Case Report

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Successful therapeutic response with sequential therapy of rituximab and belimumab in a hispanic patient with refractory lupus nephritis

Abstract

Lupus nephritis (LN) is the most common severe organ manifestation of systemic lupus erythematosus (SLE). Life expectancy and renal survival is reduced in these patients. A partial remission in LN is associated with a significantly better patient and renal survival rate compared with no remission. We report the case of a 27-year-old Hispanic patient with diffuse proliferative lupus nephritis (grade IV with high activity index) managed with induction therapy with mycophenolate mophethyl (MMF, 1000 mg daily escalating to 3000 mg daily and prednisone (PDN) 1 mg/kg/day. Progression of proteinuria with preserved renal function and extra-renal activity were observed (alopecia). Re-induction with IV cyclophosphamide (CYC, 1 gr.) and pulse IV methylprednisolone (500 mg for three days) was administered, followed by a lower starting dose of PDN (0.5 mg/kg/day). Treatment failure was observed. A second renal biopsy evidenced renal damage (chronicity index 4/12 and activity index 4/24). The patient also developed non-renal clinical manifestations (malar rash, oral ulcers and arthritis). Treatment with IV rituximab (RTX) 1000 mg X2 associated with MMF 1000 mg per day and IV methylprednisolone 500 mg X3 was initiated, followed by PDN 0.5 mg/kg/day with a dose-tapering scheme similar to CYC re-induction. Treatment continued with IV Belimumab (BLM) 600 mg every month associated with MMF 1000 mg per day. Sequential therapy with RTX + BLM showed a partial renal and complete extra-renal response in a patient with severe lupus despite two 2 immunosuppressive treatment schemes.

Keywords: renal lupus, anti-DNA antibodies, systemic lupus erithematosus

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Introduction

Lupus nephritis (LN) is the most frequent severe organ manifestation of systemic lupus erythematosus (SLE). The aim of immunosuppression therapy is to preserve kidney function and improve survival.

In the Euro-Lupus cohort, the 10-year survival of patients with LN was 88% vs 94% in patients without LN.[1] Life expectancy was 15 years lower in patients with LN.[2] In a study including 86 patients with diffuse proliferative LN, the patient survival rate at 10 years was 95% for complete remission, 76% for partial remission, and 46% for no remission. The renal survival rate at 10 years was 94% for complete remission, 45% for partial remission, and 19% for no remission.[3] Even a partial remission in lupus nephritis is associated with a significantly better patient and renal survival compared with no remission.

Hispanics represent a very heterogeneous population in terms of both genetic and socioeconomic backgrounds. Very few studies are available on the differences in epidemiology and response to treatment between this and other groups. Differences in the susceptibility/protection genes have been seen as compared to other populations. These patients have a higher prevalence and greater severity of renal involvement when compared with Caucasians. Also, they have a lower response to treatment of nephropathy with cyclophosphamide. The mortality rate is higher than among Caucasians, even though this might be a consequence of lower socioeconomic levels and a lower access to health care.[4] Between 20% and 70% of patients with LN are reported to be refractory to standard immunosuppressive therapy.[5] Data from GLADEL indicate that belonging to the *Mestizo* group (mixed Amerindian and European ancestry) is associated with greater renal damage.[6]

To date, no new approaches for the treatment of LN have been shown to be superior to CYC or MMF plus corticosteroids. Here, we present a case of refractory LN in a Hispanic patient with good response to sequential therapy with rituximab (RTX) and belimumab (BLM).

Case report

A 27-year-old Hispanic patient diagnosed with SLE (2012) based on skin-mucosal and joint involvement, positive ANA and anti-dsDNA began treatment with hydroxychloroquine 400 mg daily with good clinical response. At the end of 2013, a renal biopsy (RB) was performed due to micromehaturia, red blood cell casts and proteinuria (0.7 grams/day). Diffuse proliferative lupus nephritis (grade IV) with a full house pattern on immunofluorescence with an activity index of 10/24 and a chronicity index of 0/12 was found. At the beginning of 2014, mycophenolate mophethyl (MMF) was started as induction therapy (1000 mg per day to a dose of 3000 mg per day) with prednisone (PDN) 1 mg/kg/day in addition to enalapril 10 mg per day and hydroxychloroquine. At the beginning of the induction phase, the patient developed multi-metameric herpes zoster with good response to IV acyclovir, followed by prophylactic acyclovir for 6 months. PDN was started at a dose of 60 mg/day, then tapered every four weeks by 10 mg/day until a 40 mg/day dose was reached. The dose was then tapered by 5 mg/day until an 8 mg/day dose was reached. After 12 months of treatment and due to therapeutic failure (alopecia, 2.1 grams/day of proteinuria, preserved renal function, positive anti-

