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Review

Efficacy of rituximab in 164 patients with biopsy-proven lupus nephritis: Pooled data from European cohorts

Cándido Díaz-Lagares [a], Sara Croca [b], Shirish Sangle [c], Edward M. Vital [d], Fausta Catapano [e,j], Agustín Martínez-Berriotxoa [f], Francisco García-Hernández [g], José-Luis Callejas-Rubio [h], Javier Rascón [i], David D'Cruz [c], David Jayne [e], Guillermo Ruiz-Irastorza [f], Paul Emery [d], David Isenberg [b], Manuel Ramos-Casals [a,*], Munther A. Khamashta [c] and The UK-BIOGEAS Registry [1]

[a] *Laboratory of Autoimmune Diseases "Josep Font", Department of Autoimmune Diseases, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Hospital Clínic, Barcelona, Spain*
[b] *Centre for Rheumatology, University College London, London, UK*
[c] *Lupus Research Unit, The Rayne Institute, King's College London School of Medicine at Guy's, King's and St Thomas' Hospitals, St Thomas' Hospital, London, UK*
[d] *Section of Musculoskeletal Disease, NIHR Leeds Musculoskeletal Biomedical Research Unit, Leeds Institute of Molecular Medicine, University of Leeds, UK*
[e] *Vasculitis and Lupus Clinic, Addenbrooke's Hospital, Cambridge University, UK*
[f] *Autoimmune Diseases Research Unit, Department of Internal Medicine, Hospital Universitario Cruces, University of the Basque Country, Barakaldo, Spain*
[g] *Collagenosis and Pulmonary Hypertension Unit, Department of Internal Medicine, Hospital Virgen del Rocío, Sevilla, Spain*
[h] *Department of Internal Medicine, Hospital San Cecilio, Granada, Spain*
[i] *Department of Internal Medicine, Hospital Son Espases, Mallorca, Spain*
[j] *Department of Nephrology, S. Orsola-Malpighi Hospital, Bologna, Italy*

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ABSTRACT

Objective: To present a pooled analysis of the efficacy of rituximab from European cohorts diagnosed with biopsy-proven lupus nephropathy (LN) who were treated with rituximab.
Methods: Consecutive patients with biopsy-proven LN treated with rituximab in European reference centers were included. Complete response (CR) was defined as normal serum creatinine with inactive urinary sediment and 24-hour urinary albumin <0.5 g, and partial response (PR) as a >50% improvement in all renal parameters that were abnormal at baseline, with no deterioration in any parameter.
Results: 164 patients were included (145 women and 19 men, with a mean age of 32.3 years). Rituximab was administered in combination with corticosteroids (162 patients, 99%) and immunosuppressive agents in 124 (76%) patients (cyclophosphamide in 58 and mycophenolate in 55). At 6– and 12-months, respectively, response rates were 27% and 30% for CR, 40% and 37% for PR and 33% for no response. Significant improvement in 24-h proteinuria (4.41 g. baseline vs 1.31 g. post-therapy, $p=0.006$), serum albumin (28.55 g. baseline to 36.46 g. post-therapy, $p<0.001$) and protein/creatinine ratio (from 421.94 g/mmol baseline to 234.98 post-therapy, $p<0.001$) at 12 months was observed. A better response (CR + PR) was found in patients with type III LN in comparison with those with type IV and type V ($p=0.007$ and 0.03, respectively). Nephrotic syndrome and renal failure at the time of rituximab administration predicted a worse response (no achievement of CR at 12 months) ($p<0.001$ and $p=0.024$, respectively).
Conclusion: Rituximab is currently being used to treat refractory systemic autoimmune diseases. Rituximab may be an effective option for patients with lupus nephritis, especially those refractory to standard treatment or who experience a new flare after intensive immunosuppressive treatment.

Contents

* Corresponding author at: Servei de Malalties Autoimmunes, Hospital Clínic, C/Villarroel, 170, 08036-Barcelona, Spain. Tel.: +34 93 2275774; fax: +34 93 2271707.
E-mail address: mramos@clinic.ub.es (M. Ramos-Casals).
[1] The members of the UK-BIOGEAS are listed in the Appendix.

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1. Introduction

Systemic lupus erythematosus (SLE) is considered the most clinically and serologically diverse systemic autoimmune diseases (SAD) because it may affect any organ and display a broad spectrum of clinical manifestations [1,2]. Renal disease plays a key role in the prognosis of SLE and contributes significantly to the morbidity and mortality of the overwhelmingly-young, female SLE population [3]. Patients with glomerulonephritis have a higher mortality rate in comparison with those without renal involvement, and nearly 10% of patients with lupus nephritis (LN) develop end-stage renal failure requiring dialysis or transplantation [4–6]. Both nephritis and chronic corticosteroid and immunosuppressive agent use cause significant morbidity and reduced life expectation in SLE patients.

Rituximab is a chimeric antibody against CD20, a surface antigen expressed by B cells. Rituximab was first approved for the treatment of patients with relapsed or refractory low-grade or follicular, CD20-positive, B-cell non-Hodgkin lymphoma in 1997, and then for RA [7]. Off-label use of rituximab in SLE was first reported in 2002 and, since then, has been increasingly used in patients with SLE [8]. However, the advanced results of the LUNAR trial [9] showed that rituximab plus mycophenolate was not superior to mycophenolate in SLE patients with proliferative nephritis (types III/IV). Although definite conclusions must await full details of this trial, the negative preliminary results are discouraging [10]. This is in contrast to the good results for the off-label use of rituximab reported by various centers with long clinical experience in the management of SLE [11–17], illustrating the differences that occur between real-life and trials.

In this study, we present a pooled analysis of the efficacy of rituximab in real-life patients from European cohorts diagnosed with biopsy-proven lupus nephropathy who were treated with rituximab.

