The Renal and Systemic Impact of Rituximab in Patients with Refractory Systemic Lupus Erythematosus

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Abstract

Introduction: Lupus nephritis (LN), a severe complication of systemic lupus erythematosus (SLE), worsens the renal and vital prognosis for up to 50% of SLE patients. Standard treatment involves corticosteroids with cyclophosphamide (CyP) or mycophenolate mofetil (MMF), yet the refractory nature of some cases necessitates alternative therapies. Rituximab (RTX), na anti-CD20 monoclonal antibody, has shown potential in SLE by targeting CD20+ B-cells. However, while some trials, like LUNAR, found RTX's renal impact inconclusive, others noted its benefit in refractory cases.

Methods: This retrospective study assessed RTX's effects on renal and systemic SLE activity in patients unresponsive to conventional immunosuppression.

Results: Ten patients, with biopsy-proven refractory SLE (rSLE) received RTX and were monitored for one year. RTX led to a renal response in 80% of cases, with significant proteinuria reduction, stable kidney function, and decreased SLE Disease Activity Index scores. The response correlated with lower baseline chronic lesions and higher anti-dsDNA levels, highlighting potential predictive factors for RTX effectiveness.

Conclusion: RTX's safety profile was generally favorable, with few infections and minimal immune suppression. These findings align with previous studies suggesting RTX benefits patients with rSLE, particularly those with high serological activity. Thus, RTX may serve as a viable adjunct in rSLE management, warranting further exploration of its role in standard SLE care.

Keywords: Lupus Erythematosus, Systemic/drug therapy; Lupus Nephritis/drug therapy; Rituximab; Treatment Outcome

INTRODUCTION

Lupus nephritis (LN) is a serious complication of systemic lupus erythematosus (SLE), affecting up to 50% of the patients; the incidence and prevalence are influenced by age, gender, geographical region and applied diagnostic criteria.[1] Across SLE patients, kidney involvement confers a worse long-term renal and vital prognosis.[1,2] The current standard treatment regimens of LN include high-dose corticosteroids in combination with either cyclophosphamide (CyP) or mycophenolate mofetil (MMF), to control the degree of disease activity and subsequent kidney and systemic manifestations.[1] B cells have a major role in SLE due to the production of pro-inflammatory cytokines and auto-antibodies and activation of other cells, which amplify the inflammatory cascade. Rituximab (RTX), a chimeric anti-CD20 monoclonal antibody, was proposed by several randomized control trials (RCT) as having a beneficial role in SLE due to its depleting action of CD20+ B-cells.[3,4] Since then, the precise role of RTX in SLE patients has remained undetermined: the Lupus Nephritis Assessment With Rituximab Study (LUNAR) failed to demonstrate superiority in renal endpoints (number of responses) in comparison with the standard of care regimens (MMF or CyP plus corticosteroids); however, the group treated with RTX registered higher renal response rates and higher reductions in auto-antibodies levels, comparing to placebo.[5] Recently, some case series, meta-analyses and open-label observational studies - suggested that RTX could be beneficial in LN patients, especially in refractory disease.[6,7] [We conducted a retrospective evaluation of our in-center experience, to evaluate RTX's efficiency in controlling renal and systemic manifestations of refractory systemic lupus erythematosus

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(rSLE) patients, evaluate treatment tolerability and side effects, and identify potential predictors of response to RTX treatment.

METHODS

Study Design and Entry Criteria

We performed a retrospective observational analysis of all patients with biopsy-proven LN treated with RTX from 2015 to 2020 in our center. Patients were included if they were older than 18 years old, presented adequate follow-up (at least two appointments in the previous 12 months before RTX administration) and fulfilled the criteria for rSLE. Refractory disease was defined as persistent clinical (Systemic Lupus Erythematosus Disease Activity Index 2K (SLEDAI-2K)) ≥10) and/or serological manifestations of SLE (levels of anti-double-stranded DNA (anti-dsDNA) antibodies >50 IU/mL and/or evidence of complement consumption) despite optimized immunosuppressive therapy.