dsDNA, decreased C3, leukopenia and lymphopenia; SLEDAI score = 15), re-induction with IV cyclophosphamide (1 gr.) and pulse IV methylprednisolone (500 mg for three days) was administered, followed by a lower starting dose of PDN (0.5 mg/kg/day) for 4 weeks, tapered to an 8 mg/day dose by 6 months. Although at the beginning a decreasing trend in proteinuria was found, treatment failure was observed after 9 months (alopecia, micromehaturia, red blood cell casts, 2.6 grams/day of proteinuria, preserved renal function, positive anti-dsDNA, decreased C3, leukopenia and lymphopenia; SLEDAI score = 15).

A second RB was performed (beginning of 2016) in which, unlike the first, the presence of renal damage was observed with an activity index of 4/24 and a chronicity index of 4/12. In addition, other extra-renal clinical manifestations apart from alopecia were present (malar rash, oral ulcers and arthritis; SLEDAI score = 23). Treatment with IV rituximab (RTX) 1000 mg X2 associated with MMF 1000 mg per day and IV methylprednisolone 500 mg X3 was initiated, followed by PDN 0.5 mg/kg/day with a dose-tapering schedule similar to CYC re-induction. Proteinuria declined and complement evolved towards normal values (Figure 1). IV RTX was administered in 4 cycles over a 2 year-period. Infectious events delayed infusion every 6 months, since 2 bacterial pneumonias were reported during this period; the patient did not require hospitalization and responded to oral antibiotics. No record of a decrease in immunoglobulin levels after RTX was observed. Treatment continued with IV Belimumab (BLM) 600 mg every month associated with MMF 1000 mg per day. After 1-year follow-up (Figure 1), proteinuria decreased >50% (0.6-0.9 grams/day), hematuria resolved, normalization of white blood cells, lymphocytes and complement was observed (SLEDAI score = 6). Corticosteroid discontinuation is under consideration. To date, no complications associated with MMF + BLM therapy scheme have been reported.

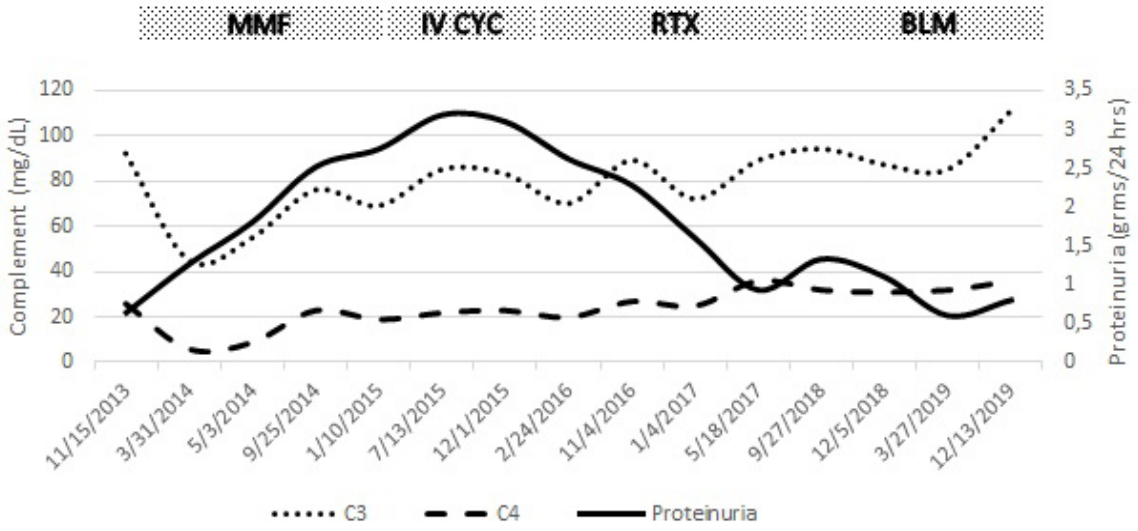

Figure 1 Evolution of proteinuria and complement along induction (MMF), re-induction (IV CYC) and sequential therapy for refractory LN (RTX + BLM). MMF = mycophenolate mofetil; IV CYC = intravenous cyclophosphamide; RTX = rituximab; BLM = belimumab.

