1. Title

Efficacy and Safety of Belimumab in the treatment of Systemic Lupus Erythematosus: a Prospective Multicenter Study.

2. Background

Systemic Lupus Erythematosus (SLE) is a chronic, autoimmune and multisystemic disease, clinically heterogenous, with remitting and relapsing periods, that predominantly affects women of childbearing age. Therapeutic approach includes antimalarials, corticosteroids, immunosuppressants and cytotoxic agents and depends on the severity of the disease, organ involvement and patient status.[1]

Pathophysiologic mechanisms remains largely unknown, but studies suggest a genetic susceptibility and environmental factors (such as virus, ultraviolet light, silica dust, smoking, medications and alcohol) that may act as triggers of the disease.[2] In spite of being one of the few rheumatic diseases with a treat-to-target recommendations approach[3], SLE have one of the highest mortality rates among them.[4] This fact highlines the need for new therapeutic targets in SLE.

Some studies have demonstrated the overexpression of BLyS (a B-lymphocyte stimulator) in SLE[5], which may explain the increased autoantibody production in the disease. In 2011, Belimumab, a human monoclonal antibody targeting BLyS, became the first biotechnologic drug available for SLE. Clinical trials with Belimumab showed reduction in the disease activity, reduction in the number and in the severity of flares, steroid-sparing effects and improvement in health-related quality of life and fatigue.[6-8] Belimumab showed better efectiveness in patients with higher disease activity, anti-dsDNA positivity and low complement levels at baseline.[9]

Belimumab is not approved for lupus nephritis or central nervous system lupus, as the clinical trials excluded these patients. A randomized, double-blinded, placebo-controlled phase III study is ongoing to evaluate the efectiveness and tolerability of Belimumab in adults with active lupus nephritis (BLISS-LN).

In the European Union, Belimumab is indicated in adult patients with active and autoantibody-positive SLE with high degree of disease activity (low complement levels and high anti-dsDNA antibodies), despite standard therapy.[10]

With the widespread use of Belimumab, it becomes necessary to evaluate its efectiveness and safety in clinical practice. We intend to study the efectiveness and safety of the use of Belimumab in SLE patients followed in the portuguese rheumatology centers.

3. Objectives

Primary Objective:

- Evaluate Belimumab effectiveness and safety in the treatment of a Portuguese SLE multicenter sample.

Secundary Objectives:

- Identify the main indications for the treatment with Belimumab in the real world setting.

-Identify possible relationships between organic involvement or other patients characteristics and the response to Belimumab.

- Acess the steroid-sparing effects of Belimumab.

Primary Outcomes:

- Efectiveness: proportion of patients that showed a >= 4-point reduction SELENA-SLEDAI score (SLE Responder Index) at 6, 12 and 24 months of treatment with Belimumab.

- Safety: any adverse events during the treatment with Belimumab, including deaths and malignancies, and necessity of suspension of Belimumab.

Secundary Outcomes:

- Proportion of patients that showed a reduction in SELENA-SLEDAI score (SLE Responder Index) at 6, 12 and 24 months of treatment with Belimumab.

- Proportion of patients that showed a reduction in SELENA-SLEDAI score (SLE Responder Index) at 6, 12 and 24 months of treatment with Belimumab according to the organic involvement.

- Proportion of patients that showed a reduction in corticoid therapy dosage at 6, 12 and 24 months of treatment with Belimumab.

- Proportion of patients still treated with Belimumab at 6, 12 and 24 monts of treatment.

- Predictors of response to belimumab, according SELENA-SLEDAI score (SLE Responder Index), at 6, 12 and 24 months.

4. Methods

Type of Study: Prospective Multicenter Cohort Study.

Inclusion Criteria: Patients diagnosed with SLE (that fulfill the 2012 SLICC diagnostic criteria[11]) treated with Belimumab.

Variables to be collected

- Demographic features: gender, ethnicity, age, body weight (at baseline, 6, 12 and 24 months of treatment with Belimumab)

- SLE data: years of disease, age at diagnosis, SLE drugs and duration, organic involvement (musculoskeletal, mucocutaneous, immunological, hematological, serositis, nephritis); SLEDAI (at baseline, 6, 12 and 24 months of treatment with Belimumab); Immunology: Anti-dsDNA antibodies levels, complement levels [C3 and C4] and immunoglobulins levels [IgG, IgM and IgA] (at baseline, 6, 12 and 24 months of treatment with Belimumab); blood cells count: leukocytes, neutrophils, lymphocytes and platelets count (at baseline, 6, 12 and 24 months of treatment with Belimumab); acute phase reactants: ESR and CRP (at baseline, 6, 12 and 24 months of treatment with Belimumab); Serum creatinine (at baseline, 6, 12 and 24 months of treatment with Belimumab); Urinalysis parameters: protein, red blood cells, white blood cells and casts (at baseline, 6, 12 and 24 months of treatment with Belimumab)

- Belimumab data: reason of choice (which disease involvement); protocol of administration and doses; duration of treatment with Belimumab (months); glucocorticoid doses (prednisolone equivalents at baseline, 6, 12 and 24 months of treatment with Belimumab); adverse events (any, including deaths: which adverse event and when); Belimumab suspension (reason and when)

5. Description of variables

Descriptive analysis: Continuous variables presented as median, mean and stardard deviation.

