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Case Report

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Use of Belimumab in a Real-World Evidence: A case of Systemic Lupus Erythematosus Refractory to Standard Therapy

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Abstract

Systemic lupus erythematosus (SLE) is an autoimmune disease of unknown cause with clinical and therapeutic protocols that include immunosuppressants, immunomodulators and corticosteroids, which increase the number of side effects. Belimumab (BLM), a monoclonal antibody, is a therapeutic alternative to control SLE activity and improve patients' quality of life. We report a clinical case of a 46-year-old female patient with SLE since 2016, hypertension and glomerulonephritis. The patient participated in a research protocol and is currently in the post-study period, where her quality of life and health were assessed in a real-world context, with a reduction in the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) and a reduction/suspension of prednisone. The patient showed a complete remission of the disease (no SLEDAI). She was also completely weaned off prednisone and remains stable. She also reported a significant improvement in her quality of life and health, with no exacerbations or need for recurrent hospitalizations, and control of laboratory values and glomerulonephritis. This demonstrates the efficacy of BLM as an adjunct in the treatment of patients with refractory SLE.

Keywords: Systemic lupus erythematosus; Belimumab; Real-world evidence.

Introduction

Systemic lupus erythematosus (SLE) is an antibody-mediated disease of unknown cause, associated with genetic, environmental and hormonal factors. It is a chronic disease that mainly affects several systems of the human body, especially the joints, skin and kidneys, promoting a significant reduction in the quality of life of lupus patients, mainly affecting women of reproductive age [1]. Although there is no cure, the disease can be controlled through the use of corticosteroids and immunosuppressive and immunomodulatory drugs. However, chronic use of corticosteroids increases the morbidity and mortality, caused by the development of infections, high blood pressure, diabetes, cardiovascular events and bone fragility [2]. Consequently, the evolution of the disease and the impacts of treatment can promote a significant reduction in the quality of life of SLE patients [3]. In this context, Belimumab (BLM) is already a previously known and approved drug for the treatment and control of SLE activity, as it is a alternative monoclonal antibody used to control disease activity in patients resistant to drugs proposed in clinical protocols [2, 4]. Therefore, the present report aims to present the effectiveness of belimumab as an adjunctive therapy in the treatment of SLE in a patient with renal involvement, who achieved remission of disease activity, reduced the

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dose of corticosteroids, ensuring a significant improvement in her quality of life.

Case Presentation, Methods, and Results

Female patient, 46 years old, mixed race, without history of pregnancies, and with systemic lupus erythematosus (SLE) diagnosed in September 2016 (symptoms since 2015). Initially, the patient presented joint, skin and renal involvement, with the presence of arthritis, alopecia, photosensitivity and malar rash. Also, proteinuria above 500 mg in 24-hour urine and systemic arterial hypertension acquired after glomerulonephritis, and positivity of some autoantibodies: antinuclear Factor (AF) with a value of 1:1280 with a dotted pattern, Anti-dsDNA (36UI/mL) and Anti-Sm (621UI/mL). She underwent a kidney biopsy, resulting in diffuse proliferative glomerulonephritis, in accordance with Society of Nephrology/Renal Pathology Society classification. In December 2016, the patient presented with her disease being active. According to the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) criteria, the patient presented activity in the following domains: diffuse alopecia, malar rash, proteinuria (PTU): 11.7 g/dL, leukocytes: 6,400/mm^3, creatinine: 1.0 mg/dL, protein/creatinine ratio: 5,439 mg/24h (reference: 50-80mg/24h), cylindruria, hematuria, pyuria, platelets 271,000/mm^3 (reference: 150-450,000/mm^3) and consumption of complement C3 fractions: 73 mg/dL (reference: 60-170 mg/dL) and C4: 18 mg/dL (reference: 10-40 mg/dL), which defined a SLEDAI score at 24 points.

She was undergoing pharmacotherapeutic treatment with Hydroxychloroquine (HCQ) 400 mg/day, Prednisone 60 mg/day, Azathioprine 100mg/day, Enalapril 20 mg/day, Amlodipine 5 mg/day, Mycophenolate Mofetil (MMF) 2 g/day, Hydrocortisone cream (application to lesions 2x/day) and $CaCO_3$ 500 mg + Vitamin D 400 IU/day. Denies allergies, other comorbidities, alcohol consumption or smoking. Despite the pharmacotherapeutic measures used to treat the patient, the disease activity remained persistent and with several relapses, affecting mainly the mucocutaneous and renal levels. In January 2017, the patient was invited to participate in a clinical protocol randomized, double-blind, placebo-controlled phase III clinical study at a research center in the city of Salvador, Bahia, Brazil, seeking to evaluate the effectiveness of Belimumab (BLM) in controlling SLE activity in patients resistant to treatment standardized by the therapeutic guidelines protocol. In January 2019, the open phase of the protocol began (lasting until July 2019) and the patient has continued to use BLM until the present day. The variations in the patient's laboratory tests was monitored throughout the study period.

