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Experience of Mass Switching to Biosimilar Drugs in Patients with Immune-Mediated Inflammatory Rheumatic Diseases: Effectiveness and Safety, Intercambiosim Project

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ABSTRACT

Objective: To evaluate the efficacy and safety of biosimilars in the treatment of immune-mediated inflammatory rheumatic diseases.

Materials and methods: Retrospective observational and descriptive study of patients with immune mediated inflammatory rheumatic disease. Patients who had switched from a biological drug to biosimilar anti TNF and rituximab, for at least 24 weeks were included. Statistical tests such as the chi-square and Mann-Whitney U tests were used to assess the independence of categorical and numerical variables, respectively.

Results: 364 patients were selected. 29.95% of patients discontinued treatment with the bio similar: inefficacy in 87 patients (52 with primary failure and 35 with secondary failure), adverse effects in 18 patients and 4 patients discontinued it by their own decision. The mean disease activity at the beginning of the medication switch was 1.73 (± 0.93) in ASDAS, 8.73 (± 12.20) in DAPSA, and 2.60 (± 1.20) in DAS28, while at 24 weeks after the switch, the mean activity was 1.79 in ASDAS, 8.39 in DAPSA, and 2.62 in DAS28.

Discussion: It was observed that 29.95% of the participants had to discontinue the use of the biosimilar drug, mainly due to its lack of efficacy, which exceeds the average reported in the current literature. Only 18

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patients experienced some type of adverse effect.

Conclusion: Our data obtained in a real-life setting suggest that biosimilar drugs can be considered an effective and safe option in the treatment of inflammatory rheumatic diseases. However, it is important to note that there is a significant rate of discontinuation of biosimilar use.

Keywords: Biosimilars bDMARDs; Rheumatic diseases; Discontinuation; Treatment

INTRODUCTION

Biological drugs (bDMARDs) have revolutionized the conventional treatment of inflammatory rheumatic diseases, significantly improving the quality of life for our patients, both in terms of joint and extra-articular outcomes [1]. Their main drawback, the economic cost, can be alleviated using biosimilars [2]. A biosimilar is a biological medicine that contains a version of the active substance found in a previously authorized original biological medicine (reference medicine). Similarity to reference medicine must be established through a comparability exercise regarding quality characteristics, biological activity, safety, and efficacy [3]. During their approval process, biosimilars have demonstrated to European and American drug agencies that the present variability and any differences from the original drug do not affect safety and efficacy [2,3]. These studies are designed to optimize the opportunity to detect clinical differences between biosimilars and reference products in homogeneous populations but do not reflect the use of biosimilars in daily practice with a heterogeneous population with associated comorbidities [4]. Given the limited clinical experience with biosimilar use, the importance of pharmacovigilance is emphasized in the drug information leaflets [4,5]. In recent years, starting in 2017, some studies have been published attempting to assess the efficacy and safety of biosimilars in real-world populations. Regarding infliximab biosimilars, studies like PLANETRA and PLANETAS conducted in patients with rheumatoid arthritis and ankylosing spondylitis, respectively, show that while PLANETRA reports an increase in adverse events leading to discontinuation, they are not considered significant compared to the pivotal study [6-8]. Both studies provide data on efficacy and tolerability in rheumatic patients. Based on the DANBIO registry (Danish registry), Glintborg's, et al., publication describes an impact on disease activity three months after the switch that is not negative, with no additional adverse effects compared to the original [9]. Other studies, such as Scheringer's, find a slight increase in adverse events with infliximab biosimilars [1]. Regarding etanercept biosimilars, a recent publication based on the DANBIO registry in 2019 describes a lower treatment retention rate in patients switching to etanercept biosimilars, but it is related to nonspecific pharmacological effects and patient-related factors [9-11]. Regarding efficacy, no negative effect is observed in the first three months, and significant adverse effects are not observed. However, certain biases are described in this study due to methodological issues such as different dosing, short follow-up duration, and cohort differences [9]. Other publications, like Bruni, et al., confirm the safety of switching from etanercept reference product to etanercept biosimilar (SB4) based on real-world population data, showing a slightly higher retention rate than other series, but it does not provide efficacy data as a limitation [12]. Regarding adalimumab biosimilars, a randomized phase III study conducted by Weinblatt was published in 2018 [13,14]. The study assessed the efficacy, safety, and immunogenicity of adalimumab reference product compared to adalimumab biosimilar (SB5) in patients diagnosed with rheumatoid arthritis who received subcutaneous injections of the standard dose of 40 mg every 14 days for 52 weeks. The study concluded that switching from an adalimumab reference product to an adalimumab

