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Efficacy and Safety of Rituximab in Patients With Active Proliferative Lupus Nephritis

The Lupus Nephritis Assessment With Rituximab Study

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Objective. **To evaluate the efficacy and safety of rituximab in a randomized, double-blind, placebo-controlled phase III trial in patients with lupus nephritis treated concomitantly with mycophenolate mofetil (MMF) and corticosteroids.**

Methods. **Patients (n = 144) with class III or class IV lupus nephritis were randomized 1:1 to receive rituximab (1,000 mg) or placebo on days 1, 15, 168, and 182. The primary end point was renal response status at week 52.**

Results. **Rituximab depleted peripheral CD19+ B cells in 71 of 72 patients. The overall (complete and partial) renal response rates were 45.8% among the 72 patients receiving placebo and 56.9% among the 72 patients receiving rituximab ($P = 0.18$); partial responses accounted for most of the difference. The primary end point (superior response rate with rituximab) was not achieved. Eight placebo-treated patients and no rituximab-treated patients required cyclophosphamide rescue therapy through week 52. Statistically significant improvements in serum complement C3, C4, and anti–double-stranded DNA (anti-dsDNA) levels were observed among patients treated with rituximab. In both treatment groups, a reduction in anti-dsDNA levels greater than the median reduction was associated with reduced proteinuria. The rates of serious adverse events, including infections, were similar in both groups. Neutropenia, leukopenia, and hypotension occurred more frequently in the rituximab group.**

Conclusion. **Although rituximab therapy led to more responders and greater reductions in anti-dsDNA and C3/C4 levels, it did not improve clinical outcomes after 1 year of treatment. The combination of rituximab with MMF and corticosteroids did not result in any new or unexpected safety signals.**

Lupus nephritis (LN) may be observed in up to 50% of patients with systemic lupus erythematosus (SLE) and is associated with a poor prognosis (1). Although renal response rates among patients receiving standard treatment of proliferative LN may approach

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50–80% at 1 year, many of these responses are only partial (2–4). Therefore, therapeutic regimens that are more effective are needed (5).

B cells produce cytokines, present antigen, interact with T cells, and mature into plasma cells that continue to produce antibodies (6–8). B cell aggregates have been observed in renal biopsy specimens obtained from patients with LN (9,10). Loss of B cell tolerance to self antigens may be a key event in lupus pathogenesis (6–8,11).

Rituximab, a chimeric monoclonal antibody, depletes CD20+ B cells while sparing stem cells and plasma cells (12,13). It is approved for non-Hodgkin's lymphoma and chronic lymphocytic leukemia, moderate to severe rheumatoid arthritis, Wegener's granulomatosis (granulomatosis with polyangiitis), and microscopic polyarteritis (14–16); it may also be effective for the treatment of relapsing-remitting multiple sclerosis (17) (for full prescribing information, see http://www.gene.com/gene/products/information/oncology/rituxan). Uncontrolled trials suggested that rituximab may be effective in treatment-refractory lupus (18–24). Although the EXPLORER (Exploratory Phase II/III SLE Evaluation of Rituximab) study in patients with active extrarenal SLE receiving immunosuppressants and corticosteroids failed to demonstrate added benefit from rituximab (25), other studies have implicated B cells in the pathogenesis of LN (26), suggesting a role for rituximab in the treatment of LN (24,27,28).

Historically, cyclophosphamide has been widely used along with corticosteroids for the initial treatment of proliferative LN. Mycophenolate mofetil (MMF) is potentially less toxic than cyclophosphamide (5,29–31), and recent data from the Aspreva Lupus Management Study (ALMS) support MMF as an alternative induction and maintenance therapy for LN (32,33).

We investigated whether the addition of rituximab to a background of MMF plus corticosteroids in patients with proliferative LN could improve renal response rates at 52 weeks. Although MMF plus corticosteroids is effective therapy for LN, the complete response rate is low (2–4), leaving considerable room for improvement. Complete renal responses are critical for preserving kidney function and attenuating the cardiovascular morbidity associated with chronic kidney disease. Because of the long-lasting pharmacodynamic effects of rituximab and the relapsing nature of LN in the months posttreatment (27,34,35), we also examined efficacy and safety at 78 weeks.