In December 2019, complete remission of skin lesions and improvement in malar rash were observed, with a SLEDAI score of 2. Prednisone, MMF, Amlodipine and Hydrocortisone were suspended. Only HCQ 400mg/day, Azathioprine 100mg/day, $CaCO_3$ 500mg + Vitamin D 400UI/day, Enalapril 20mg/day, daily use of sunscreen and and BLM infusion were maintained. Laboratory tests - Hb: 11.4 g/dL; leukocytes: 3,520/mm^3; platelets: 202,000/mm^3; creatinine: 0.8 mg/dL; C3: 109 mg/dL; C4: 38.2 mg/dL, PTU: 160 mg/24h, anti-DNA: >1 and urine summary without alterations.

In December 2020, she returned asymptomatic, with no skin or joint complaints, reporting regular use of previously prescribed drugs. Laboratory tests: Hb: 13.5 g/dL; leukocytes: 5,800/mm^3; platelets: 214,000/mm^3; creatinine: 0.7 mg/dL; C3: 126 mg/dL; C4: 51 mg/dL, anti-DNA: >1 and urine summary unchanged. She presented a bone density test that indicated the presence of osteopenia in the femoral neck. During 2021, the patient did not attend scheduled appointments, returning only 1 year and 3 months after the last appointment. In March 2022, the patient attended the consultation, reporting possible arthralgia in her hands and feet, without signs of arthritis, suppressing the pain with the use of dipyrone 1g. Denied other complaints. The dosage of HCQ was adjusted to 400mg/5x/week, according to weight, while the other drugs were maintained. She reported the regular use of medications and irregular use of sunscreen, being advised on the possibility of malar lesions and rash due to the irregular use of photoprotection. Complementary tests: Hb: 13.7 g/dL; leukocytes: 6,130/mm^3; platelets: 270,000/mm^3; creatinine: 0.9 mg/dL; anti-DNA: >1 and urine summary without changes and PTU (24h): 315 mg/24h, without other laboratory data. She returned to the follow-up appointment after 9 months (in August 2023), reporting the presence of malar rash due to sun exposure without photoprotection, occasional arthralgia without signs of arthritis. Denied any other complaints or complications since the last consultation. Laboratory tests: Hb: 12.8 g/dL; leukocytes: 6,620/mm^3; platelets: 248,000/mm^3; creatinine: 0.7 mg/dL; C3: 115 mg/dL; C4: 39.5 mg/dL and Anti-DNA: 1.0, no other data. The previous prescription was maintained, with reorientation on the need to use a sun protection factor. She was considered a patient with controlled SLE.

Patient returned to the consultation after 6 months (in February 2024), presenting mild hyperemia in the malar region, without edema and signs of arthritis. She denied any complaints related to SLE, maintaining the use of prescribed drugs, mentioning, however, irregular use of Enalapril 20mg/day and photoprotection. Reported follow-up with an ophthalmologist, with no tests available at the time of consultation. Laboratory tests: Hb: 13.1 g/dL; leukocytes: 5,320/mm^3; platelets: 233,000/mm^3; creatinine: 0.8 mg/dL; C3: 123 mg/dL; C4: 35.5 mg/dL; urine summary without changes; PTU (24h): 289 mg/24h and Anti-DNA: >1. The patient is currently undergoing specialized outpatient care at a university hospital, located in the city of Salvador, Bahia,

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Brazil. The patient reported an improvement in her self-esteem, returned to developing collective social activities and her clinical condition is currently under control, with absence of lupus activity.

Discussion

During the study, the patient showed significant changes in her laboratory tests, when compared to her initial visit (prior to the clinical protocol), demonstrating the effectiveness of BLM in reducing disease activity in the patient. According to Table 1, it was possible to evaluate disease activity through complement system proteins and other biochemical markers. Some complement system proteins, mainly C3 and C4, can be depleted in immune reactions and the low levels of these proteins in lupus patients suggest the possibility that the disease is active. However, in the period from January/2019 to February/2024, the increase in complement system proteins gradually occurred, indicating control in the disease activity. In addition, the measurement of other laboratory data, such as proteinuria (in 24-hour), indicates control of kidney damage.

