Belimumab in the treatment of Portuguese systemic lupus erythematosus patients: a real-life multicenter study

Fernandes BM[1], Barreira S[2,3], Fonseca JE[2,3], Cunha M[4], Santos MJ[3,4], Gonçalves N[5], Fernandes AL[6], Rodrigues J[7], Fontes T[8], Costa L[1], Bernardes M[1,9]

ACTA REUMATOL PORT. 2020;45:170-176

ABSTRACT

Objectives: To evaluate belimumab effectiveness and safety in real-life Portuguese patients with Systemic Lupus Erythematosus (SLE).

Materials and Methods: Multicenter cohort study including all SLE patients treated with belimumab in seven Portuguese rheumatology centers. Demographic, clinical and serological data were collected at baseline, 6, 12 and 24 months of treatment with belimumab. To evaluate effectiveness we used SLE Responder Index (SRI) rates and changes in SELENA-SLEDAI. Safety was evaluated by the number of adverse events.

Results: Thirty-eight patients were included: 37 (97.4%) female, with a mean age of 46.2±13.9 years. Mean SELENA-SLEDAI was 8.2±3.9, 78.8% had elevated anti-double-stranded DNA (anti-dsDNA) antibodies and 72.7% had complement consumption at baseline. Multiorgan involvement was the leading cause for the use of belimumab. SRI response was achieved in 51.9%, 60% and 91.7% at 6, 12 and 24 months of belimumab treatment, respectively. LUNDEX adjusted SRI response rates were 45.4%, 45.0% and 45.8% at 6, 12 and 24 months of belimumab, respectively. Mean SELENA-SLEDAI, anti-dsDNA antibodies and daily prednisolone dosage decreased significantly from baseline to 6, 12 and 24 months and C3 levels increased significantly at 12 months of belimumab treatment. Five patients presented adverse events (infections in three cases) and eleven patients discontinued belimumab (four due to inefficacy, three due to adverse events and four were lost to follow-up).

Conclusions: Our study confirmed, in real-life Portuguese patients with active SLE, the effectiveness of belimumab in reduction of disease activity, immunological response and steroid-sparing, with a good safety profile.

Keywords: Systemic Lupus Erythematosus; Belimumab.

1. Serviço de Reumatologia, Centro Hospitalar Universitário São João, Porto, Portugal;
2. Serviço de Reumatologia, Hospital de Santa Maria, Centro Hospitalar Universitário Lisboa Norte, Lisboa, Portugal;
3. Rheumatology Research Unit, Instituto de Medicina Molecular, Faculdade de Medicina, Universidade de Lisboa, Portugal;
4. Serviço de Reumatologia, Hospital Garcia de Orta, Almada, Portugal;
5. Serviço de Reumatologia, Hospital Egas Moniz, Lisboa, Portugal;
6. Serviço de Reumatologia, Centro Hospitalar Universitário do Algarve, Faro, Portugal;
7. Serviço de Reumatologia, Unidade Local de Saúde do Alto Minho, Ponte de Lima, Portugal;
8. Serviço de Reumatologia, Hospital do Divino Espírito Santo, Ponta Delgada, Portugal;
9. Departamento de Medicina, Faculdade de Medicina, Universidade do Porto, Portugal.

INTRODUCTION

In 2011 belimumab, a human monoclonal antibody targeting BLyS, became the first biotechnologic drug approved for Systemic Lupus Erythematosus (SLE). Clinical trials showed reduction of 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[1-3]. Belimumab showed greatest benefit in patients with higher disease activity, anti-double-stranded DNA (anti-dsDNA) positivity and low complement levels at baseline[4].

Belimumab is not approved for lupus nephritis or central nervous system lupus, as the initial clinical trials excluded these patients[1,2]. Recently, it was announced that a randomized, double-blinded, placebo-controlled phase III study to evaluate the efficacy and tolerability of Belimumab in adults with active lupus nephritis (BLISS-LN), has achieved its primary end-point (awaiting publication of the full results – BLISS-LN: Trial registration number NCT01639339).