2. Methods

2.1. UK-BIOGEAS Registry

In January 2009, nine centers from UK and Spain specialized in the management of SLE patients created the UK-BIOGEAS Registry, a multicenter study devoted to evaluate the efficacy of the off-label use of rituximab in adult patients with lupus nephritis in a real-life setting. By December 2010, the database included 151 consecutive patients with lupus nephritis treated with rituximab. The inclusion criteria were: i) diagnosis of SLE based on the current classification criteria [18]; ii) adult patients (age $\geq$14 years at the time of rituximab administration); and iii) lupus nephritis treated with rituximab, either following the regimen recommended for the treatment of lymphoma (375 mg/m^2 of rituximab weekly for 4 weeks) or the regimen consisting of two 1000 mg doses separated by 15 days. The majority of patients have been previously included in previous reports describing the use of rituximab in patients with SLE [19–22].

2.2. Search strategy

As complementary data to those included in the Registry, we searched MEDLINE using the MeSH term “lupus nephropathy” and the term “rituximab” with these restrictions: language (English), date (January 1, 1986 to October 14, 2010), studies (humans) and age (adults). Studies were eligible when (i) the study population included adults with lupus nephritis; (ii) the intervention consisted of therapy with rituximab; (iii) studies included European cohorts of at least 5 patients with lupus nephritis treated with rituximab (case reports were excluded); and (iv) studies contained sufficient, clear information on the effect of the drug on lupus nephritis, including an individual description of the main characteristics of each patient in a specific table. Two authors (CD-L, M-RC) read the titles and abstracts (if available) identified by the search and selected studies that might comply with the eligibility criteria. These authors fully reviewed the selected studies to determine criteria fulfillment. Disagreements between the 2 authors were discussed with the other authors until consensus was reached. We also searched the reference lists of relevant articles retrieved. Five articles [23–27] fulfilled the eligibility criteria.

2.3. Pooled analysis

With the aim to ensure the homogeneity in the patients finally included in the pooled analysis, the following inclusion criteria were applied in the two sources of patients (the Registry and the Pubmed search): i) fulfillment of SLE classification criteria; ii) age $>$ 14 years; iii) biopsy-proven lupus nephropathy; iv) homogeneous definition of therapeutic response either at 6 or 12 months. Complete response (CR) was defined as normal serum creatinine and serum albumin levels, inactive urinary sediment, and 24-hour urinary protein $<$0.5 g; partial renal remission (PR) as a $>$50% improvement in all renal parameters that were abnormal at baseline, with no deterioration in any parameter. No response was defined as no significant improvement ($<$50% of initial altered parameters) or a worsening of the disease in spite of treatment.

2.4. Data extraction

CD-L designed a standard data extraction Excel-based form and the other authors amended and validated the design of the form prior to data abstraction. Two authors (CD-L, M-RC) extracted the data independently. CD-L entered the data into the Excel file and the remaining authors checked it. The following baseline variables were entered into the Excel-based form: age, gender, SLE/LN disease duration, ethnicity, SLEDAI and BILAG scores, previous therapies, renal parameters (24-h proteinuria, protein–creatinine ratio, serum albumin and estimated glomerular filtration rate — eGFR), results of renal biopsy according to the ISN/RPS classification [28] and concomitant therapies.

2.5. Statistical analysis

Categorical data were compared using the χ^2 and Fisher's exact tests. Continuous variables were analyzed with the Student's *t*-test in large samples of similar variance and with the nonparametric Mann–Whitney *U*-test for small samples, with results indicated as mean standard error of the mean (SEM). A two-tailed value of $p<0.05$ was taken to indicate statistical significance. The statistical analysis was performed using the SPSS 18.0 program.

3. Results

3.1. General description

A total of 164 patients (99 from the UK-BIOGEAS Registry and 65 from the literature search) fulfilled the inclusion criteria for the pooled analysis (Table 1). There were 145 females and 19 males, with a mean age at LN diagnosis of 32.3 years, a mean time of evolution of SLE until LN diagnosis of 8.1 years and a mean time of evolution of LN until renal biopsy of 5.8 years. Ninety-two (56%) patients were Caucasian, 46 (28%) Black, 22 (13%) Asian and four classified as "other".

In 82 (50%) cases, rituximab was administered for LN refractory to standard therapies, in 69 (42%) for LN flare and in 13 (8%) as first-line

Table 1
Baseline characteristics at diagnosis of lupus nephritis in 164 patients treated with rituximab. Data presented in all cases and separated according to the renal biopsy.

