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ORIGINAL ARTICLE

Use of Rituximab in Systemic Lupus Erythematosus: A Single Center Experience Over 14 Years

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Objective. **To describe the clinical outcome and safety of rituximab (RTX) treatment in systemic lupus erythematosus (SLE) patients with severe manifestations or whose disease is refractory to standard immunosuppressive therapy, treated at a single center.**

Methods. **This was a retrospective analysis of all patients with SLE treated with RTX at 1 center between June 2000 and December 2013. The clinical outcome was assessed by determining British Isles Lupus Assessment Group (BILAG) scores and anti–double-stranded DNA (anti-dsDNA) and C3 levels before and 6 months after RTX treatment. For safety analysis, adverse events and deaths were recorded.**

Results. **Of a total of 115 patients, 93.9% were female, the mean ± SD age at diagnosis was 26.39 ± 11.90 years, and the mean ± SD disease duration at first RTX treatment was 91.96 ± 84.80 months. A BILAG score variation of −11.26 ± 11.38 ($P < 0.001$) was recorded 6 months after the first RTX treatment; 40% of patients had a complete response and 27% had a partial response; in 36.5% of patients, C3 levels increased more than 25%, and in 33.5% anti-dsDNA levels decreased more than 50%. Depletion of CD19+ cells was achieved in 94.0% of patients. Hypogammaglobulinemia was detected in 14.9% of patients, with significant reduction for IgM ($P < 0.001$) and IgG ($P = 0.001$) levels. Severe infections, infusion-related reactions, and hypersensitivity reactions occurred in 7%, 3.5%, and 2.6% of patients, respectively. Of the 115 patients, 62 patients had repeated RTX treatments, with an average number of 1.95 ± 1.17 cycles per patient and a mean ± SD interval between infusions of 21.44 ± 20.11 months. At the end of followup, 11 patients were deceased; 6 had cardiovascular events.**

Conclusion. **RTX treatment was effective in decreasing disease activity, with a low incidence of adverse effects.**

INTRODUCTION

Systemic lupus erythematosus (SLE) is an autoimmune disorder that can potentially affect any organ by inducing the production of pathogenic autoantibodies directed against cell components and the deposition of immune complexes. The therapeutic approach relies on the use of corticosteroids and other immunosuppressive agents, depending on the disease features. However, the rationale for the use of those agents comes mainly from uncontrolled studies, and only in 2008 did a European League Against Rheumatism task force gather some evidence-based core recommendations on the management of SLE (1). More recently, the first treat-to-target recommendations were published (2); however, the role of the available therapies was not discussed. Rituximab (RTX) is a chimeric monoclonal antibody that targets CD20+ B cells, directly inducing apoptosis or promoting antibody- or complement-dependent cell toxicity (3).

Two double-blind controlled trials have assessed the efficacy of RTX in the treatment of SLE. The Exploratory Phase II/III SLE Evaluation of Rituximab (EXPLORER) trial (4) was a randomized, double-blind, placebo-controlled trial that evaluated the efficacy and safety of RTX against placebo in the treatment of 257 patients with moderate to severe SLE, excluding lupus nephritis patients. Although a significant improvement was noted in immunologic parameters such as CD19+ B lymphocyte count, anti–double-stranded DNA (anti-dsDNA) antibody levels, and complement levels in RTX-treated patients, the study failed to meet the primary end point of demonstrating the superiority of RTX.

The Lupus Nephritis Assessment of Rituximab (LUNAR) trial (5), a phase III randomized controlled trial, evaluated

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Significance & Innovations

- There is a notable absence of long-term followup studies about systemic lupus erythematosus (SLE) patients treated with B cell depletion using rituximab.
- We address this gap by providing followup data of up to 14 years on >100 SLE patients that we have treated with B cell depletion. To our knowledge, this is the largest single-center study ever reported.
- Rituximab was an effective and safe alternative in the treatment of patients with severe or refractory SLE, demonstrating that, although not formally approved, it should remain a treatment option for such patients.

the efficacy of RTX in the treatment of 144 patients with class III/IV lupus nephritis, concomitantly with mycophenolate mofetil (MMF) and corticosteroids or versus MMF, corticosteroids, and placebo. As in the EXPLORER trial (4), RTX achieved B cell depletion and improvement in anti-dsDNA antibody levels, and complement levels, but showed no RTX superiority.