In the European Union, belimumab is indicated in patients (aged 5 years or older) with active autoanti-

body-positive SLE with high degree of disease activity (low complement levels and high titers of anti-dsDNA antibodies), despite standard therapy[5]. In Portugal, belimumab is reimbursed if used as an adjunct therapy for adults with active SLE, with SELENA-SLEDAI (SELENA-SLE Disease Activity Index) ≥ 10, anti-dsDNA antibodies ≥ 30 IU/ml and low C3 and/or C4 levels, without evidence of lupus nephritis or central nervous system involvement, despite previous treatment with corticosteroids, antimalarials and immunosuppressants (or adverse events leading to their discontinuation)[6].

Registries allow for a better understanding of real-world data on new drugs. Few studies addressed real-world use of belimumab[10-19].

This study aimed to intestigate belimumab effectiveness and safety in SLE patients followed in Portuguese rheumatology centers.

MATERIALS AND METHODS

We conducted a multicenter prospective cohort study. Adult patients with SLE diagnosis according to the 2012 SLICC classification criteria, treated with belimumab in Portuguese rheumatology departments and registered at the Rheumatic Diseases Portuguese Register (*Reuma.pt*)[7,8] until June 2019 were included. All rheumatology departments were invited and seven accepted to participate in this study. Baseline data included race, age, gender, smoking status and disease duration. SLE disease actvity measured using the SELENA-SLEDAI score, Physician Global Assessment (PGA), disease flares and serological (serum levels of anti-dsDNA antibodies, complement components levels [C3 and C4]) data were assessed at baseline and at 6, 12 and 24 months of belimumab treatment. In addition, information on previous and concomitant medication for SLE, including corticosteroid dose (mean daily prednisolone equivalent dose) at baseline and at the last evaluation was collected. The reasons for prescribing and stopping belimumab were assessed, as well as the reported adverse events.

STUDY OUTCOMES

The primary outcome was the SLE Responder Index (SRI), a composite index that combines SELENA-SLEDAI, British Isles Lupus Assessment Group (BILAG) and Physician Global Assessment (PGA). SRI response rate defined as the proportion of patiens having ≥4 point reduction from baseline in SELENA-SLEDAI score and no new BILAG A score and no more than one new BILAG B organ domain score compared with baseline and no worsening in PGA or <0.3-point increase from baseline was the primary efficacy endpoint.

Secondary outcomes were the reduction of glucocorticoid dose, SELENA-SLEDAI, anti-dsDNA titers and increase in complement levels. Additional secondary outcome was safety evaluated by the number of adverse events.

STATISTICAL ANALYSIS

Statistical analysis was performed using SPSS 24.0. Continuous variables were described as mean (± standard deviation [SD]) or median (min;max), if they were or were not normally distributed, respectively. Paired comparisons between variables at baseline and follow-up time-points (at 6, 12 and 24 months) were made using Wilcoxon test and comparison between independent subgroups was made using Mann-Whitney U test. Besides crude response rates, SRI response LUNDEX adjusted - a composite index useful for evaluating drug efficacy in observational studies that integrates clinical response and adherence to therapy, calculated as the fraction of patients adhering to therapy multiplied by the fraction of patients fulfilling the selected response criterion at a given time[9] - was also obtained in order to compensate for the missing data.

All calculations were based on observed data. Differences were considered statistically significant at $p<0.05$.

ETHICAL CONSIDERATIONS

Informed consent was obtained from all study participants and the protocol was approved in October 11th 2018 by the Ethics Committee of Centro Hospitalar Universitário São João (number 241/18). The study was run in accordance with the principles of the Declaration of Helsinki as amended in Fortaleza (2013).

RESULTS

Thirty-eight patients were included: 37 (97.4%) female, 34 (89.5%) Caucasian, 3 (7.9%) were current smokers, with a mean age of 46.2±13.9 years, a mean age at SLE diagnosis of 31.6±12.5 years and a median disease duration of 9.7 years (min:0.9; max:33.6) at the start of belimumab. Baseline mean SELENA-SLEDAI was 8.2±3.9, 26/33 (78.8%) patients had el-