PATIENTS AND METHODS

Study design. Eligible patients were 16–75 years of age and had a diagnosis of SLE according to the revised American College of Rheumatology criteria (36). They were required to have a history of antinuclear antibody (ANA) positivity, class III or class IV (± class V) LN according to the 2003 International Society of Nephrology/Renal Pathology Society (ISN/RPS) criteria and supported by renal biopsy (within 12 months), and proteinuria (urine protein:creatinine [UPC] ratio >1.0). If the biopsy was performed >3 months before screening, an active urinary sediment (>10 red blood cells [RBCs]/high-power field [hpf] or the presence of RBC casts) was also required. Patients with >50% glomerular sclerosis or interstitial fibrosis or an estimated glomerular filtration rate (eGFR) of <25 ml/minute/1.73 m^2 were excluded. The study protocol was approved by institutional review boards and ethics committees, and the participants provided written informed consent.

Treatment protocol. Patients were randomized 1:1 to receive placebo or rituximab 1,000 mg administered intravenously on days 1, 15, 168, and 182. MMF was initiated at a dosage of 1.5 gm/day in 3 divided doses, and the dosage was increased to 3 gm/day by week 4, as tolerated. Treatment with MMF at a dosage of 3 gm/day was continued through at least week 52. Methylprednisolone 1,000 mg was administered intravenously 30–60 minutes prior to the administration of study drug on day 1 and again within 3 days, as therapy for active LN. To prevent infusion reactions, methylprednisolone 100 mg was given intravenously 30–60 minutes prior to the administration of study drug on days 15, 168, and 182. Oral prednisone at a dosage of 0.75 mg/kg/day (maximum 60 mg) was administered until day 16 and tapered to ≤10 mg/day by week 16. Other immunosuppressive agents in addition to corticosteroids and MMF were not permitted and were discontinued during the screening period. The use of rescue therapy (new immunosuppressant agent and/or high-dose corticosteroids administered for >2 weeks) required discontinuation of study therapy and classification of the subject as a nonresponder. Angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs), if used, had to be initiated at least 10 days before randomization; combination treatment with the 2 agents was not allowed. Antimalarial drugs, if used, had to be maintained at a constant dose during the study, and the use of nonsteroidal antiinflammatory drugs was prohibited. Patients experiencing significant worsening of renal function (≥50% reduction in the eGFR from baseline) could be withdrawn into the safety followup period and treated at the investigator's discretion.

Study end points and assessments. The primary efficacy end point was renal response, defined as complete renal response (CRR), partial renal response (PRR), or no response (NR), at week 52. Criteria for a CRR included the following: normal serum creatinine level if it was abnormal at baseline, or a serum creatinine level of ≤115% of baseline if it was normal at baseline; inactive urinary sediment (<5 RBCs/hpf and absence of RBC casts); and UPC ratio <0.5. Patients who achieved PRR, but not CRR, met the following criteria: serum creatinine level ≤115% of baseline; RBCs/hpf ≤50% above baseline and no RBC casts; and at least a 50% decrease in the

