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ORIGINAL RESEARCH ARTICLE

Forty-Eight-Month Monitoring of Disease Activity in Patients with Long-Standing Rheumatoid Arthritis Treated with TNF-α Inhibitors: Time for Clinical Outcome Prediction and Biosimilar vs Biologic Originator Performance

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Abstract

Background and Objectives Long-term treatment of patients with rheumatoid arthritis with tumor necrosis factor-α inhibitors leads to initial changes in disease activity that can predict a late treatment response. This observational and retrospective study aimed to determine when it is possible to foresee the response to therapy in the case of long-standing rheumatoid arthritis comparing also the efficacy of the original biologics with their biosimilars.

Methods A total of 1598 patients were recruited and treated with the original biologics, adalimumab and etanercept, or with biosimilars. Patients were monitored over a period of 48 months and disease activity scores (28-Joint Disease Activity Score, Simplified Disease Activity Index, and Clinical Disease Activity Index) were measured every 6 months.

Results No differences in disease activity levels were observed in etanercept versus biosimilars (GP2015/SB4) and adalimumab versus biosimilar (GP2017) patient groups. All scores significantly decreased in all treatments during the first 18 months of therapy, and after 24 months reached a minimum that lasted up to 48 months.

Conclusions We conclude that biosimilars of adalimumab and etanercept have equivalent effectiveness over a long period of time compared to their originator drugs, and also that the levels of disease activity after 6 months of tumor necrosis factor-α inhibitors (originator drugs and biosimilars) might predict the response to therapy at 4 years in patients with long-standing rheumatoid arthritis.

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Key Points

We provided a timing to predict the long-term response to therapy with tumor necrosis factor-α inhibitors and support the use of the equally effective but less expensive biosimilars in patients with rheumatoid arthritis.

Original biologics, adalimumab and etanercept, and their biosimilars showed comparable long-term efficacy.

Levels of disease activity after 6 months of tumor necrosis factor-α inhibitors allowed the identification of long-term responders.

1 Introduction

Tumor necrosis factor-α (TNF-α) is expressed as a pro-inflammatory and immunomodulatory transmembrane cytokine by macrophages, CD4(+) T cells, mast cells, neutrophils, and natural killer cells. The binding of TNF-α with its receptors increases the expression of other pro-inflammatory cytokines (interleukin-1, interleukin-6, and interleukin-8) that drive systemic inflammation in immune-mediated diseases [1]. Rheumatoid arthritis (RA) is one of the autoimmune inflammatory disorders associated with an abnormal production of TNF-α and causes joint pain, stiffness, swelling, and systemic manifestations affecting the hands, feet, and wrists. This long-term condition leads to progressive joint damage and destruction of both cartilage and bone, reducing a patient's motility [2]. An early diagnosis is essential to start the appropriate treatment, and anti-cyclic citrullinated peptide and rheumatoid factor are considered the most important clinical biomarkers and are incorporated into the current American College of Rheumatology classification guidance [3]. Despite methotrexate and leflunomide remaining the first-line treatment, cases of inefficacy or side effects can occur. [4–7]. Hence, the 2019 updated European League Against Rheumatism recommends alternatives, such as biologic therapies based on TNF-α antagonists, to counterbalance the outcome of RA [4, 8].

Thanks to biotechnology innovations, five TNF-α inhibitors (etanercept, infliximab, adalimumab, golimumab, and certolizumab pegol) have been developed and they are currently used to manage RA symptoms [9]. Their efficacy and safety have been confirmed by clinical trials revealing also that: (i) anti-TNF-α agents are more efficacious than methotrexate alone and (ii) anti-TNF-α agents combined with methotrexate are more effective compared with anti-TNF-α monotherapy [10].

Various aspects still remain to be completely clarified, mainly the occurrence of absent or insufficient therapeutic responses and their high direct costs. Biosimilars can help solve these problems, thus they have been positively welcomed by regulatory agencies since their approval for use in Europe in 2018. They share the same mechanisms, efficacy, and safety of their biological reference drugs and offer price competition, in particular biologics with expired patents [11]. Hence, biosimilars promise a significant cost reduction for healthcare systems, improving access to therapy [1, 12]. Notwithstanding these advantages, debates on the interchangeability between reference products and biosimilars are still ongoing. Current guidelines recommend biosimilars as a first-line treatment for patients with moderate-to-severe RA who did not respond to conventional synthetic disease-modifying antirheumatic drugs. However, patients receiving TNF-α inhibitor therapy need tight control because the response to treatment varies widely [13], and initial changes in the measures of disease activity can predict a late treatment response [14, 15].