TABLE I. DEMOGRAPHIC, CLINICAL AND SEROLOGICAL FEATURES AT BASELINE

	Total n = 38
Female - n (%)	37 (97.4%)
Caucasian - n (%)	34 (89.5%)
Age - mean±SD	46.2±13.9 years
Age at SLE diagnosis - mean±SD	31.6±12.5 years
SLE duration - median (min;max)	9.7 (min:0.9;max:33.6) years
Elevated anti-dsDNA antibodies - n/total*(%)	26/33 (78.8%)
Complement consumption - n/total*(%)	24/33 (72.7%)
SELENA-SLEDAI - mean±SD	8.2±3.9
Reasons for prescribing belimumab	
Multiorgan involvement – n (%)	20 (52.6%)
Haematologic disorders – n (%)	9 (23.7%)
Cutaneous manifestations – n (%)	5 (13.2%)
Arthritis – n (%)	3 (7.9%)
Necrotizing Vasculitis – n (%)	1 (2.6%)

*accounting for missing data [5 patients]; anti-ds DNA: anti-double-stranded DNA; SLE: Systemic Lupus Erythematosus; SELENA-SLEDAI: SELENA-SLE Disease Activity Index.

evated anti-dsDNA antibodies (anti-dsDNA levels ≥ 100 IU/mL) and 24/33 (72.7%) had complement consumption (C3 levels < 83 mg/dL and/or C4 levels < 12 mg/dL). Demographic, clinical and serological features are described in detail in Table I.

Twenty-eight patients (73.7%) were concomitantly treated with hydroxychloroquine, 16 (42.1%) with azathioprine, 7 (18.4%) with methotrexate and 3 (7.9%) with mycophenolate mofetil. Regarding previous therapeutic failures, all but four patients failed to respond to hydroxychloroquine, 10 failed a second *conventional synthetic disease-modifying antirheumatic drug* (csDMARD: methotrexate in 6, azathioprine in 3 and cyclophosphamide in 1), 7 failed a third one (mycophenolate mofetil in 3, cyclophosphamide in 3 and azathioprine in 1), and 6 failed rituximab treatment (2 as monotherapy, 1 after failing response to 2 csDMARDs and 3 after therapeutic failure with 3 csDMARDs). The reasons for prescribing belimumab were: multiorgan involvement in 20 (52.6%) patients (10 with cutaneous, articular and haematologic involvement; 3 with articular and cutaneous involvement; 3 with articular and haematologic involvement; 1 with cutaneous and haematologic involvement; 1 with serositis, articular and haematologic involvement; 1 with serositis, articular and cutaneous involvement; 1 with serositis, cutaneous and haematologic involvement), haematologic disorders in 9 (23.7%) patients, cutaneous manifestations in 5 (13.2%) patients, arthritis in 3 (7.9%) patients, necrotizing vasculitis in 1 (2.6%) patient. Belimumab was administered intravenously (10mg/kg) every 4 weeks for a median of 12 (min:1; max:76) months. Data on medication at baseline can be seen in Table II.

SRI response was achieved in 14/27 (51.9%), 12/20 (60%) and 11/12 (91.7%) at 6, 12 and 24 months of belimumab treatment, respectively. Taking into account drug discontinuation and the duration of belimumab treatment, we calculated LUNDEX adjusted SRI response rates, which were 45.4%, 45.0% and 45.8% at 6, 12 and 24 months of belimumab treatment, respectively. No new BILAG A or BILAG B organ domain scores were observed at 6, 12 and 24 months of belimumab. In all the patients, the absence of a SRI response was due to the SELENA-SLEDAI score. Additionally, three patients at 12 months of belimumab also did not fulfil the PGA criteria (in addition to the SELENA-SLEDAI criteria).Mean SELENA-SLEDAI significantly decreased from 8.2±3.9 at baseline to 3.8±2.2 ($p<0.001$), 4.1±3.2 ($p<0.001$) and 3.1±1.6 ($p=0.002$) at 6, 12 and 24 months, respectively. Anti-dsDNA antibodies significantly decreased at 6, 12 and 24 months and C3 increased at 12 months of belimumab treatment; no significant increase was found at any timepoint in C4 levels. Regarding patients with high levels (≥100 IU/mL) of anti-dsDNA antibodies at baseline, 10/26 patients normalized (<100 IU/mL) at 6 months, 5/26 at 12 months and 4/26 at 24 months of beli-