However, a review (6) and many further retrospective and open-label studies (7–11) suggested that RTX is effective and safe in the treatment of moderate to severe SLE when standard treatments have failed. Some recent studies showed that RTX might be a useful steroid-sparing agent in patients with lupus nephritis (12,13) and in newly diagnosed patients (14). RTX was first used as an alternative in the treatment of refractory SLE at the University College of London Hospital (UCLH) in 2000; the clinical outcome of the first 50 patients was published in 2007, and a later assessment looking at the outcome in relation to the duration of B cell depletion was also published (15). The objective of this retrospective study was to examine data on the efficacy and long-term safety of RTX in patients with lupus at this center over a 14-year time period.

PATIENTS AND METHODS

Participants and study design. This is a single-center in-depth retrospective analysis of all patients diagnosed with SLE treated with RTX at the UCLH between June 2000 and December 2013 and followed for up to 14 years. We enrolled patients through the UCLH Rheumatology Unit database of all SLE patients treated with RTX. The treatment protocol consisted of 2 infusions of 1 gm of RTX, 2 weeks apart, with a combination of methylprednisolone (100–250 mg), antihistamines, and, up to 2007, cyclophosphamide (500–750 mg). After 2007 we reduced the cyclophosphamide to a single infusion (following the first dose of RTX). Following B cell depletion the patients continued taking hydroxychloroquine and, if possible, a reduced dose of corticosteroids. Invariably any immunosuppressive drugs being prescribed at the time of B cell depletion were stopped until the B cells had returned and the disease began to flare. CD19+ counts and total immunoglobulin levels were monitored approximately every 2 months post–B cell depletion until the CD19+ B cell count was back to normal. As this study is an audit, it did not require hospital ethics committee approval.

Data collection. The clinical records of all patients enrolled were reviewed for sex, ethnicity, age at presentation, disease duration at first RTX treatment, previous immunosuppressive treatments, indication for RTX treatment, response to RTX treatment after 6, 12, 18, and 24 months, and followup time after RTX treatment. Other data collected

Table 1. Baseline demographic and clinical characteristics of SLE patients treated with RTX*

Epidemiologic features	
Female:male sex	108:7
Ethnicity	
White	50
Afro-Caribbean	37
South Asian	20
Other	8
Age at diagnosis, mean ± SD years	26.39 ± 11.90
Disease duration at first RTX treatment, mean ± SD months	92.00 ± 84.80
Previous treatments, no. (%)	
Prednisolone	109 (94.8)
Hydroxychloroquine	90 (70.3)
Azathioprine	74 (64.3)
Mycophenolate mofetil	40 (34.8)
Cyclophosphamide	39 (33.9)
Methotrexate	35 (30.4)
Other	21 (18.3)
Serologic characterization, no. (%)	
Antinuclear antibody positivity	111 (96.5)
Anti-Ro positivity	62 (53.9)
Anti-La positivity	23 (20)
Anti-RNP positivity	53 (46.1)
Anti-Sm positivity	32 (27.8)
Anticardiolipin positivity	21 (18.3)
Anti-dsDNA	81 (70.4)
Lupus anticoagulant	12 (10.4)
Clinical features, no. BILAG A/B scores	
General	10/23
Mucocutaneous	12/29
Neurologic	8/4
Musculoskeletal	23/32
Cardiovascular and respiratory	8/7
Vasculitis	3/5
Renal	15/23
Hematologic	8/46
Disease activity	
BILAG score, mean ± SD	18.29 ± 10.62
Anti-dsDNA, mean ± SD units (n <50 U/ml)	712.60 ± 1,410.80
C3, mean ± SD units (n = 0.9–1.8 mg/liter)	0.79 ± 0.34

* SLE = systemic lupus erythematosus; RTX = rituximab; anti-dsDNA = anti–double-stranded DNA; BILAG = British Isles Lupus Assessment Group.