Baseline patient evaluations were collected from the existing patient records and included demographic data (age, gender, race), kidney function (serum creatinine and estimated glomerular filtration rate (eGFR) according to the CKD-EPI equations (reported in mL/min/1.73 m^2)), 24-hour urine protein levels and SLE's clinical activity score (SLEDAI-2K), immunity markers (anti-dsDNA levels and C3/C4 values) and treatment regimens (class and dosage). Furthermore, given that all patients had a kidney biopsy performed at least 6 months before treatment with RTX, we also re-evaluated the severity of LN, using both the modified National Institute of Health (mNIH) activity and chronicity scoring system.

All patients with rSLE received two grams of RTX as induction therapy, divided in either two (biweekly) or four (weekly) administrations, associated with the prednisolone (1 mg/kg with tapering over weeks) and either CyP (500 mg every two weeks for 12 weeks) or MMF (2000-3000 mg/day, according to leucocyte and gastrointestinal tolerance). For maximal antiproteinuric effects, angiotensin receptor blockers or angiotensin-converting enzyme inhibitors were used in combination at the highest doses tolerated.

The patient's response was re-evaluated in all the pertinent clinical and biological variables at six and twelve months. At six months, all the patients who achieved a partial response received an additional RTX infusion (500 mg).

End Points and Assessments

Our primary endpoint was to assess renal response to treatment. It was divided as: complete (24-hour urine protein <500 mg), partial (24-hour urine protein reduction ≥50% and absolute values <3000 mg) and absent (when none of the above criteria were fulfilled).

Secondary Endpoints Included:

- Variation of the eGFR during treatment;
- Evolution of clinical markers of disease activity, measured through the variation of the SLEDAI-2K score and incidence of low-activity SLE (Lupus Low Disease Activity State (LLDAS) criteria included a SLEDAI-2K score inferior to 4 and PDN dose inferior to 7.5 mg daily and no major organ involvement);
- Evolution of serological markers of disease activity (serum complement and anti-dsDNA levels);
- Variation of the dosage of adjuvant immunosuppressive drugs, particularly steroids.
- Identification of predictors of response to rituximab therapy.

Safety Assessments

Safety assessments included adverse events, with particular emphasis on adverse events of special interest, including infusion/anaphylactic reactions, cancer, infections, hypogammaglobulinemia, hospitalization and death.

Statistical Analysis

Statistical analysis was performed using IBM-SPSS Statistics v26 and the confidence interval was set at 95%. A p-value < 0.05 was considered statistically significant. The sample was described globally in terms of the distribution of the descriptive variables by summary statistics depending on the type of variable and its distribution. Categorical variables will be described as relative frequency (absolute frequency). Numerical continuous and discrete data will be described as median (interquartile range). Mann-Whitney test (U) was used to compare the medians and distribution of continuous variables between groups and $\chi 2$ test to compare the prevalence of categorical variables of interest. A comparison of continuous variables is presented as Pearson coefficient (r). To estimate the RTX's effect on clinical and analytical SLE-related variables, the Wilcoxon-signed Rank Test for paired variables (Z) was applied.

RESULTS

Patient Population

We reviewed our entire center's Lupus Cohort patients (n=127) and identified ten patients with rSLE that were treated with RTX during the study period. The baseline characteristics of these patients are exposed in Table 1.

Our sample was composed mainly of females (70.0%, n=7), with a median age of 26 years (23-50) and 9 years (4-14) of SLE vintage.

Table 1. Clinical and demographic information.

Patient	Gender	Age	Ethnicity	SLE vintage (years)	LN Class	mNIH activity	eGFR	Proteinuria (mg/24h)	dsDNA antibodies	Low C3 or C4	SLEDAI 2K	Non-renal symptoms	Previous treatment
1	F	25	C	15	IV	8	133	3330	+	+	35	MC, MS	MMF + PDN
2	M	59	C	13	III	8	100	890	+	-	11	MS	MMF + PDN
3	F	22	C	9	III	11	122	4600	+	+	26	MC	MMF + CsA + PDN
4	F	23	C	12	IV	10	84	1000	+	+	20	MC, H, G	MMF + PDN
5	F	48	C	7	III	0	111	16593	+	+	11	MS, MC	MMF + PDN
6	F	55	C	20	IV	6	63	3271	+	+	27		MMF + CsA + PDN
7	F	21	C	2	III	4	126	2832	+	+	18	MC, H	MMF + CsA + PDN
8	M	35	B	4	V + III	0	53	11354	-	-	20	MS	MMF + PDN
9	F	27	C	8	IV	4	79	4372	+	+	17	G,MS	MMF + PDN
10	F	23	C	2	V	0	72	4800	+	+	19	MC	MMF + PDN