Table 1. Patient demographics and baseline disease characteristics*

Variable	Placebo (n = 72)	Rituximab (n = 72)
Age, mean ± SD years	29.4 ± 9.3	31.8 ± 9.6
Female sex	67 (93.1)	63 (87.5)
Race		
White	26 (36.1)	19 (26.4)
Black	20 (27.8)	20 (27.8)
Hispanic	23 (31.9)	29 (40.3)
Asian/Pacific Islander	3 (4.2)	4 (5.6)
History of lupus nephritis	30 (41.7)	36 (50)
Duration since lupus nephritis diagnosis, months		
Mean ± SD	28.8 ± 51.6	32.4 ± 48.0
Median (range)	5.4 (0.4–306)	11.1 (0.4–211)
Duration since last biopsy, months		
Mean ± SD	2.2 ± 2.3	2.0 ± 2.8
Median (range)	1.6 (0.2–12.0)	1.1 (0.2–12.6)
ISN/RPS classification		
Class III	24 (33.3)	25 (34.7)
Class IV	48 (66.7)	47 (65.3)†
Segmental	17 (23.6)	18 (25.0)
Global	30 (41.7)	28 (38.9)
Class III + V or IV + V	23 (31.9)	26 (36.1)
Class III + V	8 (11.1)	17 (23.6)
Class IV + V	15 (20.8)	9 (12.5)
Serum creatinine, mean ± SD mg/dl	1.0 ± 0.5	1.0 ± 0.5
Serum albumin, mean ± SD gm/liter	2.6 ± 0.7	2.7 ± 0.8
Urine protein:creatinine ratio		
Mean ± SD	4.2 ± 3.0	3.8 ± 2.8
>3	42 (58.3)	38 (52.8)
Estimated GFR, ml/minute		
Mean ± SD	96.0 ± 51.1	87.7 ± 34.9
≥60	52 (72.2)	55 (76.4)
ANA positive at randomization‡	83.3	81.9
Anti-dsDNA, IU/ml§		
Mean ± SD	383.5 ± 702.6	449.6 ± 785.6
Geometric mean	142.5	149
Median (IQR)	168.5 (57–321)	122.5 (47–504)
≥30	61 (84.7)	59 (81.9)
≥75	46 (63.9)	46 (63.9)
Anti-ENA		
Any of 4 positive (≥120)	46 (63.9)	44 (61.1)
Anti-Sm	26 (36.1)	21 (29.2)
Anti-Ro	27 (37.5)	23 (31.9)
Anti-RNP	28 (38.9)	25 (34.7)
Anti-La	7 (9.7)	5 (6.9)
C3, mg/dl¶		
Mean ± SD	74.1 ± 27.9	73.6 ± 29.4
<90	54 (75)	53 (73.6)
C4, mg/dl¶		
Mean ± SD	13.8 ± 9.4	14.7 ± 8.5
<10	31 (43.1)	28 (38.9)
BILAG index global score, mean ± SD	15.3 ± 6.2	15.3 ± 6.4
Systolic blood pressure, mean ± SD mm Hg	129.8 ± 18.7	128.8 ± 17.8
Diastolic blood pressure, mean ± SD mm Hg	81 ± 14.2	81.4 ± 12.9

* Except where indicated otherwise, values are the number (%). ISN/RPS = International Society of Nephrology/Renal Pathology Society; GFR = glomerular filtration rate; IQR = interquartile range; anti-ENA = anti–extractable nuclear antigen; BILAG = British Isles Lupus Assessment Group.
† One patient had an unknown lupus nephritis class IV subtype.
‡ Antinuclear antibody (ANA) positive if ≥1:80 dilution.
§ Anti–double-stranded DNA (anti-dsDNA) positive at randomization if ≥30.
¶ Central laboratory normal ranges 90–180 mg/dl for C3 and 10–40 mg/dl for C4.

UPC ratio to <1.0 (if the baseline UPC ratio was ≤3.0) or to ≤3.0 (if the baseline UPC ratio was >3.0). Patients were assessed as NR if criteria for CRR or PRR were not met, for early termination from the study or inability to assess the end point due to missing data, or for initiation of a new immunosuppressant agent prior to week 52. Urinary sediment assessments were performed at local laboratories on a first morning urine sample.