Table 2. Mean BILAG score, C3 level, and anti-dsDNA titer at baseline and 6 months after RTX therapy*

	Baseline	6 months	Δ	*P*
First RTX cycle				
BILAG score (n = 109)	18.29 ± 10.62	6.79 ± 5.55	−11.22 ± 11.33	< 0.001
C3 (n = 103)	0.79 ± 0.03	0.95 ± 0.03	0.16 ± 0.03	< 0.001
Anti-dsDNA (n = 105)	712.60 ± 1,410.80	478.06 ± 1,572.33	−243.36 ± 141.32	< 0.001
Any RTX cycle				
BILAG score (n = 206)	16.18 ± 8.91	6.83 ± 4.95	−9.23 ± 10.45	< 0.001
C3 (n = 192)	0.89 ± 0.36	0.96 ± 0.33	0.20 ± 1.16	< 0.001
Anti-dsDNA (n = 199)	619.73 ± 1,197.61	486.60 ± 1,461.16	−125.56 ± 1,237.30	< 0.001

* Values are the mean ± SD unless otherwise indicated. BILAG = British Isles Lupus Assessment Group; anti-dsDNA = anti–double-stranded DNA; RTX = rituximab.

included anti-dsDNA antibody and C3 levels before and 6 months after RTX infusions. Both parameters were measured at the UCLH laboratory. Anti-dsDNA titers were evaluated by enzyme-linked immunosorbent assay (n <50 U/ml) and C3 levels (n = 0.9 → 1.8 mg/liter) by laser nephelometry. Data on B cell depletion were also recorded: acknowledgment of B cell depletion in the first 6 months after RTX treatment was reviewed. Adverse events, including allergic/anaphylactic reactions, hypogammaglobulinemia, infections, cardiovascular and cerebrovascular events, and death were reviewed.

Measurements and calculations. The indication for RTX treatment was dependent upon the severity of the organ/system involved (which was captured by British Isles Lupus Assessment Group [BILAG] assessments). For the purpose of clinical outcome assessment, response to RTX treatment was classified according to classic BILAG scoring, with full disease response being determined by BILAG A or B scores changing to C or D in every organ system; partial response by BILAG scores changing from A or B to C or D in at least 1 organ system but with a persistent A or B score in another organ system; and no improvement by BILAG A or B scores remaining unchanged after treatment. For anti-dsDNA antibody levels, the benefit of RTX treatment was recorded when a 50% reduction of the initial titer was achieved. For C3 levels, the benefit was recorded if a 25% increase occurred.

Regarding safety analysis, the proportion of patients with adverse reactions was recorded. Adverse events were divided into the following categories: severe infections (defined as requiring hospitalization or intravenous antibiotics), hypersensitivity reactions, infusion-related reactions, and others. Hypersensitivity reactions occur when the drug is recognized as an antigen by the patient's immune system; these are IgE-mediated reactions and, as such, only become evident with subsequent exposures to the culprit drug. Clinically, hypersensitivity reactions lead to urticarial rash, angioedema, bronchospasm, hypotension, and eventually anaphylaxis. Infusion reactions usually develop during the infusion or several hours afterward, have a mild to moderate intensity, and are characterized by a complex of chills, fever, nausea, asthenia, headache, and hypotension; these reactions are thought to be cytokine dependent (16). Hyponatremia-induced seizures due to cyclophosphamide, reactivation of hepatitis B, jugular thrombosis due to catheterization, abnormal liver function tests, or cyclophosphamide-induced cytopenia were classified as other adverse reactions.

Statistical analysis. Descriptive statistics were done using means and standard deviations for continuous variables and percentages with 95% confidence intervals for discrete variables. Statistical analysis was performed using SPSS, version 22.0. We applied Student's paired *t*-test to compare the values of the continuous variables before and after RTX treatment; ordered and multinomial logistic regression analyses were performed to compare the number of infusions according to the BILAG system involved and BILAG responses after RTX treatment in different organ systems. Both models included all of the BILAG systems. We set statistical significance at *P* less than 0.05.

RESULTS

Baseline characteristics. Of a total of 650 patients with an SLE diagnosis, 115 patients treated with RTX were identified after chart review. The baseline demographic and clinical characteristics of the patients are described in Table 1. Female sex and white race were predominant. Prednisolone and hydroxychloroquine were the most frequent previous treatments (94.8% and 70.3%, respectively), followed by azathioprine, mycophenolate mofetil, cyclophosphamide, and methotrexate; other less frequent previous therapies included cyclosporine A, intravenous immunoglobulin, dapsone, sulphasalazine, and plasma exchange.

