Ref: Ro J Rheumatol. 2023;32(4)
DOI: 10.37897/RJR.2023.4.7

Lupus nephritis – case report of an uncommon succession of therapies

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ABSTRACT

Background. Lupus nephritis (LN) is one of the most severe manifestations of systemic lupus erythematosus (SLE) and often occurs within the first five years after diagnosis.

Case report. A 33-year-old woman with SLE (arthritis; cutaneous involvement; Raynaud phenomena, vasculitis, pleural effusion, hematological and immunological abnormalities), under treatment with glucocorticoids and hydroxychloroquine developed focal proliferative LN, which progressed under treatment with belimumab. Consequently, intravenous cyclophosphamide and low-dose rituximab were used to induce LN remission, while maintenance therapy relied on mycophenolate mofetil.

Conclusions. The case illustrates an uncommon succession of therapies for SLE and LN, with belimumab preceding cyclophosphamide. The decision to induce remission with cyclophosphamide was based on histological aspects of the renal biopsy. Although current recommendations permit the association of belimumab and cyclophosphamide, there is very little practical experience to support it.

Keywords: lupus nephritis, systemic lupus erythematosus, belimumab, cyclophosphamide, rituximab

List of abbreviations (in alphabetical order):

ANA – Antinuclear antibodies
anti-dsDNA antibody – Anti-double-stranded DNA antibodies
ANA – Antinuclear antibodies
ANC – Absolute neutrophil count
BLISS-LN – Belimumab International Study in Lupus Nephritis
CRP – C-reactive protein
ELISA – Enzyme-linked immunosorbent assay
ESR – Elevated erythrocyte sedimentation rate
EULAR – European Alliance of Associations for Rheumatology
LN – Lupus nephritis
MMF – Mycophenolate mofetil
SLE – Systemic lupus erythematosus

INTRODUCTION

Systemic lupus erythematosus (SLE) is an autoimmune disease with multisystemic involvement, characterized by the loss of immune tolerance towards self-antigens. SLE manifestations are caused by autoantibody production and complement deposition in tissues, which leads to systemic inflammation. It is a heterogenous disease with various phenotypes and a continuum of disease manifestations that can affect any organ system [1].

Lupus nephritis (LN) represents one of the most severe organ complications of SLE, and is directly associated with higher morbidity and mortality rates. It

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Article History:
Received: 19 December 2023
Accepted: 26 December 2023

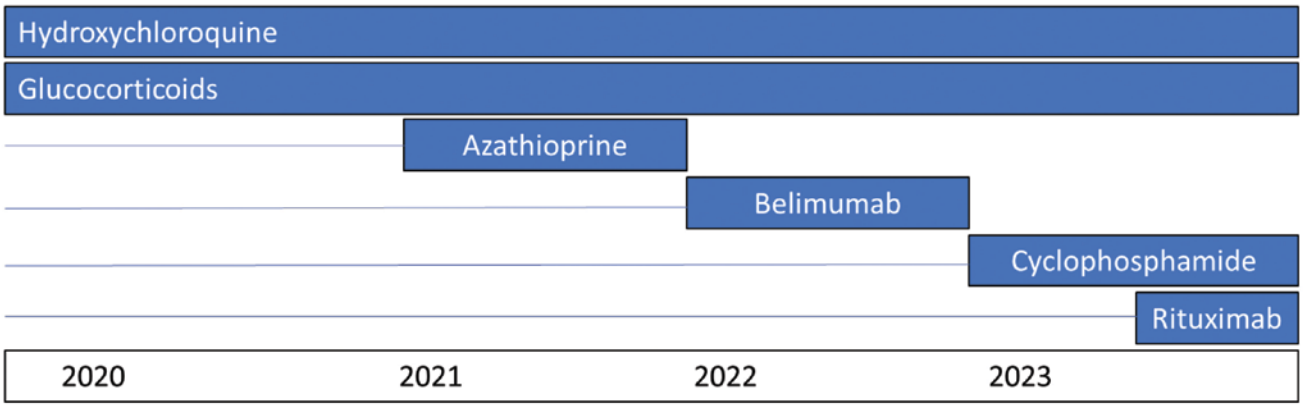

FIGURE 1. SLE treatment history

often occurs within the first 5 years after SLE diagnosis and up to 10% of patients develop kidney failure in the same span of time. The risk of death in this category of patients is thrice as high, while the risk of progression to end stage renal disease is 44 times higher. Studies show that histological signs of LN are present in most patients with SLE, even in the absence of clinical manifestations [2-5].

LN evolves with periods of inactivity, alternating with flares. Clinical presentation ranges from asymptomatic profile to rapidly progressive kidney failure, depending on various histological aspects that determine the class of LN. Other manifestations pertaining to renal involvement are arterial hypertension and susceptibility to infections [4].

