Formulário de acesso a dados do Registo Nacional de Doentes Reumáticos (Reuma.pt) da SPR

1. Title

Efficacy and safety of biosimilar infliximab CT-P13 compared to originator infliximab in rheumatoid arthritis and axial spondyloarthritis patients: data from the Portuguese Register Reuma.pt

2. Background

2.1 Current knowledge

Biosimilars are defined by the European Medicines Agency (EMA) as biological medicinal products that contain a version of the active substance of an already authorized original biological medicinal product known as reference product (1). Biosimilars were created with the sole purpose of offering the same efficacy and safety as originator drugs at lower prices, thus generating significant cost-savings (2). The first biosimilar of a monoclonal antibody was granted marketing authorization by EMA in 2013 (infliximab biosimilar CT-P13, brand names Remsima® and Inflectra®) (3) and, since then, three have followed (etanercept biosimilars SB4, brand name Benepali®, and GP2015, brand name Erelzi®; and infliximab biosimilar SB2, brand name Flixabi®) (4,5). However, many more are currently under development and will probably be approved in the near future (6). In the North American and European markets, the approval pathway is highly regulated and biosimilar candidates must undergo an intricate comparability exercise comprising quality, non-clinical and clinical testing (6). Two randomised, double-blind, parallel-group trials, PLANETAS and PLANETRA, provided the evidence for similar pharmacokinetics, clinical efficacy and safety of the infliximab biosimilar CT-P13. The first was a phase I study that demonstrated pharmacokinetic equivalence (primary endpoint) and similar efficacy and safety (secondary endpoints) between CT-P13 and originator infliximab (both intravenous 5 mg/kg every 8 weeks for 30 weeks) in 250 patients with active ankylosing spondylitis (AS) (7). The second was a phase III study that showed equivalent clinical efficacy (primary endpoint) and pharmacokinetic, pharmacodynamic, safety and immunogenicity (secondary endpoints) in 606 patients with active rheumatoid arthritis (RA), despite methotrexate therapy, treated with intravenous 3 mg/kg every 8 weeks, up to 30 weeks (8). Evidence of maintained biosimilarity at 54 weeks has been recently published for both diseases (9, 10).

Despite rigorous assessment, uncertainty remains on whether the inherent variability of biosimilar drugs may generate unexpected immunogenicity and compromise efficacy or safety. These have so far only been analysed in the context of randomized clinical trials and almost no data from registries have yet been published. Data from 'real-life' settings is crucial to further define the position of biosimilars in daily clinical practice.

2.2 Preliminary data

We have no preliminary data concerning the current study.

2.3 Hypothesis

We hypothesize that the infliximab biosimilar CT-P13 has similar efficacy compared to originator infliximab in Portuguese patients with active RA and axial spondyloarthritis (axSpA) in daily clinical practice, a 'real-life' setting. We also hypothesize these two therapies have a similar safety profile.

2.4 Innovation and significance

The arrival of biosimilar drugs promises to change the treatment landscape of immune-mediated rheumatic diseases. However, adequate answers to the uncertainties still surrounding biosimilars are necessary to guarantee their widespread use and success. While small differences in quality attributes or physicochemical properties may not be sufficient to preclude biosimilarity in preclinical testing, some authors state that these may trigger immunogenicity issues affecting efficacy and safety that may not be detected in clinical trials with limited follow-up periods and limited numbers of highly selected patients (11). There are also doubts related to the extrapolation of safety and efficacy demonstrated in one clinical indication to all the indications of the reference drug, especially in conditions with distinct pathophysiologies (6).

Clinical registries, such as Reuma.pt, can be an important tool to monitor treatment outside the context of a clinical trial. The current proposal aims to further assess biosimilarity between CT-P13 and reference infliximab in RA and axSpA patients in a real-life setting. We decided to assess CT-P13 as this was the first biosimilar of a monoclonal antibody introduced in Portugal, having the longest track record. The majority of observational studies published on infliximab biosimilar CT-P13 were performed in patients with inflammatory bowel disease (IBD), which is quite understandable considering the lack of direct interventional evidence in IBD (12-15). We found only one low-quality observational study of CT-P13 in 39 rheumatic patients currently

published (some of the reasons for low quality included small population, use of individualized instead of validated composite outcome measures and combined statistical analysis of distinct rheumatic diseases) (16).

3. Specific aims

3.1. PRIMARY AIM

To compare the efficacy of i) biosimilar infliximab CT-P13, ii) originator infliximab and iii) non-biological therapy over 24 months of follow-up in RA and axSpA patients.