In light of this, we conducted a study to compare the clinical efficacy of biosimilars with biologic agents over a long 48-month period to determine when it is possible to foresee the response to therapy in the case of long-standing RA, which refers to the chronic stage of the disease, typically spanning several years. We evaluated the effects of adalimumab (GP2017) and etanercept (GP2015 or SB4) biosimilars (in comparison with those of their biological reference drugs).

2 Methods

2.1 Study Design and Patients

The present retrospective and observational study was conducted at the Rheumatology Section of the Santa Maria della Scaletta Hospital of Imola, Italy and at San Pier Damiano Hospital in Emilia Romagna, North Italy. A total of 1598 consecutive TNF-α inhibitor-naïve patients fulfilling the 1984 modified American College of Rheumatology for RA [16] were recruited and followed up for 48 months after beginning anti-TNF-α therapy. This analysis referred to patients recruited and treated in two successive periods from June 2011 to June 2023. We compared the clinical outcomes observed in patients who received originator drugs, as biosimilars were still not available, with those obtained more recently in patients treated with biosimilars. All patients presented with high initial disease activity, had not responded to conventional synthetic disease-modifying antirheumatic drugs, and had long-standing RA (the 25th, 50th, and 75th quartile for the disease duration at the beginning of anti-TNF-α therapy was 3.7, 5.7, and 9.7 years, respectively), with documented erosions detected by conventional radiography. Patients treated with originator drugs started with a TNF-α inhibitor before the introduction of biosimilars to the market. Patients who switched to biosimilars were also included, with the exception of those in remission already after treatment with the originator drugs as recommended by the regional guidelines. This study was approved by the ethics committee of our hospital, and written informed consent was obtained from the patients.

2.2 Treatment

Participants, divided into four different groups according to treatment (etanercept; etanercept biosimilars GP2015/SB4; adalimumab; adalimumab biosimilar GP2017), were

homogeneous in terms of clinical characteristics and therefore comparable in terms of outcomes. All of them were treated in accordance with current guidelines [4], and received long-term follow-up care for 5 years (from August 2017 to August 2022). A prescription of a biosimilar was based on regional approvals: (i) SB4 was the first etanercept biosimilar to be introduced starting from August 2017; (ii) GP2015 was authorized from September 2018 to December 2020; and (iii) GP2017 was the only adalimumab biosimilar used during the whole study period. To continue, patients who had started a specific anti-TNF-α biosimilar had maintained the same treatment throughout the study period even if the drug approval was changed.

2.3 Outcome Assessment and Data Collection

Patients received routine monitoring of disease activity for 48 months and data were collected every 6 months. The monitoring period lasted 48 months for two reasons: first, the average response was stable from month 24 (Fig. 1), and second, biosimilars were available for use only since 2018. Changes in disease activity in patients were evaluated using the 28-Joint Disease Activity Score (DAS28), the Simplified Disease Activity Index (SDAI), and the Clinical Disease Activity Index (CDAI). Then, treatment efficacy was assessed comparing the three indices within each group: etanercept versus biosimilars (GP2015/SB4) and adalimumab versus biosimilar (GP2017).

Hence, DAS28, CDAI, and SDAI were used as predictors of outcomes and the criteria to continue TNF-α inhibitor therapy after 6, 12, or 18 months. Patients with a DAS28 of at least 1.2 were defined as responders and continued treatment, while those who did not reach this level of response were classified as non-responders, thus the treatment was discontinued. Finally, in our study, primary inefficacy was defined as patients who had not presented with a DAS28 improvement of at least 1.2, whereas secondary inefficacy was defined as the loss, overtime, of the efficacy of a previous treatment.

2.4 Statistical Analysis

Age and diagnosis months fall within a range, thus they were presented as mean ± standard deviation. Data acquisition and statistical analyses were performed with Jamovi software (Version 2.2.5; The Jamovi Project, Sydney, Australia) [17] using a repeated-measures analysis of variance and the Bonferroni post-hoc test to assess the differences between time and treatments.