Secondary end points included the following: CRRs sustained from week 24 through week 52, CRR rates at week 52, reduction in the baseline UPC ratio from >3.0 to <1.0 at week 52, time to first CRR, time-adjusted area under the curve minus the baseline British Isles Lupus Assessment Group (BILAG) index global score over 52 weeks using numerical scoring of flare severity or absence (37,38), and change in the physical function score for the 36-Item Short-Form Health Survey (39) from baseline to week 52. Serologic end points included changes in anti–double-stranded DNA (anti-dsDNA) antibody titers as assessed by enzyme-linked immunosorbent assay (ELISA) and complement C3/C4 levels from baseline to week 52. Peripheral B cell counts (CD19+ and other subsets) were measured, and ANA, anti-Sm, anti-Ro, anti-La, and anti-RNP antibodies, total immunoglobulin, IgG, IgM, IgA, and human antichimeric antibody (HACA) titers were determined by ELISA. The rituximab HACA ELISA used rituximab as the capture reagent and biotinylated rituximab and streptavidin–horseradish peroxidase for detection; the assay calibrator curve was prepared with affinity-purified polyclonal goat antibodies to rituximab and was confirmed by immunodepletion with rituximab.

Adverse events (AEs) were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0. Patients were monitored every 4 weeks up to week 78. If CD19+ B cell recovery was not observed by week 78, patients in the rituximab group were followed up every 12 weeks until recovery was achieved.

Statistical analysis. As a design assumption, the addition of rituximab to standard immunosuppressive treatment with MMF and corticosteroids was expected to increase CRR and PRR rates by 20% and 5%, respectively, with an overall renal response rate increase of 25%, which was deemed a clinically important increase. With this assumption, and a total of 70 patients per arm, the Wilcoxon's rank sum test for 2 ordered multinomial distributions would have ~90% power to demonstrate benefit at a significance level of 0.05 for a 2-sided test (StatXact version 5.0). The power of this test to detect a similar overall benefit that consisted mainly of an increase in PRR rates (e.g., 20% increase in the PRR rate and 5% increase in the CRR rate) was <70% with this sample size and considerably lower for a smaller overall benefit.

Dichotomous end points were analyzed using a stratified Cochran-Mantel-Haenszel chi-square test, and continuous outcomes were analyzed by analysis of covariance (ANCOVA). Time-to-event outcomes were evaluated using a stratified log rank test. The variable race (dichotomized as black versus other) was used to stratify all categorical or time-to-event efficacy end points or as a covariate in ANCOVA models. Missing data imputation for the week 52 primary end point was performed by carrying forward the last available result within 60 days of the visit. *P* values were not adjusted for multiple comparisons. Safety analyses included all data from baseline through week 78.

RESULTS

Study population. From January 2006 to January 2008, 144 patients were randomized to receive rituximab or placebo (n = 72 each) at 52 centers; 74% and 26% of patients were enrolled at US and Latin American sites, respectively. Eighty-eight percent of the placebo-treated patients and 93% of the rituximab-treated patients completed 52 weeks of study; 81% and 89%, respectively, completed 78 weeks (see Appendix Figure 1, available on the *Arthritis & Rheumatism* Web site at http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)1529-0131). The percentage of patients who discontinued therapy was larger in the placebo group (25%) than in the rituximab group (10%).

Baseline characteristics were similar between treatment groups (Table 1). The majority of patients (~90%) were female, and the mean ± SD age of the patients was 30.6 ± 9.5 years. As shown in Table 1, approximately one-third each were of Hispanic, white, or black race/ethnicity, with slightly more whites in the placebo group and more Hispanics in the rituximab group. In 69% of the patients, LN was first diagnosed within 2 years of randomization, and 54% of the patients had no prior episode of LN. The median duration of LN was somewhat lower in the placebo group (5.4 months versus 11.1 months in the rituximab group). The mean duration since biopsy was 2.1 ± 2.6 months (median 1.3 months). Two-thirds (66%) of the patients enrolled had ISN/RPS LN class IV, of whom 61% had global class IV. One-third (34%) of the patients had class V concurrent with either class III or class IV. The mean ± SD serum creatinine level at baseline was 1.0 ± 0.5 mg/dl, and the mean ± SD UPC ratio was 4.0 ± 2.9. UPC ratios >3 were observed in 56% of the patients.

