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Anti-tumor necrosis factor α: originators *versus* biosimilars, comparison in clinical response assessment in a multicenter cohort of patients with inflammatory arthropathies

C. Gioia[1], A. Picchianti Diamanti[2], R. Perricone†[3], M.S. Chimenti[3], A. Afeltra[4], L. Navarini[4], A. Migliore[5], U. Massafra[5], V. Bruzzese[6], P. Scolieri[6], C. Meschini[7], M. Paroli[8], R. Caccavale[8], P. Scapato[9], R. Scrivo[1], F. Conti[1], B. Laganà[2], M. Di Franco[1]

[1]Division of Rheumatology, Department of Clinical Internal, Anesthesiologic and Cardiovascular Sciences, Sapienza University, Rome; [2]Rheumatology, Clinical and Molecular Medicine, Sapienza University, Sant'Andrea University Hospital, Rome; [3]Rheumatology, Allergology and Clinical Immunology, Department of Systems Medicine, Tor Vergata University, Rome; [4]Allergology, Clinical Immunology and Rheumatology, Bio-Medical Campus, University of Rome; [5]San Pietro Fatebenefratelli Hospital, Rome; [6]Department of Internal Medicine, Rheumatology and Gastroenterology, Nuovo Regina Margherita Hospital, Rome; [7]General Medicine, Belcolle Hospital, Viterbo; [8]Department of Medical-Surgical Sciences and Biotechnology, Polo Pontino, Sapienza University, Latina; [9]Rheumatology, Department of Medicine, S. Camillo de Lellis Hospital, Rieti, Italy

SUMMARY

Objective. To compare etanercept and adalimumab biosimilars (SB4 and ABP501) and respective bioriginators in terms of safety and efficacy in a real-life contest.

Methods. We consequently enrolled patients affected by rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis, treated with SB4, and ABP501, or with corresponding originators, belonging to the main biological prescribing centers in the Lazio region (Italy), from 2017 to 2020. Data were collected at recruitment and after 4, 8, 12, and 24 months of therapy.

Results. The multicenter cohort was composed by 455 patients treated with biosimilars [SB4/ABP501 276/179; female/male 307/146; biologic disease-modifying anti-rheumatic drug (b-DMARD) naïve 56%, median age/interquartile range 55/46-65 years] and 436 treated with originators (etanercept/adalimumab 186/259, female/male 279/157, b-DMARD naïve 67,2%, median age/interquartile range 53/43-62 years). No differences were found about safety, but the biosimilar group presented more discontinuations due to inefficacy (p<0.001). Female gender, being a smoker, and being b-DMARD naïve were predictive factors of reduced drug survival (p=0.05, p=0.046, p=0.001 respectively). The retention rate at 24 months was 81.1% for bioriginators and 76.5% for biosimilars (median retention time of 20.7 and 18.9 months, respectively) (p=0.002). Patients with remission/low disease activity achievement at 4 months showed a cumulative survival of 90% to biosimilar therapy until 24 months (p=0.001); early adverse reactions instead represented a cause of subsequent drug discontinuation (p=0.001).

Conclusions. Real-life data demonstrated a similar safety profile between biosimilars and originators, but a reduced biosimilar retention rate at 24 months. Biosimilars could be considered a valid, safe, and less expensive alternative to originators, allowing access to treatments for a wider patient population.

***Key words**: Biosimilars, bioriginators, anti-TNF, inflammatory arthropathies.*

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INTRODUCTION

Biological disease-modifying anti-rheumatic drugs (b-DMARDs) have significantly improved the treatment of rheumatological diseases, including rheumatoid arthritis (RA) and spondylarthritis (SpA), as demonstrated by 60-70% of patients who maintain a long-term clinical response (1-3). Tumor necrosis factor α (TNFα) antagonists were the first biological drugs to be used and to show important clinical effica-

Corresponding author:
Manuela Di Franco
Division of Rheumatology,
Department of Clinical Internal,
Anesthesiologic and Cardiovascular Sciences,
Sapienza University, 00161 Rome, Italy
E-mail: manuela.difranco@uniroma1.it

cy; consequently, the experience related to their use is greater than that of other drugs with different targets/mechanism of action. Five TNF-α inhibitors are currently approved by both the Food and Drug Administration and the European Medicines Agency for the treatment of RA and SpA: infliximab, adalimumab, etanercept, golimumab, and certolizumab pegol. Their mechanism of action is expressed by blocking the binding between TNFα and its own receptors, preventing the cascade of events due to its pro-inflammatory actions (4-9).
Long-term therapy with anti-TNF-α is well tolerated; despite this, the increased risk of opportunistic infections, the development of immune-mediated diseases, and infusion reactions, especially with infliximab, requires constant monitoring. Anti-TNF safety data were initially obtained from clinical trials (10) and subsequently amplified by several post-marketing data and also compared with conventional synthetic disease-modifying antirheumatic drugs (cs-DMARDs) (11-13). Most of these data come from European and American registries (Corrona Registry in the USA), demonstrating the absence of toxicity in the long-term use of therapy with TNF-α inhibitors.
The survival of a drug as well as drug withdrawal time are influenced by different factors: ineffectiveness, loss of efficacy (immunogenicity is the principal cause), adverse events, and poor adherence. Different national registries of RA patients treated with biologics have provided useful data to assess drug survival rates. For example, an Italian registry evaluating 4 years of observation showed that etanercept has a longer survival than adalimumab and infliximab (14). Predictive factors for the continuation of therapy include the concomitant use of cs-DMARDs, and the presence of comorbidities, but not high indices of disease activity.
Biosimilars are biological products that are highly "similar" to the previously approved reference biological drug (originator) in terms of safety, purity, and potency (efficacy). Anti-TNF biosimilars were among the first to be produced and approved for the treatment of rheumatological and gastrointestinal diseases, according to the indications of the originator product. Infliximab and etanercept biosimilars were among the first to be placed on the market. In Italy, the Italian Medicines Agency authorized SB4 and GP2015 (etanercept biosimilars), SB5, ABP501, GP2017, MSB11022 (adalimumab biosimilars) after passing III-phase randomized clinical trials.
Several trials and studies carried out to evaluate the comparability of biosimilars with the reference product, first for the chemical-physical composition and pharmacokinetics and then for efficacy and clinical safety, have shown a high acceptance rate of the drug by the patients (79-99%) (15, 16). Since their marketing, numerous real-life studies have been carried out deriving from the data of their use in daily clinical practice: the acceptance rates of the new drug and the retention rate have not always been shown to be equivalent. A possible hypothesis regarding this difference is the nocebo effect (the negative counterpart of the placebo effect) and the attribution effects (attributing pre-existing or unrelated symptoms to the new treatment); consequently, there is no conclusive evidence (17, 18).
Currently, it is thought that the nocebo effect can be reduced by better collaboration with the patient in the treatment decision and information.
The purpose of this study was to evaluate the clinical efficacy, safety, and tolerability of the biosimilar drugs SB4 and ABP501, respectively, etanercept and adalimumab, in a large multicenter cohort of patients with RA, psoriatic arthritis (PsA), and ankylosing spondylitis (AS) and compare them with a cohort of patients affected by the same diseases treated with the corresponding originator drugs.