3 Results

3.1 Demographic and Monitoring Characteristics of Patients

Table 1 summarizes the demographic and monitoring characteristics of the 1598 patients (1219 female and 379 male). The mean age of patients treated with originator drugs was 65.99 ± 0.4 years for etanercept and 63.63 ± 0.5 years for adalimumab. The mean age of patients treated with etanercept biosimilars (GP2015/SB4) was 58.62 ± 0.3 years and 60.81 ± 0.4 years for adalimumab biosimilar (GP2017). No differences were seen among treatments based on methotrexate or leflunomide combined with biologic/biosimilar agents, and also in terms of positivity to anti-cyclic citrullinated peptide and rheumatoid factor. The average time between diagnosis and initial treatment was 74.53 months for the group of patients treated with etanercept, 66.55 for those patients treated with etanercept biosimilars (GP2015/SB4), 49.45 months for the adalimumab group, and 71.64 months for patients who received adalimumab biosimilar (GP2017).

4 Analysis of Diseases Activity Scores After TNF-α Inhibitor Administration

As previously described, DAS28, SDAI, and CDAI scores are useful to evaluate disease activity in RA. In the present study, these scores were collected and analyzed every 6 months from the starting point of therapy until the 48th month of monitoring. Their analysis was reported in Fig. 1 and revealed no differences in the treatment based on etanercept (original biologic) versus biosimilars (GP2015/SB4), as well as adalimumab versus biosimilar (GP2017). During the first 18 months of administration, a significant decrease was observed for all scores in all treatments ($p < 0.01$; comparison 0–6; 6–12; 12–18 months for DAS28, SDAI, and CDAI levels in both etanercept vs etanercept biosimilars [GP2015/SB4] and adalimumab versus biosimilar [GP2017]). Between 18 and 48 months, the levels of DAS28, SDAI, and CDAI were flattening in both etanercept versus biosimilars (GP2015/SB4; $p = 0.019$; $p = 1$; and $p = 1$, respectively) and adalimumab versus biosimilar (GP2017; $p = 1$ for all scores). The clinical efficacy of both originator drugs and biosimilars was maximum after 24 months of treatment and lasted up to 48 months (Fig. 1).

5 Drug Survival

Although the efficacy of biosimilars was the same for originator drugs, the analysis of survival probability curves showed significant differences ($p < 0.0001$) in the 48 months of treatment: etanercept with biosimilars (GP2015/