The main disease features that motivated RTX treatment were musculoskeletal, mucocutaneous, and renal involvement. Although there were 54 patients that scored A or B for hematologic manifestations of the disease, most of them had mild to moderate anemia or slightly low leukocyte count, not demanding aggressive intervention. The mean ± SD followup time after the last RTX cycle was 46.03 ± 41.10 months; 4 patients were lost to followup.

RTX infusions. In the considered interval, among the 115 patients who had RTX treatment, 53 had only 1 cycle of RTX; 35 had 2 cycles; 14 had 3 cycles; and 9, 1, and 3 patients, respectively, had 4, 5, and 6 cycles. The mean ± SD number of RTX cycles was 1.95 ± 1.18. The mean ± SD

Table 3. Response rate to therapy in terms of BILAG score, C3 level, anti-dsDNA titer, and depletion of CD19+ lymphocytes*

Patients	First RTX cycle (at 6 mos.), % (95% CI)	All RTX cycles (at 6 mos.), % (95% CI)
With decrease in anti-dsDNA level ≥50% or normalization	38.2 (28.9–47.5)	37.7 (30.8–44.6)
With increase in C3 level ≥25% or normalization	36.5 (27.2–45.8)	31.8 (25.5–38.1)
With complete response	43.0 (33.7–52.3)	42.4 (35.7–49.1)
With partial response	29.0 (20.5–37.5)	27.3 (21.2–33.4)
With no response	28.0 (19.6–36.4)	30.2 (23.9–36.5)
With successful depletion of CD19+ lymphocytes (n = 100)	94.0 (89.3–98.7)	92.0 (88.2–95.8)

* BILAG = British Isles Lupus Assessment Group; anti-dsDNA = anti–double-stranded DNA; RTX = rituximab; 95% CI = 95% confidence interval.

interval between the first and second cycles of RTX was 23.81 ± 22.65 months. The overall mean ± SD interval between 2 consecutive cycles was 21.75 ± 20.23 months. None of the indications for the first RTX treatment was associated with a higher number of RTX cycles ($P = 0.691$).

The reason for the second RTX treatment was the same as that for the first in 85.2% (95% confidence interval [95% CI] 76.3–94.1%) of patients. Overall, the principal involvement that motivated retreatment with RTX (n = 109) was the same as that that had led to previous treatment in 79.8% (95% CI 72.3–87.4%) of cases; in 17.4% of cases, the new flare was distinct from the ones that were previously responsible for RTX treatment, and a new RTX cycle was administered to prevent new flares in 2.8% of the cases.

Efficacy. There was a significant decrease in BILAG score after treatment with RTX, both at first and at subsequent cycles. The addressed serologic markers of disease also demonstrated a significant improvement, as shown in Tables 2 and 3. In RTX treatment, of the 6 patients who were not successfully CD19+ lymphocyte depleted, only 1 had no response; partial and complete responses were observed in 2 and 3 patients, respectively. Overall, the absence of depletion and the absence of response were coincident in 7 of the 15 patients who were not successfully depleted.

In RTX retreatment (n = 100), in 48% (95% CI 38.2–57.8%) of cases, patients were still partially depleted of CD19+ lymphocytes at the time of the new cycle. Response to therapy according to the different organs affected is shown in Table 4. Musculoskeletal and renal manifestations were associated with a higher response rate in our model ($P = 0.026$ and $P = 0.001$, respectively).

RTX effects on immunoglobulins (IgA, IgM, and IgG). With respect to the first RTX treatment, a statistically significant decrease 6 months posttreatment was found in both IgM (mean ± SD 1.26 ± 1.05 gm/liter at 0 months and 0.94 ± 0.97 gm/dl at 6 months; $P < 0.001$) and IgG levels (mean ± SD 15.15 ± 6.92 gm/liter at 0 months and 13.52 ± 6.84 at 6 months; $P < 0.001$). No such difference was found for IgA ($P = 0.112$). At 6 months after first RTX cycle, low levels of IgA, IgG, and IgM, respectively, were detected in 2.1% (95% CI 0.0–5.0%), 14.9% (95% CI 7.7–22.1%), and 23.4% (95% CI 14.8–32.0%) of patients (n = 94). Considering all RTX cycles, only IgM levels decreased significantly after 6 months (mean ± SD 1.22 ± 1.02 gm/liter to 0.92 ± 0.92 gm/liter; $P < 0.001$); and low IgA, IgG, and IgM levels, respectively, were identified in 3.3% (95% CI 0.7–5.9%), 12.2% (95% CI 7.7–17.0%), and 27.2% (95% CI 20.7–33.7%) of patients (n = 180).