	All patients N = 164	Type IV N = 93	Type III N = 26	Type V N = 20	Mixed types N = 19	Type II N = 6
Sex (female)	145 (88%)	85 (91%)	22 (85%)	18 (90%)	15 (79%)	5 (83%)
Age at LN diagnosis (yrs)	32.31 ± 0.84	32.32 ± 1.07	31.12 ± 1.69	35.85 ± 2.92	29.47 ± 2.29	34.5 ±
SLE disease duration (yrs)	8.15 ± 0.49	8.54 ± 0.70	7.42 ± 1.0	9.1 ± 1.67	6.87 ± 1.05	6.17 ± 2.20
LN disease duration (yrs)	5.79 ± 0.44	6.4 ± 0.62	4.65 ± 1.14	5.47 ± 1.10	4.88 ± 0.90	5.20 ± 2.54
Ethnicity						
- White	92 (56%)	61 (66%)	14 (54%)	9 (45%)	6 (32%)	2 (33%)
- Black	46 (28%)	17 (18%)	9 (35%)	9 (45%)	8 (42%)	3 (50%)
- Asian	22 (13%)	11 (12%)	3 (11%)	2 (9%)	5 (26%)	1 (17%)
- Other	4 (2%)	4 (4%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
SLEDAI at LN diagnosis	16.4 ± 0.85	16.60 ± 1.33	15.50 ± 1.65	14.2 ± 1.79	18.78 ± 2.02	16.75 ± 3.50
BILAG A	35/41 (85%)	28/31 (90%)	5/7 (71.4%)	1/1 (100%)	0/0 (0%)	1/2 (50%)
Previous therapies						
- CYC[2]	131 (80%)	81 (87%)	21 (81%)	10 (50%)	15 (79%)	4 (67%)
- AZA	105 (64%)	52 (56%)	17 (65%)	13 (65%)	14 (74%)	2 (33%)
- MMF	98 (60%)	53 (57%)	18 (69%)	16 (80%)	14 (74%)	4 (67%)
- MTX	23 (14%)	10 (11%)	7 (27%)	3 (15%)	3 (16%)	0 (0%)
- CsA	10 (6%)	7 (7%)	1 (4%)	2 (10%)	0 (0%)	0 (0%)
Cumulated CYC grams	8.1 ± 1.06	10.04 ± 1.70	4.49 ± 1.01	6.94 ± 1.78	4.92 ± 0.69	4.75 ± 1.25
RTX indication						
- First-line therapy	13 (8%)	8 (9%)	2 (8%)	1 (5%)	2 (11%)	0 (0%)
- Refractory LN	82 (50%)	53 (57%)	8 (31%)	10 (50%)	7 (37%)	4 (67%)
- LN flare	69 (42%)	32 (34%)	16 (61%)	9 (45%)	10 (53%)	2 (33%)
Renal presentation						
- 24-h proteinuria (gr)^	4.4 ± 0.38	4.33 ± 0.47	2.54 ± 0.49	4.86 ± 0.77	6.56 ± 1.70	3.85 ± 1.01
- Protein/creatinine ratio (g/mmol)	421.9 ± 66.2	508.1 ± 89	174.2 ± 63.4	310.6 ± 98.0	289.7 ± 66.0	167.0 ± 32.0
- Albumin (g)[1]	28.55 ± 0.71	28.31 ± 0.93	34.73 ± 1.54	26.75 ± 1.77	25.73 ± 1.88	27.67 ± 3.68
- eGRF (ml/min)[1]	28.6 ± 0.71	70.66 ± 4.19	90.36 ± 6.92	99.32 ± 9.18	69.51 ± 7.08	77.0 ± 16.34
- 24-h proteinuria > 3 g[1]	57/99 (58%)	30/52 (58%)	4/16 (25%)	10/13 (77%)	10/14 (71%)	3/4 (75%)
- Prot/ProtCreat Ratio > 3g*,[1]	79/146 (54%)	48/85 (56%)	6/23 (26%)7	11/16 (69%)	11/16 (69%)	3/6 (50%)77
- Cr Cl < 60 ml/min	41/139 (30%)	30/82 (37%)	3/23 (13%)	2/15 (13%)	5/14 (36%)	1/5 (20%)
Activity renal index[2]	7.71 ± 0.47	8.55 ± 0.61	5.4 ± 0.48	Nd	8.46 ± 1.02	Nd
Chronicity renal index	3.23 ± 0.30	3.23 ± 0.39	2.0 ± 0.77	Nd	4.31 ± 0.59	Nd
CD19+ depletion	91/101 (90%)	50/53 (87%)	15/19 (79%)	10/11 (94%)	11/13 (85%)	5/5 (100%)
CD19+ depletion (months)	12.80 ± 1.74	14.82 ± 2.86	8.79 ± 1.26	8.17 ± 1.47	16.29 ± 3.74	7.00 ± 1.26
Concomitant therapies						
- CYC[2]	58 (35%)	43 (46%)	8 (31%)	1 (5%)	3 (16%)	3 (50%)
- MMF	55 (33%)	30 (32%)	8 (31%)	8 (40%)	8 (42%)	1 (17%)
Therapeutic response (6 m)[2]						
- Complete remission	30/110 (27%)	10/62 (16%)	10/21 (48%)	3/11 (27)	8/16 (50%)	1/6 (17%)
- Partial remission	44/110 (40%)	28/62 (45%)	6/21 (27%)	5/11 (46%)	4/16 (50%)	2/6 (33%)
- No response	36/110 (33%)	24/62 (39%)	5/21 (24%)	3/11 (27%)	4/16 (50%)	3/6 (50%)
Therapeutic response (12 m)^						
- Complete remission	38/126 (30%)	16/71 (22%)	10/16 (62%)	3/17 (18%)	8/16 (50%)	1/6 (17%)
- Partial remission	46/126 (37%)	29/71 (41%)	3/16 (19%)	8/17 (47%)	4/16 (25%)	2/6 (33%9
- No response	42/126 (33%)	26/71 (37%)	3/16 (19%)	6/17 (35%)	4/16 (25%)	3/6 (50%)

Significant differences between groups: ^$p<0.10$. [1]$p<0.05$. [2]$p<0.01$. [3]$p<0.001$.
LN: lupus nephritis; SLE: systemic lupus erythematosus; RTX: rituximab; CYC: cyclophosphamide; MMF: mycophenolate; AZA: azathioprine; MTX: methotrexate; CsA: cyclosporin A; eGRF: creatinine clearance; SEM: standard error of the mean. *Prot/ProtCreat Ratio: 24-h proteinuria > 3 g, and/or protein/creatinine ratio > 3 mg/g; Cr Cl: creatinine clearance.

therapy in patients with newly diagnosed LN. Previous immunosuppressive therapies included cyclophosphamide in 131 (80%) patients, mycophenolate in 105 (64%), azathioprine in 98 (60%), methotrexate in 23 (14%) and cyclosporine A in 10 (6%). The cumulated dose of cyclophosphamide was detailed in 104 patients, with a mean of 8.1 g.

Renal biopsy showed type IV LN in 93 (57%) patients, type III in 26 (16%), type V in 20 (12%), type II in 6 (4%) and mixed membranous LN with proliferative lesions in 19 (12%). The renal activity and chronicity scores were detailed in 56 patients; the mean activity score was 7.7 and the mean chronicity index 3.2. The main baseline features according to histopathological LN type are summarized in Table 1.