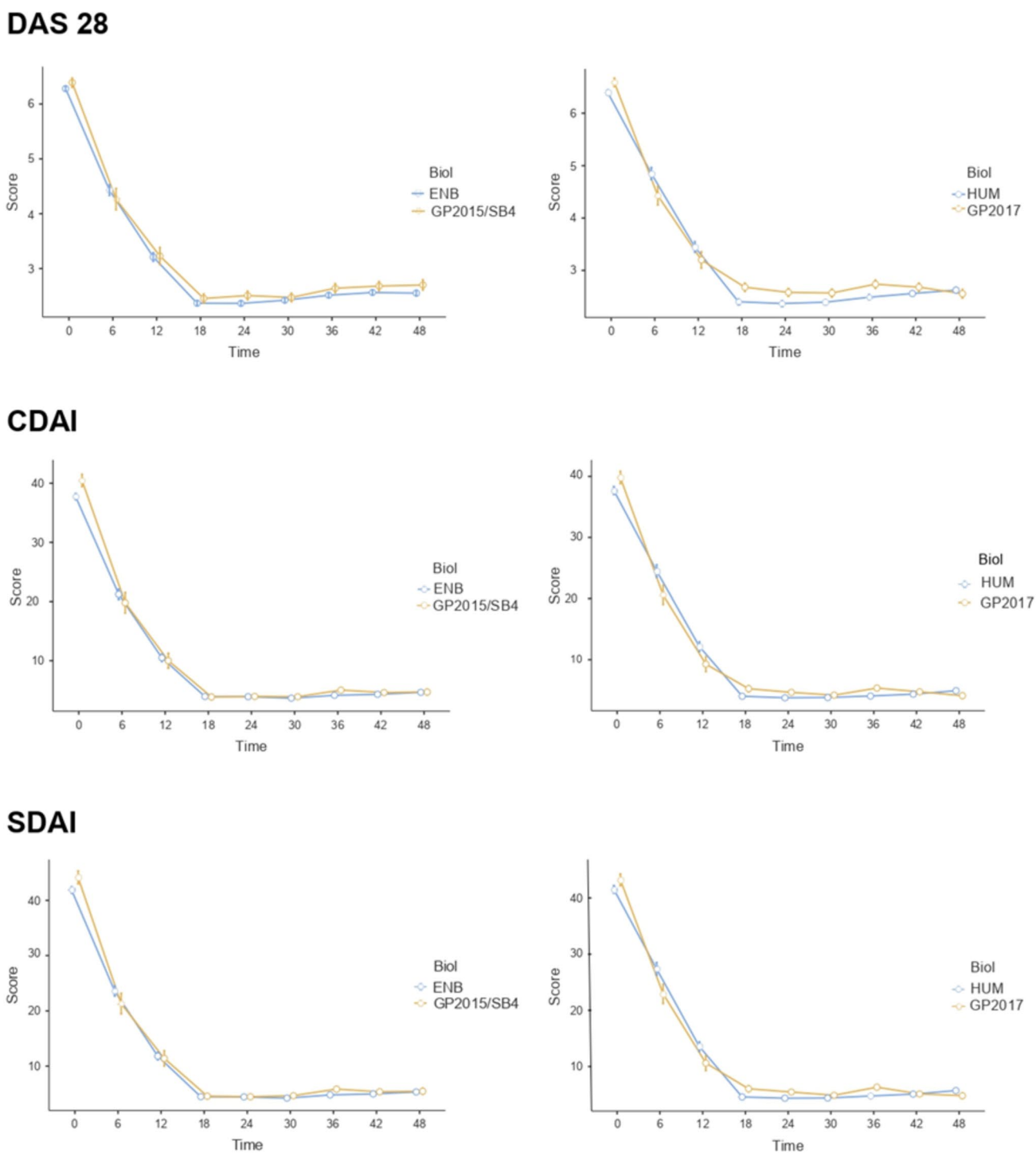

Fig. 1 Comparison of the clinical efficacy of originator drugs with biosimilars (BIO). Graphical representation of 28-Joint Disease Activity Score (DAS28), Clinical Disease Activity Index (CDAI), and Simplified Disease Activity Index (SDAI) values collected every 6 months during 48 months of tumor necrosis factor-α-inhibitor administration. Time was expressed in months and abbreviations were indicated as follows: etanercept; etanercept BIO (GP2015 or SB4); adalimumab; adalimumab BIO (GP2017)

SB4; Fig. 2A), and adalimumab with its biosimilar GP2015 (Fig. 2B). In both treatments, the biosimilar survival remains approximately high until the first 24 months of administration. Then, the increased distance between curves greatly increases in both cases, notwithstanding the overall drug survival curve of the biosimilar GP2017 versus

Table 1 Demographic and monitoring characteristics of patients

Items	Etanercept	Etanercept biosimilar	Adalimumab	Adalimumab biosimilar
Patients, *n* (%)	553 (35%)	284 (18%)	442 (28%)	319 (20%)
MTX, *n* (%)	429 (78%)	226 (80%)	329 (74%)	244 (76%)
LEF, *n* (%)	55 (10%)	23 (8%)	55 (12%)	40 (13%)
Anti-CCP, *n* (%)	166 (30%)	197 (69%)	290 (65%)	209 (66%)
RF, *n* (%)	166 (30%)	87 (31%)	295 (67%)	207 (65%)
Min age (years), *n*	29	41	36	36
Max age (years), *n*	90	71	91	79
Mean age (years) ± SD	65.99 ± 0.4	58.62 ± 0.3	63.63 ± 0.5	60.81 ± 0.4
Female patients, *n*	416	213	344	246
Male patients, *n*	137	71	98	73
Min Δdiagnosis-treatment (months), *n*	1	0	2	1
Max Δdiagnosis-treatment (months), *n*	486	319	598	466
Mean Δdiagnosis-treatment (months) ± SD	74.53 ± 3.4	66.55 ± 5.8	49.45 ± 2.6	71.64 ± 3.3

CCP cyclic citrullinated peptide, *LEF* leflunomide, *Max* maximum, *Min* minimum, *MTX* methotrexate, *RF* rheumatoid factor, *SD* standard deviation, Δ Delta is the time that elapses between diagnosis and the start of treatment

adalimumab seems to be slightly more favorable than that of etanercept biosimilars (GP2015/SB4) versus etanercept treatment. There are no data available for the causes of dropout (e.g., death, serious adverse events, change in treatment plan). However, we observed a notable high percentage of patients stopped the study among those treated with originator drugs, who are also the oldest, suggesting the influence of age: etanercept (21.48%), adalimumab (29.86%), etanercept biosimilar (GP2015/SB4; 58.62%), adalimumab biosimilar (GP2017; 60.56%).