MATERIALS AND METHODS

From January 2017 to September 2020, patients with RA, PsA, and AS treated with biosimilar drugs (SB4 and ABP501) have been consecutively enrolled at the Department of Internal, Anesthetic, and Cardiovascular Clinical Sciences of the complex operative unit of Rheumatology of the Poli-

clinico Umberto I and at the main prescribing centers of Rheumatology in the Lazio region (Italy). This multicenter, phase IV observational study also included a retrospective phase, from January 2014 to December 2016, evaluating patients suffering from the same diseases and treated with corresponding originators, considered the Lazio region's provision to prescribe biosimilars for naïve patients from January 2017. In summary, while the first part of the study from 2014 to 2016 was retrospective, the second one from 2017 to 2020 was observational-prospective.

Every 4 months, study participants underwent monitoring visits. Data about diagnosis and patients' history were collected at screening (T0). The subsequent evaluations were carried out at 4 (T1), 8 (T2), 12 (T3) and 24 months (T4). In addition, the patients enrolled in both the prospective and retrospective phases were administered the health assessment questionnaire (HAQ) to assess their quality of life. The inclusion criteria used included:

1) both sexes;
2) age between 18 and 80 years;
3) diagnosis of RA according to the American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) 2010 criteria (19), of SpA according to the Assessment of SpondylArthritis International Society (ASAS) criteria 2009 (20, 21), and of PsA according to the Classification Criteria for Psoriatic Arthritis (CASPAR) (22);
4) moderate/severe disease activity in naïve patients: disease activity score (DAS28) >3.2 or clinical disease activity index (CDAI) >2.8 in RA patients, disease activity index for psoriatic arthritis (DAPSA) >14 in PsA patients, ankylosing spondylitis disease activity score ($ASDAS_{PCR}$) ≥1.3 or Bath ankylosing spondylitis disease activity index (BASDAI)≥4 in patients with axial SpA;
5) clinical remission/low disease activity sustained for at least 6 months, in patients who switched from the originator biologic drug: DAS28<3.2 or CDAI<2.8 in RA patients, DAPSA<14, $ASDAS_{PCR}$ <1.3 or BASDAI<4 in patients with axial SpA;
6) patients able to read and understand informed consent.

The exclusion criteria were:

1) any contraindication to the administration of anti-TNF-biological drugs α as per technical data sheet (hypersensitivity to the active ingredient, ongoing infections including TB, heart failure NYHA class III/IV etc.);
2) age <18 years.

After obtaining informed consent, data were collected at the baseline visit and follow-up visits after 4 and 8 months and subsequently 12 and 24 months of biologic drug treatment. They included the main demographic, clinical, and therapeutic parameters as follows: anamnestic collection [body mass index (BMI), cigarette smoking, comorbidities, therapy, etc.]; clinical examination with evaluation of disease activity using the main clinimetric indices for RA and SpA (DAS28, CDAI, ASDAS, DAPSA, BASDAI) and functionality; quality of life and work disability (HAQ); evaluation of the main laboratory data [rheumatoid factor, anti-citrullinated protein antibody (ACPA), human leukocyte antigen, erythrocytes sedimentation rate (ESR), C-reactive protein –(CRP)]; and adverse events and therapeutic efficacy. Therapeutic ineffectiveness was assessed in accordance with the EULAR response criteria for RA and SpA and considering the minimal disease activity (MDA). The HAQ was used as a self-assessment tool for measuring functional capacity in carrying out normal routine activities, such as dressing and eating, to assess the quality of life.

Ethics

The study was approved by the local institutional ethics committee and conducted in accordance with the Declaration of Helsinki.

Statistical analysis

Demographic data, patient features, clinical response parameters, questionnaire measures, and safety data have been reviewed descriptively. For continuous variables, the following measures were reported: mean, standard deviation, median, quartiles (Q1 and Q3), minimum, maximum, and number

and proportion of patients with missing data (n, % of total). The summary of the baseline change included 95% confidence intervals. For categorical variables, these were summarized through counts and percentages. Time-to-event data were analyzed using Kaplan-Meier estimates or cumulative incidence curves. Mixed models were used for repeated measures. All statistical analyses were performed with SPSS (IBM, Armonk, NY, USA).

RESULTS

From January 2017 to September 2020, a total of 455 patients with RA according to the ACR/EULAR 2010 criteria, with axial-SpA according to the ASAS 2009 criteria, and with PsA according to the CASPAR criteria, belonging to the different prescribing centers in the Lazio region, treated with biosimilars SB4 (Benepali®) and ABP501 (Amgevita®), have been enrolled. As a control group, data obtained from January 2014 were considered retrospectively for 436 patients with RA, axial-SpA and PsA in treatment with their corresponding originators (Enbrel® and Humira®) followed at the Rheumatology of the Policlinico Umberto I. Among 455 patients in the biosimilar treatment group, 194 (42.6%) were diagnosed with RA, 189 (41.5%) with PsA, and 72 (15.8%) with AS. As regards the group of 436 patients treated with the originator, 160 (36.7%) patients with RA, 171 (39.2%) with PsA, and 105 (24.1%) with AS were observed. The clinical, demographic, and serological characteristics of these patients are summarized in Table I.

