1. Title

Persistence in treatment with TNF-alpha inhibitors in Spondyloarthritis: comparison between original and biosimilar drugs - a multicenter study

2. Abstract

Biosimilars have demonstrated comparable efficacy, safety and immunogenicity to original drugs in randomized clinical trials, with subsequent extrapolation of their therapeutic indications to those of the original drug. Some studies with real-world data supporting this biosimilarity have been published. However, long-term data on their use in Spondyloarthritis (SpA), particularly regarding persistence beyond 52 weeks, remain scarce.

In an exploratory analysis of 127 patients with SpA followed in our department, we observed a significantly higher persistence rate at 3-years under original TNF-alpha inhibitors (iTNF) (61.4%), with an average drug use time of 27.2 months; compared to 33.3% under biosimilar iTNF, with an average drug use time of 23.7 months (p=0.012). The main cause of treatment discontinuation was secondary failure, with a higher proportion observed under biosimilar iTNF (52.8% vs 18.1%, p<0.01), with no differences found regarding the rate of AEs. These results suggest greater efficacy of the original iTNF, with no significant differences observed in the safety profile, compared to biosimilars. However, the number of missing data and the relatively small sample size were a limitation of the study, which limits the extrapolation of our conclusions.

The aim of this study is to further evaluate the therapeutic persistence of the original iTNF (Humira®, Enbrel®, Simponi®) compared to biosimilar agents (Amgevita®, Hulio®, Hyrimoz®, Idacio®, Imraldi®, Yuflima®, Benepali®, Erelzi®) in a larger cohort of patients, as a measure of their medium and long term efficacy and safety. Additionally, this study also aims to compare disease activity rates between the groups at 6, 12, 24 and 36 months of therapy, assess the reasons for discontinuation and compare the frequency and severity of adverse events.

3. Background

Biotechnological drugs have drastically altered the prognosis and quality of life of patients with inflammatory rheumatic diseases and constitute a fundamental therapeutic array in their current management. However, these therapies have high economic costs, especially when the original molecule is prescribed (1). Biosimilar drugs, introduced more recently, are an economically viable alternative to the original drugs, given their lower associated costs (1, 2), and have demonstrated equivalent clinical efficacy, safety and immunogenicity in phase III clinical trials (1-6). For this reason, preference has been given to their use as first-line treatment in naïve patients and even to switching patients already on treatment from the original drug to the biosimilar, with the aim of expanding access to this therapy to a greater number of patients (1, 2).

The efficacy and safety of the biosimilar Benepali® were evaluated in a randomized, double-blind clinical trial in patients with Rheumatoid Arthritis (RA). Subsequently, the drug was approved by extrapolation for the remaining therapeutic indications of the original drug Enbrel®, including Spondyloarthritis (SpA) (5, 6). Several retrospective studies have evaluated real-world data from patients diagnosed with RA, Psoriatic Arthritis (PsA) and SpA, confirming the similarities between the original and biosimilar drugs in terms of efficacy and safety (7-11). Focusing on the data from SpA, Pinto et al. (7) reported a persistence rate (PR) of 78.4% for Benepali®, with a mean time on drug of 27.4 months, and 71.5% for Enbrel®, with a mean time on drug of 28.0 months (p=0.816), at 36-months of follow-up; no statistically significant differences were found in the adjusted cumulative risk of adverse events or disease activity scores

(BASDAI, BASFI, ASDAS, ASDAS response and BASDAI response) at 24-months of follow-up. Rojas-Giménez et al. (9) found a PR of 70% for Benepali®, with a mean time on drug of 12 months, and 81.4% for Enbrel® (p=0.117), with a mean time on drug of 12 months, at 12-months of follow-up; no differences were observed in the proportion of patients achieving remission or low disease activity at 12 months of follow-up (50.6% with Benepali®, 52.5% with Enbrel®, p=0.659). Ditto et al. (10) reported no significant differences in BASDAI scores before and after switching Enbrel® to Benepali® over 6 and 12 months of follow-up (p=0.901; p= 0.750).