biosimilar did not increase adverse reactions, immunogenicity, or loss of efficacy [15]. There are ongoing extension studies to evaluate the effectiveness and safety of transitioning from the reference product to adalimumab biosimilar, such as the studies by Moots and Cohen [16,17]. Another biologic available for treating rheumatoid arthritis is rituximab, for which a biosimilar has been available since 2017 [18]. Its clinical use is limited as it is considered a second-line treatment according to the recommendations of EULAR (European League Against Rheumatism), ACR (American College of Rheumatology), and SER (Spanish Society of Rheumatology). Studies like the one conducted by Park, et al., which was a phase III clinical trial, demonstrated equivalence with the original product in terms of pharmacokinetics, immunogenicity, safety, and efficacy, although the study only covered a period of up to 2 weeks [19,20]. In Spain, we have had the BIOBADASER registry since 2000. It includes patients with any type of rheumatic disease undergoing treatment with original and biosimilar biologic drugs, as well as small molecules. The most frequent adverse events reported were infections [21,22]. Despite the economic benefits of biosimilars, as they contribute to the sustainability of the healthcare system, there are still uncertainties in daily clinical practice regarding safety, clinical effectiveness, immunogenicity, and special situations related to the interchangeability of the reference drug or another biosimilar. Therefore, it is necessary to conduct comparative exercises that demand that the biosimilar demonstrates sufficient similarity to the reference product and prove that any minor differences between them do not have a relevant impact on the biosimilar's activity, efficacy, and safety.

In November 2019, the Official Gazette of Castilla-La Mancha published the Framework Agreement for the selection of suppliers of medications, fluid therapy, and contrast agents for public healthcare centers in the region. This agreement highlighted the inclusion of batches of new biosimilar medications, including adalimumab, etanercept, infliximab, and rituximab, by the Castilla-La Mancha Health Service. Additionally, the framework agreement allowed for the continuation of biological drug treatments when deemed clinically necessary. In compliance with this agreement, the pharmacy and therapeutics committee at the general university hospital of Ciudad Real decided to include the corresponding batches of these drugs in the pharmacotherapeutic guide and carry out a mass switching of eligible patients. Therefore, the objective of our study is to determine the effectiveness and safety of biosimilar drug use in immune-mediated inflammatory rheumatic diseases following the interchange.

MATERIALS AND METHODS

Study design

This study is an observational and descriptive study. A retrospective review of a database of patients with inflammatory immune-mediated rheumatic diseases is under consideration and who have undergone a prior biologic switch to a biosimilar drug.

Patients

Patients with inflammatory immune-mediated rheumatic diseases, including spondyloarthritis predominantly axial (radiographic and non-radiographic axial spondyloarthritis) and predominantly peripheral (psoriatic arthritis, reactive arthritis, spondyloarthritis associated with inflammatory bowel disease, undifferentiated spondyloarthritis) according to ASAD 2009 criteria, rheumatoid arthritis according to EULAR 2010 criteria and other rheumatic inflammatory diseases like systemic lupus erythematosus, Behçet, Sjögren, myopathies and syndrome. From PAPAsh. Patients were treated during outpatient visits in the Rheumatology Department of General University Hospital of Ciudad Real, for at least 24 weeks.

Variables

The collected variables were as follows: demographic data (sex and age) and the diseases studied. The biosimilar biologic drug used (infliximab, etanercept, adalimumab, and rituximab) was collected, as whether and which

concomitant conventional DMARD was used and the patients' associated comorbidities. Furthermore, as a variable of interest for our study, the disease activity variables were collected as ASDAS-CRP (Ankylosing Spondylitis Activity Score) for axial involvement in patients diagnosed with axial spondyloarthritis and psoriatic arthritis with axial involvement, which includes both subjective variables such as questions about spinal pain, global assessment of the patient, peripheral pain or swelling, or duration of stiffness, in addition to an objective variable of inflammation such as CRP and inactive disease being defined when the score is <1 .3, moderate activity if 1.3-2.1, high activity if 2.1-3.5 and very high activity if >3.5; DAPSA index (Disease Activity for Psoriatic Arthritis) was used for those patients suffering from psoriatic arthritis and was calculated by adding 5 variables in a linear fashion: (1) number of swollen joints, (2) number of tender joints, (3) pain measured using a 0-10 Visual Numeric Scale (VNS), (4) patient global assessment using a 0-10 VNS, and (5) CRP (mg/dl); DAS28-RCP index for patients with rheumatoid arthritis and is calculated using the 28-joint score (joint pain and inflammation), C-Reactive Protein (CRP), and the patient's subjective assessment of their level of pain, defining it as inactive disease when the score is <2.6, low activity if 2.6-3.2, moderate activity if 3.2-5.1, and high activity if >5.1. In addition, the acute phase reactants ESR (mm/1 h) and CRP (mg/dl) are measured. In addition, other variables related to biosimilar DMARDs such as drug survival, optimization, reason for discontinuation, and adverse events, were assessed. All this was measured at the start of switching and 24 weeks.