3.2. Therapeutic response

3.2.1. Response rates

Response rates could be evaluated at 6 months in 110 patients. A favorable therapeutic response (CR or PR) was achieved in 74 (67%) patients (44 were classified as PR, 30 as CR). The remaining 36 (3%) patients were classified as having no response (NR). A favorable response (CR or PR) was found in 16/21 (76%) patients with type III LN, in 38/62 (61%) of those with type IV, in 8/11 (73%) of those with type V and in 8/10 (80%) of those with mixed membranous-proliferative LN. The highest rates of CR were obtained in patients with mixed types (75%) and type III LN (48%), while patients with pure type V and type IV had the lowest rates (27% and 16%, respectively).

Response rates could be evaluated at 12 months in 126 patients. A favorable therapeutic response (CR or PR) was achieved in 84 (67%) patients (46 were classified as PR, 38 as CR). The remaining 42 (33%) patients were classified as having no response (NR). A favorable response (CR or PR) was found in 13/16 (81%) patients with type III LN, in 45/71 (63%) of those with type IV, in 11/17 (65%) of those with type V and in 12/16 (75%) of those with mixed membranous-proliferative LN. The highest rates of CR were obtained in patients with type III LN (62%) and mixed types (50%), while patients with type IV and pure type V had the lowest rates (22% and 18%, respectively). A better response was found in patients with type III LN in comparison with those with type IV and type V ($p = 0.007$ and 0.03, respectively).

3.2.2. Response of laboratory parameters

In addition to the standardized definitions of therapeutic response (CR, PR and NR), we also analyzed the response of renal parameters to rituximab therapy at 12 months. An improvement in 24-h proteinuria was observed in 56/62 (90%) patients (from 4.41 g. baseline to 1.31 g. post-therapy, $p = 0.006$), improvement in serum albumin in 86/106 (81%) (from 28.55 g. baseline to 36.46 g. post-therapy, $p < 0.001$), improvement in protein/creatinine ratio in 32/45 (71%) (from 421.94 g/mmol baseline to 234.98 post-therapy, $p < 0.001$) and improvement in eGFR in 62/112 (55%) patients (from 74.96 ml/min to 79.58 ml/min post-therapy, $p = 0.101$) (Fig. 1).

3.2.3. Prognostic factors

The prognostic value of the main baseline features at LN diagnosis with respect to achieving a CR to rituximab at 12 months is summarized in Table 2. Patients who achieved CR had a lower mean 24-h proteinuria (3.2 g vs 5.7 g, $p = 0.006$) and higher mean levels of serum albumin (31.4 g/l vs 27.4 g/l, $p = 0.026$), and a lower frequency of nephrotic syndrome (36% vs 82%, $p < 0.001$) and renal failure (15% vs 38%, $p = 0.024$) in comparison with those who did not achieved CR.

Subanalysis of prognostic factors for each type of LN disclosed that patients with CR and with type IV LN were less likely to have received mycophenolate (31% vs 69%, $p = 0.009$) and had a lower mean 24-h proteinuria (2.2 g vs 5.7 g, $p = 0.009$) and a lower frequency of nephrotic syndrome (22% vs 84%, $p = 0.002$), while patients with CR and type III LN had a lower mean 24-h proteinuria (2.3 g vs 5.6 g, $p = 0.036$) in comparison with those who did not achieve CR.

The lower rate of CR was observed in patients with refractory LN (26% vs 60% in the other patients, $p < 0.001$), a result that also was statistically significant in patients with type IV LN (25% vs 64%, $p = 0.01$).

3.3. Adverse events

Thirty-four (21%) patients suffered 45 adverse events. Eight (5%) patients developed infusion reactions, which was severe in 2 cases. Twenty (12%) patients had a total of 21 infections: 7 respiratory infections (4 pneumonia, 3 respiratory tract infections), 5 sepsis, 2 urinary tract infections, 2 osteoarticular infections (1 septic arthritis, 1 necrotizing fascitis), 4 viral infections (3 herpes zoster, 1 CMV viremia) and 1 pneumococcal meningitis. In 6 (4%) patients, neutropenia (3 febrile neutropenia) was observed after rituximab administration. A small number of patients developed other adverse events; one patient (apL positive) suffered two thrombotic events (one pulmonary embolism, one stroke), and there was one brain hemorrhage, three posterior reversible leukoencephalopathies and one pancreatitis. Three patients died during the follow-up period (due to septic shock, brain hemorrhage and disease progression, respectively).

4. Discussion

SLE is not a benign disease. Patients with SLE have a 1.5 to 5-fold increased risk of mortality [29] and nearly 10% die within 10 years of the diagnosis [30]. Clinically, therapeutic decisions in SLE are based on personal experience and reported studies since there are no standardized therapeutic guidelines, with the exception of very recent EULAR proposals [31,32]. The small number of RCTs in SLE may be explained by the low prevalence, the heterogeneous clinical presentation (often multiorgan) and the lack of consensual endpoints. In patients with LN, only three controlled therapeutic trials in large series of patients have been published (Euro-Lupus, ALMS and MAINTAIN trials) [33–35]. The complexity of the therapeutic approach in LN is increased by the large number of patients who do not respond to first-line therapies and by relapses after initial clinical remission [36]. In these patients, there is less scientific evidence available for the use of second-line drugs, which are often prescribed according to individual clinical decisions.

Biological agents are being used for a rapidly expanding number of systemic autoimmune diseases, even though they are not yet licensed for this use by the FDA or the EMEA [37–39]. This off-label use is centered on treating patients with either life-threatening situations or those who are refractory or intolerant to standard therapy. B-cell targeted therapies are included in the therapeutic armamentarium for patients with SLE [40]. Various uncontrolled studies have found rituximab beneficial in small series of LN patients [41,42]. In contrast, the advance results of the LUNAR trial show that rituximab plus mycophenolate was not superior to mycophenolate alone [9]. Thus, rituximab in LN currently seems to be good in real life, but bad in controlled trials [43,44].