Adverse events. Adverse events are presented in Table 5. Four severe infections occurred in patients with low IgM levels: 3 infections (1 soft tissue infection, 1 gastroenteritis, and 1 septic shock of unknown origin) occurred within 6 months of the first RTX cycle, and 1 was registered after the second RTX cycle (cystitis). Human antichimeric antibodies were identified in 2 patients, although they were not routinely investigated. In 80.4% (95% CI 75.2–85.6%) of 224 RTX infusions, no adverse events were recorded.

From 2000 to 2013, 6 patients had at least 1 cardiovascular event: 1 patient presented with stroke, 4 patients had a

Table 4. Changes in British Isles Lupus Assessment Group scores in responders to rituximab treatment

	General	Mucocutaneous	Neurologic	Musculoskeletal	Cardiorespiratory	Vascular	Renal	Hematologic
Total A/B	33	41	12	55	15	8	38	54
A → B	0	2	0	6	0	0	7	3
A → C	7	4	2	7	1	2	6	2
A → D	2	3	2	5	6	1	1	2
B → C	9	11	0	13	0	0	11	21
B → D	13	13	4	15	4	5	10	6

Table 5. Adverse events occurring within 6 months of rituximab therapy

Adverse event	First (n = 115)	Second (n = 62)	Third (n = 27)	Fourth (n = 13)	Fifth (n = 4)	Sixth (n = 3)
Severe infections	8	5	0	0	0	0
Hypersensitivity reactions	3	5	4	1	0	0
Infusion-related reactions	4	6	1	1	0	1
Other	10	11	0	1	1	0
None	91	51	23	10	3	2

myocardial infarction, and 1 had arterial insufficiency in the legs due to femoral artery plaque. During the same period, 11 patients died: 3 patients died due to disease activity; 2 patients committed suicide; 1 patient had a fatal acute respiratory distress syndrome attributed to cyclophosphamide infusion; 1 patient had a fatal cerebrovascular accident; 1 patient had a fatal myocardial infarction; and in 3 patients the cause of death was unknown.

DISCUSSION

Although the use of B cell depletion in lupus is not novel, there is a marked paucity of long-term followup data on patients treated this way. This study attempts to fill that gap with the real-world experience of >100 lupus patients followed for periods of up to 14 years. To our knowledge, this is the largest analysis of a single-center experience of the use of RTX in SLE. Edwards and Cambridge were the first to suggest that since corticosteroids, cyclophosphamide, and RTX were able to reduce peripheral B cell numbers, B cell depletion might best be achieved by combining these drugs (16). Their studies in patients with rheumatoid arthritis fully validated this approach (17), and we extended its use to patients with lupus (8,14,18).

In this cohort, the efficacy analysis was largely favorable. Most of the patients treated with RTX at UCLH presented with clinical features refractory to more than 1 immunosuppressive agent; however, a small minority of patients (those with florid presentation of the disease or severe renal involvement) in recent years was treated with RTX at the time of diagnosis. In any case, RTX was able to reduce disease activity, with a response rate (partial or complete) of about 70%. The response to RTX was better in patients with musculoskeletal and renal involvement. These data are in line with recent evidence suggesting that RTX is useful, not only in cases of lupus nephritis refractory to standard immunosuppressive agents but also as a steroid-sparing agent in the induction of remission (12,13,19–23).

Notably, many of the patients who flared and needed to be retreated with RTX were still partially depleted of CD19+ lymphocytes at the time of the flare. The safety profile was also favorable, with a low incidence of serious adverse events; in particular, no patient developed multifocal leukoencephalopathy, but there were serious infections, 1 case of reactivation of hepatitis B, and 1 death due to an acute respiratory distress syndrome secondary to cyclophosphamide infusion. The infusion-related and hypersensitivity reactions were mostly mild to moderate.