Among 436 patients treated with originators, 293 (67.2%) were b-DMARD naïve; 255/455 (56%) biosimilar treatment patients were naïve, with no significant difference between the groups. No differences were found in the RA, PsA, and AS subgroups. In the non-naïve originator group, the b-DMARDs used were in 84% the second choice of treatment: patients treated with Enbrel® had failed previous therapy with Humira® (or abatacept in the RA group) and patients treated with Humira® had failed previous therapy with Enbrel®. The other 16% was composed of patients who had failed more previous anti-TNF treatments. In the biosimilar group, 78 (39%) non-naïve patients switched from originator to biosimilar, both for Benepali® and Amgevita®. In the RA non-naïve and non-switch groups, previous b-DMARDs were anti-TNF, abatacept, and tocilizumab, while 5 (2.5%) failed rituximab. In the AS and PsA groups, secukinumab over anti-TNFs was used before bioriginators choice.

Age was significantly higher in the cohort of patients treated with biosimilars compared to originators (p=0.005).

Regarding the other demographic characteristics (disease duration, BMI), no significant differences were found between the 2 groups.

Patients were also analyzed for their comorbidities: in the biosimilar group, 179 (39.3%) suffered from cardiovascular diseases, 212 (46.6%) from endocrine/metabolic diseases, and 30 (6.6%) were affected by fibromyalgia. Similar comorbidities were found in the originator group. Analyzing disease activity indices, both considering the cohort of patients as a whole and considering disease subgroups, a higher disease activity was observed at baseline, expressed by DAS28 for patients with RA in the group candidate for biosimilars treatment (p=0.001); in contrast, BASDAI was lower in AS patients who had to start biosimilar treatment (p=0.027). The differences in DAS28 and BASDAI did not translate into statistically significant differences in the number of patients in MDA. No differences were observed about inflammation markers, other disease activity indices, and quality of life.

Regarding the trend during follow-up of the inflammation markers and clinimetric indices between the 2 groups, it was observed that (Figure 1):

1) there were higher ESR values in the total group of patients treated with biosimilars than in the group of patients treated with originators after 4, 8 and 12 months of treatment ($p<0.05$);
2) there were no statistically significant differences between the 2 groups regarding the CRP values;
3) there were persistently higher $DAS28_{ESR}$ values in patients of the biosimilar

group from T0 up to 24 months of therapy ($p<0.05$);

4) except for the BASDAI value higher at T0 in patients who had to start therapy with the originator as previously described, there were no differences in this index in the subsequent follow-up. Also, there were no differences regarding the 2 groups about DAPSA values at all times considered.

Table I - Clinical, demographic and serological data.

	Total		RA		PsA		AS		p
	Biosimilar N=455	**Originator N=436**	**Biosimilar N=194**	**Originator N=160**	**Biosimilar N=189**	**Originator N=171**	**Biosimilar N=72**	**Originator N=105**	
Naïve, n (%)	255 (56)	293 (67.2)	114 (58.7)	107 (66.8)	105 (55.5)	122 (71.3)	36 (50)	64 (69.9)	ns
Age, median (IQR)	*55 (46-65)*	*53 (43-62)*	59 (50-68)	60 (46-65)	55 (44-64.5)	54 (46-62.5)	51 (44-57)	44 (34-54.5)	*0.005*
F/M	307/148	279/157	157/37	126/34	112/77	110/61	38/34	43/62	ns
Adalimumab/ etanercept	179/276	259/186	40/154	77/83	87/102	97/74	42/30	78/27	ns
Disease duration (months), median (IQR)	84 (27-156)	84 (48-161)	90 (36-180)	60 (43-180)	72 (24-144)	96 (48-162)	72 (24-144)	90 (36-141)	ns
BMI, median (IQR)	24.7 (22-28.2)	24.7 (22.8-25.5)	24.1 (22-27.8)	24.3 (22-28)	25.7 (22.3-29.2)	24.7 (22.8-26.6)	24.6 (22-27.6)	24.2 (22-27.1)	ns
Smokers, n (%)	107 (23.5)	212 (48.6)	38 (19.5)	39 (24.3)	54 (28.5)	59 (34.5)	15 (20.8)	26 (24.7)	ns
ACPA, n (%)	–	–	116 (60)	131 (81.8)	–	–	–	–	ns
RF, n (%)	–	–	109 (56.1)	129 (80.6)	–	–	–	–	ns
HLA-B27, n (%)	–	–	–	–	–	–	45 (62.5)	69 (65.7)	ns
GC, n (%)	159 (24.9)	180 (41)	93 (47.9)	84 (52.5)	54 (28.5)	70 (40.9)	12 (16.6)	26 (24.7)	ns
MTX, n (%)	172 (37.8)	154 (35.3)	98 (50.5)	70 (45)	62 (32.8)	70 (40.9)	12 (16.6)	14 (13.3)	ns
SSZ, n (%)	44 (9.6)	46 (10.5)	11 (5.6)	7 (4.3)	21 (11.1)	23 (13.4)	12 (16.6)	16 (15.2)	ns
CYA, n (%)	3 (0.6)	1 (0.2)	0 (0)	1 (0.6)	3 (1.5)	0 (0)	0 (0)	0 (0)	ns
AZA, n (%)	2 (0.4)	2 (0.4)	0 (0)	0 (0)	0 (0)	1 (0.5)	2 (2.7)	1 (0.9)	ns
LEF, n (%)	21 (4.6)	11 (2.5)	10 (5.1)	9 (5.6)	11 (5.8)	2 (1.1)	0 (0)	0 (0)	ns
HCQ, n (%)	4 (0.8)	17 (3.8)	4 (2)	12 (7.5)	0 (0)	5 (2.9)	0 (0)	0 (0)	ns
DAS28, median (IQR)	*3.9 (2.9-4.6)*	*3.5 (2.7-4.3)*	4.1 (3.1-4.8)	3.2 (2.9-4.3)	*3.5 (2.7-4.4)*	*3.2 (2.5-4.1)*	–	–	*0.001*
DAPSA, median (IQR)	17.9 (11.4-23.5)	18.2 (12.1-23.1)	–	–	17.4 (11.1-23.3)	18.2 (12.1-23.4)	–	–	ns
BASDAI, median (IQR)	*5.05 (2.9-6.9)*	*5.5 (3.7-7.2)*	–	–	5.8 (3.3-7.4)	6 (4.5-7.2)	*4.7 (2.9-6.1)*	*5.1 (3-7.2)*	0.027
HAQ, median (IQR)	1 (0.5-1.27)	0.8 (0.5-1.3)	0.9 (0.3-1.26)	0.8 (0.5-1.5)	0.8 (0.3-1.2)	0.8 (0.5-1.25)	1 (1-1.3)	0.7 (0.3-1.2)	ns
BASFI, median (IQR)	4.1 (1.9-6.4)	4.4 (2.2-6.6)	–	–	4.6 (0.1-0.9)	5.2 (3.1-7.6)	4 (3.6-5.4)	3.8 (1.7-6)	ns
ESR, median (IQR)	17 (8.2-30)	17 (8-30)	21 (12-34.5)	24.5 (10.2-33.2)	12 (7-26)	16 (8-28)	13.5 (6-25.5)	14 (7-30.5)	ns
CRP, median (IQR)	0.46 (0.1-1)	0.4 (0.1-1.3)	0.5 (0.2-1.1)	0.3 (0.2-33.2)	0.4 (0.1-0.9)	0.4 (0.1-1.2)	0.4 (0.1-1)	0.5 (0.2-2.1)	ns