We present the results of the use of rituximab in 164 patients with biopsy-proven LN, the majority of whom were refractory to standard therapies (corticosteroids and immunosuppressive drugs, mainly cyclophosphamide, mycophenolate and azathioprine) or had a flare despite their use. We found a clinical response in two thirds of patients at both 6 and 12 months, and a rate of CR of 27% at 6 months rising to 30% at 12 months. In addition, we found a different rate of response according to the ISN/RPS histopathological classification, with a 4-fold higher rate of CR at 12 months in patients with mixed proliferative-membranous LN (70%) in comparison with those with type IV LN (22%). This low rate of CR in type IV LN may help to explain the non-significant results found in the LUNAR trial, in which two thirds of patients have type IV LN [9].

The main baseline features associated with not achieving CR were nephrotic syndrome and renal failure. Other variables that were at the limit of statistical significance ($p < 0.10$) included previous treatment

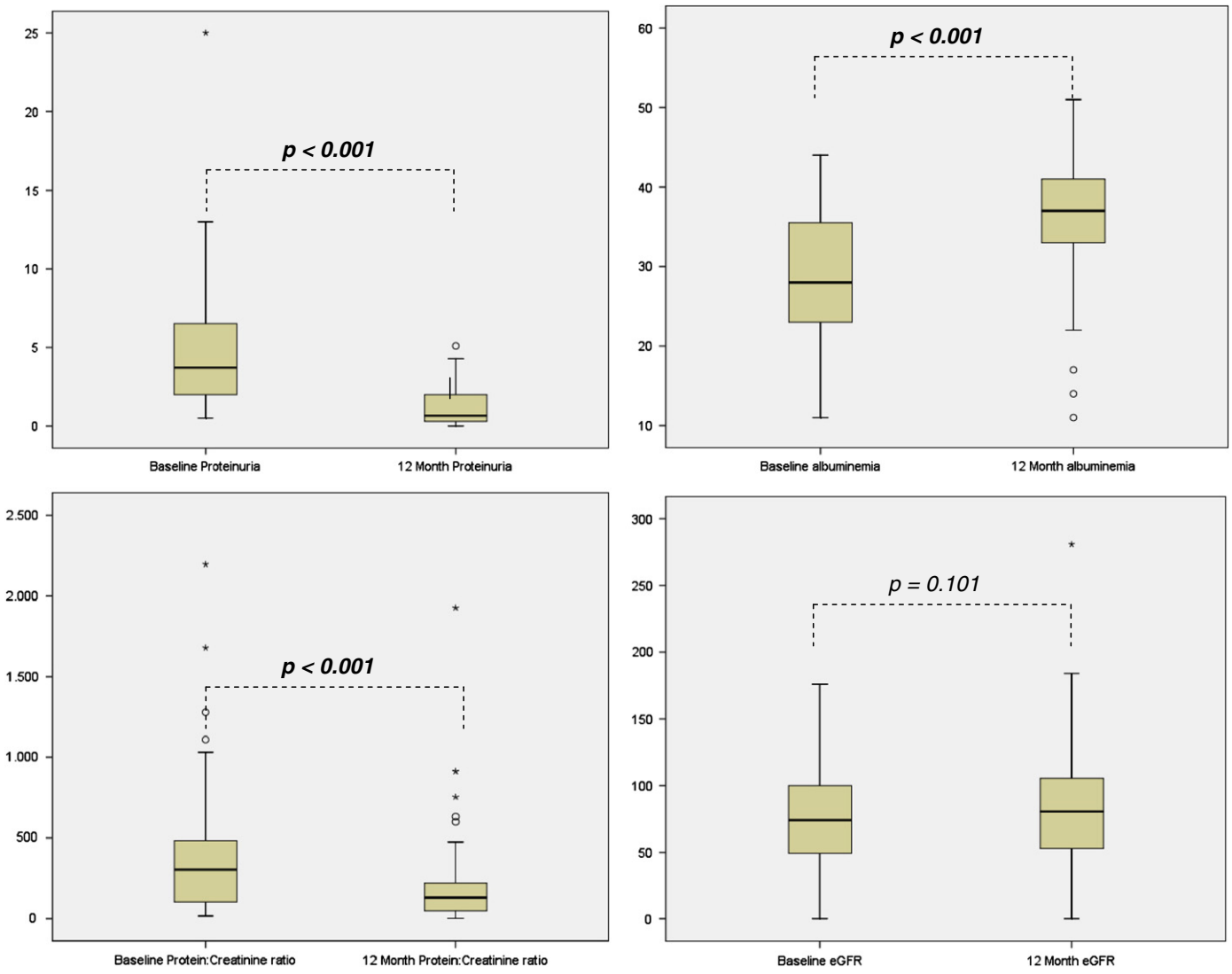

Fig. 1. Response of renal parameters (baseline vs 12-month post-treatment values) in patients with LN treated with rituximab: 24-h proteinuria (from 4.41 g. baseline to 1.31 g. post-therapy, p = 0.006), serum albumin (from 28.55 g. baseline to 36.46 g. post-therapy, p<0.001), protein/creatinine ratio (from 421.94 g/mmol baseline to 234.98 post-therapy, p<0.001) and eGRF (from 77.37 ml/min to 77.94 ml/min post-therapy, p = 0.142).

with mycophenolate and renal chronicity index score. Advance results of the LUNAR trial [9] have also identified renal damage (measured by SLICC SDI) and eGRF <60 ml/min as variables associated with a lack of renal response to rituximab. In addition, we found a lower rate of CR in patients who received concomitant cyclophosphamide. In 2004, van Vollenhoven et al. [45] reported a good response when rituximab was added in two patients refractory to cyclophosphamide. However, a recent study [20] suggested that concomitant cyclophosphamide may not provide additional benefit to rituximab. These data underline the importance of analyzing the effect of concomitant immunosuppressive therapies in LN patients treated with rituximab. Studies in general cohorts of SLE patients have reported other factors associated with no response including shorter disease duration [46], the presence of human anti-chimeric antibodies [26], a shorter B-cell depletion period [25] and the lack of B cell depletion 1 month after rituximab administration, suggesting the importance of early B-cell depletion in achieving a therapeutic response [26]. In our study, the percentage of patients who achieved B-cell depletion was higher in patients with a clinical response (CR or PR) compared with those who did not (95% vs 79%), although the difference was not statistically significant (p = 0.056).