Statistical analysis

The numeric variables with a normal distribution are expressed as means and standard deviation. Frequency measures and central tendency/dispersion measures are used with

The other variables are described accordingly. We performed a hypothesis test with $\alpha=0.05$ for the independence of categorical variables with the chi-square test. On the other hand, we performed a U-Mann Whitney test to test the independence between categorical and numeric variables, checking the heteroscedasticity of the groups.

RESULTS

Of the 380 patients being treated with biosimilar bDMARDs, a total of 364 patients who met the inclusion criteria were selected (3 did not meet the inclusion criteria, and 13 were lost to follow-up). The mean age was 52.50 years (± 12.11), with 168 women and 196 men selected. By number of patients, the drugs used were: 203 adalimumab, 130 etanercept, 13 infliximab, and 18 rituximab. Regarding concomitant treatments, 125 patients had taken corticosteroids at some point, and in relation to conventional bDMARDs, 89 patients had methotrexate, 25 leflunomide, 21 sulfasalazine, and four hydroxychloroquine. Of the total, 173 had spondyloarthritis, 68 had psoriatic arthritis, 112 had rheumatoid arthritis (90 seropositive and 22 seronegative), and 11 had other systemic autoimmune diseases (Behçet's disease, systemic lupus erythematosus, Sjögren's syndrome, dermatome Yositis, and Papash syndrome). Variables related to activity and switching of biosimilars, discontinuation, etc., were found to be independent according to the results of the chi-square tests ($p=0.05$). With the Mann-Whitney U test for the study on the independence of the days that the biosimilar has been taken and the activity of the patient, together with a Levene test of homogeneity of the variances, it is observed that in patients who present activity shows dependence on the number of days that they had a biosimilar that was significantly lower than the number of days that patients without activity took it ($p<0.01$). Disease activity at the start of the switch was 1.73 (± 0.93) in ASDAS-CRP, 8.73 (± 12.20) in DAPSA, and 2.60 (± 1.20) in DAS28-CRP, while at 24 weeks after the switch, it was 1.79 (± 0.96) in ASDAS-CRP, 8.39 (± 9.05) in DAPSA and 2.62 (± 1.23) in DAS28-CRP. In serological markers, at the beginning of the switch, the CRP was 0.51 mg/dl (± 1.18) and the ESR was 10.77 mm (± 9.75), while at 24 weeks after the switch, the CRP was 0.54 mg/dl (± 2.17) and the ESR was 10.48 mm (± 10.23) (Table 1) .

Table 1. Activity of the disease, at the beginning of switching and 24 weeks after switching.

Activity	At the start of switching	24 weeks after switching
ASDAS-CRP	1,73 (± 0,93)	1,79 (± 0,96)
DAPSA	8,73 (± 12,20)	8,39 (± 9,05)
DAS28-CRP	2,60 (± 1,20)	2,62 (± 1,23)
ESR (mm/h)	10,77 (± 9,75)	10,48 (± 10,23)
CRP (mg/dl)	0,51 (± 1,18)	0,54 (± 2,17)

The number of patients, measured by ASDAS-CRP (for patients with spondyloarthritis with axial involvement), increased in the groups of inactive disease, high activity, and very high activity after 24 weeks of switching. If measured by DAPSA (for psoriatic arthritis patients), the number of patients increased in the low-activity and high-activity groups at 24 weeks post-switching. And if it is measured by DAS28-CRP (rheumatoid arthritis), the number of patients increases in the groups of moderate activity and high activity at 24 weeks after switching (Figures 1-3).

Figure 1. Activity measured by ASDAS-RCP for patients with axial spondyloarthritis, at the beginning and 24 weeks after switching. **Note:** (■) At the start of switching; (■) 24 Weeks after switching.