RA, rheumatoid arthritis; PsA, psoriatic arthritis; AS, ankylosing spondylitis; IQR, interquartile range; BMI, body mass index; ACPA, anti-citrullinated protein antibody; RF, rheumatoid factor; HLA-B27, human leukocyte antigen; GC, glucocorticoids; MTX, methotrexate; SSZ, sulfasalazine; CYA, cyclosporyne A; AZA, azathioprine; LEF, leflunomide; HCQ, hydroxychloroquine; DAS28, disease activity score 28; DAPSA, disease activity in psoriatic arthritis; BASDAI, Bath ankylosing spondylitis disease activity index; HAQ, health assessment questionnaire; BASFI, Bath ankylosing spondyltis functional index; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; ns, not significant.

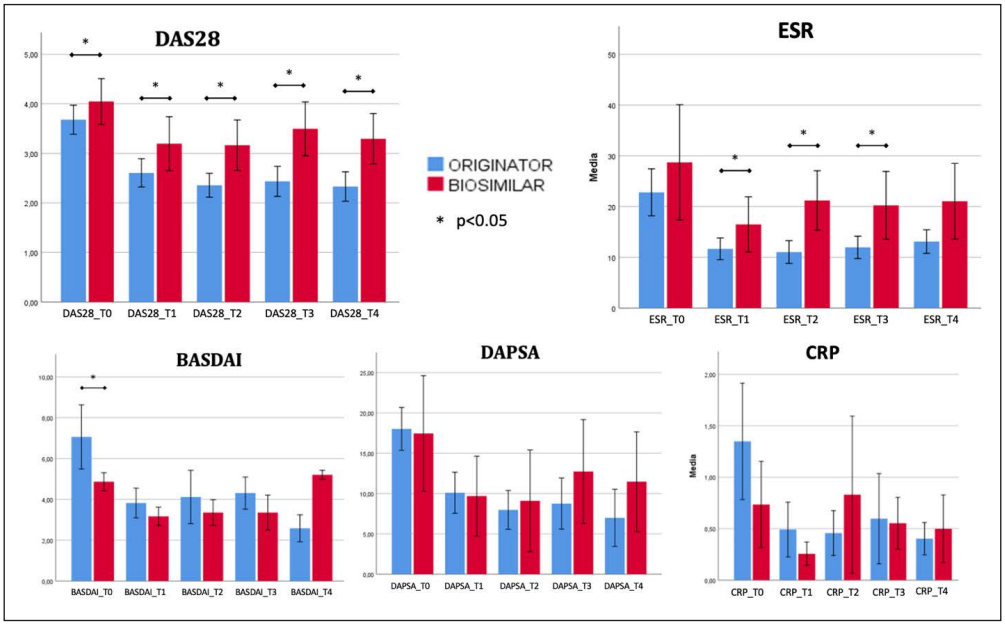

Figura 1 - Inflammation markers and clinimetric indices trend at different times. DAS was significantly higher in patients treated with biosimilars, at all times; ESR was higher at 4, 8 and 12 months in patients treated with the biosimilar. There was no difference in mean BASDAI, disease activity in psoriatic arthritis and CRP values.
DAS28, disease activity score 28; DAPSA, disease activity in psoriatic arthritis; BASDAI, Bath ankylosing spondylitis disease activity index; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; T0, screening, T1, 4 months; T2, 8 months; T3, 12 months; T4, 24 months.

Considering the whole patient cohort, drug discontinuations (both bioriginators and biosimilars) were observed starting from the first 4 months of the follow-up evaluation, both due to ineffectiveness and adverse events. At each time considered (T4, T8, T12, and T24), there was a different frequency of the various outcomes between the 2 groups: at all times, the biosimilar group had a higher frequency of drug discontinuation due to ineffectiveness (p=0.017; p=0.02; p=0.002 and p=0.012, respectively), while there were no differences between the 2 groups regarding intolerance and adverse events (Figure 2).

Analyzing the survival of the drug and therefore using the stopping event as an outcome (both for adverse effects and for ineffectiveness), there was a significant difference between patients receiving originator and biosimilar therapy. On average, patients on originator therapy retained the drug for 20.7 months, while patients on biosimilars retained it for 18.9 months. The 24-month retention rate was 81.1% for originators and 76.5% for biosimilars. Regarding the discontinuation due to adverse effects, no differences were found between the 2 groups, showing comparable drug safety. In the assessment of discontinuation due to ineffectiveness, the originator-treated group showed a lower incidence, with a statistically significant difference in the whole cohort (p<0.0001) and in the subgroups of RA patients (p=0.013) and PsA (p<0.0001) (Figure 3a).

