ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Use of belimumab in a patient with systemic lupus erythematosus refractory to conventional treatment: case report

Uso de belimumabe em paciente com lúpus eritematoso sistêmico refratário ao tratamento convencional: relato de caso

Maria Eduarda Castanhola[1], Sandra Silva[1], Camila Ferreira Bannwart-Castro[1,2]

ABSTRACT

Systemic lupus erythematosus is an immune-mediated disease caused by hormonal, environmental and genetic factors. It is characterized by the presence of reactive autoantibodies to different cells and tissues, with diverse clinical manifestations and periods of exacerbation and remission, which complicates treatment. This case report highlights progress with the use of a human monoclonal antibody in a woman diagnosed with systemic lupus erythematosus in May 2019 (at age 30). Since she was refractory to conventional drugs, belimumab treatment was begun in September 2019. Belimumab is a human monoclonal antibody that binds to soluble B lymphocyte-stimulating proteins, including self-reactive ones, and reduces the differentiation of B lymphocytes into plasma cells, decreasing the serum IgG and anti-dsDNA antibody levels, in addition to improving patient clinical status. Despite being a high-cost biological drug, it drastically reduces the clinical symptoms of systemic lupus erythematosus, enabling reduced used of corticosteroids and their effects, in addition to reestablishing laboratory parameters altered by the disease, without changing liver and kidney indicators. Since systemic lupus erythematosus has no cure, the goal of treatment is to reduce symptoms and the active phases of the disease.

Keywords: Immunotherapy, systemic lupus erythematosus, monoclonal antibodies, belimumab.

RESUMO

O lúpus eritematoso sistêmico (LES) é uma doença de caráter imunomediado, ocasionada por fatores hormonais, ambientais e genéticos. Caracteriza-se pela presença de autoanticorpos reativos para diferentes células e tecidos, apresentando manifestações clínicas diversificadas, períodos de exacerbação e remissão, o que dificulta o tratamento desses pacientes. Este relato de caso destaca o progresso do uso de anticorpo monoclonal humano em uma paciente do gênero feminino, diagnosticada com LES em maio de 2019, aos 30 anos, e, por ser refratária ao tratamento medicamentoso convencional, utilizou o tratamento com anticorpo monoclonal humano belimumabe, com início em setembro de 2019. O belimumabe é um anticorpo monoclonal humano que se liga à proteína estimuladora de linfócito B (BLyS) solúvel, inclusive dos autorreativos, e desta maneira, reduz a diferenciação de linfócitos B em plasmócitos, diminuindo os níveis de IgG sérica e dos anticorpos anti-dsDNA, além de melhorar o quadro clínico dos pacientes. Apesar de ser um medicamento biológico de alto custo, diminui drasticamente os sintomas clínicos do LES, possibilitando a redução do uso do corticoide e os efeitos consequentes de seu uso, além de reestabelecer os parâmetros laboratoriais alterados pela doença, sem alteração de indicadores hepáticos e renais. O LES não tem cura, logo, o objetivo do tratamento é diminuir os sintomas e conter as fases ativas da doença.

Descritores: Imunoterapia, lúpus eritematoso sistêmico, anticorpos monoclonais, belimumabe.

1. Centro Universitário Sudoeste Paulista UNIFSP - Avaré, SP, Brazil.
2. Universidade Estadual Paulista UNESP, Departamento de Patologia, Faculdade de Medicina de Botucatu - Botucatu, SP, Brazil.

Submitted: 06/14/2022, accepted: 09/16/2022.

Arq Asma Alerg Imunol. 2022;6(4):544-50.

http://dx.doi.org/10.5935/2526-5393.20220065

Introduction

Systemic lupus erythematosus (SLE) is an autoimmune inflammatory disease of unknown etiology related to genetic, environmental, and hormonal factors. It predominantly affects females of fertile age, because of the regulatory role that estrogens play in the immune system.[1] Since it is a multisystemic disease, its clinical manifestations are heterogeneous, with periods of exacerbation and remission triggered by exposure to the sun and physical or emotional stress.[2]

The clinical manifestations are caused by auto-antibodies that interact with the body's own genetic material, present in apoptotic cells, forming immune complexes (antibodies bound to antigens) which build up in tissues, causing lesions.[2] These auto-antibodies may also attack the body's own proteins, found in cells such as red blood cells, lymphocytes, and platelets, activating a reaction in cascade in the complement system, causing lysis of the target cells. Reductions in these cells can be used as a parameter for diagnosis of SLE and for classification of disease activity.[3]