A randomized, double-blind clinical trial in patients with RA demonstrated that the biosimilar Imraldi® exhibited comparable efficacy, safety, and immunogenicity to the original drug (3,12). The data were subsequently extrapolated to the therapeutic indications of the original drug Humira®, including SpA. Subsequently, three retrospective observational studies evaluated the efficacy and safety of Imraldi® in patients with SpA: Bruni et al. (13) reported no statistically significant differences in BASDAI and ASDAS indicators at 6 months after switching from Humira® to Imraldi®. However, they observed a significant increase in the number of painful joints at 6 months in the group of patients with predominantly axial involvement (p=0.003); Scrivo et al. (14) found a reduction in the number of patients in remission or with low disease activity after switching from Humira® to Imraldi® (89% and 80.9%; p=0.009), with no differences in ASDAS-CRP or BASDAI; Müller-Ladner et al. (4) described a high treatment PR after switching to Imraldi® at week 48 (0.80; 95% CI: 0.71–0.86).

The efficacy, safety, and immunogenicity profile of the biosimilar Hyrimoz® were equivalent to the original drug Humira® in a randomized, double-blind clinical trial involving patients with Plaque Psoriasis (15). The data were extrapolated to the therapeutic indications of the original drug Humira®, including SpA. Subsequently, the same results were obtained in a randomized, double-blind clinical trial with 353 patients diagnosed with RA (16).

Martins Fernandes et al. (17) conducted a retrospective observational single-center UK study evaluating the long-term effectiveness and safety of adalimumab and etanercept original drugs and biosimilars in bDMARD-naïve patients and those who switched from original to biosimilars for SpA. The study found no significant differences in 3-year drug PR: adalimumab PR were 73.5% for original drugs, 64.5% for biosimilars, and 77.5% in the switching group (p=0.959); etanercept PR were 96.0% for original drugs, 97.0% for biosimilars and 93.8% in the switching group (p=0.449).

A study conducted by Jourdain et al. (18) assessed the persistence and safety of biosimilars iTNF compared to the original drugs using data from the French National Health Data System. This real-world study compared the biosimilars Benepali®, Hyrimoz® and Imraldi® (among others) with the original drugs across all approved indications of these molecules (RA, SpA, PsA and Psoriasis for Etanercept, RA, SpA, PsA, Psoriasis, Crohn's disease, Ulcerative colitis, Hidradenitis suppurativa and Uveitis for Adalimumab). The results showed that each biosimilar product subgroup had either better or similar PR compared to the originator groups, and similar adverse event rates at 12-months of follow-up.

Overall, these observational studies (4, 7-11, 13, 14, 17, 18) demonstrated comparable treatment PR for biosimilars and the original drugs, aligning with the results from clinical trials (3, 5, 6, 12, 15, 16) and suggesting similar effectiveness and safety in real-world practice. However, the majority of these studies included patients with various rheumatic conditions, with only a small subset of individuals with SpA. For instance, Rojas-Giménez et al. (9) studied 29 patients with SpA, 9 on Enbrel® and 20 on Benepali®; Ditto et al. (10) included 13 patients previously treated with Enbrel® and switched to Benepali®; Bruni et al. (13) evaluated 32 patients previously treated with Humira® and switched to Imraldi®; Scrivo et al. (14) included 37 patients previously treated with Humira® and switched to Imraldi®; and Müller-Ladner et al. (4) assessed 127 patients, previously treated with Humira® and switched to Imraldi®.

Another limitation of most studies is their relatively short follow-up period. Rojas-Giménez et al. (9), Ulf et al. (11) and Jourdain et al. (18) evaluated treatment retention rates, while Ditto et al. (10) compared

disease activity scores, only after 12-months of treatment. Müller-Ladner et al. (4) assessed PR at week 48, Bruni et al. (13) evaluated disease activity scores at 6-months, and Scrivo et al. (14) compared disease activity at 4-months of follow-up. The limited duration of these studies constrains the ability to draw robust conclusions regarding the comparative long-term effectiveness of the original and biosimilar iTNF.

Pinto et al. (7) conducted a real-world study that evaluated the long-term effectiveness and safety of the original Enbrel® and biosimilar Benepali® in a large cohort of bDMARD-naïve patients in Portugal. This is, to the best of our knowledge, the only real-world study confirming the efficacy of this therapeutic alternative over an extended follow-up period (36-months), involving a substantial Portuguese cohort of 494 patients (368 on Enbrel® and 126 on Benepali®). Despite the valuable insights provided by this study, data regarding the use of adalimumab biosimilars and other etanercept biosimilars in the Portuguese population remain limited.

When therapeutic failure occurs, patients may need to switch to a biotechnological drug with a different mechanism of action, such as IL-17 inhibitors and JAK inhibitors. This alternative treatment option, however, typically comes at a substantially higher cost compared to maintaining therapy with iTNF.