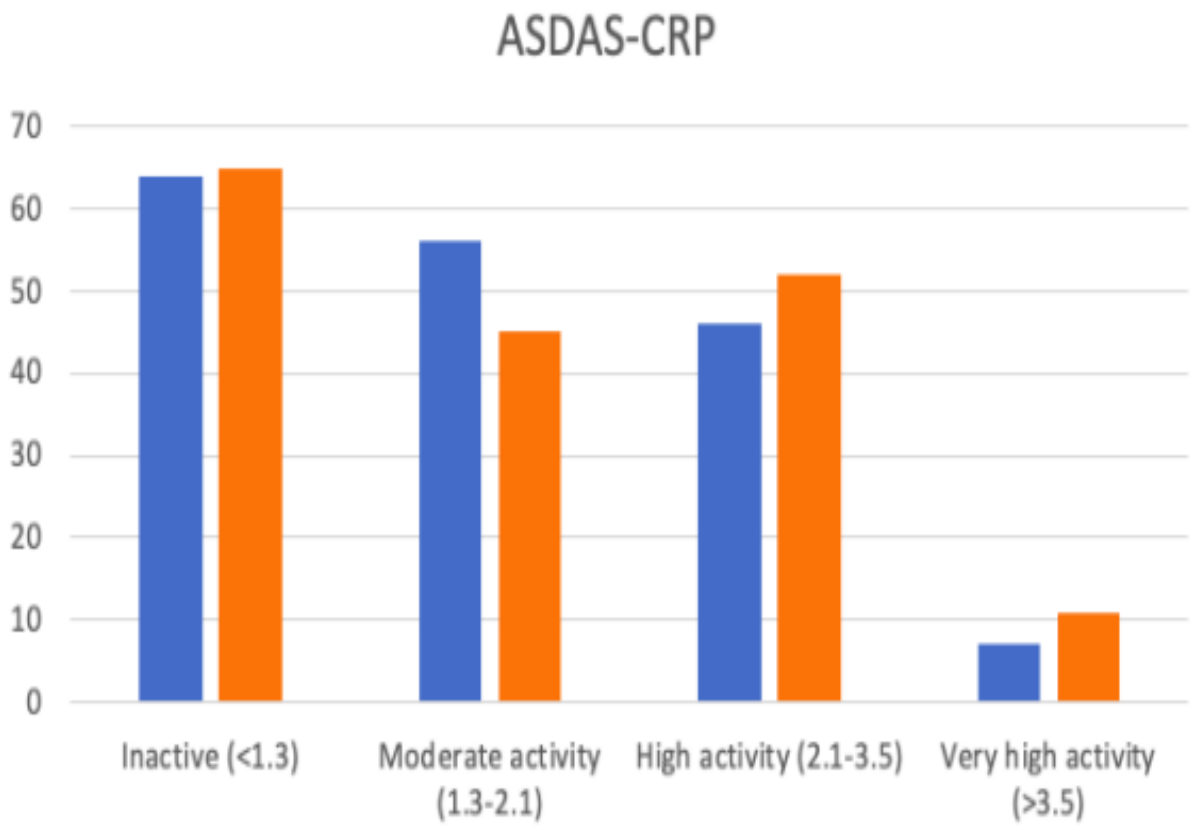


Figure 2. Activity measured by ASDAS-RCP for patients with axial spondyloarthritis, at the beginning and 24 weeks after switching. **Note:** (■) At the start of switching; (■) 24 Weeks after switching.

