Pedido de acesso a dados do Registo Nacional de Doentes Reumáticos (Reuma.pt) da Sociedade Portuguesa de Reumatologia

1. TITLE

EFFECTIVENESS, SAFETY, QUALITY OF LIFE, COSTS AND PERSISTENCE OF BIOSIMILAR ETANERCEPT COMPARED TO REFERENCE ETANERCEPT IN JUVENILE IDIOPATHIC ARTHRITIS PATIENTS – DATA FROM THE PORTUGUESE REGISTER REUMA.PT.

2. INTRODUCTION

Biosimilars are biological medicinal products containing a version of the active substance of an already authorized original biological medicinal product (reference or originator product), for which they are required to have similar efficacy, safety and immunogenicity. Biosimilars are being introduced in clinical practice for the sole purpose of mitigating the economic burden put on healthcare systems by biological therapies, which are currently the main driver for direct costs with rheumatic patients. In adult patients with rheumatic diseases, switching to biosimilar etanercept is becoming a reality in Portuguese Centers of Rheumatology.

The data of biosimilars in juvenile idiopathic arthritis (JIA) are scarce in terms of clinical trials and real-world data. Patients with JIA have so many specificities that studies in this group are warranted and we think they should be mandatory.

We intend to study the effectiveness, safety, quality of life, costs and persistence of biosimilar etanercept compared to originator etanercept, in children and adolescents with juvenile idiopathic arthritis (JIA).

3. STUDY HYPOTHESIS

We hypothesize that the biosimilar etanercept (Benepali) has similar effectiveness, safety, quality of life and persistence profile, at a lower cost, when compared to reference etanercept (Enbrel), in Portuguese children and adolescents with JIA, based on Reuma.pt.

4. OBJECTIVES

- To compare the effectiveness of biosimilar etanercept (Benepali) with reference etanercept (Enbrel) at 6, 12, 18 and 24 months of follow-up in JIA patients.

- "To evaluate the persistence in remission of biosimilar etanercept (Benepali) after switching from reference etanercept (Enbrel)." - To compare the safety profile of biosimilar etanercept (Benepali) with reference etanercept (Enbrel) at 6, 12, 18 and 24 months of follow-up in JIA patients.

- To compare the quality of life, physical function, difficulties with medication administration, school problems caused by the disease, psychosocial health and satisfaction with the outcome of the illness of patients treated with biosimilar etanercept (Benepali) with reference etanercept (Enbrel) at 12 and 24 months of follow-up in JIA patients.

- To compare the persistence rates of biosimilar etanercept (Benepali) with reference etanercept (Enbrel) in JIA patients.

- To compare the costs of JIA patients treated with biosimilar etanercept (Benepali) and with reference etanercept (Enbrel) at 12 and 24 months of follow-up.

5. METHODS

5.1. Study Design

This is a multicenter, prospective, observational study, using data from the Rheumatic Diseases Portuguese Register (Reuma.pt). Recruitment will be done in JIA patients starting biosimilar etanercept, reference etanercept and in patients that switch from etanercept reference to etanercept biosimilar during the first 24 months after the beginning of the study. We will extend the recruitment phase to 36 months if the number of patients is less than 50 patients in each arm of the study.

The patients will make the switch from reference etanercept (Enbrel) to biosimilar etanercept (Benepali), according to the decision of the attending rheumatologist and institutional policy. This study is based on daily clinical practice and does not condition any type of switch.

5.2. Population:

Inclusion criteria: patients with less than 16 years-old at baseline, with the diagnosis of JIA, according to the ILAR criteria, treated with biosimilar etanercept or reference etanercept.

3 arms of the study:

1. biosimilar etanercept arm (Benepali): all biological-naive patients starting biosimilar etanercept (Benepali) due to inefficacy or intolerance to conventional/non-biological therapies.
2. reference etanercept arm (Enbrel): biological-naive patients starting reference etanercept due to inefficacy or intolerance to conventional/non-biological therapies.
3. Switch arm: JIA patients on stable low disease activity or disease remission after treatment with reference etanercept (Enbrel) during at least the previous 6 months, that agreed to switch to biosimilar etanercept (Benepali).

5.3. Study duration: 24 months.

6. VARIABLES

The following variables will be collected from the Reuma.pt database at baseline, 6, 12, 18 and 24 months after the beginning of biosimilar etanercept (Benepali) and reference etanercept (Enbrel):