The promising results in uncontrolled studies of LN patients are in clear contrast to the advance results of the recently completed LUNAR trial, a phase III, randomized, double-blind, placebo-controlled, multicenter study that evaluated rituximab in type III/IV LN. In this trial, patients treated with cyclophosphamide, calcineurin inhibitors or mycophenolate within the 3 months prior to screening were excluded. The rituximab arm (n = 72) had a higher percentage of response than the placebo arm (n = 72), although the difference was not statistically significant (57% vs 46%, p = 0.18) [38]. However, there was a statistically significant reduction in anti-DNA titers (p = 0.007) and an increase in C3 levels (p = 0.025) [47]. It will be interesting to know whether type III and type IV LN patients responded differently in the LUNAR trial, since our study showed a 3-fold higher rate of CR in patients with type III LN than in type IV.

The overall and long-term risks of biological agents in patients with SLE are unknown, and the decision to use these agents should be governed by the clinical manifestations. Patients should also be counseled about the potential risks of using biological therapies. The two reported cases of progressive multifocal leukoencephalopathy (PML) in SLE patients treated with rituximab [48], together with the recent reports of additional cases in other diseases (RA) [49] and using other biological agents (etanercept, efalizumab) [50–51], only strengthen the need for careful evaluation of the risk/benefit profile of using biological agents. However, the two reported cases of PML

Table 2
Main baseline characteristics of 126 patients with lupus nephritis according to the response to rituximab at 12 months.

	All patients		Type IV		Type III		Type V		Mixed	
	CR n = 38	PR/NR n = 88	CR n = 16	PR/NR n = 55	CR n = 10	PR/NR n = 6	CR n = 3	PR/NR n = 14	CR n = 8	PR/NR n = 8
Sex (male)	5 (13%)	7 (8%)	2 (12%)	3 (5%)	1 (10%)	1 (17%)	0 (0%)	1 (7%)	2 (25%)	1 (12%)
Age (yrs)	32.0 ± 1.6	32.1 ± 1.2	30.3 ± 2.1	32.5 ± 1.5	31.9 ± 2.8	29.0 ± 4.0	32.3 ± 7.6	35.7 ± 3.9	32.8 ± 4.5	26.0 ± 2.5^
SLE disease duration (yrs)	8.1 ± 1.0	8.1 ± 0.7	9.1 ± 2.0	8.8 ± 0.9	5.9 ± 1.0	6.3 ± 1.6	6.7 ± 3.2	8.8 ± 2.0	8.4 ± 2.1	6.4 ± 0.9
LN disease duration (yrs)	6.2 ± 1.0	6.0 ± 0.5	7.0 ± 2.2	7.1 ± 0.7	4.2 ± 0.7	2.6 ± 0.9	5.3 ± 2.4	5.9 ± 1.3	6.0 ± 4.5	4.5 ± 0.8
Ethnicity										
Caucasian	20 (53%)	45 (51%)	12 (75%)	29 (53%)	4 (40%)	4 (67%)	2 (67%)	6 (43%)	2 (25%)	4 (50%)
Black	11 (29%)	26 (29%)	2 (12%)	13 (24%)	4 (40%)	2 (33%)	0 (0%)	7 (50%)	4 (50%)	2 (25%)
Asian	7 (18%)	13 (15%)	2 (12%)	9 (16%)	2 (20%)	0 (0%)	1 (33%)	1 (7%)	2 (25%)	2 (25%)
Previous therapies										
CYC	30 (79%)	70 (80%)	12 (75%)	48 (87%)	7 (70%)	6 (100%)6	3 (100%)3	6 (43%)	7 (87%)	7 (87%)
MMF	22 (58%)^	66 (75%)	5 (31%)[2]	38 (69%)	8 (80%)	6 (100%)	3 (100%)	11 (79%)	6 (75%)	7 (87%)
Laboratory parameters										
24-h proteinuria (g)	3.2 ± 0.5[2]	5.7 ± 0.6	2.2 ± 0.3[2]	5.7 ± 0.7	2.3 ± 0.5[1]	5.6 ± 2.1	4.2 ± 1.6	5.1 ± 0.9	5.6 ± 1.7	7.3 ± 2.8
PCR ratio (g/mmol)	422.8 ± 141.3	432.8 ± 86.6	493.3 ± 182.4	497.4 ± 105.4	Nd	Nd	Nd	Nd	Nd	Nd
Albumin (g/l)	31.4 ± 1.4[1]	27.4 ± 0.9	182.4	105.4	35.0 ± 2.4	36.0 ± 2.6	30.0 ± 5.6	25.1 ± 1.7	29.0 ± 2.7	22.6 ± 2.6
eGRF (ml/min)	86.3 ± 4.3^	73.9 ± 4.4	30.6 ± 2.2 82.7 ± 6.9	27.9 ± 1.2 69.2 ± 5.9	88.6 ± 6.5	84.2 ± 12.7	94.0 ± 21.0	100.4 ± 11.7	84.5 ± 14.1	59.9 ± 7.6
Nephrotic syndrome	10/28 (36%)[4]	40/49 (82%)	2/9 (22%)[3]	21/25 (84%)	2/10 (20%)	2/2 (100%)	2 (67%)	8/10 (80%)	4/6 (67%)	6 (75%)
Renal failure[b]	5/34 (15%)[1]	29/77 (38%)	3/15 (20%)	21/48 (44%)	0 (0%)	2/6 (33%)	1 (33%)	1/11 (9%)	1/5 (20%)	4 (50%)
Activity renal index	7.6 ± 0.7	8.0 ± 0.8	7.7 ± 0.4	9.4 ± 1.1	5.8 ± 0.6	3.0 ± 0.0	Nd	Nd	9.6 ± 2.4	7.7 ± 0.8
Chronicity renal index	2.4 ± 0.3^	3.7 ± 0.5	2.7 ± 0.3	3.5 ± 0.3	1.0 ± 0.4	Nd	Nd	Nd	3.6 ± 0.7	4.7 ± 0.9
Indication										0.097
First line therapy	6 (16%)[3]	4 (4%)	4 (25%)[2]	3 (5%)	1 (10%)	0 (0%)	0 (0%)	1 (7%)	1 (12%)	0 (0%)
Flare	22 (58%)	31 (35%)	8 (50%)	17 (31%)	7 (70%)	3 (50%)	1 (33%)	6 (43%)	6 (75%)	3 (37%)
Refractory	10 (26%)	53 (60%)	4 (25%)	35 (64%)	2 (20%)	3/6 (50%)	2 (67%)	7 (50%)	1 (12%)	5 (62%)
CD19+ depletion	26/28 (93%)	51/58 (88%)	12/12 (100%)	30/33 (91%)	7/9 (78%)	4/5 (80%)	1/1 (100%)	8/9 (89%)	5/5 (100%)	5/7 (71%)
CD19+ depletion (months)	13.1 ± 3.1	14.9 ± 2.7	13.7 ± 6.4	18.6 ± 4.0	9.3 ± 2.1	7.5 ± 2.6	8.2 ± 1.8	Nd	18.4 ± 4.8	16.0 ± 0.0
Coexisting CYC	6 (16%)	33 (37%)[1]	4/16 (25%)	27/55 (49%)	1 (10%)	3 (50%)	0 (0%)	1/14 (7%)	0 (0%)	0 (0%)
Coexisting MMF	13 (34%)	26 (29%)	8/16 (50%)	15/55 (27%)	2 (20%)	2/6 (33%)	0 (0%)	6 (43%)	3 (37%)	2 (25%)