The limitations of this study have to be carefully taken into account. The cohort was highly heterogeneous in terms of affected systems, and interobserver variability has to be considered when judging BILAG scores. However, all of the clinicians assessing the BILAG scores were trained by one of the authors (DI), and the single-center approach allows for uniformity of serologic assessment. There was wide variability in disease duration, as well as in the number of previous immunosuppressive agents used.

There were some missing data, for several reasons. First, 4 patients were lost to followup. Some patients were not seen in the outpatient clinic at 6 months; therefore, clinical and laboratory data could not be easily obtained for that period. In some cases, laboratory tests were not available. Another limitation was that some patients (n = 4) had the last RTX cycle less than 6 months before data collection. The lack of a control group also limits the measure of efficacy and safety of RTX in SLE patients.

Even though a new anti–B lymphocyte stimulator monoclonal antibody, belimumab, has been approved for the treatment of SLE, its role in the treatment of lupus nephritis and lupus with neuropsychiatric features has not yet been established. Long-term data on efficacy and safety are still lacking for this drug. RTX is the biologic agent with the most extensive off-label use in the treatment of refractory SLE and with the most observational studies. Much of the published data seems to contradict the results from the 2 available randomized controlled trials (4,5), suggesting a possible role for this drug in the treatment of SLE patients. It is notable that both the American College of Rheumatology and European League Against Rheumatism guidelines on the treatment of lupus nephritis consider RTX a viable therapeutic option (24,25).

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Isenberg had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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REFERENCES