Lupus nephritis is a disease caused by the deposition of immune complexes in kidney tissues, causing damage and ischemic atrophy of the cortex, increasing the risk of high blood pressure, insufficiency or even kidney failure [5]. Around 50% of SLE patients develop glomerulonephritis within the first year of diagnosis, mainly in patients who present high proteinuria, high protein/creatine ratio, hematuria and presence of urinary cyllinders. The presence of low titers of complement system proteins C3 and C4 and high titers of anti-DNA and anti-dsDNA corroborate the diagnosis of nephritis. Renal biopsy is indicated to determine the histological characteristics of the renal lesion, indicating the prognosis of the disease, as well as directing pharmacotherapeutic treatment [6]. This study corroborates the findings of Furie et al. [7] who carried out a phase 3, randomized, double-blind, placebo-controlled clinical trial lasting 104 weeks, carried out in 21 countries for 2 years (including Brazil), which evaluated the efficacy and safety of BLM in patients with active lupus nephritis, as adjuvant therapy to standard therapy (MMF, Cyclophosphamide and Azathioprine). With the use of BLM as adjunctive therapy, the primary outcome was the improvement in renal responses, with a decrease in proteinuria levels indicating the conservation of renal function, even reducing the possibility (by approximately 50%) of risk of renal exacerbation [7]. The patient presented periods of inactivation and exacerbation of SLE, with variation in SLEDAI. Initially, the patient had a SLEDAI score of 24 points, showing that the disease was very active. The SLEDAI criteria and score were created in accordance with the American College Rheumatology (ACR) in 1999, as a way to facilitate the diagnosis of SLE, in which the patient must meet at least 4 criteria, among the 11 described. The evaluation of the variation in the SLEDAI criterion is important to determine, because if there is an increase in the score, it is suggested that the disease is active. If the score is maintained, it can be inferred that the disease persists even after the use, or not, of the placebo drug [8]. The expected outcome with the use of BLM was the reduction of the SLEDAI score to values below 4, indicating a reduction in disease activity or, until its complete inactive disease, clearly demonstrating the benefit of the drug in controlling SLE.

Furthermore, the reduction of high doses of prednisone or cessation of use, ensuring a quality of life for the patient. The use of HCQ, MMF and azathioprine are generally associated with doses of corticosteroids, to control the activity and exacerbations of SLE symptoms, due to the chronicity and capabilities (relapse and inactive disease) of the disease [1-3]. The use of steroids in high doses and continuously is associated with high morbidity and mortality, due to the damage caused to the body [7]. Due to their low selectivity and not acting only on autoreactive cells, corticosteroids (such as prednisone) cause systemic involvement, suppressing

Table 1: Evaluation of the disease activity by laboratory tests evolution.

Period	Hemoglobin (12-16 g/dL*)	Leukocytes (4,000-10,000/mm³*)	Platelets (150,000-450,000/mm³*)	C3 (60-170 mg/dL*)	C4 (10-40 mg/dL*)	Creatinine (0.5-1.1 mg/dL*)	Proteinuria (in 24 hours) (50-80 g/24h*)
December/2016	11.7	6,400	2,71,000	73.0	18.0	1.0	5,439
November/2019	11.4	3,520	2,02,000	88.0	25.0	0.8	160
December/2020	16.5	5,800	2,14,000	126.0	51.0	0.7	-
March/2022	13.7	6,130	2,70,000	-	-	0.9	315
August/2023	12.8	6,620	2,84,000	115.0	39.5	0.7	280
November/2023	12.5	7,210	2,42,000	150.0	37.0	0.6	120
February/2024	13.1	5,320	2,33,000	123.0	35.5	0.8	289

*Reference values

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the action of monocytes and neutrophils, favouring the emergence of infections, comorbidities such as high blood pressure and diabetes mellitus, cataracts, poor wound healing, cardiovascular damage, in addition to depleting calcium from the bones, favouring the development of osteoporosis [3-6]. In the real-life context (in November 2023), during the patient's visit, she was asked to fill out the questionnaire (Portuguese version) World Health Organization Quality of Life (WHOQOL) [9], which aimed to assess the quality of life and health, from the patient's point of view, after using the BLM. Despite being a self-administered instrument, a direct interview was chosen, given the difficulty in reading, visual problems and the patient's low level of education. When answering the first question about: "How would you evaluate your quality of life?", the patient reported that she considered it "good", since before using BLM she suffered from relapses and recurrent hospitalizations. Regarding the question: "How satisfied are you with your health?" the answer was "satisfied", reporting that she is currently free from skin lesions and that her alopecia is under control, as she suffered for a long time from hair loss, a period in which she felt very vulnerable and had low self-esteem. When asked about the drugs currently in use, the patient reported that she uses HCQ 400 mg/day, azathioprine 100 mg/day and enalapril 20 mg/day. She reported the absence of SLE symptoms, therefore remaining asymptomatic, with no SLEDAI score. Therefore, it was possible to define that the primary efficacy outcome was achieved, showing control of disease activity with the use of BLM, as adjuvant therapy. Despite the disease exacerbation processes and pre-existing kidney damage, the patient achieved an excellent response to BLM therapy, with the secondary outcome being the gradual reduction of prednisone until its total suspension. Furthermore, the effectiveness of the treatment, using the perception of quality of life and health reported by the patient, promoted a significant improvement in both, since the patient is asymptomatic.

Ethics declaration

The study design was approved by the ethics committee of State University of Bahia. The Ethics committee approval number is 5.431.372/2022. Written informed consent was obtained from the patient.

Data availability statement

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Author contributions

Isabella Vargas de Souza Lima and Mittermayer Barreto Santiago defined the study protocol, contributed to the laboratory work, analyzed the data, and drafted the manuscript. Larissa Milena de Moura Maia Senna analyzed the data, provided the final revision of the manuscript Aníbal de Freitas Santos Júnior analyzed the data and drafted the manuscript. All the authors have given the final approval of the version to be published and they take responsibility for appropriate portions of the content.

Conflicts of interest

The authors declare no potential conflict of interest.

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