6 Discussion

Tumor necrosis factor-α inhibitors have revolutionized the treatment of RA, but despite all advances, clinical response varies widely among patients. Those with a long disease duration as well as those with high baseline disease activity are more sensitive to TNF-α inhibitors [18]. In light of this, efforts to establish a clinical response for a single patient are crucial in moving towards personalized RA therapy. It is known that the biologic process of RA changes early in the disease, lowering the clinical response over the time, thus patients need to be monitored consistently throughout the course of treatment in order to promptly identify potential long-term responders [18, 19]. Thus, our goal was to determine how to predict the response to treatment in the case of

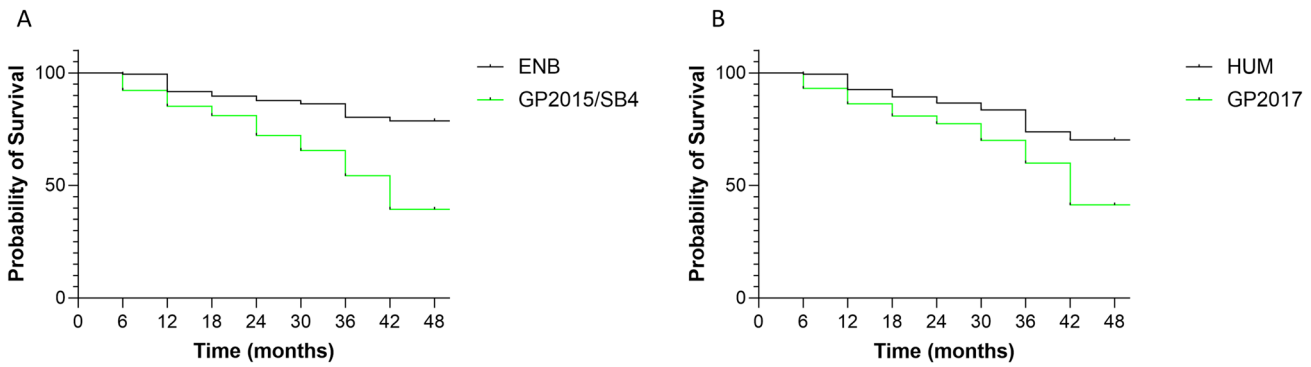

Fig. 2 Kaplan–Meier plot of patient dropouts over time. Kaplan–Meier curve showing the survival probability in patients with rheumatoid arthritis over 48 months treated with originator drugs and their respective biosimilars (BIO). **A** Probability of survival for treatments with etanercept vs BIO (GP2015/SB4); **B** probability of survival in treatments with adalimumab vs BIO (GP2017). Analysis was performed using GraphPad Prism 10.0.2

long-standing RA, taking into account also the administration of biosimilars.

To our knowledge, this is the first study that compared the impact of both originator biologics and their biosimilars on RA management over a long 48-month monitoring period. This study revealed some important findings. First, it correlates decreased levels of disease activity at the 6-month follow-up with a good and persistent response to therapy in patients with long-standing RA and highly active disease at baseline. Second, levels of disease activity after 6 months of treatment predict the response to therapy at 4 (and perhaps more) years and provide information that identifies long-term responders and allows adequate clinical decisions and personalized therapy. Finally, we demonstrated efficacy in real life of etanercept and adalimumab over a long period of time and showed, for the first time, a fully comparable trend of long-term efficacy between etanercept, adalimumab, and their biosimilars. However, this finding may seem not supported by the drug survival curves that showed significant differences in favor of originator drugs. The extended survival of originator drugs compared with biosimilars can be explained by several factors. First, originator drugs were the exclusive treatment option in the past, benefiting from a long presence in the market and accumulated clinical experience and long-term data. Therefore, the familiarity that patients and physicians have with originator drugs plays a crucial role, it tends to cultivate greater trust, leading to a more persistent utilization of these drugs. Second, current guidelines are more focused on an early clinical response, leading to the termination of treatment with delayed effectiveness. However, in contrast to the past, there is an expanding number of biosimilars/biologics that can be used as an alternative therapeutic option, allowing the personalization of therapy. This means that those patients who previously did not tolerate or respond adequately to the originator drug now have better chances of treatment. While originator drugs and biosimilar formulations demonstrated the same efficacy, the medical perspective has changed over time. To date, clinical demand is driven by an enhanced attention to disease prognosis and an increased array of therapeutic alternatives as described by the 2023 update of the European League Against Rheumatism [20, 21]. Overall, this study presents a speculative approach to designing future scenarios and possibilities for RA management.