In an exploratory analysis of 127 patients with SpA followed in our department, we observed a significantly higher PR at 3-years under original iTNF (61.4%), with an average drug use time of 27.2 months; compared to 33.3% under biosimilar iTNF, with an average drug use time of 23.7 months ($p=0.012$). The main cause of discontinuation was secondary failure, with a higher proportion observed under biosimilar iTNF (52.8% vs 18.1%, $p<0.01$). No differences were found regarding primary failure or the rate of adverse events. Our results suggest greater efficacy of the original iTNF, with no differences in the safety profile, compared to biosimilars. However, the number of missing data and the sample size were a limitation of the study, which limits the extrapolation of our conclusions (19).

Given the divergent findings from our pilot study compared to the current state of the art, that affirms the biosimilarity between original drugs and their biosimilars, this larger study with a Portuguese patient cohort aims to provide robust real-world data to verify the results. The implications for clinical practice could be significant. If we observe similar retention rates and therapeutic responses, it may allow for broader use of these more affordable biosimilar drugs. However, if biosimilars demonstrate lower retention rates and higher disease activity scores, it may be prudent to prioritize the use of original drugs to avoid or delay the need to switch to morce costly biologics with different mechanisms of action.

4. Study hypothesis

We hypothesize that the biosimilars Amgevita®, Hulio®, Hyrimoz®, Idacio®, Imraldi®, Yuflima®, Benepali® and Erelzi® have similar persistence in treatment, effectiveness and safety profile, when compared to reference Humira®, Enbrel® and Simponi®, in Portuguese adults with SpA, based on data from Reuma.pt.

5. Objectives

1) Compare treatment persistence at 3-years of follow-up between original iTNF (Humira®, Enbrel®, Simponi®) and biosimilars (Amgevita®, Hulio®, Hyrimoz®, Idacio®, Imraldi®, Yuflima®, Benepali®, Erelzi®) (primary endpoint);

2) Compare the therapeutic response between the group of patients receiving the original iTNF and the group using biosimilar drugs at 6, 12, 24 and 36 months of therapy, using the following indices:

2.1) For patients with predominant or exclusive axial involvement: BASDAI, BASDAI response, ASDAS-CRP and ASDAS response;

2.2) For patients with predominant or exclusive peripheral involvement: DAS28-3V-CRP, DAS28-4V-CRP and EULAR response (secondary endpoint);

3) Evaluate the reasons for treatment discontinuation (primary/secondary failure, severe adverse events, sustained remission, other reasons) (secondary endpoint);

4) Compare the frequency and severity of adverse events between original and biosimilars iTNF (secondary endpoint).

6. Methods

6.1. Study design

A multicenter, retrospective, observational cohort study with a 3-years period of follow-up in patients with SpA, using real-world data from the Rheumatic Diseases Portuguese Register (Reuma.pt).

6.2. Population

Inclusion criteria:

- Patients aged 18 years or older;
- Patients diagnosed with Spondyloarthrtitis, in axial and/or peripheral forms, according to the attending rheumatologist;
- Patients receiving treatment with original iTNF (Humira®, Enbrel®, Simponi®) or biosimilars (Amgevita®, Hulio®, Hyrimoz®, Idacio®, Imraldi®, Yuflima®, Benepali®, Erelzi®);
- Patients under rheumatology care for at least 36 months after the first administration of the biotechnological drug;
- Patients included in the Portuguese registry of rheumatic diseases - Reuma.pt (www.reuma.pt) and who have signed informed consent.

Exclusion criteria:

- Patients aged younger than 18 years at the start of treatment; OR
- Patients who do not meet the diagnostic criteria; OR
- Patients who do not consent to participation in Reuma.pt; OR
- Patients whose information recorded in Reuma.pt is considered insufficient.

7. Variables

1. For characterization of the study population, the following data will be collected at baseline (defined as the date of initiation of the iTNF):

  - Demographic data: age, gender and body mass index (BMI);
  - Smoking status (smoker, non-smoker or former smoker);
  - Date of diagnosis (month and year);
  - Clinical characteristics: radiographic axial SpA, non-radiographic axial SpA or peripheral SpA; HLA-B27 positive or negative;
  - Comorbidities (hypertension, dyslipidemia, diabetes, hyperthyroidism, hypothyroidism, heart failure, solid or hematologic tumors);
  - Concomitant medication (cDMARDs, corticosteroids and NSAIDs).