3.2. SECONDARY AIM

To compare the safety of i) biosimilar infliximab CT-P13, ii) originator infliximab and iii) non-biological therapy over 24 months of follow-up in RA and axSpA patients.

4. Methods

4.1. Study design

We will perform a prospective multicentre observational cohort-study using data from the Portuguese Register Reuma.pt (17). For each rheumatic disease, we will compare biological-naive patients starting infliximab biosimilar CT-P13 with biological-naive patients starting originator infliximab, and patients treated with non-biological therapy (conventional synthetic DMARDs [csDMARDs] in RA; non-steroidal anti-inflammatories [NSAIDs] in axSpA) from 2014 onwards (2014 was the year CT-P13 entered the Portuguese market). Although we are mostly interested in the comparison between the biosimilar CT-P13 and originator infliximab, we have decided to include a third arm in the comparison because we anticipate having a small number of patients treated with the biosimilar CT-P13. Therefore, and in order to avoid a possible type II error, we will also look at the effect sizes across the 3 arms and base our interpretations on these comparisons. If the number of biological-naive patients starting originator infliximab from 2014 onwards is not sufficient for comparison, we will broaden our inclusion period to 2013 and eventually 2012.

As depicted below, we will focus our analysis on efficacy rather than safety. This decision comes from the fact that we will probably find a limited number of patients treated with infliximab biosimilar and limited follow-up times, adding to possible reporting bias from incomplete filling of the database (which is usually greater for safety outcomes). Focusing on

efficacy and using the previously mentioned study design, we will be able to increase our statistical power to detect any differences between the three treatment arms.

4.2. Inclusion and exclusion criteria

Inclusion criteria

- adult patients (>18 years old) with RA or axSpA according to their treating rheumatologists.
- patients naive for biotechnological therapies.
- biosimilar infliximab arm: all biological-naive patients starting biosimilar infliximab (CT-P13) due to inefficacy, intolerance or adverse events to conventional/non-biological therapies, according to their treating rheumatologists.
- originator infliximab arm: biological-naive patients starting originator infliximab due to inefficacy, intolerance or adverse events to conventional/non-biological therapies, according to their treating rheumatologists. Since we are aiming for an identical number of patients in the biosimilar and originator arms, if the number of biological-naive patients starting originator infliximab from 2014 onwards is not sufficient for comparison, we will broaden our inclusion period to 2013 and eventually 2012. If during the follow-up period the patient is switched to biosimilar infliximab, the efficacy and safety analysis will be performed till the time of swtich. The same applies for a biosimilar to originator switch.
- non-biological therapy arm: we will randomly select one conventional/non-biological treated patient for each biosimilar treated patient from the biosimilar prescribing centres. The multivariable analyses will be adjusted for relevant baseline characteristics that expectedly will differ between groups given the observational design of the study.

Exclusion criteria

- patients that are not naive for biotechnological therapies.

4.3. Efficacy analysis

4.3.1. Efficacy outcome measures

Clinical data from baseline and at each 3 months up to 24 months of follow-up will be used.

RA

- primary endpoint: disease activity score (DAS) 28 - ESR variation from baseline at 3, 6, 9, 12, 15, 18, 21 and 24 months.
- secondary endpoints: DAS28-ESR remission (DAS 28-ESR < 2.6) and low disease activity (2.6 ≤ DAS 28-ESR ≤ 3.2), clinical disease activity index (CDAI) remission (CDAI ≤ 2.8) and low disease activity (2.8 < CDAI ≤ 10), simplified disease activity index (SDAI) remission (SDAI ≤ 3.3) and low

disease activity (3.3 < SDAI ≤ 11), proportion of EULAR good responders (DAS28-ESR ≤ 3.2 and improvement > 1.2 from baseline), proportion of patients achieving the ACR/EULAR Boolean-based definition of remission, variation in CDAI and SDAI from baseline, and HAQ-score at 3, 6, 9, 12, 15, 18, 21 and 24 months.

AxSpA

- primary endpoint: ankylosing spondylitis disease activity score (ASDAS) variation from baseline at 3, 6, 9, 12, 15, 18, 21 and 24 months.
- secondary endpoints: ASDAS inactive disease (ASDAS < 1.3) and moderate disease activity (1.3 ≤ ASDAS < 2.1), ASDAS clinically important improvement (ASDAS Δ ≥ 1.1 from baseline), ASDAS major improvement (ASDAS Δ ≥ 2.0 from baseline), BASDAI 50 response, BASDAI, BASDAI improvement from baseline and BASFI at 3, 6, 9, 12, 15, 18, 21 and 24 months.

