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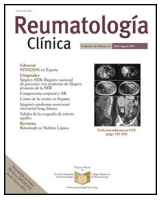

Letter to the Editor

Biological sequential therapy with rituximab-belimumab in patients with recurrent lupus nephritis☆

Terapia biológica secuencial con rituximab-belimumab en pacientes con nefritis lúpica recurrente

Dear Editor,

Despite advances in our knowledge and therapeutic approach, lupus nephritis (LN) remains a serious complication, with recurrences and remission failures, and its management is not yet fully established.

We present 2 cases in which sequential therapy with rituximab and belimumab resulted in adequate control of recurrent lupus nephritis.

Case 1: a 31-year-old woman diagnosed with systemic lupus erythematosus (SLE) at the age of 18, presenting with malar erythema, non-erosive arthritis predominantly in the carpal and interphalangeal joints of both hands, haemolytic anaemia with mild thrombocytopenia, together with complement consumption and positive ANA with elevated anti-dsDNA, with negative anti-Ro and anti-La. Antiphospholipid antibodies were also negative. Treatment with hydroxychloroquine and azathioprine was prescribed, with improvement of the clinical picture, and normalisation of the parameters of biochemical lupus activity and haematological abnormalities. Over the following years, the patient achieved excellent clinical and analytical control, remaining on antimalarials alone. At 29 years of age, normal gestation, with no significant complications. Six months after delivery, at a routine visit, she reported slight oedema in the legs, with evidence of complement consumption and positive anti-dsDNA, lymphopenia, and urine sediment with cylindruria, microscopic haematuria, and 3 protein crossmatches. Creatinine was 1.8 g/dl (clearance 59 mL/min) and 24 h proteinuria was 2,360 mg. Renal biopsy showed global diffuse proliferative glomerulonephritis, with a disease activity index of 10/24 and chronicity of 2/12, together with extracapillary proliferation, without thrombopathy or tubulo-interstitial involvement. Treatment was indicated with a Euro-lupus regimen and adjuvant therapy (ACE inhibitors, statin), achieving partial remission of renal involvement and improvement of lupus activity. At 4 months, haemolytic anaemia (Hb 7.4 g/dl) and severe thrombocytopenia (12,000/dl) were observed, with no evidence of thrombotic microangiopathy, requiring steroid pulses (500 mg methylprednisolone/3 consecutive days) and later prednisone (60 mg/day) together with mycophenolic acid. Despite initial improvement, the patient required high-dose steroids, and developed skin lesions on her hands and legs, with a biopsy of lupus necrotising vasculitis. In addition, worsening kidney function was noted, with nephrotic proteinuria and creatinine of 2.1 mg/dl (clearance 42 mL/min). The patient refused a further renal biopsy. Given the presence of lupus vasculitis, haematological involvement and progression of renal involvement, rituximab was prescribed (2 doses of 1 g separated by 2 weeks) and one month after the anti-CD20 treatment, belimumab was started at the usual dose and regimen. At 6 months, under belimumab, mycophenolic acid (1,080 mg/d, due to digestive intolerance it was not possible to progress to higher doses), and hydroxychloroquine, not only were haemolysis controlled and platelet counts normalised, but also the analytical parameters of lupus activity were negative and kidney function improved (CrCL 72 mg/dl, proteinuria 24 h/320 mg, sediment normal). She remains without renal recurrence after 19 months with belimumab.

Case 2: A 32-year-old woman, diagnosed at 17 years of age with SLE based on mucocutaneous lesions, carpal arthritis, and positive ANAS, with anti-dsDNA; anti-Sm, anti-RNP, antiphospholipid negative. During the first year of the disease, she was treated with NSAIDs, low doses of prednisone and hydroxychloroquine. At 26 years of age, an abnormality was detected in urinary sediment with nephrotic proteinuria and complete urine consumption, and therefore a renal biopsy was performed, showing focal proliferative and membranous lupus nephropathy. Induction treatment was started with cyclophosphamide according to the classic NIH regimen for 6 months, and mycophenolate mofetil as maintenance therapy, achieving a complete response after one year of treatment. At 2 years, after changing from mycophenolate to azathioprine due to her wish to become pregnant, she developed renal recurrence with nephrotic syndrome, microhaematuria, impaired kidney function (creatinine 1.29, ClCr 54 mL/min) and decreased complement. A further renal biopsy revealed the presence of diffuse and membranous proliferative nephritis with a disease activity index of 6/24 and chronicity of 2/12. This new renal flare was treated with 3 boluses of methylprednisolone and triple therapy with prednisone, mycophenolate mofetil and tacrolimus, with the addition of hydroxychloroquine. Despite this, not even partial remission was achieved, with deterioration of kidney function (creatinine 1.38, ClCr 45 mL/min) and development of up to 8 g of proteinuria/per 24 h. Rituximab was prescribed (2 doses of 1 g separated by 2 weeks), together with cyclophosphamide (Euro-lupus regimen) and hydroxychloroquine, achieving partial renal response after 3 months. At that time, belimumab was prescribed at the usual dose. After 14 monthly infusions, the patient remained free of extrarenal manifestations, with no complement consumption, negative anti-dsDNA, proteinuria less than 1 g/24 h, with normal renal sediment and function. Currently, after 6 years, the patient has achieved complete renal and extrarenal remission.