TABLE II. SYSTEMIC LUPUS ERYTHEMATOSUS MEDICATION DATA

	Total n = 38
Prednisolone dose at baseline - mean±SD	10.8±5.1 mg
Belimumab duration - median (min;max)	12 (min:1;max:76) months
Concomitant SLE medication	
Hydroxychloroquine – n (%)	28 (73.7%)
Azathioprine – n (%)	16 (42.1%)
Methotrexate – n (%)	7 (18.4%)
Mycophenolate mofetil – n (%)	3 (7.9%)

SLE: Systemic Lupus Erythematosus

TABLE III. SRI RESPONSE AND EVOLUTION OF SELENA-SLEDAI, ANTI-DSDNA ANTIBODIES AND C3 LEVELS AT 6, 12 AND 24 MONTHS OF BELIMUMAB AND ITS STATISCAL COMPARISON WITH BASELINE VALUES

	Baseline (n=38)	6 months (n=28)	12 months (n=21)	24 months (n=12)
SRI response n(%)	-	14 (51.9%) (n=27*)	12 (60%) (n=20*)	11 (91.7%) (n=12*)
SRI response LUNDEX adjusted (%)	-	45.4%	45.0%	45.8%
SLEDAI mean±SD	8.2±3.9 (n=37*)	3.8±2.2 (p<0.001) (n=28*)	4.1±3.2 (p<0.001) (n=20*)	3.1±1.6 (p=0.002) (n=12*)
Anti-dsDNA antibodies (IU/mL) mean±SD	255.8±277.4 (n=33*)	175.5±189.0 (p=0.015) (n=26*)	177.4±333.9 (p=0.031) (n=20*)	111.4±129.1 (p=0.001) (n=11*)
C3 (mg/dL) mean±SD	82.6±28.8 (n=33*)	89.6±27.1 (p=0.223) (n=27*)	94.6±25.8 (p=0.018) (n=21*)	100.9±36.9 (p=0.139) (n=12*)

*number of patients with available information at each time-point; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index; SRI: Systemic Lupus Erythematosus Responder Index. Statistical test – Wilcoxon test.

mumab.

We found a significant reduction in mean daily prednisolone dose from baseline (10.8±5.1mg) to 6 months (7.5±3.9mg, p=0.001), 12 months (6.6±3.8mg, p<0.001), 24 months (6.5±3.3mg, p=0.017) and up to the last evaluation under belimumab (5.5±3.0mg, p<0.001). Three patients were able to completely stop corticosteroids. Detailed data are shown in Table III.

No significant differences in SELENA-SLEDAI reduction or SRI response rate were observed in subgroup comparison analysis at any time-point (elevated vs non elevated dsDNA levels at baseline; complement consumption vs no complement consumption at baseline) nor in the baseline variables by clinical response (SRI reponders vs not SRI responders; SELENA-SLEDAI improvement vs no SELENA-SLEDAI improvement).

Five patients (13.2%) presented adverse events (3 infections, 1 acute myocardial infaction and 1 breast cancer). The three infections occurred during treament with belimumab were: skin infection, upper respiratory tract infection and urinary tract infection (reason for discontinuation in one patient).

Reasons for belimumab discontinuation (11 patients, 28.9%) were: inefficacy in 4 patients (at 2, 5, 7 and 54 months of belimumab), loss to follow-up in 4 patients (at 2, 6, 8 and 21 months of belimumab), and adverse events in 3 patients (1 due to recurrent urinary tract infections [after 47 months of belimumab], 1 due to acute myocardial infarction [after 1 month of beli-

mumab] and 1 due to breast cancer [after 18 months of belimumab]). Interestingly, the clinical manifestation that led to the discontinuation of belimumab after 5 months of treatment, in a particular patient, was a lupus nephritis class III, which was subsequently treated with mycophenolate mofetil. Given the limited number and the heterogeneity of these patients, it was not possible to determine a population prone to the discontinuation of belimumab.

DISCUSSION

Our results, based on *Reuma.pt*, showed not only belimumab effectiveness, but also a pattern of immunological response and steroid-sparing effect in real-life Portuguese SLE patients at 6, 12 and 24 months of treatment, with a good safety profile. Demographic features of our population were similar to those of clinical trials[1,2] in terms of gender distribution, age, duration of disease, rise in anti-dsDNA antibody levels, complement consumption, SLE medication and mean daily prednisolone equivalent dose. However, our population had a higher predominance of Caucasian patients and a lower mean SELENA-SLEDAI at baseline.