F: feminine; M: masculine; C: caucasian; B: black; dsDNA antibodies quantitative assay: negative: <30 umol/L; Low C3: <0.7 g/L; Low C4:<0.16 g/L; Non-renal symptoms (according to the British Isles Lupus Assessment Group (BILAG) Index8): MS: musculoskeletal, MC: mucocutaneous, H: hematological, G: general MMF: mycophenolate mofetil; CsA cyclosporine; PDN: prednisolone

Histological Findings

LN class IV was the most common finding (40.0%, n=4) on kidney biopsy, followed by class III (40.0%, n=4) and class V (20.0%, n=2). Amongst patients with associated or primary proliferative LN (class III and IV), the median mNIH score for activity and chronicity was 5 (4-9) and 2.5 (2-4), respectively. Additionally, one patient presented with histological signs of vascular LN, in the form of acute glomerular thrombotic microangiopathy associated with the presence of a lupus anticoagulant.

Baseline Biochemistry and Immunology

Our sample had a baseline value for serum creatinine of 0.9 mg/dL (0.7-1.1) and 24-hour proteinuria of 3851 mg (2374-6438). The severity of kidney involvement varied according to the biopsy's histology, with higher serum creatinine (U=16, *p*=0.044) and higher 24-hour urine protein (U=14, *p*=0.09) seen in patients with class V LN. Median baseline levels of anti-dsDNA antibodies were 88 IU/mL (16-929) and were similar across all LN classes and presented no correlation with disease's activity (r=-0,1; *p*=0,8). The majority of the cohort (80.0%, n=8) had levels of C3 and/or C4 below the normal range, reflected in a median value for C3 of 0.64 (0.58-0.89) and C4 of 0.09 (0.07-0.12). Despite not reaching statistical significance, serum complement levels tended to be lower in patients with active LN class III or IV (C3: U=2.0, *p*=0.17; C4: U=4, *p*=0.24).

Baseline Clinical Disease Activity

Active clinical disease activity- measured using the SLEDAI--2K and assuming a cut-off score of ≥12 - was present in all our patients. Accordingly, the median score for the SLEDAI-2K was 20 (16-26). Patients with higher disease vintage tended to present a more clinically severe SLE score (r=0.54, *p*=0.12). Extra-renal manifestations of SLE were predominantly mucocutaneous (acute or chronic) (60.0%, n=6), followed by musculoskeletal (50.0%, n=5), hematological (20.0%, n=2) and constitutional (10.0%, n=1).

Treatment Regimen Before Rituximab

Before RTX, all our cohort was treated with an association of hydroxychloroquine, MMF and prednisolone (PDN), with a median daily dosage in the previous six months of 3000 mg (2000-3000) and 10.0 mg (5,0-10,0) of MMF and PDN, respectively. In addition, three patients were also treated with cyclosporine (100 mg/day).

Renal Outcomes and Predictors of Response

One year after RTX administration, eight out of ten patients had achieved a renal response, either complete (n=4) or partial (n=4), at a median time of 29 weeks (12--36). A renal response associated with a lower baseline mNIH score for chronicity (if class III or IV) (U=0, *p*=0.046), higher dsDNA titres (U=14, *p*=0.078) and lower SLEDAI--2K (U=2.5, *p*=0.06). Furthermore, when severe chronic

lesions were present (mNIH index for chronicity ≥5) the probability of a renal response was significantly lower ($\chi2$=9, *p*=0.025). Age, gender, disease vintage, LN class/activity score and administration of an additional dosage of RTX did not influence the rate of renal response.