Early detection of LN and prompt treatment initiation are key to reducing the impact on patient outcome, therefore patients should be regularly monitored for signs of kidney disease. Although there are no available specific biomarkers, renal function is usually monitored through serum creatinine, urine albumin to creatine ratio and the presence of proteinuria in urinalysis. However, renal biopsy remains the most relevant for correct diagnosis and assessment of disease progression, as well as for treatment decisions [2,3].

CASE REPORT

A 33-year-old, non-smoking, urban-dwelling woman was initially referred for evaluation in June 2020 when the patient complained of fatigue and presented with hands and knees arthritis, malar erythema, erythematous skin lesions on the right hemithorax and livedo reticularis of the lower legs. Laboratory tests revealed the presence of antinuclear antibodies (ANA) in both enzyme-linked immunosorbent assay (ELISA) and indirect immunofluorescence, with high count of anti-double-stranded DNA antibodies (anti-dsDNA antibody) and anti-Smith antibodies, as well as low complement levels. Systemic inflammation was also present through high levels of C-reactive protein (CRP) and elevated erythrocyte sedimentation rate (ESR). SLE was diagnosed and the patient received treatment with hydroxychloroquine 400 mg daily and glucocorticoids 20 mg prednisone-equivalent daily (Figure 1).

A positive evolution was observed for more than a year, after which, in September 2021, the patient relapsed and presented with additional clinical manifestations, namely Raynaud phenomena, splinter hemorrhages and dyspnea. The chest plain radiography revealed massive bilateral pleural effusion and emergency thoracentesis was performed. After the initial thoracentesis, subsequent interventions were required until the pleural effusion remitted. Alongside, the patient continued hydroxychloroquine and glucocorticoids and azathioprine 50 mg daily was initiated (maximum tolerated dose because of gastrointestinal side effects). Testing for antiphospholipid syndrome was performed twice, at a three-month interval, with negative results for lupus anticoagulant, anticardiolipin antibodies and anti-beta2-glycoprotein I antibody.

While under treatment with glucocorticoids (15 mg prednisone-equivalent), hydroxychloroquine and azathioprine, the patient continued to present disease flairs with extensive joint and skin involvement (persistent arthritis of the hands, knees, ankles, Raynaud phenomena, livedo reticularis), hematological and immunological abnormalities (lymphopenia, low complement levels, high count of anti-dsDNA antibodies) and began to exhibit signs of kidney involvement (urinalysis indicated the presence of proteinuria), but without pulmonary manifestations. Further testing showed a 24-hour urine proteinuria of 900 mg and the patient was referred to a nephrology department for renal biopsy which she declined.

In May 2022, biological treatment with belimumab was initiated, according to the national protocol for SLE treatment. In subsequent evaluations the patient presented fewer clinical complaints (regarding skin and joint involvement), but persistent hematological, immunological and renal manifestations were observed. The 24-hour proteinuria

escalated to 1,300 mg and the patient acquiesced to the renal biopsy.

The renal biopsy revealed class III focal lupus glomerulonephritis, with both active and chronic lesions. Together with the nephrologist the decision was made to initiate intravenous cyclophosphamide treatment in low-dose (EuroLupus) [6], while continuing hydroxychloroquine and glucocorticoids (15 mg prednisone-equivalent). Low doses of rituximab 100 mg were used off-label twice during induction with cyclophosphamide, specifically during the fourth and fifth cyclophosphamide administrations. Starting from the induction phase with cyclophosphamide, belimumab was permanently discontinued. As maintenance therapy, mycophenolate mofetil (MMF) 2 g daily was chosen.

The patient responded to the aforementioned therapies with a significant decrease in the 24-hour proteinuria, from 1,300 mg to 700 mg. From a clinical standpoint, constitutional symptoms as well as arthritis and arthralgias were less frequent, while immunological abnormalities such as anti-dsDNA antibodies and low complement levels were observed. It is important to note that the patient has been unable to reduce glucocorticoids to less than 10 mg prednisone-equivalent.

DISCUSSION

The patient had been under our observation since disease onset and was closely monitored following current European Alliance of Associations for Rheumatology (EULAR) recommendations [7,8]. Disease activity and organ involvement were assessed at all clinical visits for the purpose of treatment adjustment. A turning point in the patient's disease development was at the first sign of new-onset renal involvement, through the presence of proteinuria in urinalysis and a 24-hour urine proteinuria of 900 mg.

The decision to escalate treatment to a biological agent was based on two factors. Firstly, the patient was not responding to combined therapy of hydroxychloroquine 400 mg/day and azathioprine 50 mg/day, in addition to chronic use of glucocorticoids (15 mg prednisone-equivalent). The patient weighed 55 kg therefore the dose of azathioprine was considered appropriate and was well tolerated. Secondly, kidney involvement was a sign of disease progression and required a more aggressive therapeutic approach.