Analyzing the single anti-TNF, we observed different results for etanercept and adalimumab in the 2 groups. For the etanercept molecule, we observed a 74% 24-month retention rate in the biosimilar group and a 78.2% in the originator group, with a statistically significant difference (p=0.038). In etanercept bioriginators group, we observed a lower incidence of discontinuations due to ineffectiveness (p<0.001) than in the biosimilar group; no differences were described about safety. About adalimumab, the origi-

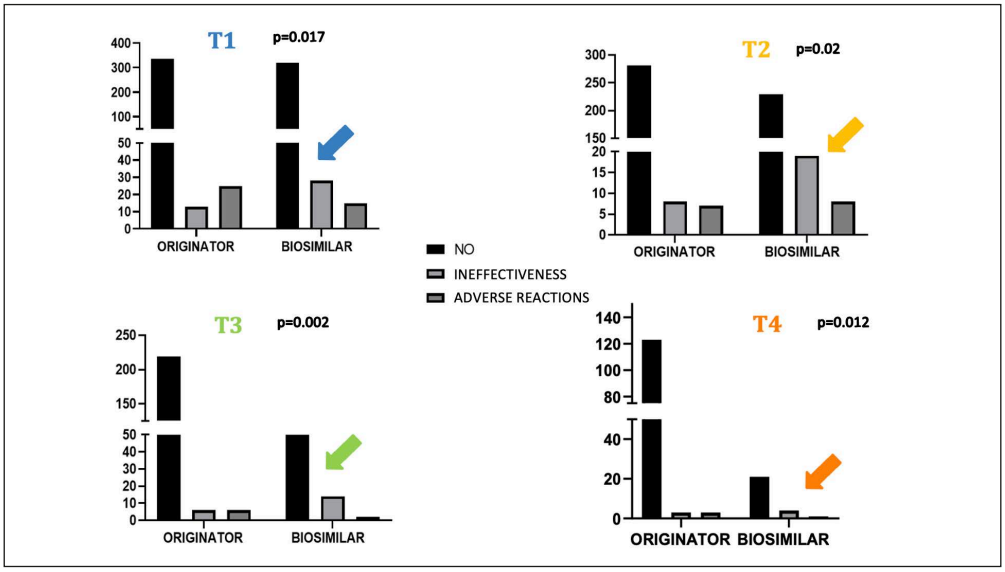

Figura 2 - Biological drugs discontinuations distribution. The biosimilar group had a higher frequency of discontinuations, due to ineffectiveness at all times, as indicated by the arrows.
T1, 4 months; T2, 8 months; T3, 12 months; T4, 24 months.

nator group showed a 24-month retention rate of 83.3%, while the biosimilar group showed a 24-month retention rate of 80% (p=0.036). Regarding discontinuation due to adverse effects, no differences were found between the 2 groups, while regarding discontinuation due to ineffectiveness, the adalimumab biosimilar group showed a higher but not significant frequency (p=0.09). No differences were found in the biosimilar group or in the originator group between etanercept and adalimumab (Figure 3b).

Considering disease activity, we observed a higher originators' retention rate (80.6%) than biosimilars' (72.9%) in moderate/severe disease activity patients (p<0.001), while no differences were found in patients in remission or low disease activity.

We also evaluated possible response predictors at baseline for the drug and, therefore, its discontinuation at 24 months, using a model generated by Cox regression. The model was found to be highly significant for specific covariates such as sex, smoking, and biosimilar/originator therapy (p=0.005, p=0.046 and p<0.0001, respectively). Female sex was associated with a reduced cumulative survival on therapy, with a risk of discontinuation at 24 months of 34% *versus* about 20% of males. Similarly, current smoker status was associated with reduced therapy survival, with a 24-month risk of discontinuation of 36%. Finally, considering the drug used, biosimilar therapy was the main predictor of discontinuation, with a cumulative risk of drug discontinuation at 24 months of 40% compared to approximately 22% with the originator drug. Another significant factor considered was the b-DMARD naïve and/or non-naïve state at the start of therapy with biosimilars or originators. A significantly better cumulative survival of the originator drug compared to the biosimilar was observed in b-DMARD naïve patients (respectively, mean 21.2 months *versus* 18.4 months, retention rate 83% *versus* 71%). In contrast, drug survival was similar in patients receiving both the originator drug and the biosimilar, either as a second line or for subsequent lines (Figure 4).

A further regression model was constructed by evaluating covariates present at T4, observing significance in relation to the achievement of MDA (p<0.0001) and the occurrence of adverse reactions (p<0.0001). Notably, patients who achieved a 4-month MDA had a cumulative therapy survival of