A number of scientific publications on the use of belimumab in real-life SLE patients has been published. OBSErve (evaluation Of use of Belimumab in clinical practice SEttings) is an international cohort program designed to describe the clinical outcomes of belimumab therapy in real-life setting, with data published in some countries like USA[10], Germany[11] and Switzerland[12]. Also, data reflecting the reality of other countries have been published, like Italy[13], Brazil[14] and Israel[15] and a review of real-life data on belimumab, including some OBSErve studies, was also published[16]. The population size varies among real-life studys and ranges from 18 patients in an Italian study[13] to 91 patients in a Greek study[17]. Our sample of 38 Portuguese SLE patients, although not large enough to allow more complex statistical analysis or subgroup analyses, allowed us to draw some interesting conclusions. Also, being a multicenter study, more national representative findings could be obtained. Regarding the duration of follow-up, our last time point (24 months) is equal or superior to most of the previous published data, an important aspect in a chronic, lifelong disease. Most studies had a follow-up period of 6[11,12,18] and 12 months[13,14]. Concerning baseline demographic characteristics, a marked female predominance is observed in all studies. A predominance of Caucasion race is also observed, but in a smaller scale in most studies as compared to our results, probably reflecting the characteristics of the Portuguese SLE population. Other baseline disease-related characteristics are similar to our study population: mean SLEDAI between 8[17] and 12.4[10], mean age at start of belimumab between 32.6[14] and 46.7[12] years and mean disease duration between 9.7[17] years and 171.8[19] months (14.3 years). The percentage of patients with high anti-dsDNA antibody levels was highly variable among studies (36.3%[17] to 83%[19]) and the same was observed regarding complement consumption (48.3[17] to 78%[19]) and mean daily prednisolone equivalent dose (10.2mg/day[19] to 30mg/day[14]).

On the other hand, the reasons for starting belimumab are difficult to compare across studies due to differences in their coding methodologies. Our national registry (*Reuma.pt*) classifies as "multiorgan involvement" when the involvement of more than one system is the reason to start the drug, but this limits the identification of the type of organ involvement that might have been the main contributor to the clinical decision. Differently, other studies describe all the organs involved at baseline[14,17], the most involved one[19] or specific reasons[12] (like inefficacy or intolerance to previous treatment or to spare corticosteroids). Multiorgan involvement was the leading cause for the use of belimumab in our sample, with haematologic disorders as the second cause. Caution should be taken interpreting this finding, as the "multiorgan involvement" may include several different combinations of organic systems involved. Most data showed articular and cutaneous involvement as the main reasons to start belimumab. The later represents the fourth and third main single reasons to prescribe the drug in our SLE patients.

Previous and concomitant SLE medication in most studies was also similar to ours, with hydroxychloroquine being the most frequently used drug in all studies, followed by azathioprine[15,17] or mycophenolate mofetil[11,19] in most of them. Curiously, in our sample, the use of methotrexate came in second place as previous therapy to belimumab (just after hydroxychloroquine), and in third place as concomitant drug (after azathioprine). Few studies included patients previously treated with rituximab and these patients constituted between 4%[12] and 13.2%[17] of the total. In our sample, 15.8% of patients had previously failed rituximab, which may be a potential indicator of disease severity.

Regarding results, SRI response rate at 52 weeks fol-

low-up in clinical trials with belimumab administered at a dose of 10 mg/kg every 4 weeks was 58%[1] and 43.2%[2], respectively in BLISS 52 and in BLISS 76 studies. These results are similar to our LUNDEX adjusted SRI response rates. Also, statistically significant changes were also noted in anti-dsDNA levels, complement components and daily corticosteroid dosage. Most real-life studies, like ours, demonstrate a statistically significant decrease in SLEDAI and/or in mean daily prednisolone equivalent dose[10-15,17-19], some of them showing also a decrease in anti-dsDNA antibodies levels[10-12,15,19] and an increase in complement components[10-12,14,15,19]. The fact that there was no significant increase in C4 levels in any of the time-points analyzed in our study can be explained by the limited number of patients and the worse sensitivity of low C4 levels in SLE (compared to C3 levels)[20]. Additionally, we evaluated SRI response rate which is not always feasible in clinical practice, given the need to have BILAG and PGA, but data from our national registry allowed us to calculate it. Some studies have used other outcomes and even shown potential predictors of response to belimumab, like limited/no organ damage prior to belimumab[21] and baseline polyarthritis, SLEDAI ≥10 or prednisolone ≥7.5mg/day[22]. Our study did not identify any differences in subgroup analysis or possible predictors of response (elevated vs non elevated dsDNA levels at baseline; complement consumption vs no complement consumption at baseline; SRI reponders vs not SRI responders; SELENA-SLEDAI improvement vs no SELENA-SLEDAI improvement) probably due to the sample size not powered to detect small effects.