We registered a decrease in 24-hour proteinuria values by 73.2% (53.6%-93.6%) (Fig. 1A), reaching a median value of 1275 mg (168-2788) at the end of the follow-up. These results represented a significant decrease when compared to the baseline values (Z=-2.3, *p=0*.017). A lower baseline proteinuria was found in patients reaching a complete response (U=4, *p*=0.11), which probably reflects the different clinical purposes for RTX treatment.

Overall, there was no significant change in median serum creatinine (Z=0.9, *p*=0.89) or respective eGFR one year after treatment (Fig. 1B). As expected, higher baseline chronic mNIH scores were associated with higher serum creatinine (r=0.43, *p*=0.23) and lower eGFR at one year, irrespective of the renal response. During the follow-up period, we did not register any renal relapses. Nevertheless, all patients with a partial renal response at six months (n=5) received an additional administration of RTX. This supplemental dose translated to one additional complete response at 12 months.

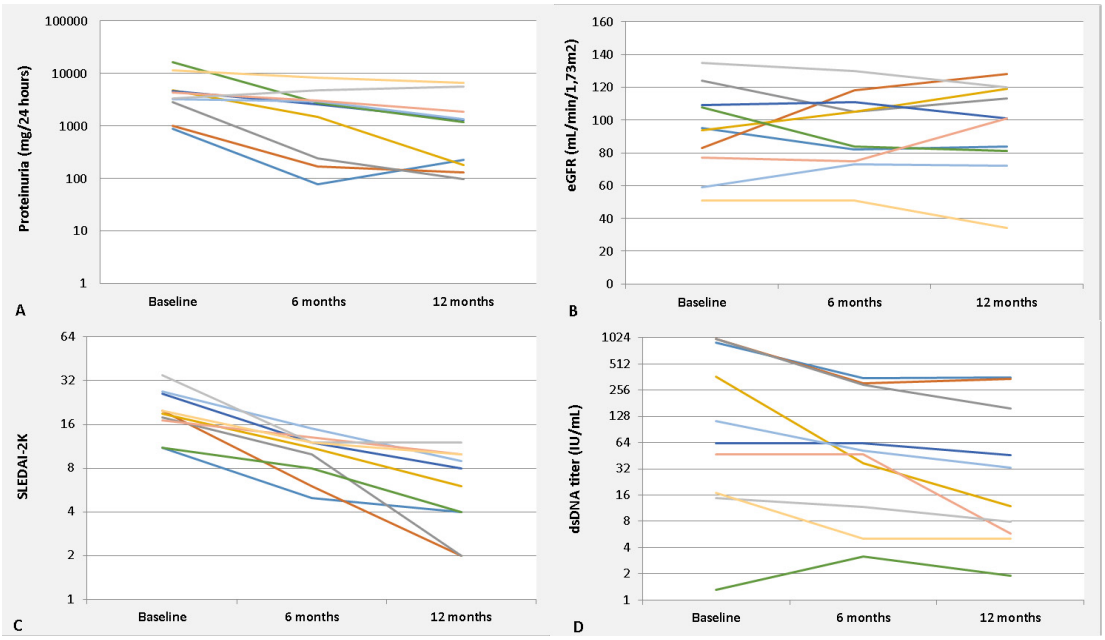

Figure 1. Evolution of different clinical and analytical SLE-related variables across the observation period after treatment with rituximab (each coloured line represents a specific patient).

Clinical and Serological Response and Predictors of Response

A significant clinical improvement was registered at 12 months amongst our entire cohort (Fig. 1C). There was a decrease in the SLEDAI-2K score, averaging 65.1% per patient (47.8-74.1), which translated to lower median scores (Z=-2.8, *p*=0.005) and higher prevalence (90.0%, n=9) of patients with inactive clinical disease (LLDAS) at the end of the follow-up.

There was also a clear link between clinical and renal responses: both the proteinuria Δ (r=0.8, *p*=0.009) and the incidence of a renal response (U=1, *p*=0.039) were associated with higher SLEDAI-2K Δ. Interestingly, older patients presented higher clinical amelioration (r=0.69, *p*= 0.01). No significant association was found between LN class or activity index and the SLEDAI-2K Δ.