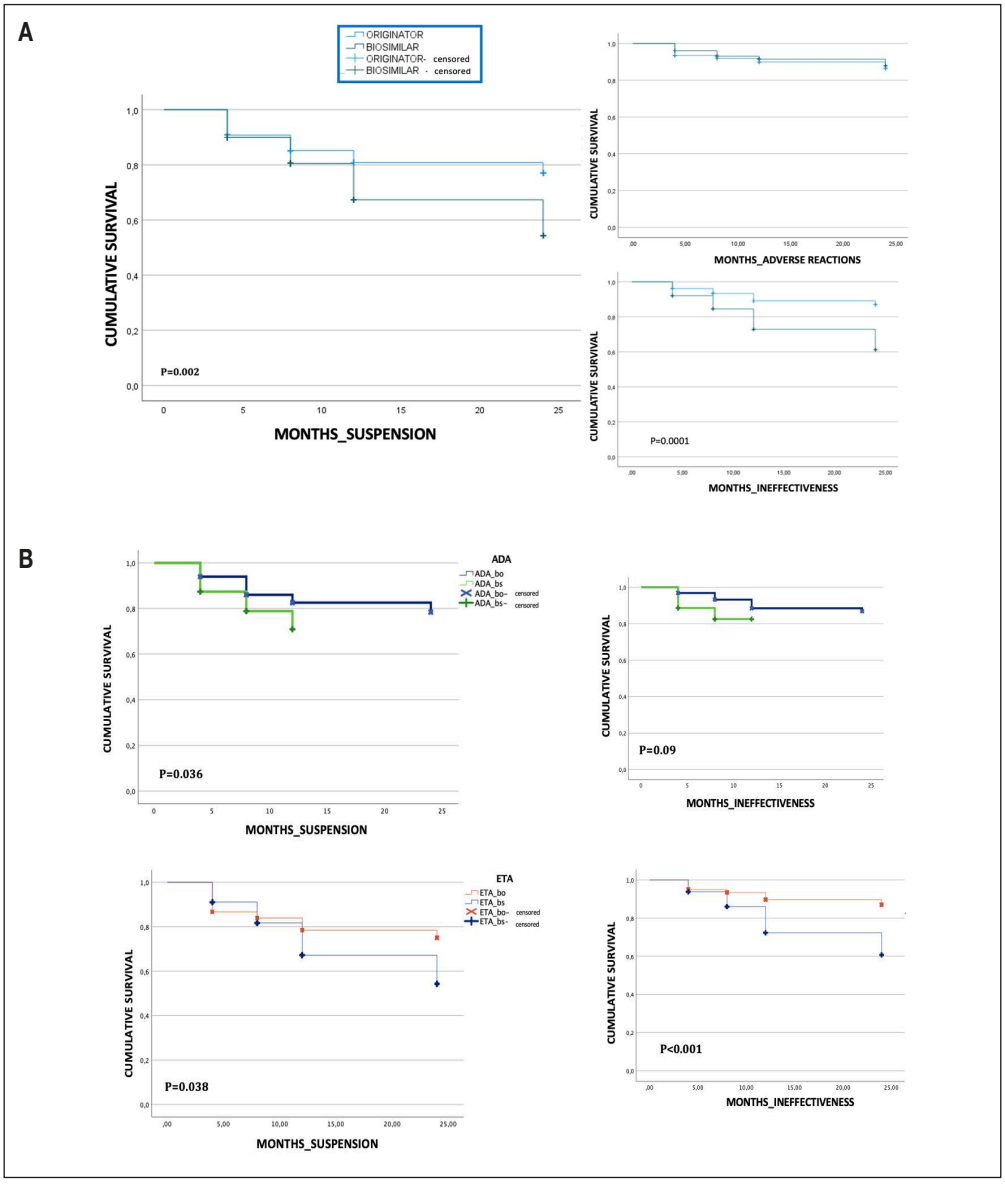

Figura 3 - Drugs survival.
a) Cumulative survival. Considering discontinuation event as an outcome, there was a significant difference between patients receiving originator and biosimilar therapy. Patients on originator therapy retained the drug for 20.7 months while patients on biosimilar 18.9 months. The 24-month retention rate was 81.1% for originators and 76.5% for biosimilars. There were no differences in treatment survival using discontinuation due to an adverse event as the outcome. Considering suspension due to ineffectiveness, the originator showed a lower incidence of suspensions, significant in the entire cohort and in the subgroups of patients with rheumatoid arthritis and psoriatic arthritis;
b) cumulative survival of adalimumab and etanercept. For etanercept, a 24-month retention rate of 74% in the biosimilar group and 78.2% in the originator group was observed, with a statistically significant difference. In the group of bioriginators with etanercept, there was a lower incidence of suspensions due to ineffectiveness compared to the group of biosimilars, without differences regarding safety. About adalimumab, the originator group showed a 24-month retention rate of 83.3%, while the biosimilar group showed a 80% retention rate (p=0.036). As regards suspension due to adverse effects, no differences were found between the 2 groups, while as regards suspension due to ineffectiveness, the group treated with the adalimumab biosimilar showed a higher but not significant incidence (p=0.09).

90% at 24 months. On the contrary, adverse events were an important cause of subsequent discontinuation, with a rapid fall in the survival curve. Among the adverse effects reported (Table II), laboratory changes (changes in blood counts and liver enzymes) and skin reactions were the most frequent, while infections (mainly of the upper respiratory tract and genitourinary tract) were less associated with drug withdrawal (Figure 5).

DISCUSSION

Adalimumab and etanercept were the first-line anti-TNFs used in clinical practice for the treatment of SpA and RA, in agreement with EULAR recommendations (23). These agents markedly improved the management of patients affected by inflammatory arthritis, but their high cost has created possible inequality in access to care. The introduction of biosimilars has led to reduced healthcare costs, thus allowing access to treatment for a higher number of patients (24).

Our study aimed to investigate the efficacy, safety, and tolerability of the biosimilar drugs SB4 and ABP501 in a large cohort of patients suffering from inflammatory arthritis during an observation period of at least 2 years and compare them with patients treated with the corresponding originator drugs. Regarding the retention rate of biosimilar drug (both Benepali® and Amgevita®) in line with previous real-life studies and registries such as BIOBADASER (25), we found an overall retention rate of 76.5% at 24 months, confirming the effectiveness of these drugs.

However, the 24-month retention rate was lower for biosimilars than for originators (81%). Patients on originator therapy retained the drug for 20.7 months, while patients on biosimilars retained it for 18.9 months. The 24-month retention rate of Benepali® was 74%, lower than Enbrel®; also, the Amgevita® 24-month retention rate was lower than Humira®, about 80%. No significant differences were found between the 2 groups regarding the discontinuation due