SLE has no cure, but with pharmacological treatment the immunological changes can be regulated, attenuating its consequences. Medications used to modulate the immune system in SLE include glucocorticoids, anti malaria drugs, and immunosuppressants.[4] However, the human monoclonal antibody belimumab is indicated for patients refractory to conventional drug treatment who are over the age of 18 years.[5]

Belimumab is a human monoclonal antibody that binds to a soluble B-lymphocyte stimulator (BLyS) protein, also known as B cell activating factor, part of the tumor necrosis factor (TNF) family, and a type II transmembrane protein that can exist both in a membrane-bound form or in a soluble form.[6] Use of belimumab causes reduction of B lymphocyte differentiation into immunoglobulin-producing plasmacytes, thus achieving the objective of treatment, which is to reduce serum IgG and anti double-stranded DNA (anti-dsDNA) antibodies, improving patients' clinical status.[7]

The objective of this paper is to present the progress achieved using human monoclonal antibodies in a patient with SLE refractory to treatment with conventional medications.

Methods

This is a case report with the objective of presenting the progress achieved using human monoclonal antibodies in a patient with SLE refractory to treatment with conventional medications. Data were collected from medical reports and laboratory tests provided by the patient and personal accounts reported orally to the authors of the patient's main experiences with the disease since her first symptoms in mid-September of 2018, until the most recent laboratory tests on June 7, 2021.

Case report

A female patient was diagnosed with SLE in March 2019, at 30 years of age, after having noticed enlarged lymph nodes in her cervical region in mid-September of 2018. After consultation with a head and neck surgeon, cervical ultrasonography with Doppler was ordered to attempt to understand the palpable enlargement, suspected of being Hodgkin's lymphoma.

The cervical Doppler ultrasonography report described unusual cervical lymphadenomegaly in the left cervical region, with rounded, hypoechogenic lymph nodes, some with no obvious central hilum, others with the hilum extruded, with no areas of cystic permeation and no internal microcalcifications. Cervical lymph nodes with a normal elongated appearance and preserved hilum were also noted. There was intense hilar and subcapsular vascularization with vascular structures with normal path and caliber. The remaining cervical structures assessed, such as thyroid and salivary glands, were normal.

In view of the Doppler ultrasonographic analysis of the cervical region, in conjunction with the lymphadenomegaly of the cervical region observed during the medical consultation, the physician responsible for the case ordered another ultrasonography examination with Doppler, but at level III of the cervical region, with the intention of analyzing the abnormal area in greater detail. This confirmed the enlargement and abnormality of the left supraclavicular lymph nodes. Therefore, combined with puncture examination and biopsy results, the primary hypothesis of Hodgkin's lymphoma was ruled out, but no definitive diagnosis was achieved.

The patient complained of severe joint pain, fatigue, and hives, and was therefore referred to a rheumatologist, in March of 2019, who ordered

laboratory tests to attempt to make a conclusive diagnosis. An antinuclear factor (ANF) assay and a full blood test were conducted (Table 1).

The patient was diagnosed with SLE on the basis of the rheumatologist's clinical assessment in conjunction with the positive ANF result, with a thick speckled nucleus and titers of 1/640, and analysis of the blood test results, which showed leukopenia, neutropenia, and low serum C3 concentration. Initially, conventional drug treatment for SLE was employed (Table 2), in addition to vitamin supplements to control hair loss, a third-generation hormonal contraceptive, desogestrel 75 mg, to avoid a risk of pregnancy during active disease periods, and factor 50 sun protection on the body and factor 70 on the face, because of the risks of exposure to sunlight.

This treatment was maintained until the start of July 2019, but without results, when the rheumatologist substituted methotrexate 2.5 mg with azathioprine 50 mg, 1-3 mg/kg/day. However, the substitute was only maintained for approximately 1 month, because of worsening fatigue, urticaria, and joint pain and onset of depressive symptoms. For these reasons, the patient was instructed to withdraw azathioprine and

Table 1
Analytes at abnormal levels in the blood test performed before diagnosis of SLE

Analytes	Normal reference values for women	Results 03/20/2019
Leukocytes	5,000 to 10,000/mm^3	2,930
Neutrophils	1,700 to 7,000/mm^3	1,440
C3	Age 31 to 49 years: 84 to 160 mg/dL	56

Abnormal results of blood test on March 20, 2019, showing leukopenia, neutropenia, and low serum C3 concentration, characteristic of autoimmune diseases. Other analytes were normal according to the reference values.