Anti-dsDNA antibodies were reduced by 68.0% (41-89) with RTX; median absolute values after one year were inferior compared to baseline values (Z=-2.7, *p*=0.007) (Fig. 1D). No correlation was found between the dsDNA antibodies Δ and the corresponding clinical score or the probability to reach a renal response. The serological impact of RTX was further amplified by an increase in complement factors C3 (Z=1,8, *p*=0.07) and C4 (Z=2.36, *p*=0.01), reaching a median increase of 37.9% (-5-84) and 77.8% (28-129), respectively. Additionally, after adjustment for baseline levels, a significant number of patients (n=9) evidenced normalization of complement values ($\chi2$=9.4, *p*=0.002).

Post-Rituximab Treatment Regimens

By the end of the follow-up period, all our patients were treated with an association of MMF and prednisolone. However, median daily dosages of MMF had decreased by 33% (8-50) and were significantly lower (Z=-2.8, *p*= 0.01) compared to baseline. Prednisolone obtained similar

positive results: we registered a 65.7% (50-90) decrease in daily dosage and lower absolute values (Z=-2.5, *p*= 0.002). Furthermore, in all patients initially treated with CyP (Table 1), the drug was discontinued.

Adverse Events

Five patients developed gastrointestinal discomfort after titration of the MMF dosage, which required an individual adjustment of the maximal dosage. Two patients developed infectious intercurrences, both of bacterial origin (erysipelas and community-acquired pneumonia), but were treated in an ambulatory. We registered one case of immunoparesis (immunoglobulin G below the lower limit of normal); however, this side effect did not result in any infectious complications. No deaths occurred during the follow-up.

DISCUSSION

We conducted a retrospective cohort study with patients with rSLE treated with RTX, to determine its efficacy in reducing renal and systemic manifestations of the disease. We hypothesized that the addition of RTX to the standard of care (SOC) regimens would lead to an important reduction of different renal and clinical-related variables, without significant associated morbidity.

The LUNAR study was the first large randomized study to evaluate the effect of RTX on lupus nephritis: despite a higher rate of renal responses and reductions in several parameters related to disease activity, no significant difference was found compared to the SOC.[5] At this time, these results went against the results of several non-randomized studies that demonstrated clear benefits, especially in cases refractory to standard immunosuppressive therapy.[3,4] Several reasons were put forward to explain the disparity in results, including different trial designs and inclusion criteria: the LUNAR study did not include patients with refractory disease, while the other studies focused especially on this population. Also, from a biological perspective, RTX efficacy is thought to result mainly from its impact on the generation of short-lived antibody-secreting cells (plasmablasts), through the depletion of their direct precursors, including activated and germinal center B cells.[8] In this perspective, RTX failure could be due to antibody production being mediated by refractory, long-lived, CD20-negative, auto-reactive plasma cells, residing in tissues and bone marrow or to the persistence of RTX-resistant B cells in peripheral blood and in the protected microenvironment of lymphoid structures or tissues such as the renal tubulointerstitium.[8]Supporting this last hypothesis, a reanalysis of available data from 68 participants of LUNAR showed that only 53 patients (78%) achieved complete peripheral B depletion.[9] The achievement of a stringent complete depletion, as well as the rapidity and duration of this response, is associated with a complete response to RTX at week 78, although not at 52 weeks.[9] This data suggests that there may be a role for more potent anti-CD20 drugs (such as obinutuzumab), and that the time frame for evaluation of results with these therapies should be longer, requiring adjustments in trial designs.

Nonetheless, in a systematic review of 26 studies, identifying 300 patients with refractory LN, the addition of RTX to the SOC immunosuppressive therapy resulted in 40% of the patients achieving complete renal clinical response with a further 34% having a partial response.[10] Another meta-analysis of 31 studies describing 1112 patients with refractory lupus, of which 10 studies included 223 patients with refractory LN achieved similar results, with 78% of the patients showing renal response (46% complete and 32% partial).[11] In this scientific context, the RITUXILUP trial emerged. It was a single-center observational study that enrolled 50 patients, using a rituximab-based therapeutic regimen without oral corticosteroids, consisting in two intravenous doses of 1 g rituximab with 500 mg EV methylprednisolone (D1 and D15) and maintenance treatment with MMF. By 52 weeks, CR and PR had been achieved in 52% (n=26) and 34% (n=17) respectively; 22% of the patients experienced flares and there was a good safety profile, with only 2 patients of the responding group requiring the use of oral steroids for more than 2 weeks.[6] This study defied conventional wisdom and rules for the treatment of lupus nephritis and remains, to this day, and to the best of our knowledge, the only study completely avoiding oral steroids in the treatment of LN. Sadly, a RCT comparing the RITUXULUP protocol with an arm using SOC with oral steroids was prematurely terminated due to difficulties in recruiting patients, after enrolling only 24 patients.