LN: lupus nephritis; SLE: systemic lupus erythematosus; MP: methylprednisolone; CYC: cyclophosphamide; MMF: mycophenolate; eGRF: creatinine clearance. PCR: protein creatinine ratio; Nd: not done.
[b] Renal failure: eGRF<60 ml/min.
^ p<0.10.
[1] p<0.05.
[2] p<0.01.
[3] p<0.005.
[4] p<0.001.

in SLE patients do not seem to provide a high-enough level of concern to warrant eliminating the off-label use of rituximab in this disease, in view of the lack of new reported cases and the limited options (and the risks associated with those options) in refractory patients with severe organ involvement.

The need for new therapeutic agents in LN is urgent, as no new drugs have been approved for more than 50 years [52]. Since 2002, rituximab off-label has been increasingly used in SLE patients. However, it is not yet possible to make definite recommendations for this off-label use of rituximab in LN. Our results and those obtained by other groups suggest that the use of rituximab in LN is effective and relatively safe, although the data must be interpreted with caution. The advance results of the LUNAR trial show no significant superiority of rituximab over standard treatment, but this does not rule out the possible benefits of using rituximab in patients with refractory or severe LN. The premature halting of the BELONG trial (ocrelizumab in type III/IV LN) due to an increased rate of severe infections [53] and the limited benefits shown by advance data for the renal component of the BLISS-52 and 76 trials (belimumab in SLE) [54,55] only emphasize the difficulties of finding effective and safe biological therapies for patients with LN. Currently, the safety profile of rituximab in the treatment of LN appears to be sufficiently positive to support its off-label use in severe or refractory cases.

Disclosure statement

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Take-home messages

- Rituximab in lupus nephritis (LN) currently seems to be good in real life, but bad in controlled trials.
- We present the results of the use of rituximab in 164 patients with biopsy-proven LN, the majority refractory to standard therapies, with a clinical response in two thirds of patients at both 6 and 12 months, and a rate of CR of 27% at 6 months rising to 30% at 12 months.
- We found a different rate of response according to the ISN/RPS histopathological classification, with a 4-fold higher rate of CR at 12 months in patients with mixed proliferative-membranous LN (70%) in comparison with those with type IV LN (16%).
- The main baseline features associated with not achieving CR were nephrotic syndrome and renal failure.

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Appendix A. Members of the UK-BIOGEAS Study Group