It is a known fact that rituximab has not been able to find a position in the large trials designed for this purpose (EXPLORER, LUNAR) as a treatment for lupus or, more specifically, lupus nephritis. However, we also know the benefit of the drug as off-label rescue

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for patients in these same scenarios,[1] and there are even single-centre trials that position it as the pivotal drug in the approach to nephritis.[2] However, a frequent problem after the induction phase is the difficulty in achieving remission and preventing relapse. One of the known causes of relapse is the reappearance of autoreactive B-lymphocytes after initial potent treatment, hence the importance of optimal maintenance therapy. In the case of rituximab induction, BAFF (BLyS) increases with B-cell depletion. B-cell repopulation in a BAFF-rich environment will favour the emergence of autoreactive B-cells, with the consequent risk of relapse. In this area, belimumab may prevent the development of such autoreactive cells, helping to control lupus disease activity.[3,4] Furthermore, there is evidence of the clinical utility of the combination of rituximab and belimumab in reducing excessive neutrophil extracellular trap (NET) formation in SLE patients.[5] NETosis is involved in the development of self-perpetuating mechanisms of reactivity against antigens, a substrate for disease onset.

Several trials, such as CALIBRATE and SynBiose, have explored these findings. In the CALIBRATE trial (NCT02260934), researchers showed that a combination of rituximab and cyclophosphamide followed by belimumab may be safe, but with the small population studied, no clinical benefit was demonstrated in lupus nephritis. In the SynBioSe trial (NCT02284984), the main objective was to evaluate the reduction of autoantibodies, and its impact on clinical improvement, by analysing the safety profile and feasibility of long-term B-cell depletion. The recently published BEAT-Lupus trial has shown that belimumab, initiated 4–8 weeks after rituximab, significantly reduced serum levels of IgG anti-dsDNA antibodies and reduced the risk of severe flare in patients with SLE refractory to conventional therapy at 52 weeks of follow-up.[6]

The optimal timing of the sequential combination of rituximab and belimumab is unclear; especially how soon to wait to start belimumab after anti-CD20, or whether anti-BLyS should be started with reconstitution of anti-CD19/CD20 or independently.

Belimumab is a useful drug in patients with clinically and immunologically active SLE who do not respond to standard therapy. There are data on the usefulness of belimumab in renal lupus nephritis,[7] and the medium- and long-term progress of our patients also suggests this, maintaining the improvement achieved and reducing the frequency of flares. Therapy with belimumab sequentially or in combination with other drugs may enhance the benefits of the various prescribed molecules, even in recurrent forms and scenarios, such as renal, where the best strategy has not been defined.[8,9]

References

1. Diaz-Lagares C, Croca S, Sangle S, Vital EM, Catapano F, Martínez-Berriotxoa A, et al. Efficacy of rituximab in 164 patients with biopsy-proven lupus nephritis: pooled data from European cohorts. Autoimmun Rev. 2012;11:357–64.
2. Condon MB, Ashby D, Pepper RJ, Cook HT, Levy JB, Griffith M, et al. Prospective observational single-centre cohort study to evaluate the effectiveness of treating lupus nephritis with rituximab and mycophenolate mofetil but no oral steroids. Ann Rheum Dis. 2013;72:1280–6.
3. Kraaij T, Huizinga TWJ, Ton J, Rabelink TJ, Teng YKO. Belimumab after rituximab as maintenance therapy in lupus nephritis. Rheumatology. 2014;53:2122–4.
4. Gualtierotti R, Borghi MO, Gerosa M, Schioppo T, Larghi P, Geginat J, et al. Successful sequential therapy with rituximab and belimumab in patients with active systemic lupus erythematosus: a case series. Clin Exp Rheumatol. 2018;36:643–7.
5. Kraaij T, Kamerling SWA, de Rooij ENM, van Daele PLA, Bredewold OW, Bakker JA, et al. The NET-effect of combining rituximab with belimumab in severe systemic lupus erythematosus. J Autoimmun. 2018;91:45–54.
6. Shipa M, Embleton-Thirsk A, Parvaz M, Santos LR, Muller P, Chowdhury K, et al. Effectiveness of belimumab after rituximab in systemic lupus erythematosus: a randomized controlled trial. Ann Intern Med. 2021, http://dx.doi.org/10.7326/M21-2078. Epub ahead of print. PMID: 34698499.
7. Furie R, Rovin BH, Houssiau F, Malvar A, Teng YKO, Contreras G, et al. Two-year, randomized, controlled trial of belimumab in lupus nephritis. N Engl J Med. 2020;383:1117–28.
8. Shipa M, Embleton-Thirsk A, Parvaz M, Santos LR, Muller P, Chowdhury K, et al. OP0129 Belimumab after rituximab significantly reduced igg anti-dsdna antibody levels and prolonged time to severe flare in patients with systemic lupus erythematosus. Ann Rheum Dis. 2021;80:74.
9. Atisha-Fregoso Y, Malkiel S, Harris KM, Byron M, Ding L, Kanaparthi S, et al. Phase II randomized trial of rituximab plus cyclophosphamide followed by belimumab for the treatment of lupus nephritis. Arthritis Rheumatol. 2021;73:121–31. Erratum in: Arthritis Rheumatol. 2021;73:2356.

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