At the time of study entry, 44% of patients were receiving an antimalarial drug, and 47% of patients had received either an ACE inhibitor or an ARB for >3 months prior to screening. In addition, 55% of patients had been treated with corticosteroids for ≥6 months. The mean ± SD daily MMF doses achieved over the 52-week treatment period were 2.4 ± 0.6 gm and 2.7 ± 0.4 gm in the placebo and rituximab groups, respectively.

Efficacy. *Primary end point*. Renal response rates (CRR/PRR/NR) at week 52 were not statistically different between the rituximab and placebo groups (*P* = 0.55) (Table 2 and Figure 1A). At 52 weeks, CRR was

Table 2. Clinical and serologic end points*

End points	Placebo (n = 72)	Rituximab (n = 72)	*P*
Primary			0.55
CRR	22 (30.6)	19 (26.4)	
PRR	11 (15.3)	22 (30.6)	
NR	39 (54.2)	31 (43.1)	
Sensitivity analysis: renal response excluding the urine sediment criteria			0.36
CRR	23 (31.9)	25 (34.7)	
PRR	12 (16.7)	18 (25)	
NR	37 (51.4)	29 (40.3)	
Secondary clinical			
No. of patients/no. of patients assessed (%) with a baseline UPC ratio of >3 who achieved a UPC ratio of <1 at week 52	22/41 (53.7)	18/38 (47.4)	0.51
Median number of months to first CRR	12.12	11.99	0.63
Time-adjusted AUCMB of BILAG index global score, mean ± SD	−8.58 ± 5.14	−8.49 ± 5.79	0.93
Change from baseline to week 52 in the SF-36 physical function score, mean ± SD	5.7 ± 9.4	4.8 ± 10.4	0.59
Achievement of a CRR from week 24 to week 52	5 (6.9)	1 (1.4)	0.21
Achievement of a CRR at week 52	22 (53.7)	19 (46.3)	0.58
Secondary serologic†			
Relative change from baseline in anti-dsDNA, geometric mean week 52:baseline ratio			
Week 52	0.50	0.31	0.007
Week 78	0.56	0.31	0.002
Change from baseline in C3, mean ± SD			
Week 52	25.9 ± 32.5	37.5 ± 28.7	0.03
Week 78	26.0 ± 34.4	34.9 ± 32.2	0.11
Change from baseline in C4, mean ± SD			
Week 52	6.6 ± 8.9	9.9 ± 7.5	0.02
Week 78	5.8 ± 9.4	8.9 ± 8.2	0.04
Exploratory			
CRR at week 78	23 (47.9)	25 (52.1)	0.72
Overall (at least partial) response			
Week 52	33 (45.8)	41 (56.9)	0.18
Week 78	32 (44.4)	40 (55.6)	0.18
Overall response in subgroups, no. of patients/no. of patients assessed (%)			
Black			
Week 52	9/20 (45)	14/20 (70)	0.20
Week 78	7/20 (35)	12/20 (60)	0.20
Hispanic			
Week 52	11/23 (47.8)	16/29 (55.1)	0.78
Week 78	10/23 (43.5)	13/29 (44.8)	1.00
White			
Week 52	13/26 (50)	10/19 (52.6)	1.00
Week 78	13/26 (50)	13/19 (68.4)	0.24
At least 50% reduction from baseline in UPC ratio			
Week 52	41 (56.9)	48 (66.7)	0.23
Week 78	39 (54.2)	51 (70.8)	0.04
Complete or partial proteinuria response‡			
Week 52	41 (56.9)	48 (66.7)	0.18
Week 78	41 (56.9)	53 (73.6)	0.04
Started cyclophosphamide prior to:			
Week 52	8 (11.1)	0	0.006§
Week 78	11 (15.3)	2 (2.8)	0.02§
BILAG renal domain C or better at week 52	28 (38.9)	39 (54.2)	0.07
Average daily oral steroid dose between weeks 16 and 52, mean ± SD mg¶	12.8 ± 6.5	10.9 ± 4.1	0.05
Cumulative steroid dose up to week 52, mean ± SD gm	6.7 ± 2.5	6.3 ± 2.1	0.34

