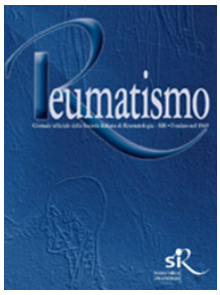

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A comprehensive evaluation of the transition to a biosimilar of adalimumab in rheumatoid arthritis and psoriatic arthritis: a single-center experience with a focus on imaging outcomes

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Summary

Objective. Limited data in Latin America exists regarding the efficacy of switches from original biologicals to biosimilars in real-life scenarios. Currently, no studies assess this switch using imaging. The objective of this study was to evaluate clinical, functional, ultrasonographic, and radiological responses in a group of patients with rheumatoid arthritis (RA) and psoriatic arthritis (PsA) switched from original adalimumab (oADA) to biosimilar (bADA) (GP2017).

Methods. A prospective cohort study included diagnosed RA and PsA patients undergoing oADA treatment. At the baseline visit, blood analysis, X-rays, ultrasound, and an interview for sociodemographic and clinical data were conducted. Evaluators were unaware of each other's data. Patients switched to bADA during follow-up and were assessed in the same program within 3 to 12 months post-switch (only including patients with all evaluations).

Results. Out of 270 RA cohort patients, 35 met the criteria for complete pre-and-post control post-switch to bADA (GP2017), along with 15 PsA patients. The mean time between the switch and the second evaluation was 4.1 months (interquartile range 7). No statistical differences were observed in disease activity or functional capacity. Regarding imaging, no difference was found in X-ray erosion number; however, ultrasonography revealed decreased power Doppler (PD) activity, but not grayscale findings. No differences in acute phase reactants, joint count, or patient visual analog scale were observed between controls.

Conclusions. In this analysis of the switch between oADA and bADA, no differences were found in disease activity, functional capacity, or radiographic progression. Ultrasonography indicated improvement of PD findings.

Introduction

Rheumatoid arthritis (RA) and psoriatic arthritis (PsA) are chronic autoimmune conditions characterized by joint inflammation and damage, contributing significantly to patient morbidity (1, 2). The arrival of biological therapies, particularly adalimumab (ADA), has changed the management of these conditions, demonstrating improved clinical outcomes and enhanced quality of life (3).

The implementation of biosimilars in rheumatic diseases has gained a place, emphasizing their comparable efficacy and safety to reference products. Not only do biosimilars offer potential economic benefits, but they also enhance accessibility to effective treatments for a broader patient population (4).

The introduction of a biosimilar of tumor necrosis factor (TNF) blockers, especially ADA, raises the need to perform evaluations of the efficacy and safety associated with the switch from the original ADA (oADA) to the biosimilar counterpart (bADA) in real-life scenarios, beyond the clinical trials that support the evidence (5). One of the primary challenges is the potential development of anti-drug antibodies, which could impact the efficacy and safety of these therapies. Additionally, the nocebo effect, where negative expectations from patients or clinicians regarding the biosimilar may influence treatment outcomes, poses a significant hurdle in clinical practice. Its use in Latin America is widespread, but published data is scarce (4, 5).

The increasing role of imaging, notably ultrasonography (US), in assessing disease activity and treatment response has become integral to rheumatological practice. However, the impact of transitioning from oADA to bADA on imaging parameters remains an underexplored area in the existing body of literature (6).

The primary objective of this research is to comprehensively evaluate the clinical, functional, ultrasonographic, and radiological responses in RA and PsA patients under the first biological treatment, undergoing a switch from oADA to bADA.

Materials and Methods

This prospective longitudinal study included consecutive patients older than 18 years with a diagnosis of RA and PsA, treated with oADA as a first line of biological treatment (failure to conventional synthetic disease-modifying anti-rheumatic drugs) who were evaluated by the Reuma-Check program and switched to bADA (GP2017) within one year. The baseline evaluation was performed between August 2022 and December 2023. In brief, the Rheuma-Check Program is a circuit designed for the early diagnosis of rheumatic conditions and the systematic follow-up of patients. The different physicians involved included laboratory, imaging, and clinical specialists. This setup is integral to the Reuma-Check program, which operates through a station-based evaluation process. Each evaluator conducts its assessment independently, without access to the results obtained by others. This design aims to prevent any potential bias and ensures that the findings from one domain do not influence the evaluations in another. After switching to bADA, a second evaluation under the same standardized protocol was conducted within one year of the baseline assessment (7, 8).

Baseline assessment

Demographic features were assessed. Clinical data including disease duration and comorbidities, were collected. The musculoskeletal assessment was performed according to standard clinical procedures and included: tender joint count (TJC 28), swollen joint count (SJC 28), visual analog scale for patient's (VAS patient global) and physician's (VAS physician global) global perception of disease activity. The function was evaluated by the Argentinean version of the Health Assessment Questionnaire-Disability Index (9).