Table 2
Medications and dosages used in conventional treatment for SLE

Medication		Administration		
Name	Concentration	Quantity	Route	Frequency
Methotrexate	2.5 mg	6 pills	Oral	1x/week
Folic acid	5 mg	1 pill	Oral	6x/week, except on day methotrexate taken
Prednisone	5 mg	2 pills	Oral	1x/day
Hydroxychloroquine	400 mg	1 pill	Oral	5x/week

resume methotrexate 2.5 mg, 6 pills 1x/week, with the addition of venlafaxine 150 mg, a selective serotonin reuptake inhibitor antidepressant, and noradrenaline, at a dosage of 1 pill 1x/day.

However, even continuing this treatment for 6 months (March 2019 to September 2019), the patient did not improve, proving refractory to the medications employed. The rheumatologist therefore suggested adding the monoclonal antibody belimumab to the treatment regimen.

The monoclonal antibody belimumab was administered for the first time on September 23, 2019, 10 mg/kg via intravenous infusion, for 1 hour, allowing a 2 week interval between administrations to elapse for the first three doses, and then administering doses every 4 weeks. The patient described a gradual improvement in symptoms from the third administration onwards. The last administration was on August 29, 2020.

Treatment with belimumab resulted in more rapid and significant improvements than the conventional drug treatment, as shown by the laboratory tests summarized in Table 3.

In January of 2020, while still on belimumab, the rheumatologist adjusted the drug treatment, increasing the frequency of hydroxychloroquine 400 mg to 1 pill 6x/week, to help contain the disease.

After treatment with belimumab, while the laboratory test result values were still not within normal reference ranges, they revealed little variation, which is evidence of a reduction in disease activity. In the last urine test, conducted on June 7, 2021, microscopy of sediments revealed numerous epithelial cells, sparse crystals of calcium oxalate, sparse amorphous urate crystals, and abundant mucus filaments, which had not been present in previous samples, and there was a significant increase in erythrocyte levels, which had been absent in the previous test, on April 5, 2021.

Discussion

SLE is diagnosed on the basis of many different clinical and laboratory parameters proposed by the American College of Rheumatology (ACR) in 1997,[8] and universally accepted, which can be used at any time of life. At least 4 of the 11 classification criteria are needed for a positive diagnosis, as follows: malar rash, discoid rash, photosensitivity, mouth sores, arthritis, serositis, renal changes, neurological changes, hematological changes, immunological changes, and positive antinuclear factor (ANF) titers.[9]

The assay to detect ANF is most often used in suspected SLE cases. ANF constitutes a group of autoreactive antibodies that attack nuclear structures such as ribonucleoproteins, histones, and the double-strand of DNA. The test is based on staining a sample with immunofluorescence, so that the autoreactive antibodies in the sample become fluorescent and can be seen with microscopy. The result is positive if fluorescence is still present after 40 or more dilutions of the stained sample (result 1/40 or 1:40). The greater the number of dilutions needed to eliminate fluorescence from the sample, the more severe the disease state.[2]

Pharmacological treatment should be individualized, paying attention to which organs or systems are being comprised during the current phase of the disease and its severity. The Brazilian Unified Health System (SUS) national technology commission recommendations[10] adopt the following drugs for treatment of SLE: chloroquine or hydroxychloroquine, dexamethasone and betamethasone, methylprednisolone and prednisone, azathioprine, cyclosporine, cyclophosphamide, danazol, methotrexate and thalidomide, all of which are distributed by the SUS. Notwithstanding, treatment with the human monoclonal antibody belimumab is indicated for patients over the age of 18 who are refractory to these medications and are taking corticosteroids, non-steroidal anti-inflammatories, anti malaria drugs, or immunosuppressants.[5]

Belimumab is the first biological drug for patients with SLE. It was developed by Human Genome Sciences Inc., (HGS, Rockville, MD) in conjunction with GlaxoSmithKline (Research Triangle Park, NC) and was only approved in 2011 by the US Food and Drug Administration (FDA) and the European Medications Agency.[11] Belimumab is a human monoclonal IgG1λ antibody that binds to the human B-lymphocyte stimulator (BLyS), also known as the B cell activating factor of the TNF family (BAFF), inhibiting its biological activity. BLyS is a type II transmembrane protein that exists both in a form bound to the surface membranes of a wide variety of cell types, such as monocytes, activated neutrophils, T cells, and dendritic cells, when in the soluble form after cleavage.[6] When soluble, it becomes a ligand for three receptors on B lymphocytes: BLyS receptor 3 (BR3), transmembrane activator and calcium-modulator and cyclophilin ligand interactor 1 (TACI), and B-cell

maturation antigen (BCMA).[11] Belimumab blocks soluble BLyS, causing a reduction in lymphocyte B differentiation into plasmacytes, reducing serum IgG and anti-dsDNA antibodies, improving patients' clinical status. BLyS is overexpressed in patients with SLE, so there is a robust association between SLE activity and plasma BLyS concentrations.[7]