2. For assessing treatment persistence, the elapsed time from the start of therapy to the definitive discontinuation of the drug will be calculated in months.

3. For characterization of disease activity, treatment response, and adverse events occurring in all patients, the following data will be collected at baseline and at 6, 12, 24 and 36 months of therapy:

- Patient Global Assessment of Disease using Visual Analog Scale (VAS);
- Physician Global Assessment of Disease using VAS;
- Patient Assessment of Pain using VAS;
- Adverse events: infections, neoplasms, allergic reactions or hematologic changes;
- Severity of adverse events categorized into the following groups:
    - Mild: requiring only symptomatic measures;
    - Moderate: necessitating temporary discontinuation of the drug;
    - Severe: resulting in permanent discontinuation of the drug.

- For patients with predominant or exclusive axial involvement, the following data will be collected:
    - BASDAI (Bath Ankylosing Spondylitis Disease Activity Index);
    - BASDAI response:
        - BASDAI Δ ≥2 or ≥50% (improvement of at least 2 units or at least 50%): yes or no;
    - ASDAS-CRP (Ankylosing Spondylitis Disease Activity Score using C-reactive protein);
    - ASDAS-CRP response:
        - Clinically significant improvement (ASDAS-CRP Δ ≥1.1): yes or no;
        - Major improvement (ASDAS-CRP Δ ≥2): yes or no.

- For patients with predominant or exclusive peripheral involvement, the following data will be collected:
    - Count of swollen and tender joints;
    - DAS28-3V-CRP (Disease Activity Score, 3 variables, with C-reactive protein);
    - DAS28-4V-CRP (Disease Activity Score, 4 variables, with C-reactive protein);
    - EULAR response:
        - Good responder (DAS28-4V-CRP Δ > 1.2 and DAS28-4V-CRP ≤ 3.2): yes or no;
        - Moderate responder (DAS28-4V-CRP Δ > 1.2 and DAS28-4V-CRP ≥ 3.2 OR DAS28-4V-CRP Δ > 0.6 and ≤ 1.2 and DAS28-4V-CRP ≤ 5.1): yes or no.

4. The reasons for treatment discontinuation will be categorized into the following groups:

- Primary failure (lack of response within the first 6 months of treatment);
- Secondary failure (loss of response after having sustained a positive effectiveness outcome for ≥12 months from treatment initiation);
- Adverse events;
- Sustained remission (inactive disease according to ASDAS-CRP);
- Other reasons (patient preference, loss to follow-up, pregnancy, etc.).

Missing data from the platform will be identified and requested to be filled in by each participating center based on hospital clinical registries.

8. Statistical analysis

Data retrieved from the Reuma.pt platform will be exported and aggregated into a single document in Microsoft Excel format. Subsequently, they will be imported and subjected to statistical analysis using the Statistical Package for the Social Sciences (SPSS) and R software.

Missing data analysis will be conducted. Variables associated with missingness will be identified using appropriate statistical tests, such as the chi-square test. Furthermore, Little's test will assess whether data are missing completely at random (MCAR). Imputation by mean/median or multiple imputation will be employed.

For continuous variables, if normally distributed, mean and standard deviation will be reported. If not normally distributed, median and quartiles will be reported. For categorical variables, frequency or proportion will be reported.

To compare treatment persistence at 3-years of follow-up between original iTNF and biosimilars, the Kaplan-Meier test and Cox regression will be used to estimate survival probability over time and compare the survival curves between the groups.

Therapeutic response between patients using original iTNF and those using biosimilar iTNF will be compared. Chi-square tests will be employed for categorical variables, while Student's t-tests or Mann-Whitney U tests will be used for numerical variables. These tests will compare the following disease activity indices at 6, 12, 24 and 36 months of follow-up:

1.1) For patients with predominant or exclusive axial involvement:
- ΔBASDAI (change in BASDAI score);
- Proportion of patients with BASDAI response;
- ΔASDAS-CRP (change in ASDAS-CRP score);
- Proportion of patients with clinically significant improvement by ASDAS;
- Proportion of patients with major improvement by ASDAS.

1.2) 1.2) For patients with predominant or exclusive peripheral involvement:
- ΔDAS28-3V-CRP (change in DAS28-3V-CRP score);
- ΔDAS28-4V-CRP (change in DAS28-4V-CRP score);
- Proportion of patients with good EULAR response;
- Proportion of patients with moderate EULAR response.