* Except where indicated otherwise, values are the number (%). CRR = complete renal response; PRR = partial renal response; NR = no response; AUCMB = area under the curve minus baseline; BILAG = British Isles Lupus Assessment Group; SF-36 = 36-Item Short-Form Health Survey; anti-dsDNA = anti–double-stranded DNA.
† Week 78 outcomes were determined from exploratory analyses.
‡ At least 50% reduction from baseline in the urine protein–to-creatinine (UPC) ratio, and a reduction of <1 if the baseline value was >3.
§ By Fisher's exact test.
¶ Not all patients were able to maintain an oral steroid dosage of ≤10 mg/day after week 16, particularly nonresponders.

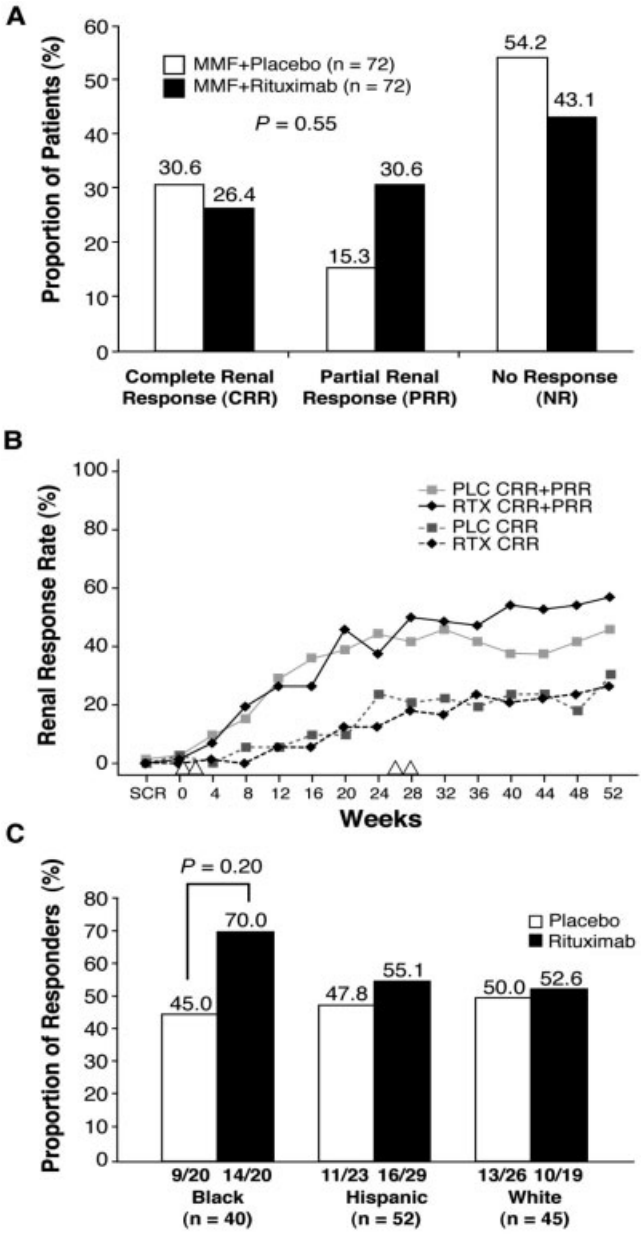

Figure 1. Efficacy end points. **A,** Proportions of patients with a complete renal response, a partial renal response, or no response. **B,** Complete and partial renal responses over 52 weeks. **C,** Subgroup analysis of renal responses in black, Hispanic, and white patients. The *P* value was derived from a stratified Wilcoxon's rank sum test comparing the proportions of responders between the rituximab (RTX) and placebo (PLC) arms. MMF = mycophenolate mofetil (mean ± SD dose 2.4 ± 0.62 gm in the placebo group and 2.7 ± 0.41 gm in the rituximab group); SCR = screening; Δ = rituximab infusion.