1. Bertsias G, Ioannidis JP, Boletis J, Bombardieri S, Cervera R, Dostal C, et al. EULAR recommendations for the management of systemic lupus erythematosus: report of a task force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics. Ann Rheum Dis 2008;67:195–205.
2. Van Vollenhoven RF, Mosca M, Bertsias G, Isenberg D, Kuhn A, Lerstrøm K, et al. Treat-to-target in systemic lupus erythematosus: recommendations from an international task force. Ann Rheum Dis 2014;73:958–67.
3. Sanz I, Lee FE. B cells as therapeutic targets in SLE. Nat Rev Rheumatol 2010;6:326–37.
4. Merrill JT, Neuwelt CM, Wallace DJ, Shanahan JC, Latinis KM, Oates JC, et al. Efficacy and safety of rituximab in moderately-to-severely active systemic lupus erythematosus: the randomized, double-blind, phase II/III systemic lupus erythematosus evaluation of rituximab trial. Arthritis Rheum 2010;62:222–33.
5. Rovin BH, Furie R, Latinis K, Looney RJ, Fervenza FC, Sanchez-Guerrero J, et al, for the LUNAR Investigator Group. Efficacy and safety of rituximab in patients with active proliferative lupus nephritis: the Lupus Nephritis Assessment with Rituximab study. Arthritis Rheum 2012;64:1215–26.
6. Ramos-Casals M, Soto MJ, Cuadrado MJ, Khamashta MA. Rituximab in systemic lupus erythematosus: a systematic review of off-label use in 188 cases. Lupus 2009;18:767–76.
7. Eisenberg RA, Khan S, Stansberry J, Tsai D, Kolasinski S, Rieder E, et al. An open-label safety and efficacy study of an anti-CD20 antibody (rituximab, Rituxan) for anti-B-cell therapy in the treatment of systemic lupus erythematosus [abstract]. Arthritis Res Ther 2004;6 Suppl 3:92.
8. Lu TY, Ng KP, Cambridge G, Leandro MJ, Edwards JC, Ehrenstein M, et al. A retrospective seven-year analysis of the use of B cell depletion therapy in systemic lupus erythematosus at University College London Hospital: the first fifty patients. Arthritis Rheum 2009;61:482–7.
9. Terrier B, Amoura Z, Ravaud P, Hachulla E, Jouenne R, Combe B, et al. Safety and efficacy of rituximab in systemic lupus erythematosus: results from 136 patients from the French AutoImmunity and Rituximab registry. Arthritis Rheum 2010;62:2458–66.
10. Witt M, Grunke M, Proft F, Aringer M, Burmester G, Chehab G, et al. Clinical outcomes and safety of rituximab treatment for patients with systemic lupus erythematosus (SLE): results from a nationwide cohort in Germany (GRAID). Lupus 2013;22:1142–9.
11. Iaccarino L, Bartoloni E, Carli L, Ceccarelli F, Conti F, De Vita S, et al. Efficacy and safety of off-label use of rituximab in refractory lupus: data from the Italian Multicentre Registry. Clin Exp Rheumatol 2015;33:449–56.
12. Pepper R, Griffith M, Kirwan C, Levy J, Taube D, Pusey C, et al. Rituximab is an effective treatment for lupus nephritis and allows a reduction in maintenance steroids. Nephrol Dial Transplant 2009;24:17–23.
13. Condon MB, Damien A, Pepper R, Cook HT, Levy JB, Griffith M, et al. Prospective observational single-centre cohort study to evaluate the effectiveness of treating lupus nephritis with rituximab and mycophenolate mofetil but no oral steroids. Ann Rheum Dis 2013;72:1280–6.
14. Ezeonyeji AN, Isenberg DA. Early treatment with rituximab in newly diagnosed systemic lupus erythematosus patients: a steroid-sparing regimen. Rheumatology (Oxford) 2012;51:476–81.
15. Dias SS, Rodriguez-Garcia V, Nguyen H, Pericleous C, Isenberg D. Longer duration of B cell depletion is associated with better outcome. Rheumatology (Oxford) 2015;54:1876–81.
16. Edwards JC, Cambridge G. Sustained improvement in rheumatoid arthritis following a protocol designed to deplete B-lymphocytes. Rheumatology (Oxford) 2001;40:205–11.
17. Edwards JC, Szczepanski K, Szechinski J, Filipowicz-Sosnowska A, Emery P, Close DR, et al. Efficacy of B-cell targeted therapy with rituximab in rheumatoid arthritis. New Engl J Med 2004;35:2572–81.
18. Ramos L, Isenberg DA. Rituximab: the lupus journey. Curr Treat Opt Rheum 2015;1:30–41.
19. Días-Lagares C, Croca S, Sangle S, Vital EM, Catapano F, Martínez-Berriotxoa A, et al. Efficacy of rituximab in 164 patients with biopsy-proven lupus nephritis: pooled data from European cohorts. Autoimmun Rev 2012;11:357–64.
20. Jónsdóttir T, Zickert A, Sundelin B, Henriksson EW, van Vollenhoven RF, Gunnarsson I. Long-term follow-up in lupus nephritis patients treated with rituximab: clinical and histopathological response. Rheumatology (Oxford) 2013;52:847–55.
21. Moroni G, Raffiotta F, Trezzi B, Giglio E, Mezzina N, Del Papa N, et al. Rituximab vs mycophenolate and vs cyclophosphamide pulses for induction therapy of active lupus nephritis: a clinical observational study. Rheumatology (Oxford) 2014;53:1570–7.
22. Tanaka Y, Takeuchi T, Miyasaka N, Sumida T, Mimori T, Koike T, et al. Efficacy and safety of rituximab in Japanese patients with systemic lupus erythematosus and lupus nephritis who are refractory to conventional therapy. Mod Rheumatol 2016;26:80–6.
23. Roccatello D, Sciascia S, Baldovino S, Rossi D, Alpa M, Naretto C, et al. A 4-year observation in lupus nephritis patients treated with an intensified B-lymphocyte depletion without immunosuppressive maintenance treatment: clinical response compared to literature and immunological reassessment. Autoimmun Rev 2015;14:1123–30.
24. Hahn BH, McMahon MA, Wilkinson A, Wallace WD, Daikh DI, Fitzgerald JD, et al. American College of Rheumatology guidelines for screening, treatment, and management of lupus nephritis. Arthritis Care Res (Hoboken) 2012;64:797–808.
25. Bertsias GK, Tektonidou M, Amoura Z, Aringer M, Bajema I, Berden JH et al. Joint European League Against Rheumatism and European Renal Association–European Dialysis and Transplant Association (EULAR/ERA-EDTA) recommendations for the management of adult and paediatric lupus nephritis. Ann Rheum Dis 2012;71:1771–82.