The hematological abnormalities generally present for diagnosis of SLE are: hemolytic anemia with reticulocytosis; leukopenia with values below 4,000/mm^3 on two or more occasions; lymphopenia less than 1,500/mm^3 on two or more occasions; thrombocytopenia less than 100,000/mm^3 in the absence of drugs responsible for this.[8] In the current case, the patient had sufficient hemolytic anemia, leukopenia, and lymphopenia for a diagnosis of SLE, but never had thrombocytopenia during the entire period analyzed.

Table 3
Progression of results of laboratory tests during the period analyzed, from September 23, 2019 to August 29, 2020

Analytes	Normal reference for women	Results					
		Before*			During*	After*	
		April 25, 2019	July 4, 2019	July 7, 2019	January 25, 2020	April 5, 2021	June 7, 2021
Erythrocytes	4.0 to 5.40 milh./mm^3	4.01	3.88	3.47	4.09	4.03	3.96
Hemoglobin	11.50 to 16.30 g/dL	12.1	12.1	11.0	13.1	12.40	12.10
VCM	82.0 to 98.0 fL	89.5	94.3	101.4	96.8	–	–
Leukocytes	5,000 to 10,000/mm^3	4,050	2,710	2,400	4,700	5,330	4,760
Neutrophils	1,700 to 7,000/mm^3	2,090	1,320	1,330	3,160	–	–
Eosinophils	100 to 400/mm^3	60	40	100	40	59	52
Lymphocytes	1,000 to 4,000/mm^3	1,410	1,030	610	860	981	1,309
VHS	Up to 15 mm/1st hour	19	21	30	16	–	18
Total complement	72 to 140 units	–	60	–	35	–	–
C3	Age 31 to 49 years: 84 to 160 mg/dL	56	60	49	74	–	96
Platelets	150,000 to 450,000/mm^3	238,000	284,000	221,000	261,000	234,000	266,000
Quantitative erythrocyte assay, urine	Up to 5,000/mL	< 10,000	< 10,000	< 10,000	22,000	Absent	< 26,000

* Before, during and after treatment with belimumab.

In this case, the clinical and laboratory improvement exhibited by the patient after the third dose of belimumab was in line with the reduction in disease activity, as demonstrated by the significant reduction in VHS levels, which is a test often used to screen for inflammatory conditions, such as infections, autoimmune diseases, and cancers.[12] Despite frequent use of VHS as a nonspecific marker of diseases in clinical practice, VHS tends to accompany disease activity in chronic inflammatory diseases and levels generally fall when there is a clinical response to treatment, as seen in the laboratory results in this report, in which VHS increased exponentially until treatment with belimumab was initiated.[13]

Urine analysis should be ordered in SLE cases to detect inflammatory processes in the initial stages, since renal inflammation only causes symptoms in severe and advanced states. The elevated erythrocyte counts in urine after treatment with belimumab seen in this case reveal the renal inflammation described in the drug leaflet.[14]

A case similar to this one was described by Bazílio AP,[15] in which a female patient diagnosed with SLE in 2004 was treated successfully with the conventional drug regimen until 2011, when renal function worsened significantly and joint involvement set in, with arthritis of the hands and knees. Despite changes to the drugs used, in 2014 the patient still had intense disease activity and was refractory to treatment. At this point, belimumab 10 mg/kg was indicated in combination with the treatment. After 6 months' treatment the drug dosages were reduced significantly because of clinical and laboratory improvement, manifest as absence of fatigue, increased lymphocytes, leukocytes, hemoglobin, platelets, C3, and C4 and reduced VHS levels. These factors are all evidence of reduced disease activity and successful treatment. In September 2014, it proved possible to completely withdraw corticoid therapy.