Multiple studies have determined that belimumab 10 mg/kg lowers autoantibody levels and has a positive impact on overall disease activity of SLE patients [9]. Although recommendations regarding the use of belimumab were initially focused on non-renal SLE, recent studies have validated its benefits in the treatment of LN. Efficacy of belimumab in LN was assessed in Belimumab International Study in Lupus Nephritis (BLISS-LN), which showed better renal response, with glomerular filtration rate preservation, for patients receiving combination therapy of belimumab plus standard therapy (induction with either MMF or cyclophosphamide) versus standard therapy alone [10]. Also, the risk of flares decreased by 55% [11].

After belimumab was initiated, the patient presented positive clinical evolution with less joint inflammation and fewer constitutional symptoms; however, a significant increase in 24-hour proteinuria was noted (1,300 mg). Renal biopsy was essential for diagnosis as well as assessment of disease development [12]. Further treatment decisions were made with the involvement of nephrologists who considered histological features of the renal biopsy as key to choosing between either MMF or cyclophosphamide as induction of remission therapy.

The renal biopsy showed mesangial hypercellularity, with active focal endo-capillary hypercellularity, and extra-capillary hypercellularity with non-circumferential crescents. Chronic lesions, such as interstitial fibrosis, were also present. Crescents are considered active lesions and a mark of severity. They can be found in almost half on LN cases and the long-term renal outcome is determined by the crescentic type. Studies show that circumferential cellular crescents present in more than a fourth of examined glomeruli are independent determinants of evolution towards end stage kidney disease [13,14].

Given the histopathological features, cyclophosphamide was chosen as induction of remission therapy. Although cyclophosphamide - and MMF-based treatment regimens have similar efficiency in LN, induction with cyclophosphamide has been observed to provide better long-term outcomes, through sustained remission and a better preservation of renal function [15-17].

The patient received low-dose cyclophosphamide in line with the EuroLupus protocol, which was administered in the nephrology clinic. At this point in time, the question of whether to continue treatment with belimumab was posed. Current EULAR recommendations state that the association of a biological agent with an immunosuppressant "should be considered" in the treatment of active LN, but ultimately the decision is to be made by the primary physician in each respective case [15].

It is important to note that in the BLISS-LN study, belimumab was initiated after induction treatment with either MMF or cyclophosphamide, and was afterwards associated with maintenance therapy (either MMF or azathioprine) [10]. The association of belimumab and cyclophosphamide is rarely cited in the literature, therefore belimumab was discontinued for safety reasons pertaining to possible excessive immunosuppression. Nevertheless, the nephrol-

ogist considered that a biological agent was needed and intravenous rituximab 100 mg was added off-label during the fourth and fifth cyclophosphamide administrations. The association of cyclophosphamide and rituximab has been previously studied but the results did not affirm any added benefit compared to their individual use. Furthermore, a higher susceptibility towards infections was noted [15,18].

After the induction phase, the patient was initiated on MMF, currently 2 g daily, while continuing treatment with hydroxychloroquine 400 mg/day and glucocorticoids (10 mg/day prednisone equivalent). Current treatment principles in SLE aim for flare prevention, minimizing organ impact, and even for complete remission [7,8]. Subsequent evaluations in the following 8 months showed that the patient had achieved partial renal response according to 2019 EULAR/ERA-EDTA targets that state that proteinuria of 500-700mg/24h and below is acceptable after a year of treatment, as in some cases complete renal response can be achieved after almost 24 months of treatment. Regarding other manifestations of SLE, the patient had fewer complaints regarding arthritis or arthralgias, but it is important to note that the dose of daily glucocorticoids exceeds acceptable maintenance doses (≤ 5 mg prednisone equivalent daily). The patient has tried on several occasions to taper glucocorticoids but has been unsuccessful because of recurrent arthritis [15]. Therefore, an argument can be made that the patient's current status of remission is partly due to the underlying glucocorticoid treatment, which would not be sustainable long term.

CONCLUSION

The case illustrates an uncommon succession of therapies for SLE and LN, with belimumab preceding cyclophosphamide. The decision to induce remission with cyclophosphamide was based on histological aspects of the renal biopsy. Although current recommendations permit the association of belimumab and cyclophosphamide, there is very little practical experience to support it.

Patient consent:
Patient consent was given for the publication of medical information.
Anonymity was guaranteed.

Conflict of interest:
The authors declare that they have no conflicts of interest

Author's contributions:
Conceptualization, AR and LE; methodology, AR, LE, CP, CC; software, AR, CP; validation, AR, LE, CP, CC; investigation, AR, LE; writing—original draft preparation, AR, CP; writing—review and editing, AR, LE, CP, CC. All authors have read and agreed to the published version of the manuscript.

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