Erythrosedimentation rate (ESR), and C-reactive protein (CRP) were determined in all patients on the same day of the clinical and image evaluation.

All US examinations were performed by the same rheumatologist with extensive experience on this imaging technique, on the same day of the clinical assessment. Patients were asked not to talk with the operator during the US examination. A MyLab 25 Gold (Esaote) machine with a multifrequency

linear transducer (6-18 MHz) was used. The following joints were bilaterally investigated: wrist, 2nd to 5th metacarpophalangeals and 2nd to 5th proximal interphalangeals, giving a total of 22 assessed joints per patient. The standardized scanning method recommended by the European Alliance of Associations for Rheumatology was used and joint cavity widening (10), due to the presence of synovial fluid and/or synovial hypertrophy (grayscale synovitis) according to the OMERACT ("Outcomes Measures in Rheumatology") preliminary definitions (11), was evaluated at each joint. All joints were evaluated with the power Doppler (PD) technique to assess the presence of increased, abnormal synovial vascularization. Intraarticular PD signal was scored on a semiquantitative scale from 0 to 3 (grade 0 = no intraarticular PD signal; grade 1 = presence of a single PD signal; grade 2 = more than two confluent foci of PD signal but occupying less than 50% of intra-articular area; grade 3 = PD signal in more than 50% of the intraarticular area). To maximize PD sensitivity and trying to avoid artifacts, the settings of PD were adjusted as follows: low pulse frequency repetition (between 500 and 1000 Hz), dynamic range 20-40 dB, low wall filters (2, 3), and PD gain below the level at which color noise appeared in the underlying bone (12-14). For the purposes of this study, patients were considered to have positive US if they had at least one joint with a positive PD signal grade 2-3 and to be improved when the PD signal dropped to grade 0 or 1. Findings were defined as absence or presence (yes/no). X-rays of both hands and feet were performed on the same day. The presence or absence (yes/no) of bone erosions was determined by an experienced medical rheumatologist, at any joint included on the Sharp/van der Heijde score.

Follow-up

Clinical, laboratory, and imaging data at baseline were uploaded to an electronic clinical system report. After one year, an evaluation identical to the baseline was carried out in the same circuit with the same evaluations, in those patients who had been switched from oADA to bADA (GP2017) for less than one year. All procedures and steps of the Reuma-Check program are detailed in the cited publications (7, 8).

Statistical analysis

Descriptive statistic was used to summarize patients' characteristics. Continuous variables were expressed as medians and interquartile range (IQR) or as means and standard deviation, and categorical variables were expressed as percentages with their corresponding 95% confidence intervals. The comparison between disease activity assessments, Health Assessment Questionnaire (HAQ) results, laboratory parameters, and images was performed using parametric and non-parametric tests for continuous variables and the chi-squared test for categorical variables.

Results

Of the 270 patients in our RA cohort, 35 met the criteria: first biological treatment, switch from oADA to bADA (GP2017) with complete pre-and post-monitoring in the Reuma-Check circuit. Of the PsA cohort (70 patients), 15 patients met this premise. Table 1 shows the baseline characteristics before the switch.

The mean number of months of treatment with the oADA was 4 (IQR 6) and the mean time between the switch (and the second evaluation was 4.1 months (IQR 7).

No statistical differences were observed in terms of median disease activity pre- and post-switch: Disease Activity Score-28 3.7 (IQR: 2) *vs.* 3.5 (IQR: 1.8), p=0.6 or functional capacity (HAQ) 0.8 (IQR: 0.1) *vs.* 1.1 (IQR: 0.11), p=0.7. Figure 1 shows the values of Simplified Disease Activity Index and Clinical Disease Activity Index.

Regarding the images evaluation, no difference was found in the proportion of erosions in X-rays (47% *vs.* 48%, p=0.7); the comparison of US examinations showed a decreased activity by PD (27% *vs.* 12%, p=0.03), but not by greyscale evaluation, after the switch (Figure 1).

There was no difference between visits in acute phase reactants (ESR mm/hr.: 30 *vs.* 27.5, p=0.2, CRP mg/L: 3 *vs.* 4, p=0.09), tender and swollen joint count (TJC: 4 *vs.* 5, p=0.4, SJC: 2.9 *vs* 3.1, p=0.6) and VAS of the patient's activity (51 *vs.* 47 mm, p=0.08).

Discussion

This study evaluates the impact of switching from oADA to its biosimilar in patients with RA and PsA and analyzes clinical, functional, ultrasonographic, and radiological responses in patients undergoing this transition.

In the development of biosimilars, physical-chemical characterization and preclinical studies are more important than clinical trials, which are limited to transition or switch studies, or interchangeability studies in the most sensitive indications for the drug (15, 16). However, once approval is achieved by regulatory agencies, the development of real-world evidence (RWE) is essential for the development of evidence in the switch (17).

