylser, 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) 2654-2664, https://doi.org/10.1002/art.30463.

P. Nash, S. Navigaier, M.C. Genovese, A.J. Kivitz, K. Okle, C. Ludivico, et al., Immunogenicity, safety, and efficacy of abatacept administered subcutaneously without or with 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. Strubberg, 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, doi:10.1136/annrheumdis-2011-200344.

E.C. Keystone, J.M. Kremer, A. Russell, J. Box, C. Abud-Mendoza, M.G. Ellizondo, et al., Abatacept in subjects who switch from intravenous to subcutaneous therapy: results from the phase IIb 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-Gonzalez, A. Rojas-Villarraga, et al., Ankylosing spondylitis in patients with rheumatoid arthritis: a real-life experience, Ann Rheum Dis 75 (2016) 1024, https://doi.org/10.1136/annrheumdis-2016-eular.5165.

Garriston 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.:326-335. doi:10.1111/j.1524-4733.2007.00186.x.

H.G. Nülein, R. Alten, M. Galeazzi, H.-M. Lorenz, D. Boumpas, M.T. Nurmontohamed, et al., Real-world effectiveness of abatacept for rheumatoid arthritis treatment in European and Canadian populations: a 6-month interim analysis of the 2010 ACR/EULAR rheumatoid arthritis classification criteria, Ann. Rheum. Dis. 73 (2014) 516-528, https://doi.org/10.1136/annrheumdis-2013-204577.

J.K. Heijde, P. van Riel, G. van Gestel, T. van Rijswijk, R. de Jong, et al., The impact of patient heterogeneity and socioeconomic factors on abatacept retention in rheumatoid arthritis across nine European countries, RMD Open 1 (2015) 1-7, https://doi.org/10.1136/rmdopen-2014-000406.

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) 1-7, https://doi.org/10.1136/rmdopen-2014-000406.
V.B. Katkade, K.N. Sanders, K.H. Zou, Real world data: an opportunity to
J. Sarmiento-Monroy, E. Rodríguez-Mantilla, N. Molano-González, M. Rodríguez-Jiménez, R.D. Manilla, 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. Convov. Rheumatol. Autoimmun. CORA 2017, 2017. Bologna, Italy,
T. Pincus, C.J. Sweaingien, M. Bergman, Y. Yuzici, 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.
J.M. Kremer, H.K. Genant, L.W. Moreland, A.S. Russell, P. Emery, C. Abd-El-Meda, et al., Effects of abatacept in patients with methotrexate-resistant active rheumatoid arthritis: a randomized trial, Ann. Intern. Med. 144 (2006) 865–876.
M.C. Genovese, J.-C. Becker, M. Schiﬀ, M. Luggen, Y. Sherrr, 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.
Mola EM, Balsa A, Martínez Taboada V, Marenco 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.
M. Desplats, T. Pascart, G. Jelin, L. Norberciaï, P. Philippe, E. Houvenaegel, et al., Are abatacept and tocilizumab intravenous users willing to switch to the subcutaneous route of administration? A questionnaire-based study, Clin. Rheumatol. 36 (2017) 1395–1400, https://doi.org/10.1007/s10067-017-3587-8.
Conitec, Abatacepte para o tratamento da Artrite Reumatoide Moderada a Grave.
T. Pincus, C.J. Swearingen, M. Bergman, Y. Yazici, RAPID3 (Routine Assessment of Patient Index Data 3) and disease activity score 28 (DAS28) in patients with rheumatoid arthritis treated with subcutaneous abatacept, in: 4th Int. Congr. Convov. Rheumatol. Autoimmun. CORA 2017, 2017. Bologna, Italy.
M.-A. D., Conitec, Abatacepte para o tratamento da Artrite Reumatoide Moderada a Grave.
J.E. Gottenberg, P. Ravaud, A. Cantagrel, B. Combe, R.M. Filip, T. Schaeverbeke, 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.
J. Sokolove, M. Schiﬀ, R. Fleischmanna, M.E. Weinblatt, S. Johsenn, 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 AMPLEx trial, Ann. Rheum. Dis. 75 (2016) 709–714, https://doi.org/10.1136/annrheumdis-2015-207942.
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.
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.
K. Ebina, M. Hashimoto, W. Yamamoto, A. Ohnishi, D. Kabata, T. Hiranoh, 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.
J.E. Gottenberg, D.S. Courvoisier, M.V. Hernandez, F. Iannone, E. Lie, H. Chanho, 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.
L.R. Harrold, H.J. Litzman, S.E. Connolly, S. Kelly, W. Hua, E. Alemoa, 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.1700007.
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.1600051.
J. Blument, 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.
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.