Discussion

Several studies conducted in the United States have included Latin American patients, and usually refer to them as "Hispanics", a term that is mainly related to language rather than ethnic background, which may vary between and within Latin American countries. Most of our knowledge about SLE in Hispanics comes from two cohorts. One is the GLADEL study (Latin American Group for the Study of Lupus) a pioneering study in nine Latin American countries which included *Mestizo* (mixed Amerindian and European ancestry), white and African-Latin American (the rest were classified as Native Americans of various countries or Asians).[6] The other is the LUMINA cohort (Lupus in Minorities: Nature vs. Nurture), an incipient cohort recruited in southern USA and Puerto Rico which includes patients from four main groups: Caucasians, Afro-Americans, and Hispanics; the latter group consisting of Texan Hispanics, overwhelmingly of Mexican origin (95%), and Puerto Rican Hispanics.[7] Data from GLADEL indicate that belonging to the *Mestizo* group is associated with greater renal damage, even after considering clinical and socio-demographic variables.[6]

The EULAR/ERA-EDTA guidelines consider RTX as a therapeutic option in the setting of refractory or relapsing disease.[8] There is currently a mismatch between the perceived value of rituximab for the treatment of LN and the published data. The efficacy of RTX in 164 patients with biopsy-proven LN from European cohorts (majority refractory to standard therapies) showed clinical response in two thirds of the patients at both 6 and 12 months.[9] However, RTX has been unsuccessful in the LUNAR trial.[10] In a detailed review, Houssiau et al. discussed the speculative reasons why biologic therapy failed in LN trials and included poor trial design, inadequate definition of the primary outcome measure, immunosuppressive co-medications, too short an exposure to the drug, superiority design required by the medical agencies and underestimation of the role of ethnicity.[11]

Sequential B cell depletion therapy (BCDT) may promote ever-increasing levels of circulating B-cell activating factor (BAFF), accompanied by rising anti-dsDNA antibody levels and disease flare even at a low B cell count.[12] Therefore, the judicious use of BAFF blockade in a subgroup of lupus patients after BCDT justifies the sequential therapy with RTX + BLM. In a translational study, this therapeutic intervention led to specific reductions in humoral autoinmune phenomena, excessive neutrophil extracellular trap (NETs) formation and clinical responses in 16 refractory SLE patients (13 patients with LN and renal response was observed in 11 with 5 complete responders).[13] An interim analysis of data from a phase 2

trial (CALIBRATE study) showed that anti-BAFF following anti-CD20 for LN did not improve clinical outcome at week 24.[14] Further analyses at 48 weeks and beyond will address how anti-BAFF therapy affects the long-term clinical outcome. In a subgroup of lupus patients, after a second cycle of BCDT, and despite increases in both anti-dsDNA antibody and BAFF levels during disease relapse following the first treatment cycle, a decline in serum BAFF and anti-dsDNA antibody levels was observed.[13] Studies in general cohorts of SLE patients have reported that a shorter B-cell depletion period was identified in persisting active disease.[15]

Finally, despite the fact that in our patient treatment with IV methylprednisolone might have been an option at the beginning of LN, our concern about adverse effects, lack of solid evidence supporting the use of a very high dose of glucocorticoids, concurrent capitalization of MMF and the presence of mild proteinuria favored corticosteroid therapy at the dose described above. Thus, in our patient considering the previous treatment failures, increased disease activity despite IV CYC therapy, residual activity in the second RB and the SLE characteristics in Hispanics, we decided that more than 1 cycle of RTX was necessary in order to extend the B-cell depletion period (induction stage) beyond follow up with BLM (maintenance stage).

As the information regarding the long-term safety profile of IV RTX in renal or extra-renal lupus and the effect that might cause a persistent BCDT is scarce in SLE extension of induction therapy beyond 2 years was considered unsafe.[16–20] Regarding the maintenance stage with BLM, a pooled post-hoc analysis of the BLISS trials has shown anti-proteinuric effect and fewer renal relapses in a mixed new-onset and refractory LN population.[21] A recent phase III RCT (n=448) of BLM compared to placebo (both combined with standard of care) in LN showed that more patients receiving BLM plus standard therapy had a primary efficacy renal response than those who received standard therapy alone at week 104.[22] In this regard, the European Commission has approved the expanded use of intravenous and subcutaneous BLM in combination with background immunosuppressive therapies for the treatment of adult patients with active LN in Europe, in addition to SLE. The EU marketing authorization follows the recent approval for the similar expanded LN indication in the U.S. Finally, a Phase II randomized trial (n=43) of RTX plus CYC followed by BLM for the treatment of refractory LN in the US showed that clinical efficacy was not improved although standard treatment (or background immunosuppressive medications) in the maintenance (or BLM) phase was not allowed and the number of patients included in the study was too small to make definite conclusions.[23]

Partial response may be an acceptable outcome when all treatment options have been used. Sequential therapy with RTX and BLM with MMF as background treatment might be a suitable option for refractory LN in Hispanics. Adequately designed studies are necessary in order to confirm our clinical experience.

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Conflicts of interest

The authors declare no conflict of interest.

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