achieved in 26.4% and 30.6% of patients in the rituximab and placebo groups, respectively; PRR rates were 30.6% in the rituximab group and 15.3% in the placebo group. Overall renal response rates (CRR or PRR) were 56.9% for rituximab and 45.8% for placebo ($P = 0.18$); this difference was driven by higher PRR rates (Figure 1B). Additional assessments of partial responses were performed in order to evaluate the influence of individual components of the responder index on overall response. Among partial responders, 7 (32%) of 22 patients in the rituximab group but just 1 (9%) of 11 patients in the placebo group achieved a complete response with respect to proteinuria; however, other components of response were insufficient to allow classification of these patients as complete responders. In comparison, the serum creatinine criteria for complete response were achieved by 19 (86%) of 22 patients in the rituximab group and by 7 (64%) of 11 patients in the placebo group. Finally, with respect to urinary sediment, 13 (59%) of 22 patients in the rituximab group and 7 (64%) of 11 patients in the placebo group achieved the complete response criteria. However, a sensitivity analysis of the primary end point, in which the criteria for improvement in hematuria was excluded, did not alter the outcome.

Prespecified subgroup analysis. LN is associated with a worse prognosis in certain ethnic groups, and in the EXPLORER study of patients with active extrarenal SLE, rituximab had a beneficial effect on the primary end point in the black and Hispanic subgroups (25). Therefore, a prespecified subgroup analysis of the overall renal response at week 52 according to race and ethnicity was performed. Differences in overall response between treatment arms were <10% (Table 2), except in the subgroup of blacks, in which rituximab-treated patients had higher response rates (70%) compared with placebo-treated patients (45%) at week 52 (Figure 1C). The difference in overall response between treatments in this subgroup, consisting of 20 patients (28%) in each arm, was 25% (95% confidence interval [95% CI] −4.6, 54.6; $P = 0.20$). This difference was also driven by a higher PRR rate (35% versus 5%). An ad hoc analysis of renal response in other subgroups is shown in Appendix Figure 2, available on the *Arthritis & Rheumatism* Web site at http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)1529-0131.

Secondary end points. There were no statistically significant differences between the rituximab and placebo groups in secondary clinical end points at week 52. The median time to first CRR was 12 months in both groups (hazard ratio 1.13, $P = 0.63$). At week 52, the difference (10%) in the proportion of patients with