Currently, there is still a lack of information about the real-world effectiveness of TNF-α inhibitors, notwithstanding their ability to slow RA progression recorded in several randomized clinical trials [22]. Indeed, few results produced from these studies revealed that adalimumab and etanercept may be effective treatment options for patients with an inadequate response to infliximab, but they reflect a small sample size of patients that limits generalizability to real-world subjects [22, 23]. Noteworthy, adalimumab and etanercept biosimilars demonstrated comparable efficacy to the corresponding original biologics in real-life cohorts of patients with RA [24, 25]. This similarity was observed in studies concerning different RA populations at baseline in terms of demographic characteristics with comparable phenotypes, disease activity indices, and conventional synthetic disease-modifying antirheumatic drug treatment [26, 27]. These studies had a short 6-month follow-up period, but the occurrence of their pharmacological effect in real-life patients highlights the importance of the introduction of biosimilars as treatment.

Despite advances in a treat-to-target strategy, achieving clinical remission remains the critical aspect of RA management and monitoring disease activity must be integrated during routine assistance. As recommended by the American College of Rheumatology and also by the European League Against Rheumatism, several RA disease activity measures need to be considered. These indices allow the collection of information on patient-reported measures, provider assessments, and laboratory results including imaging [4, 28]. In accordance with these guidelines, we regularly collected and analyzed DAS28, CDAI, and SDAI scores that were significantly decreased in all treatments over the long study period, highlighting the efficacy of both originator drugs and biosimilars. Furthermore, it is important to emphasize that biologic drugs are costly, contributing to the inequity of access to therapy in both national and international healthcare systems. To date, few clinical studies demonstrating the equivalent efficacy and safety of biosimilars with respect to their originator drugs are available [29, 30], and more effort is needed to solve this economical question. Our study contributes data to support switching to biosimilars, and also overcomes the reluctant attitude of both physicians and patients towards these alternative approaches.

However, there are some study limitations that impact all of the findings discussed until now. First, the retrospective nature of our investigation followed by the lack of an evaluation of previous treatments and baseline characteristics may have affected the outcome, and the lack of reasons for discontinuing treatment with the originator drug by few patients. As obesity, sex, smoking habit, and seropositivity for autoantibodies influence the response to treatment [18, 31, 32], both demographic and clinical characteristics should be considered to make more personalized predictions. This becomes particularly relevant in light of TNF secretion by adipose tissue, raising important considerations for the appropriateness of anti-TNF prescription in overweight patients, regardless of whether the prescribed drug is a biosimilar or the original formulation. In our study, we specifically recorded the body mass index (BMI) for past patients who were treated with the original medication. Despite having this BMI information, anti-TNF therapy was still administered to these patients as it represented the

sole available therapeutic option at that time. Conversely, for recent patients treated with biosimilars, BMI data were not documented, as current guidelines require anti-TNF treatment without regard to this information.

This regulatory shift presents a substantial challenge, hindering a direct comparison between the two patient groups. The implications of such a divergence in treatment approaches, especially in relation to the potential impact of BMI on TNF secretion, underscore the need for further exploration and discussion to optimize therapeutic outcomes across diverse patient populations.

7 Conclusions

In summary, this investigation provides a timing to predict the long-term response to therapy with TNF-α inhibitors and supports the use of the equally effective but less expensive, etanercept biosimilars (GP2015, SB4) and adalimumab biosimilar (GP2017) to minimize disease activity in patients with RA. The prevalent use of these biosimilars will certainly bring durable clinical benefits to patients and economic advantages to the healthcare system.

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Declarations

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Conflicts of Interest Matteo Colina, Micheline Khodeir, Roberto Rimondini, Marco Valentini, Federica Campomori, Stefania Corvaglia, and Gabriele Campana have no conflicts of interest that are directly relevant to the content of this article.

Ethics Approval The program was approved by the Italian Local Health Authority and notified to the site's ethics committee. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and all applicable local regulations (institutional review board number 6747 BIOCO).

Consent to Participate Written informed consent was obtained from each patient prior to start of treatment in accordance with local practice and regulations.

Consent for Publication Not applicable.

Availability of Data and Material The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request, with the exception of sensitive data.

Code Availability Not applicable.

Authors' Contributions Study conception, design, patient recruitment, data collection, and characterization were performed by MC, MK, FC, SC, and MV. Statistical analyses were performed by GC and RR. All authors read and approved the final manuscript.

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