To evaluate the reasons for treatment discontinuation, we will use descriptive statistics to summarize the reasons and the Chi-square test to compare the group of patients using original iTNF and the group using biosimilar drugs.

To compare the frequency and severity of adverse events between original and biosimilars iTNF, we will use the Chi-square test.

In all analyses significance level will be set at 0.05.

9. Timeline

Timelines for the several steps of this project are presented in Table I. Globally, this study will take 9 months to be concluded.

Table 1: Timelines for the project

	May-Aug 2025	Sep-Nov 2025	Dec-Jan 2026
Data extraction	x		
Data analysis		x	
Final report/notification			x

10. Ethical considerations

This study will be conducted according to the Declaration of Helsinky and the International Guidelines for Ethical Review of Epidemiological Studies. It was submitted and approved by the ULS Viseu Dão-Lafões' Ethics Committee and Data Protection Officer. All the participants have signed free and informed consent for their data to be used in clinical studies. Results will be presented in an objective way, and will not be hidden or manipulated.

11. Research team and institutions

Proponents: Inês Almeida[1]; Liliana Saraiva[1]; Carla Henriques[2,3]; Ana Matos[2,4]; Maura Couto[1].

1- Rheumatology Unit, ULS Viseu Dão-Lafões
2- School of Technology and Management, Polytechnic Institute of Viseu, Portugal
3- Centre for Mathematics of the University of Coimbra - CMUC, Portugal
4- CISeD – Research Centre in Digital Services, Polytechnic Institute of Viseu

Centers involved: participation is open to all the Portuguese centers interested in collaborating in this project, according to the Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals (Vancouver Convention). Co-authorship will be granted to a maximum of 2 co-authors per centre, actively collaborating in the project. Authors will be listed in the Title Page of the manuscript and in a Collaborative Authorship List, at the end of the manuscript, according to the definitions bellow:

- The Title Page will include first author (lead author of the project), last author (senior author of the project) and researchers from each center, listed in descending order according to the number of valid patients finally included per center;

- The Collaborative Authorship List at the end of the manuscript will list all investigators/centres by alphabetical order;

- A minimum of 30 valid patients will be the criterion to be included on the Title Page of the manuscript;

- Centres with at least 1 valid patient but less than 30 valid patients will have 1 co-author included in the Collaborative Authorship List;

- Centres with 30 to 59 valid patients will have 1 co-author on the Title Page; centres with 60 or more valid patients will have 2 co-authors on the Title Page.

12. Funding and conflicts of interests

There are no conflicts of interest or external funding to declare in this study.

13. References

1. Huizinga TWJ, Torii Y, Muniz R. Adalimumab Biosimilars in the Treatment of Rheumatoid Arthritis: A Systematic Review of the Evidence for Biosimilarity. Rheumatology and therapy. 2021;8(1):41-61.

2. Ishii-Watabe A, Kuwabara T. Biosimilarity assessment of biosimilar therapeutic monoclonal antibodies. Drug metabolism and pharmacokinetics. 2019;34(1):64-70.

3. Weinblatt ME, Baranauskaite A, Dokoupilova E, Zielinska A, Jaworski J, Racewicz A, et al. Switching From Reference Adalimumab to SB5 (Adalimumab Biosimilar) in Patients With Rheumatoid

Arthritis: Fifty-Two-Week Phase III Randomized Study Results. Arthritis & rheumatology (Hoboken, NJ). 2018;70(6):832-40.

4. Müller-Ladner U, Dignass A, Gaffney K, Jadon D, Matucci-Cerinic M, Lobaton T, et al. The PROPER Study: A 48-Week, Pan-European, Real-World Study of Biosimilar SB5 Following Transition from Reference Adalimumab in Patients with Immune-Mediated Inflammatory Disease. BioDrugs : clinical immunotherapeutics, biopharmaceuticals and gene therapy. 2023;37(6):873-89.

5. Emery P, Vencovský J, Sylwestrzak A, Leszczyński P, Porawska W, Baranauskaite A, et al. A phase III randomised, double-blind, parallel-group study comparing SB4 with etanercept reference product in patients with active rheumatoid arthritis despite methotrexate therapy. Annals of the rheumatic diseases. 2017;76(1):51-7.

6. Emery P, Vencovský J, Sylwestrzak A, Leszczyński P, Porawska W, Stasiuk B, et al. Long-term efficacy and safety in patients with rheumatoid arthritis continuing on SB4 or switching from reference etanercept to SB4. Annals of the rheumatic diseases. 2017;76(12):1986-91.