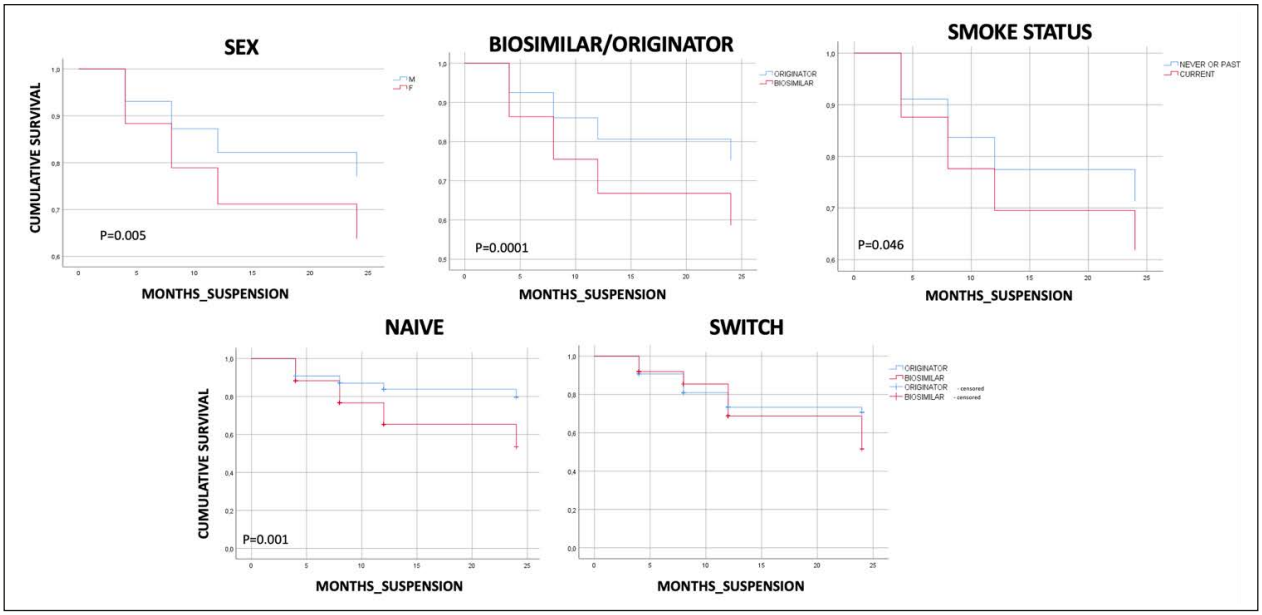

Figure 4 - Predictive T0 factors to drug discontinuation at 24 months. Using Cox regression, a highly significant model was built which highlighted sex, smoking and biosimilar/originator therapy as the covariates present at baseline associated with the discontinuation outcome in the 24-month follow-up. Female gender was associated with a reduced cumulative survival of therapy, with a risk of discontinuation of 34% at 24 months compared to approximately 20% for male sex; current smoking status was associated with reduced survival of therapy, with a 24-month risk of 36%. The main predictive factor appeared to be biosimilar therapy, which was associated with a cumulative risk of drug discontinuation at 24 months of 40% compared to 22% for the originator.

Table II - Adverse events reported in the 2 groups (p>0.05).

Adverse events	Originators n=65	Biosimilars n=70
Infections, n (%)	16 (25)	18 (25)
Skin reaction	33 (52)	35 (50)
Liver enzymes alteration	8 (12)	9 (13)
Blood cells count alteration	9 (14)	9 (13)
Others	18 (28)	19 (27)

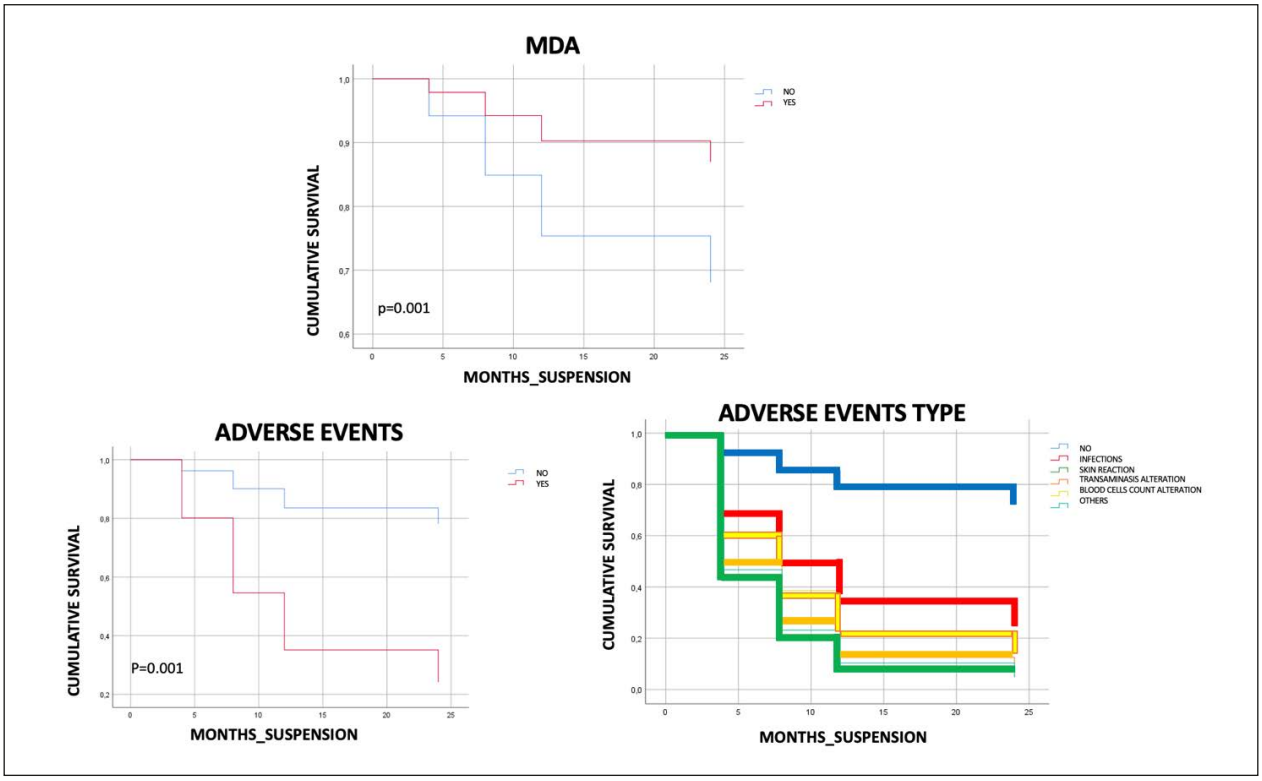

Figure 5 - Predictive T1 factors to drug discontinuation at 24 months. A further regression model built with covariates present at T1, the minimal disease activity (MDA) achievement and the adverse reactions appearance, was significant. Patients achieving MDA at 4 months had a cumulative therapy survival of 90% at 24 months. On the contrary, adverse reactions were an important cause of subsequent discontinuation, with a rapid fall in the survival curve. Infections were the adverse event least associated with discontinuation, overtaken by laboratory alterations and skin reactions.

to adverse effects. Indeed, the safety of biosimilars appears comparable to that of the respective originators, showing a low rate of adverse events responsible for drug discontinuations. No serious adverse events were observed; most of the adverse events were mild in severity, generally involving changes in laboratory tests such as blood counts and liver enzymes, similarly to bioriginators. Infectious episodes reported by the patients were mild, mainly affecting the upper airways and the genitourinary system, requiring in most cases only temporary suspensions of therapy.