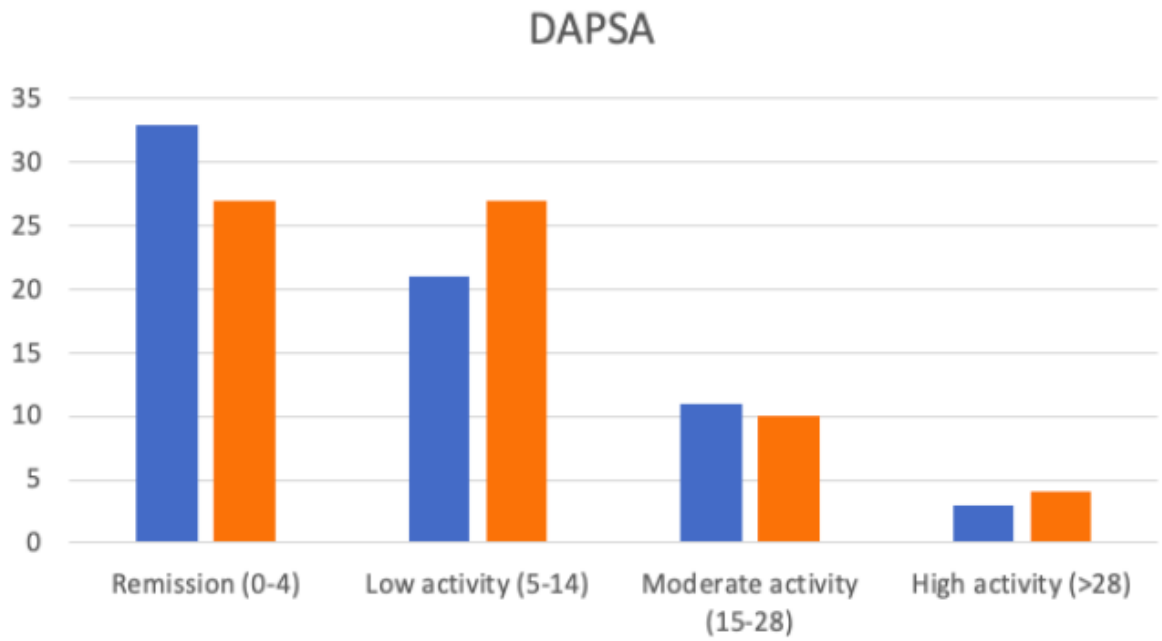
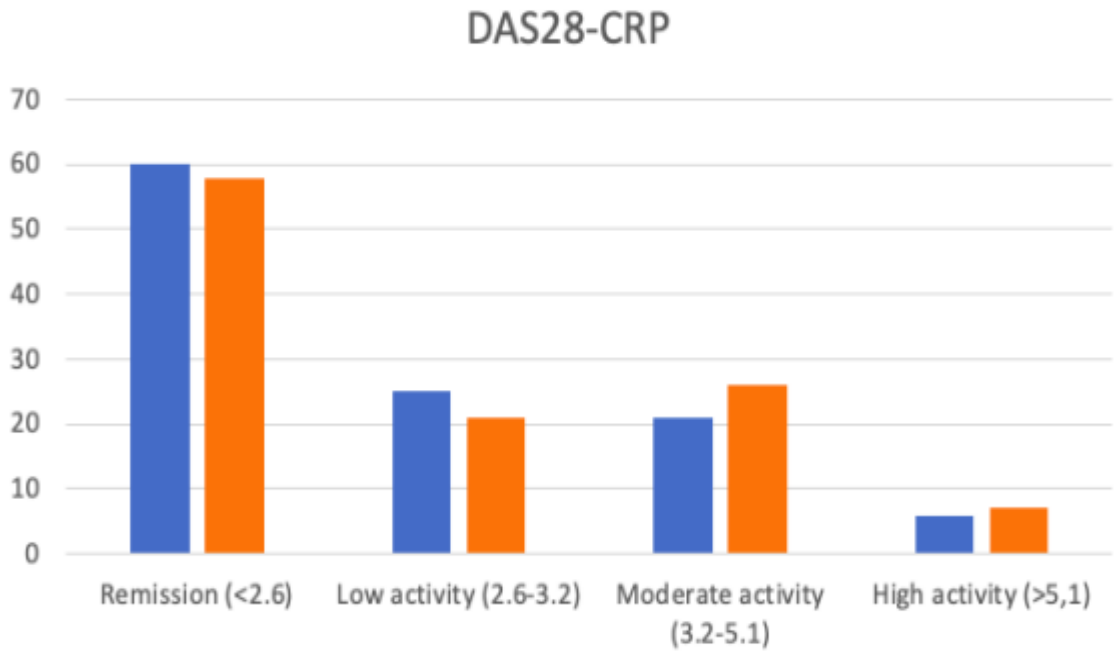


Figure 3. Activity measured by DAS28-RCP for patients with rheumatoid arthritis, at the beginning and 24 weeks after switching. **Note:** (■) At the start of switching; (■) 24 Weeks after switching.



A total of 29.95% of patients discontinued treatment with the biosimilar (109 of 364 patients). The reasons for discontinuation were ineffectiveness in 87 patients (52 with primary failure and 35 with secondary failure), adverse effects in 18 patients, and four patients discontinued it by their own decision. Of all the patients who discontinued

treatment, 76 of the 203 who were on adalimumab discontinued it, 26 of the 130 patients with Etanercept discontinued it, 2 of the 13 on infliximab discontinued, and 5 of the 18 patients on rituximab discontinued it. In contrast, the biosimilar optimization rate was 13.74% (50 patients out of 364).