Changes in SELENA-SLEDAI score before and after treatment with Belimumab will be calculated through Wilcoxon signed rank test.

The association between baseline immunology values (complement factors, immunoglobulins levels and anti-dsDNA antibodies) and changes in SLEDAI will be calculated using linear correlation.

Influence of specific organ involvement and other disease or patients characteristics in the response to the treatment with Belimumab will be accessed through Chi-square test. We also aim to determine the major predictors of a ≥4-point reduction from baseline in the SELENA– SLEDAI score. The magnitude of the associations between clinical and laboratorial variables and the presence of this SELENA– SLEDAI score reduction will be assessed using logistic regression models in order to estimate crude and adjusted odds ratios (OR) and their 95% confidence intervals (CI). All analysis were two-sided and p-values <0.05 were considered statistically significant. Alternatively, the magnitude of these associations could also be estimated from linear regression coefficients and respective 95% confidence intervals.

6. Expected results and possible limitations

We anticipate that missing data will be a limitation.

We expect to confirm the effectiveness of Belimumab in SLE population with high disease activity and positive immunology, particularly in musculoskeletal, mucocutaneous and immunological domains.

Concerning safety, we expect to confirm the good tolerability of belimumab, particularly regarding infections.

7. Calendar of tasks

Data collection: October 2018

Data analysis: November 2018

8. Proponent

Bruno Miguel Fernandes – Department of Rheumatology, São João Hospital Center, Porto.

9. Research Team

Bruno Miguel Fernandes, Miguel Bernardes, Lúcia Costa – Department of Rheumatology, São João Hospital Center, Porto.

10. Institutions

The project is open to all Nacional Rheumatology Centers interested in participate.

11. Co-authors

All clinicians who actively work on the project will be co-authors, with a maximum of two co-authors per participating center, according to the rules of Vancouver.

12. Conflits of interest

There are no conflicts of interest to declare.

13. Ethical considerations

This study will be submitted for approval to the Committee of Ethics of São João Hospital Center and will be carried out according to the Declaration of Helsinki.

References

1- Bertsias G, Ioannidis JP, Boletis J, Bombardieri S, Cervera R, et al, *EULAR recommendations for the management of systemic lupus erythematosus. Report of a Task Force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics,* Annals of the Rheumatic Diseases 2008;67:195-205;
2- Fortuna G, Brennan MT, *Systemic Lupus Erythematosus – Epidemiology, Phatophysiology, Manifestations, and Management*, Dental Clinics of North America 2013;57(4):631-655;
3- Van Vollenhoven RF, Mosca M, Bertsias G, Isenberg D, Kuhn A, et al, *Treat-to-target in Systemic Lupus Erythematosus Recommendations from an international task force,* Annals of the Rheumatic Diseases 2014;3:958–967.
4- Centers dor Disease Control and Prevention, *Trends in Deaths from Systemic Lupus Erythematosus – United States, 1979-1998,* Journal of the American Medical Association 2002;287:2649-50.
5- Hui-Yuen JS, Li XQ, Askanase AD, *Belimumab in Systemic Lupus Erythematosus: a Prespective Review*, Therapeutic advances in musculoskeletal disease 2015;7(4):115-121
6- Navarra SV, Guzmán RM, Gallacher AE, Hall S, Levy RA, et al, *Efficacy and safety of belimumab in patients with active systemic lupus erythematosus: a randomised, placebo-controlled, phase 3 trial,* The Lancet 2011;26;377(9767):721-31
7- Furie R, Petri M, Zamani O, Cervera R, Wallace DJ, et al, *A phase III, randomized, placebo-controlled study of belimumab, a monoclonal antibody that inhibits B lymphocyte stimulator, in patients with systemic lupus erythematosus,* Arthritis & Rheumatology 2011;63(12):3918-3930.
8- Blair HA, Duggan ST, *Belimumab: A Review in Systemic Lupus Erythematosus,* Drugs 2018;78(3):355-366
9- Van Vollenhoven RF, Petri MA, Cervera R, Roth DA, Ji BN, et al, *Belimumab in the treatment of systemic lupus erythematosus: high disease activity predictors of response,* Annals of the Rheumatic Diseases 2012;71(8):1343-9.

10- European Medicines Agency - Benlysta® (belimumab): summary of product characteristics. http://www.ema.europa.eu/ema. Acessed 25, July, 2018.)
11- Petri M, Orbai A-M, Alarcón GS, Gordon C, Merrill JT, et al, *Derivation and Validation of Systemic Lupus International Collaborating Clinics Classification Criteria for Systemic Lupus Erythematosus,* Arthritis & Rheumatology 2012;64(8):2677–2686