- Demographic characteristics (age, gender, ethnicity)
- Age at disease onset

- Age at diagnosis
- Disease duration
- Rheumatoid factor
- ACPA
- HLA B27
- Antinuclear antibodies
- Erythrocyte Sedimentation Rate and C-reactive protein
- Co-medication: corticosteroids, NSAIDs, DMARDs
- JADAS10 and JADAS27
- Number of swollen and tender joints
- Physician Global Assessment (measured on a 10 cm Visual Analog Scale)
- Parent/Patient Global Assessment (measured on a 10 cm Visual Analog Scale)
- Juvenile Arthritis Multidimensional Arthritis Report (JAMAR) – patients and parent's version. JAMAR will allow to evaluate the quality of life, physical function, difficulties with medication administration, school problems caused by the disease, psychosocial health and satisfaction with the outcome of the illness
- CHAQ
- Number of medical visits registered in Reuma.pt in 24 months
- Costs with medication (biological therapy) (the price per administration of the medication in each hospital will registered)
- Monitoring safety will be assessed by adverse drug reactions (like injection-site reactions), adverse events (severe and opportunistic infections, tumors, cardiovascular events, demyelinating disorders, lupus-like disease), physical examination, and clinical laboratory parameters.
- In patients who have been switched from reference etanercept (Enbrel) to biosimilar etanercept (Benepali), included in the switch-arm of the study, the analysis of the variables will be performed till the time of switch and after the switch to biosimilar.

Primary endpoints:

We intend to compare the persistence rate of biosimilar etanercept (Benepali) when compared to the reference etanercept (Enbrel) from baseline to 24 months, and over the recruitment period.

Secondary endpoints:

We intend to compare biosimilar etanercept (Benepali) with reference etanercept (Enbrel) from baseline to 24 months, and over the recruitment period, in the following variables:

- JADAS27 variation
- JAMAR data variation
- CHAQ variation
- Number of adverse events
- Costs with medication

7. STATISTICAL ANALYSIS

Categorical variables will be described using absolute and relative frequencies. For continuous data mean, standard deviation, median, 25th and 75th percentiles, minimum, and maximum will be calculated. A descriptive analysis of the disease activity (assessed by JADAS10 and JADAS27), adverse events of the medication, quality of life (assessed by the visual analogue scales, CHAQ and JAMAR), costs and persistence rates will be performed. Subsequently patients will be grouped according to the therapeutic arm (biosimilar etanercept vs reference etanercept vs transition arm (switching of reference etanercept to biosimilar etanercept)) in order to compare effectiveness, safety, quality of life, costs and persistence rates. Univariate analysis will be performed to assess the possibility of confounders. We will use multivariate linear regression models in order to adjust for the differences between the groups. Possible associations between covariables and effectiveness, presence of adverse events, patient reported outcomes, and costs will be evaluated using uni and multivariate linear regression.

In all analyses significance level will be set at 0.05. All analyses will be performed using Stata IC version 12 (StataCorp. 2011. Stata Statistical Software: Release 12. College Station, TX: StataCorp LP).

8. LIMITATIONS AND EXPECTED RESULTS

One of the limitations of the study is the possible low number of patients treated with biosimilar etanercept (Benepali).

We expect to assess the effectiveness, safety, quality of life, physical function, difficulties with medication administration, school/university/work problems caused by the disease, psychosocial health, satisfaction with the outcome of the illness and costs with the illness, in JIA patients treated with biosimilar etanercept compared to reference etanercept, in a daily life clinical practice setting.

9. TIMELINE

Centers will be informed and asked to participate in the study as soon as we have the approval of the Scientific Committee of Reuma.pt.

Final data will be collected in 24 months, with preliminary extraction of data at 6 and 12 months, in order to check if the centers are registering all the variables needed to conduct the study.

After 24 months of the beginning of the study we will have the final extraction of the data and publish in a journal with impact factor.

10. ETHICAL CONSIDERATIONS

This study will be conducted according to the Declaration of Helsinki 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.

11. RESEARCH TEAM

Proponents: Ana Filipa Mourão, Helena Canhão, Maria José Santos, Filipa Ramos, Raquel Marques, João Eurico-Fonseca, Marta Conde, José António Melo-Gomes.

Ana Filipa Mourão - study design, protocol development, interpretation and discussion of the results, preparation and revision of communications and scientific papers.
Helena Canhão - study design, protocol development, statistical analysis, interpretation and discussion of the results, preparation and revision of communications and scientific papers.
Maria José Santos - study design, protocol development, statistical analysis, interpretation and discussion of the results, preparation and revision of communications and scientific papers.
Filipa Ramos - study design, protocol development, interpretation and discussion of the results, preparation and revision of communications and scientific papers.
Raquel Marques - study design, protocol development, interpretation and discussion of the results, preparation and revision of communications and scientific papers.
João Eurico-Fonseca - study design, protocol development, statistical analysis, interpretation and discussion of the results, preparation and revision of communications and scientific papers.
Marta Conde - study design, protocol development, interpretation and discussion of the results, preparation and revision of communications and scientific papers.
José António Melo-Gomes - interpretation and discussion of the results, preparation and revision of communications and scientific papers.

Centers involved: participation is open to all the Portuguese centers interested in collaborating in this project. Co-authorship will be granted to a maximum of 2 coauthors per center, actively collaborating in the project.

12. FUNDING AND CONFLICTS OF INTERESTS

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