DISCUSSION

Our study is a real-life practice study of biosimilar bDMARDs, in a population with a large number of patients. It was observed that 29.95% of the participants had to discontinue the use of the biosimilar drug, mainly due to its lack of efficacy, which exceeds the average reported in the current literature, as in the Glintborg study, which was only 7 % [9]. Only 18 patients experienced some adverse effect, of which only 2 cases were severe, a slightly lower number than in the Bruni study (4.74% of our research vs. 22.73%) [12]. Biosimilar drugs were effective and did not show significant interference in inflammatory activity.

The mean activity levels measured by ASDAS, DAPSA, and DAS28 remained similar both at the beginning and at 24 weeks after the treatment switch, although patients with higher activity at the beginning of the switch presented higher activity levels at 24 weeks.

Recently, in September 2022 (and the last update of April 2023), the European Medicines Agency (EMA) and the Heads of Medicines Agencies (HMA) have emphasized that biosimilars approved in the European Union are scientifically interchangeable, which means that a biosimilar can be used in place of its reference product, or vice versa. Furthermore, a biosimilar can be used instead of another biosimilar of the same reference product. Any exchange should only take place after careful consideration of the product information. But the EMA emphasizes that automatic substitution at the pharmacy level is subject to the member state's decision [23].

In Spain, the substitution of biological medicines (including biosimilars) is prohibited by Order SCO/2874/2007, of September 28, which establishes the drugs that constitute an exception to the possible substitution by the pharmacist in accordance with article 86.4 of Law 29/2006, of July 26, on guarantees and rational use of medicines and health products, although we believe that this legislation should be updated due to the rise and increase in the use of biosimilar bDMARDs [24]. Carrying out massive switching in our rheumatology service has led to savings of €513,617.92 during the study period, and we have gone from an annual expense of €3,333,554 in 2019 (pre-switching) to an expense of €2,850,956 in the year 2021 (post-switching).

On the contrary, and due to the discontinuation of a large number of biosimilar bDMARDs due to lack of efficacy (primary and secondary failures), we have observed an increase in the prescription of other drugs with other targets (anti-IL17, JAKinibs).

The limitations of our study in real life are the following: it is a descriptive study of a very heterogeneous sample of patients due to the drugs used and concomitant ones, systemic autoimmune rheumatic diseases, and comorbidities, among others, and it was not measured the concentrations of drugs or levels of neutralizing antibodies to differentiate between primary failure and secondary failure accurately or that it could be the nocebo effect.

CONCLUSION

Our data obtained in a real-life setting suggest that biosimilar drugs can be considered an effective option in the treatment of inflammatory rheumatic diseases, as evaluated by ASDAS, DAPSA, and DAS28, as well as PCR and ESR markers. However, it is important to note that there is a significant discontinuation rate of biosimilar use. On the other hand, these drugs can be considered safe, as a low frequency and severity of adverse effects were observed. In addition, biosimilar drugs constitute a revolution within biological therapies in rheumatology. At present, more and more patients are being treated with them, and their lower cost helps the sustainability of the

health system. New comparative studies with original bDMARDs performed in daily clinical practice are needed to achieve greater confidence.

ETHICAL APPROVAL INFORMATION

We have a document with the final approval of the Clinical Research Ethics Committee of the General University Hospital of Ciudad Real, approved on October 25, 2022 (act 10/2022, C-567). In addition, we have obtained the patient's written informed consent to publish the material.

DECLARATIONS

Ethics approval and consent to participate and Consent for publication: We have a document with the final approval of the Clinical Research Ethics Committee of the General University Hospital of Ciudad Real, approved on October 25, 2022 (act 10/2022, C-567). In addition, we have obtained the patient's written informed consent to publish the material.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIAL

The data and material can be requested from the main author, with prior justification, since the data is protected.

COMPETING INTERESTS

The authors declare that they do not have any conflict of interest.

FUNDING

All authors declare that they have no source of funding for this work.

Authors' contributions

DCC: Substantial contributions to study conception and design, Substantial contributions to acquisition of data, Substantial contributions to analysis and interpretation of data, Drafting the article or revising it critically for important intellectual content, Final approval of the version of the article to be published.

LACP: Substantial contributions to study conception and design, Substantial contributions to analysis and interpretation of data, Drafting the article or revising it critically for important intellectual content, Final approval of the version of the article to be published.

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MAPH: Substantial contributions to study conception and design, Drafting the article or revising it critically for important intellectual content, final approval of the version of the article to be published. All authors read and approved the final manuscript.

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