In rheumatology, ADA stands out as the TNF blocker with the most extensive range of indications, encompassing conditions such as RA and PsA. Notably, ADA serves as the benchmark drug in the advancement of more sophisticated therapies for these diseases (18). At present, it is the treatment with the highest number of biosimilars developed in rheumatology, all of which adhere to the rigorous quality standards mandated by major regulatory agencies (19). Among these biosimilars, GP2017, developed by Sandoz (Basel, Switzerland), has a comprehensive development program that includes the ADMYRA study for RA (20) and ADACCES for psoriasis (21). Importantly, the latter incorporates multiple switch arms, providing compelling evidence of GP2017 interchangeability with the oADA.

The Nord-Switch study of infliximab was the pioneer in rheumatology for the switching from an original biologic to a biosimilar based on clinical evidence with pharmacoeconomic bases (22). The body of evidence regarding the transition from original drugs to biosimilars within rheumatology has been steadily expanding, owing to investigations conducted by independent research centers, real-life/pharmacovigilance registries, and data derived from healthcare payers. These studies unequivocally indicate switching does not escalate the frequency of adverse events or events associated with immunogenicity. Moreover, compelling information emerges from this body of evidence since the adoption of biosimilars yields substantial economic benefits for the healthcare system. These advantages manifest in the form of resource savings and increased accessibility to advanced therapies in rheumatology (17, 23-25). Among others, the validation of GP2017 in real-life studies, supported by the research of Nabi *et al*. from the DANBIO registry, underscores the robustness of the findings and adds confidence to the observed positive outcomes (26).

The aforementioned evidence originates predominantly from the European continent. Despite the presence of regulations about the utilization of biosimilars by health authorities or regulatory agencies in Latin America, the lack of RWE in the region accentuates the significance of our research findings. Our study not only addresses this gap, but also contributes insights into the decision-making processes of specialist physicians and the broader healthcare system together with the guidelines developed in our region by the Pan-American League of Associations for Rheumatology (27, 28).

In addition to the efficacy results, our research introduces a distinctive element by providing evidence regarding the impact of the switch on imaging, a facet not explored in RWE studies of biosimilars. We have demonstrated that there is no discernible impact from a radiographic perspective in a qualitative manner, albeit acknowledging that the evaluation time (less than one year) may be insufficient to establish conclusions. US evaluation, a secure and accessible method, indicates improved PD findings, potentially indicating that patients mantained a positive response to ADA regardless of the switch to its biosimilar.

Importantly, the utilization of objective assessments, such as imaging, serves to mitigate the nocebo effect that may arise from biosimilar switching. This approach enhances the credibility of our findings and underscores the objective nature of the observed improvements. Another positive aspect of the study lies in the method of obtaining patient information, conducted within the Reuma-Check circuit,

a protocolized evaluation program validated in various publications, enabling the collection of comprehensive and standardized data (29).
Finally, we must recognize several weaknesses in our study. Firstly, the study is hampered by a relatively small sample size, as it exclusively encompasses patients initiating their treatment with biological therapies, in a single center. This approach introduces selection and indication biases that warrant consideration. Moreover, the small sample size limits the power of the study to detect subtle differences associated with biosimilar switching. This constraint significantly impacts the generalizability of our findings to broader patient populations and reinforces the necessity of larger multicenter studies to validate our results and draw more definitive conclusions. Furthermore, the absence of a control group that continued treatment with the oADA limits our ability to distinguish whether the observed outcomes were specifically related to the biosimilar switch or attributable to other factors. Additionally, the study is constrained by a limited evaluation period (1 year) and, as of the time of this publication, lacks an ongoing follow-up.

Conclusions

In conclusion, the study suggests that transitioning from oADA to bADA (GP2017) as the first-line biological treatment for RA and PsA patients does not appear to lead to significant alterations in disease activity or functional capacity. Radiographic assessments exhibited no changes of X-ray erosions before and after the transition. However, US evaluations indicated a decreased PD activity following the switch. Acute phase reactants, joint count, and patient-reported activity did not change. While these findings are encouraging, they should be interpreted in the context of the study's limitations, including the small sample size and the absence of a control group continuing with oADA.