Conclusions

SLE is an autoimmune inflammatory disease that can be controlled with drug treatments. However, as analyzed in this paper, some patients are refractory to these treatments, in which case monoclonal antibodies such as belimumab can be used. While this is an expensive drug, it yields rapid improvement in clinical symptoms, enabling corticoids to be reduced, along with the effects consequent to them, in addition to reestablishing the laboratory parameters affected by the disease, without changing hepatic or renal indicators. Considering the progress in terms of laboratory results seen in the patient described, in conjunction with the efforts of the treating physician, and also the patient's own testimony, it can be concluded that treatment with belimumab was successful.

References

1. Enderle D, Machado D, Mendes K, Costa F, Carvalho A. Manifestações clínicas do Lúpus Eritematoso Sistêmico (LES). FACIDER - Revista Científica. 2019;12(12). Available at: http://revista.sei-cesucol.edu.br/index.php/facider/article/view/182/210. Accessed on: 07/24/2021.
2. Barasuol LL, Figueiredo MO. Análise comparativa dos aspectos clínicos e sorológicos de pacientes com Lúpus Eritematoso Sistêmico com e sem anticorpo Anti-RNP. Curitiba, PR. Trabalho de conclusão de curso [Graduação em Medicina]. Faculdade Evangélica Mackenzie do Paraná; 2019.
3. Abbas AK, Lichtman AK, Pillai S. Imunologia Celular e Molecular. 9ª ed. Guanabara Koogan; 2019. p. 576.
4. Wallace DJ, Gladman DD. Clinical manifestations and diagnosis of systemic lupus erythematosus in adults. UpTotDate. 2020. Available at: https://www.uptodate.com/contents/clinical-manifestations-and-diagnosis-of-systemic-lupus-erythematosus-in-adults. Accessed on: 07/24/2021.
5. Nakata KCF, Riveros BS. Uso de belimumab em pacientes lúpicos refratários ao tratamento convencional: avaliação de impacto orçamentário. Rev. Gestão & Saúde (Brasília) Vol. 09, nº 01, Jan. 2018.
6. Moore PA, Belvedere O, Orr A, Pieri K, LaFleur DW, Feng P, et al. BLyS: member of the tumor necrosis factor family and B lymphocyte stimulator. Science. 1999 Jul 9;285(5425):260-3.
7. Frieri M, Heuser W, Bliss J. Efficacy of novel monoclonal antibody belimumab in the treatment of lupus nephritis. J Pharmacol Pharmacother. 2015 Apr-Jun;6(2):71-6.
8. Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum. 1997 Sep;40(9):1725.
9. BRASIL. Ministério da saúde. Protocolo Clínico e Diretrizes Terapêuticas do Lúpus Eritematoso Sistêmico. Portaria nº 100. 2013. Available at: http://conitec.gov.br/images/Protocolos/LupusEritematoso_Sistemico.pdf. Accessed on: 08/10/2021.
10. BRASIL. Ministério da Saúde. Secretaria de Atenção à Saúde. Protocolos clínicos e diretrizes terapêuticas: volume 3. Brasília;2014. p.604.
11. Chiche L, Jourde N, Thomas G, Bardin N, Bornet C, Darque A, et al. New treatment options for lupus - a focus on belimumab. Ther Clin Risk Manag. 2012;8:33-43.
12. Santos VM, Cunha SFC, Cunha DF. Velocidade de sedimentação das hemácias: utilidade e limitações. Rev Assoc Med Bras. 2000;6(3):232-6.
13. Oliveira JFC. Relação da atividade clínica do lúpus eritematoso b sistêmico medida pelo VHS, PCR E SLEDAI. Rev Med Paraná, Curitiba. 2017;75(1):67-72.

14. Belimumabe: Pó liofilizado para solução para infusão intravenosa. Responsável técnico Monique Lellis de Freitas. Rio de Janeiro: Glaxo Operations UK Ltd, 2012. Bula - Profissional de saúde. Available at: https://consultas.anvisa.gov.br/#/medicamentos/25351699419201015/?nomeProduto=BenlysTa. Accessed on: 08/01/2021.

15. Bazílio AP. Caso clínico uma experiência real com Benlysta®. 2015. Available at: https://gskpro.com/content/dam/global/hcpportal/pt_BR/Areas%20Terapeuticas/Imunologia%20-%20LES/PDF/Caso%20Ana%20Paula.pdf. Accessed on: 08/11/2021.

No conflicts of interest declared concerning the publication of this article.

Corresponding author:
Maria Eduarda Castanhola
E-mail: me.castanhola@gmail.com