On the other hand, the originator-treated group showed a significantly lower incidence of discontinuation due to ineffectiveness both in the subgroups of RA patients (p=0.013) and PsA (p<0.0001).

There may be different explanations for

these data. At first, the cohort with biosimilars presented a significantly higher DAS28 than bioriginators before starting therapy. We also observed that PsA and AS patients in the originator group suffered from longer disease duration *versus* the comparator group; although not significant, we could suppose that they failed more previous b-DMARDs, thus having fewer therapeutic opportunities and then better retention on therapy with bio-originators TNFi, influencing global results. Besides age, some imbalances between biosimilar and originator groups might have contributed to results in favor of the latter; in the originator b-DMARD group, indeed, we observed fewer women, more SpA patients, more b-DMARD naïve patients, less active RA, and shorter RA disease duration. These factors were not significant between the 2 groups, but they may have influenced the better originator retention rate. Moreover, as evidenced by several studies (17, 26), the concept of biosimilars being associated with a lower cost is automatically associated with the perception of lower efficacy. This could contribute to the nocebo effect, a further bias in the overall evaluation of the efficacy of the drug, as well as in the patient's perception of the disease activity, pre-existing disorders, or disorders not related to the disease and/or its therapy. Finally, we observed a higher number of patients lost to follow-up during the first pandemic period caused by the COVID-19 lockdown (first months in 2020). Despite the initial and growing use of telehealth, the impossibility of evaluating patients through an effective clinical approach in the first months of the pandemic period, corresponding to the first months of many biosimilar treatments, contributed to the loss of T1 and T2 data. This could be considered a possible concomitant reason explaining the different survival rates of biosimilar drugs from originators.

Previous studies, especially trials, evaluated the similarity and biochemical equivalence of SB4 and ABP501 molecules, observing no major structural alterations due to post-translational changes in antibody-dependent direct cytotoxicity and Fc receptor binding on inflammatory cells, and no clinical differences, counterpart of local and systemic inflammatory activity (27, 28). Bruni et al. observed how some parameters, both objective and patient's related, could be higher in the first 3 months of therapy with biosimilar (SB5) than in the originator, but they return similar and remain stable over time after 6 months of therapy (29).

We have then evaluated possible predictive factors associated with drug discontinuation. Both female sex and current cigarette smoking were associated with a reduced cumulative survival of therapy. Different studies conducted on b-DMARDs and anti-TNFs demonstrated that the female gender could be a predictor of reduced drug survival and therefore of a lower clinical response to drugs. The increase in the subjective evaluation indices rather than objective parameters in women could be related to the different perceptions of the disease in relation to the social, cultural, and working context. In particular, the nocebo effect has been reported to be higher in women, with different perceptions of both the disease and its treatment (30). Cigarette smoking is the main environmental risk factor in rheumatoid arthritis, where it seems to stimulate the formation of ACPAs in the pulmonary mucosa of genetically predisposed subjects and play a role in the pathogenesis of spondyloarthritis. In addition, it is known that cigarette smoking is associated with a lower response to therapy (31). The initial response to the biosimilar, evaluated after 4 months of therapy, appears to be one of the main factors for the survival on the drug, and the non-response due to primary ineffectiveness is confirmed to be one of the main reasons for the suspension of the biological. In the context of personalized medicine, a good response to the drug in the first months of therapy is probably an indication of a correct therapeutic target. Interestingly, a significantly better cumulative survival of the originator drug compared to the biosimilar was observed in b-DMARD naïve patients, whereas no differences were observed for patients who had already performed therapies with other b-DMARDs. Data from the literature in this regard are contrasting. In a recent study, Kearsley-Fleet et al. demon-

strated in one of the largest analyses of RA patients that biologic-naïve RA patients treated with etanercept originator showed similar outcomes *versus* those on biosimilars, using real-world data. Drug survival and disease activity after 6 and 12 months of therapy were similar between cohorts (32). A study on a French cohort observed that the maintenance of b-DMARDs in naïve patients was superior to bioriginator, particularly for etanercept, and in the context of RA, with also a role on the retention of treatment (33).
This was the first study including "real life" data in the Lazio region with a large cohort of patients, but it presented some limits due to its retrospective nature and the fact that it did not treat the issue of switching between different biosimilars.

CONCLUSIONS

This study showed a good retention rate at 24 months for the biosimilar drugs SB4 and ABP501 in a large cohort of patients, thus confirming the use of these drugs as a valid and less expensive alternative to originators. However, the 24-month retention rate of biosimilars was slightly lower than that of originators, and this difference seemed to be mainly driven by a higher discontinuation rate due to ineffectiveness rather than safety. Female gender, smoking status, and lack of initial drug response emerged as possible predictors of a lower response to biosimilars. Biosimilars could be considered a valid, safe, and less expensive alternative to originators, allowing access to treatments for a wider patient population.
With a view to personalized medicine, the identification of all the demographic and anamnestic characteristics of the patient will be essential for the identification of a patient profile more suitable for a b-DMARD rather than another.

Contributions
All the authors made a substantial intellectual contribution, read and approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

Conflict of interest
The authors declare that they have no competing interests, and all authors confirm accuracy.

Ethics approval and consent to participate
This study was approved by the local institutional ethics committee and conducted in accordance with the Declaration of Helsinki.

Patient consent for publication
Informed consent was obtained.

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Availability of data and materials
Data and materials are available from the corresponding author upon request.

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