Reports from other registers also found that a majority of patients who were receiving biologics would not have been eligible for participation in RCTs, either because they were too ill or disabled to participate, or because the disease was not active enough to be eligible. In our sample, a considerable percentage of SLE patients did not meet the current Portuguese reimbursement criteria for prescribing belimumab (74%; data not shown). However, some of them got access to belimumab before the widespread implementation of these criteria. Of interest, at 6 months, 50% of these patients presented a significant decrease in SLEDAI and 25% exhibited SRI response (data not shown) leading us to consider that these criteria should be revisited taking into account national real-life data.

Concerning safety, as in clinical trials[1,2] and in other real-life studes[13-15,17,19], non-serious infections were the most frequent adverse events, but only in one patient led to drug discontinuation. Our rate of discontinuation (28.9%) was similar to what was observed in the USA OBSErve data (22.4%)[10] and is partly explained by the significant number of lost to follow-up (4 patients).

STUDY LIMITATIONS

Registries are important to assess drug effectiveness and safety in real-life setting and allow the comparison between different populations. To the best of our knowledge there are no data in the literature assessing real-life use of belimumab in Portuguese SLE patients, where the drug reimbursement slightly differs from the EU indication approval. As an observational study, the main limitation was missing data. Also, our sample was to small to allow subgroup analysis and to identify possible predictors of response.

CONCLUSIONS

In conclusion, in line with previous real-life studies, our study confirmed belimumab effectiveness, immunological response and steroid-sparing effect in real-life Portuguese patients with active SLE, with a good safety profile.

CORRESPONDENCE TO
Bruno Miguel Fernandes
Serviço de Reumatologia
Centro Hospitalar Universitário São João
Porto, Portugal
E-mail: bfernandesmg@gmail.com

REFERENCES

1. Navarra SV, Guzmán RM, Gallacher AE, Hall S, Levy RA, Jimenez RE et al. Efficacy and safety of belimumab in patients with active systemic lupus erythematosus: a randomised, placebo-controlled, phase 3 trial. Lancet 2011; 377(9767): 721-31.
2. Furie R, Petri M, Zamani O, Cervera R, Wallace DJ, Tegzová D 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 Rheum 2011; 63(12): 3918-3930.
3. Blair HA, Duggan ST. Belimumab: A Review in Systemic Lupus Erythematosus. Drugs 2018; 78(3): 355-366.
4. Van Vollenhoven RF, Petri MA, Cervera R, Roth DA, Ji BN, Kleoudis CS et al. Belimumab in the treatment of systemic lupus erythematosus: high disease activity predictors of response. Ann Rheum Dis 2012; 71(8): 1343-9.
5. Benlysta® (belimumab): summary of product characteristics (European Medicines Agency). https://www.ema.europa.eu/en/medicines/human/EPAR/benlysta. Accessed in February 12th 2020.
6. Belimumab – Relatório de avaliação prévia do medicamento para uso humano em meio hospitalar. https://www.in-