7. Pinto AS, Cunha MM, Pinheiro F, Bernardes M, Assunção H, Martins-Martinho J, et al. Effectiveness and safety of original and biosimilar etanercept (Enbrel® vs Benepali®) in bDMARD-naïve patients in a real-world cohort of Portugal. ARP rheumatology. 2022;1(2):109-16.

8. Codreanu C, Popescu CC, Mogoșan C, Enache L, Daia S, Ionescu R, et al. Efficacy and safety of original and biosimilar etanercept (SB4) in active rheumatoid arthritis - A comparison in a real-world national cohort. Biologicals : journal of the International Association of Biological Standardization. 2019;62:27-32.

9. Rojas-Giménez M, Mena-Vázquez N, Romero-Barco CM, Manrique-Arija S, Ureña-Garnica I, Diaz-Cordovés G, et al. Effectiveness, safety and economic analysis of Benepali in clinical practice. Reumatología Clínica (English Edition).

10. Ditto MC, Parisi S, Priora M, Sanna S, Peroni CL, Laganà A, et al. Efficacy and safety of a single switch from etanercept originator to etanercept biosimilar in a cohort of inflammatory arthritis. Scientific reports. 2020;10(1):16178.

11. Ulf L, Bente G, Daniela Di G, Dan N, Sella Aarrestad P, Bjorn G, et al. Treatment retention of infliximab and etanercept originators versus their corresponding biosimilars: Nordic collaborative observational study of 2334 biologics naïve patients with spondyloarthritis. RMD Open. 2019;5(2):e001079.

12. Weinblatt ME, Baranauskaite A, Dokoupilova E, Zielinska A, Jaworski J, Racewicz A, et al. Switching From Reference Adalimumab to SB5 (Adalimumab Biosimilar) in Patients With Rheumatoid Arthritis: Fifty-Two-Week Phase III Randomized Study Results. Arthritis & rheumatology (Hoboken, NJ). 2018;70(6):832-40.

13. Bruni C, Bitti R, Nacci F, Cometi L, Tofani L, Bartoli F, et al. Efficacy and safety of switching from reference adalimumab to SB5 in a real-life cohort of inflammatory rheumatic joint diseases. Clinical rheumatology. 2021;40(1):85-91.

14. Scrivo R, Castellani C, Mancuso S, Sciarra G, Giardina F, Bevignani G, et al. Effectiveness of non-medical switch from adalimumab bio-originator to SB5 biosimilar and from ABP501 adalimumab biosimilar to SB5 biosimilar in patients with chronic inflammatory arthropathies: a monocentric observational study. Clinical and experimental rheumatology. 2023;41(3):613-9.

15. Blauvelt A, Lacour JP, Fowler JF, Jr., Weinberg JM, Gospodinov D, Schuck E, et al. Phase III randomized study of the proposed adalimumab biosimilar GP2017 in psoriasis: impact of multiple switches. The British journal of dermatology. 2018;179(3):623-31.

16. Wiland P, Jeka S, Dokoupilová E, Brandt-Jürgens J, Miranda Limón JM, Cantalejo Moreira M, et al. Switching to Biosimilar SDZ-ADL in Patients with Moderate-to-Severe Active Rheumatoid Arthritis: 48-Week Efficacy, Safety and Immunogenicity Results From the Phase III, Randomized, Double-Blind ADMYRA Study. BioDrugs : clinical immunotherapeutics, biopharmaceuticals and gene therapy. 2020;34(6):809-23.

17. Martins Fernandes A, Pinto A, flora K, matharu d, isaacs a, Machado P. Long-term Follow-up of Starting and Switching from Bio-originator to Biosimilar: Real-world Data in Axial Spondyloarthritis Patients Treated with Adalimumab and Etanercept [abstract]. Arthritis Rheumatol. 2022; 74 (suppl 9).

18. Jourdain H, Hoisnard L, Sbidian E, Zureik M. Persistence and safety of anti-TNF biosimilars versus originators in immune-mediated inflammatory diseases: an observational study on the French National Health Data System. RMD Open. 2024;10(1).

19. Almeida I, Saraiva L, Tavares M, Teixeira A, Couto M. Persistence in treatment with TNF-alpha inhibitors in Spondyloarthritis: comparison between original and biosimilar Drugs - a pilot study. ARP rheumatology. 2024;3(suppl):124-125.