4.3.2. Potential confounders

Age, gender, ethnicity, body mass index, education, smoking status, alcohol intake, co-morbidities, co-medication and disease duration.

4.3.3. Interactions of interest

We will test if the effect of treatment on the different outcomes is modified by other factors (interactions), such as seropositivity (RA) and fulfilment of the modified New York criteria (axSpA).

4.3.4. Statistical analysis

The effect of treatment on the response criteria will be assessed using two approaches: i) multivariable logistic (or linear, depending on the outcome) regression using as outcome the response criteria at 24 months and adjusting for potential confounders (selected a priori on clinical grounds); ii) multivariable binomial (or linear, depending on the outcome) generalized estimating equations (GEE), where the effect of treatment at baseline will be tested against the outcome over 24 months of follow-up (3-month intervals), while accounting for the correlation of repeated measurements within patient. The goal of the second (longitudinal) approach is to increase the statistical power to detect possible differences between treatments, thus strengthening the robustness of a negative finding. For each final model, interactions will be tested and if significant ($p<0.15$) the model is fitted in each subgroup. Goodness-of-fit statistics will be used to get an impression on how much of the outcome-variability is explained by each model: i) logistic regression (area under the ROC curve; AUC);

GEE (quasi-likelihood under the independence model criterion; QIC). All analyses will be performed in Stata V12.1.

4.4. Safety analysis

4.4.1. Safety outcome measures

We will assess the type and proportion of adverse events in the three treatment groups, including infusion-related reactions, infections and laboratorial abnormalities, over the 24 months follow-up period.

4.4.2. Statistical analysis

The proportion of adverse events (occurring during follow-up) will be compared between the three treatment groups using the chi-squared test.

5. Limitations and expected results

Expected results:

- We expect to assess and compare the efficacy and safety of biosimilar infliximab CT-P13 with reference infliximab in RA and axSpA patients in a daily life clinical practice setting. We know that biosimilars can never be exact copies of their reference drugs and, in fact, CT-P13 exhibited slightly less basic variants in charge isoforms (attributed to C-terminal lysine) and a lower level of afucosylated glycans in preclinical testing (6). Despite these differences, neither the PLANETAS nor the PLANETRA studies showed any clinically meaningful variation in safety or efficacy between biosimilar and originator. We expect to further confirm this biosimilarity in everyday practice.

Limitations include:

- Possible treatment selection bias due to Rheumatology centre biosimilar availability and rheumatologists' preconceived ideas on biosimilars.
- Possible low number of patients treated with biosimilar infliximab. As previously mentioned, the inclusion of a third arm treated with non-biological therapy and the "generalized estimating equations longitudinal analysis" assessing the outcomes at 3-month intervals will increase the statistical power to detect differences between groups.

- Possible information bias due to incomplete filling of database fields. Rheumatologists from originator and biosimilar infliximab prescription centres will be included in this study to assure all missing data is adequately filled in, when available.

6. Timeline

	March 2017	April-June 2017	June 2017	(…)	November 2017
Data extraction					
Data evaluation and analysis					
Abstract submission			ACR 2017 meeting		
Data presentation					ACR 2017 meeting
Manuscript preparation					
Manuscript submission					

7. Ethical considerations

This study will be conducted according to the Declaration of Helsinky and the International Guidelines for Ethical Review of Epidemiological Studies.

This study will be submitted for validation and approval to an Ethics Committee. Results will be presented in an objective way, and will not be hidden or manipulated.

8. Research Team

- Filipe Araújo, MD, Rheumatology Unit, Hospital de Sant'Ana, Cascais, Portugal. Microbiology, Faculdade de Medicina da Universidade de Lisboa, Lisboa, Portugal.

Contribution: Study design, protocol writing and revision, processing of the database, statistical analysis, oral/poster presentation and article conception and revision.

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Contribution: Study design, protocol writing and revision, application for funds, oral/poster presentation and article conception and revision.

9. Conflicts of interest

Filipe Araújo: FA has received consultant and speaker fees from Pfizer LDA.

Alexandre Sepriano: none

Sofia Ramiro: none

Nélia Gouveia: none

Jaime C. Branco: none

João Gonçalves: JG has received consultant and speaker fees from Pfizer, MSD and Abbvie.

João Eurico Fonseca: JEF has received research grants and speaker fees from Pfizer, Hospira, Biogen, MSD and Abbvie.

10. Co-authors

All clinicians who actively work on the project will be co-authors with a maximum of 3 co-authors per participating institution

11. Funding

This project will apply for research grants from Pfizer and Biogen.

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