farmed.pt/documents/15786/1424140/belimumab-Benlysta_LES_ParecerNet.pdf/62cee154-2778-48e0-9a45-f254a922cf98. Accessed in February 12th 2020.
7. J Santos M, Canhão H, Faustino A, Fonseca JE et al. Reuma.pt - case study. Acta Med Port 2016; 29(2): 83-4.
8. Canhão H, Faustino A, Martins F, Fonseca JE et al. Reuma.pt - the rheumatic diseases portuguese register. Acta Reumatol Port 2011; 36(1): 45-56.
9. Kristensen LE, Saxne T, Geborek P. The LUNDEX, a new index of drug efficacy in clinical practice: results of a five-year observational study of treatment with infliximab and etanercept among rheumatoid arthritis patients in southern Sweden. Arthritis Rheum 2006; 54(2): 600-6.
10. Collins CE, Dall'Era M, Kan H, Macahilig C, Molta C, Koscielny V et al. Response to belimumab among patients with systemic lupus erythematosus in clinical practice settings: 24-month results from the OBSErve study in the USA. Lupus Sci Med 2016; 11; 3(1):e000118. doi: 10.1136/lupus-2015-000118.
11. Schwarting A, Schroeder JO, Alexander T, Schmalzing M, Fiehn C, Specker C et al. First Real-World Insights into Belimumab Use and Outcomes in Routine Clinical Care of Systemic Lupus Erythematosus in Germany: Results from the OBSErve Germany Study. Rheumatol Ther 2016; 3(2): 271-290.
12. von Kempis J, Duetsch S, Reuschling N, Villiger R, Villiger PM, Vallelian F et al. Clinical outcomes in patients with systemic lupus erythematosus treated with belimumab in clinical practice settings: a retrospective analysis of results from the OBSErve study in Switzerland. Swiss Med Wkly. 2019; 10;149:w20022. doi: 10.4414/smw.2019.20022.
13. Andreoli L, Reggia R, Pea L, Frassi M, Zanola A, Cartella S et al. Belimumab for the treatment of refractory systemic lupus erythematosus: real-life experience in the first year of use in 18 Italian patients. Isr Med Assoc J 2014; 16(10): 651-3.
14. Scheinberg M, de Melo FF, Bueno NA, Costa CM, de Azevedo Bahr ML, Reis ER. Belimumab for the treatment of corticosteroid-dependent systemic lupus erythematosus: from clinical trials to real-life experience after 1 year of use in 48 Brazilian patients. Clin Rheumatol 2016; 35(7): 1719-23.
15. Sthoeger Z, Lorber M, Tal Y, Toubi E, Amital H, Kivity S et al. Anti-BLyS Treatment of 36 Israeli Systemic Lupus Erythematosus Patients. Isr Med Assoc J 2017; 19(1): 44-48.
16. Trentin F, Gatto M, Zen M, Maddalena L, Nalotto L, Saccon F et al. Effectiveness, Tolerability, and Safety of Belimumab in Patients with Refractory SLE: a Review of Observational Clinical-Practice-Based Studies. Clin Rev Allergy Immunol 2018; 54(2): 331-343.
17. Fanouriakis A, Adamichou C, Koutsoviti S, Panopoulos S, Staveri C, Klagou A et al. Low disease activity-irrespective of serologic status at baseline-associated with reduction of corticosteroid dose and number of flares in patients with systemic lupus erythematosus treated with belimumab: A real-life observational study. Semin Arthritis Rheum 2018; 48(3): 467-474.
18. Scheinberg M, Golmia R. Real life experience on the effect of Belimumab in patients with active systemic lupus. Springerplus 2014; 3: 758.
19. Anjo C, Mascaró JM Jr, Espinosa G, Cervera R. Effectiveness and safety of belimumab in patients with systemic lupus erythematosus in a real-world setting. Scand J Rheumatol 2019; 48(6): 469-473.
20. Ricker DM, Hebert LA, Rohde R, Sedmak DD, Lewis EJ, Clough JD. Serum C3 levels are diagnostically more sensitive and specific for systemic lupus erythematosus activity than are serum C4 levels. The Lupus Nephritis Collaborative Study Group. Am J Kidney Dis 1991; 18(6):678-685.
21. Parodis I, Johansson P, Gomez A, Soukka S, Emamikia S, Chatzidionysiou K. Predictors of low disease activity and clinical remission following belimumab treatment in systemic lupus erythematosus. Rheumatology (Oxford) 2019; 58(12): 2170-2176.
22. Iaccarino L, Andreoli L, Bocci EB, Bortoluzzi A, Ceccarelli F, Conti F et al. Clinical predictors of response and discontinuation of belimumab in patients with systemic lupus erythematosus in real life setting. Results of a large, multicentric, nationwide study. J Autoimmun 2018; 86:1-8.