- M. Ramos-Casals (Coordinator, Hospital Clinic, Barcelona, Spain)
- M.M. Ayala (Hospital Carlos Haya, Málaga, Spain)
- M.J. Barragán-González (Hospital Valle del Nalón, Asturias, Spain)
- M.L. Bertolaccini (St Thomas Hospital, London, UK)
- X. Bosch (Hospital Clinic, Barcelona, Spain)
- A. Bové (Hospital Clinic, Barcelona, Spain)
- P. Brito-Zerón (Hospital Clinic, Barcelona, Spain)
- G. Calvo (Hospital Clinic, Barcelona, Spain)
- J.L. Callejas (Hospital San Cecilio, Granada, Spain)
- L. Caminal-Montero (Hospital Central Asturias, Spain)
- M.T. Camps (Hospital Carlos Haya, Málaga, Spain)
- J. Canora-Lebrato (Hospital Universitario de Fuenlabrada, Madrid, Spain)
- M. J. Castillo-Palma (Hospital Virgen del Rocío, Sevilla, Spain)
- A. Castro (Hospital Universitari Sant Joan, Reus, Spain)
- F. Catapano (S.Orsola-Malpighi Hospital, Bologna, Italy)
- A. Colodro (Complejo Hospitalario de Jaen, Spain)
- S. Croca (University College London, London, UK)
- M.J. Cuadrado (St Thomas Hospital, London, UK)
- D. D'Cruz (St Thomas Hospital, London, UK)
- E. de Ramón (Hospital Carlos Haya, Málaga, Spain)
- S. Dass (LMBRU, Leeds Institute of Molecular Medicine, University of Leeds, UK)
- R. Davies (St Thomas Hospital, London, UK)
- C. Díaz-Lagares (Hospital Clínic, Barcelona, Spain)
- C. Donate (Hospital Clínic, Barcelona, Spain)
- E. Dunn (Leeds Teaching Hospitals NHS Trust, Leeds, UK)
- M.V. Egurbide (Hospital Cruces, Barakaldo, Spain)
- P. Emery (LMBRU, Leeds Institute of Molecular Medicine, University of Leeds, UK)
- O. Escoda (Hospital Clínic, Barcelona, Spain)
- D. Galiana (Hospital de Cabueñes, Gijón, Spain)
- F.J. García Hernández (Hospital Virgen del Rocío, Sevilla, Spain)
- R. Gómez-de-la-Torre (Hospital San Agustín, Avilés, Spain)
- R. González-León (Hospital Virgen del Rocío, Sevilla, Spain)
- D. Isenberg (University College London, London, UK)
- D.W. Jayne (Addenbrooke's Hospital, Cambridge University, UK)
- J. Jiménez-Alonso (Hospital Virgen de las Nieves, Granada, Spain)
- M.A. Khamashta (St Thomas Hospital, London, UK)
- M. Martin (LMBRU, Leeds Institute of Molecular Medicine, University of Leeds, UK)
- A. Martínez-Berriotxoa (Hospital Cruces, Barakaldo, Spain)
- F. Medrano (Hospital Universitario de Albacete, Spain)
- M.L. Micó (Hospital La Fe, Valencia, Spain)
- S. Muñoz (Hospital Clinic, Barcelona, Spain)
- C. Ocaña (Hospital Virgen del Rocío, Sevilla)
- J. Oristrell (Hospital Parc Taulí, Sabadell, Spain)
- N. Ortego-Centeno (Hospital San Cecilio, Granada, Spain)
- L. Pallarés (Hospital Son Dureta, Mallorca, Spain)
- C. Pease (LMBRU, Leeds Institute of Molecular Medicine, University of Leeds, UK)
- I. Perales-Fraile (Hospital Universitario de Fuenlabrada, Madrid, Spain)
- M. Pérez-de-Lis (Hospital Meixoeiro, Vigo, Spain)
- R. Perez-Alvarez (Hospital Meixoeiro, Vigo, Spain)
- J. Rascón (Hospital Son Dureta, Mallorca, Spain)
- S. Retamozo (Hospital Clinic, Barcelona, Spain)
- G. Ruiz-Irastorza (Hospital Cruces, Barakaldo, Spain)
- L. Saez (Hospital Universitario Miguel Servet, Zaragoza, Spain)
- G. Salvador (Hospital de Sagunt, Valencia, Spain)
- J. Sánchez-Roman (Hospital Virgen del Rocío, Sevilla, Spain)
- S. Sangle (St Thomas Hospital, London, UK)
- G. Sanna (St Thomas Hospital, London, UK)
- A. Selva-O'Callaghan (Hospital Vall d'Hebron, Barcelona, Spain)
- A. Sisó (CAPSE/GESCLINIC, Barcelona, Spain)
- E.M. Vital (LMBRU, Leeds Institute of Molecular Medicine, University of Leeds, UK)

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We don't need to treat with antivirals (all) patients with autoimmune diseases and chronic hepatitis B virus infection who start biologics

The problem of treating with antivirals patients with a rheumatic condition who start therapy with a biologic drug but who suffer from chronic hepatitis B virus (HBV) infection is actual and pushing.

First of all, the patients with HBV should be categorized properly in those who have seroreversion, those who have reactivation and those who have active disease. According to these definitions, patients should be studied not only for the HBV-DNA concentrations, but also for the presence/absence of hepatitis B e antigen and anti-hepatitis B c antigen antibodies.

Then, we do not have to forget that the risk of developing a more severe liver disease is higher per se in patients with autoimmune conditions, as they are immunosuppressed, and may assume hepatotoxic chemotherapies. Nonetheless, at the suspension of chemotherapic drugs, the immune-mediated reconstitution of infected hepatocytes can cause from hepatitis to hepatic failure and death.

These are good reasons to support the usage of antiviral medications that are usually safe in these patients. Nonetheless, patients with rheumatic conditions can be treated with biologics, that by lowering the immune responses, could represent an addictive risk factor to worsening of infection activity leading into tissue damage.

Marignani et al. (Eur J Intern Med. 2011;22:576-81) performed a systematic review on the course of HBV in biologic response modifiers treated rheumatologic patients. They found no reactivations in patients treated with anakinra, abaacept, golimumab certolizumab pegol. Two patients who were taking tocilizumab as a third line therapy, showed reappearance of HBV-DNA, but did not develop hepatitis, and only in one case entecavir was added.

The major concerns stand for rituximab, with poor data in the literature when analyzing rheumatic patients and contrasting when considering those patients with hematologic conditions. Interestingly, a large number of patients who started biologics were inactive carriers who did not receive prophylaxis, but who did not develop liver complications.

Of this paper, the final suggestions on the possible management strategies are of particular interest and could be considered in the routinary clinical practice. Thus, patients should at first be deeply studied and subcategorized, and then, therapy should be individually set.

Carlo Perricone, MD