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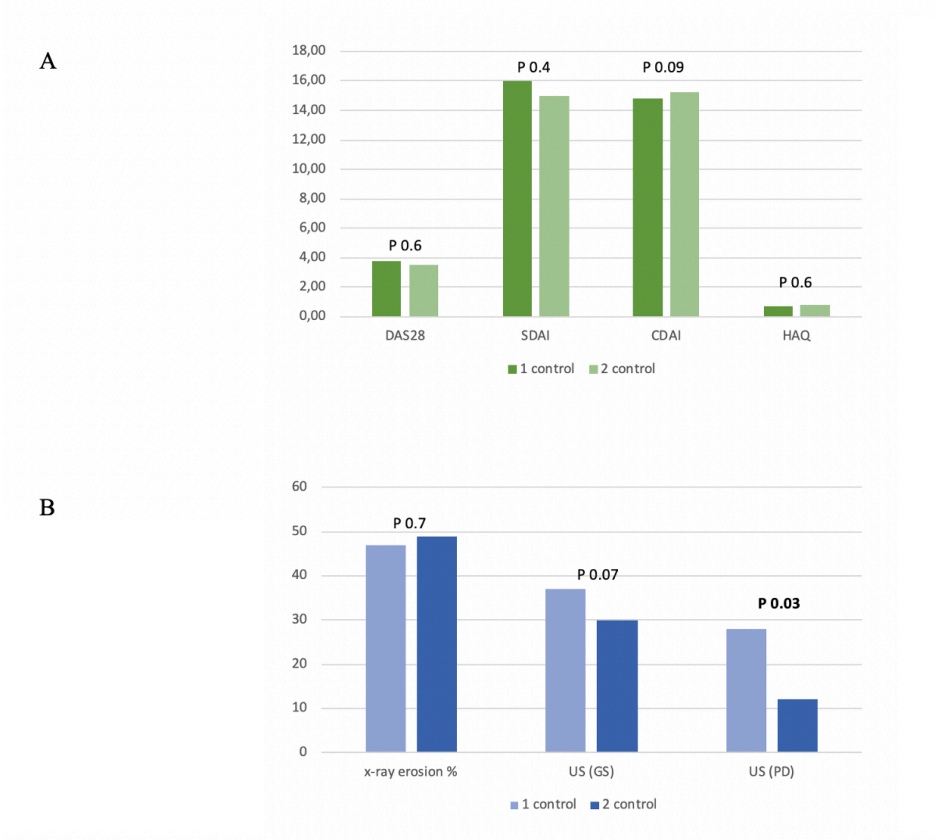

Figure 1. Clinical, functional, and imaging assessments before and after the switch from original adalimumab (oADA) to its biosimilar (GP2017). A) Comparison of disease activity (DAS28, SDAI, CDAI) and functional status (HAQ) between baseline (1st control) and follow-up (2nd control) evaluations; B) imaging outcomes including proportion of patients with radiographic erosions, grayscale ultrasonographic synovitis (US-GS), and power Doppler activity (US-PD). A significant decrease in PD activity was observed after the switch (p=0.03). No significant changes were found in the other parameters.

Table 1. Baseline characteristics of the rheumatoid arthritis and psoriatic arthritis cohort.

	n: 50
Baseline characteristics	
Female sex, %	60
Age (years), mean (SD)	54 (14)
Disease duration (months), median (IQR)	24 (50)
School years, mean (SD)	12.5 (3)
Weight (kg), mean (SD)	78 (17)
TBQ, %	34
Early disease (≤2 years), %	50
RF+, %	74
ACPA +, % (RA: 35)	53
Double seropositive, % (RA: 35)	48
X-ray hands erosions +, %	47
Synovitis US (grayscale), %	37
Ultrasonographic synovitis (power-doppler), %	28
TJC (28), mean (SD)	2.9 (2.1)
SJC (28), mean (SD)	4 (3.5)
CRP + (>5 mg/L), %	35
CRP titer (mg/L), median (IQR)	3 (9)
ESR (mm 1 h), mean (SD)	30 (24)
VAS patient (mm), mean (SD)	51 (21)
VAS physician (mm), mean (SD)	37 (19)
DAS28, mean (SD)	3.8 (1.2)
SDAI, mean (SD)	16 (11)
CDAI, mean (SD)	14.8 (8)
HAQ, mean (SD)	0.75 (0.48)
Comorbidities	
Comorbidities (any),%	55
Anemia (Hb≤12), %	18
Cardiovascular disease, %	39
Diabetes, %	17
Interstitial lung disease, %	9
Cancer, %	8
MACE, %	5
Dyslipidemia, %	16
Associated treatment	
Methotrexate, %	83
Oral corticosteroids (any dose), %	43
Oral corticosteroids (>10 mg), %	16

SD, standard deviation; TBQ, tobacco smoking; RF+, rheumatoid factor positive; ACPA, anti-citrullinated peptide antibody; RA, rheumatoid arthritis; US, ultrasound; TJC, Tender joint count; SJC, swollen joint Count; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; VAS, visual analog scale; DAS28, Disease Activity Score-28; SDAI, Simplified Disease Activity Index; CDAI, Clinical Disease Activity Index; HAQ, Health Assessment Questionnaire; Hb, hemoglobin; MACE, major adverse cardiac events. ACPA and RF were assessed only in patients with rheumatoid arthritis.