In our series, treatment with RTX was associated with both clinical and renal improvement. A renal response was achieved in 80% of the patients, which reflected both a significant decrease of the 24-hour proteinuria without an associated deterioration of the baseline kidney function. These results are in line with the before-mentioned published trials.[10,11] Among patients with class III or IV LN, the ability to reach a renal response was severely impacted by the presence of histological chronicity signs (glomerulosclerosis, fibrous crescents, tubular atrophy and interstitial fibrosis). Furthermore, although baseline demographical, clinical and analytical variables were comparable amongst responders and non-responders, baseline severe chronic lesions (modified NIH score ≥ 5) were only present in the latter, which reflects the overall worse renal prognosis associated with chronic lesions.[12] These data emphasize the importance of early and aggressive treatment of LN, to minimize the development of chronic lesions, that condition worse treatment response and renal outcomes.

Another predicting factor of response was the presence of high dsDNA titres, suggesting that patients with high serological activity may derive, potentially, the most benefit from RTX treatment. This data is consistent with analysis concerning anti-B cell therapy with other drugs.

Particularly, post hoc analyses from the phase 2 and the phase 3 BLISS (a study of Belimumab in Subjects with Systemic Lupus Erythematosus) trials have suggested that patients with serological activity at baseline (ie, elevated anti-dsDNA titres and/or low complement levels) show better responses to B-lymphocyte stimulator (BlyS) inhibition.[7,13] All our patients improved clinically: we registered a significant decrease in the SLEDAI-2K scores compared to baseline, which led to all patients presenting inactive clinical disease by the end of the follow-up. There was also a clear link between clinical and renal responses: both the proteinuria decrease and the incidence of a renal response were associated with higher SLEDAI-2K Δ. RTX also had a serological impact, as we registered a reduction in anti-dsDNA titres and normalization of complement values. Most importantly, it permitted a reduction of the median dosage of the normally prescribed immunosuppressants and also discontinuation of one drug in case of triple therapy. This becomes especially important when it comes to corticosteroids, given the high incidence of complications arising from long-term therapy.

We found no significant adverse effects following RTX administration, despite two cases of bacterial infections being recorded.

Our study was limited by the retrospective nature of many collected variables and the missing data from patients' records. However, we corrected these limitations by assessing patient's records from the hospital's clinical archive. Secondly, our results are heavily limited due to a low study population; this is explained by the fact that not only RTX treatment is associated with higher health-related costs when compared to SOC but also is considered an off-label therapy in this population.

Despite recent scientific advances, the exact role of RTX in patients with SLE and lupus nephritis remains undefined: individualization of therapy (considering previous therapeutic history, age and pre-existing comorbidities) and the prescriber's experience are still the main deciding factors. In our experience, RTX therapy in patients with rSLE had a favorable impact on the regression of renal and systemic activity markers, without any significant adverse effects. Additionally, it also allowed a significant reduction in the dose of immunosuppressive therapy necessary to control the disease. A lower baseline mNIH score for chronicity, higher dsDNA titres and lower SLEDAI-2K were predictors of good response to RTX therapy.

Ethical Disclosures

Conflicts of Interest: The authors have no conflicts of interest to declare.
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Confidentiality of Data: The authors declare that they have followed the protocols of their work center on the publication of patient data.
Protection of Human and Animal Subjects: The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and those of the Code of Ethics of the World Medical Association (Declaration of Helsinki as revised in 2024).
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PAC: Responsible for collecting, analyzing patient's data and writing the manuscript.
NO and HP: Responsible for writing the manuscript.
RA: Editing and reviewing of the final version of the article.
All authors approved of the final version to be published.

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