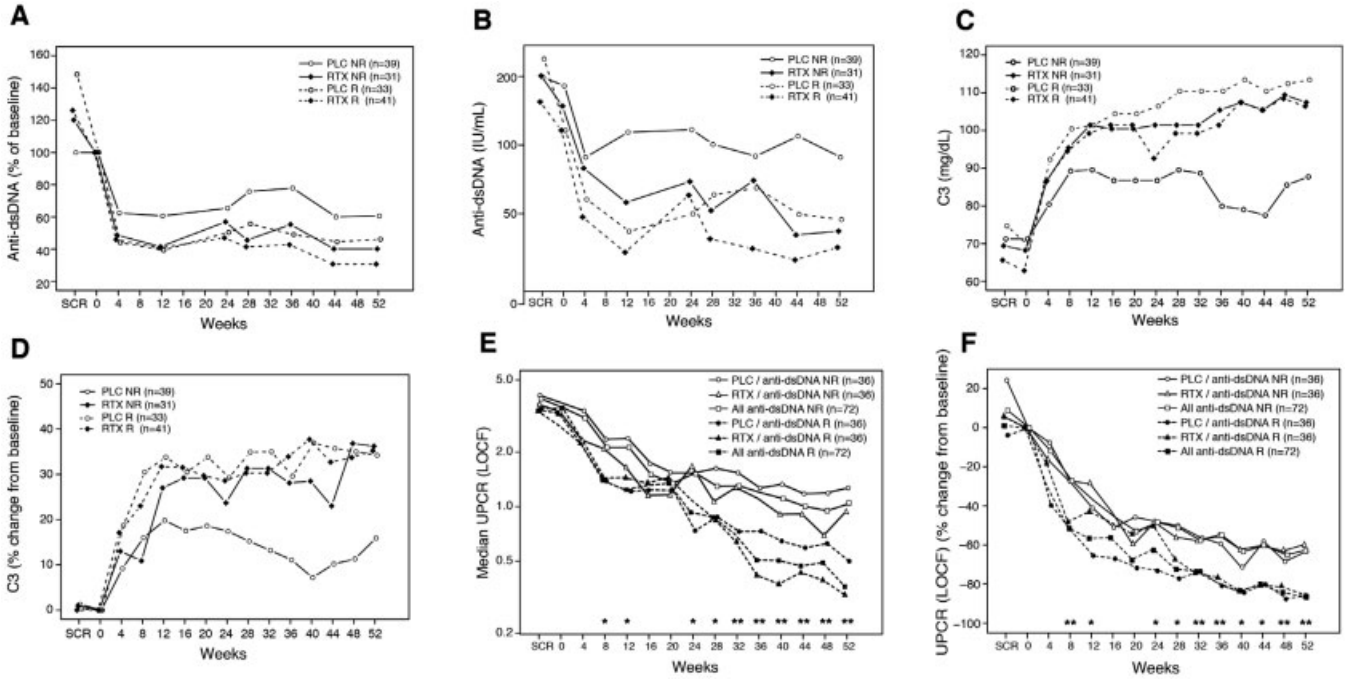

Figure 2. Changes from baseline to week 52 in anti–double-stranded DNA (anti-dsDNA) and complement C3 levels in responders (R) and nonresponders (NR) in the rituximab and placebo groups. **A,** Median percent change in anti-dsDNA level. **B,** Median anti-dsDNA levels. **C,** Mean C3 levels. **D,** Median percent changes in C3 levels. **E,** Median urine protein:creatinine ratio (UPCR) stratified by week 52 anti-dsDNA response status (defined as a reduction in the anti-dsDNA level greater than the median reduction in the patient's own treatment group). **F,** Median percent change in the UPC ratio stratified by week 52 anti-dsDNA response status. $* = P < 0.05$; $** = P < 0.01$, all anti-dsDNA responders versus all nonresponders. LOCF = last observation carried forward (see Figure 1 for other definitions).

≥50% reduction in proteinuria favored rituximab treatment; the difference increased to 17% at week 78 ($P = 0.04$) (Table 2). Similarly, the rituximab group was more likely to achieve a complete or partial response with respect to proteinuria at week 78 ($P = 0.04$) (Table 2). The serum creatinine criteria for the primary end point at week 52 were achieved by 80.6% and 68.1% of patients in the rituximab and placebo groups, respectively. At week 78, this value remained unchanged in the rituximab group but increased to 79.2% in the placebo group.

Due to worsening disease, more placebo-treated patients than rituximab-treated patients received cyclophosphamide (8 versus 0 [$P = 0.006$] at week 52; 11 versus 2 [$P = 0.02$] at week 78). In addition, the average daily oral steroid dose was lower in rituximab-treated patients (Table 2).

Serologic improvement and responder status. At week 52, a greater reduction in the anti-dsDNA level was observed in rituximab-treated patients compared with controls ($P = 0.007$). Although reductions in anti-dsDNA levels were not significantly correlated with renal response, more responders than nonresponders in both groups had normalized anti-dsDNA levels (Figures 2A and 2B). At week 52, a greater mean increase in C3 was observed in the rituximab group compared with the placebo group ($P = 0.03$). Responders in the placebo group exhibited a greater increase in C3 (Figure 2C) and more frequent C3 normalization compared with nonresponders (Figure 2D) at week 52. An increase in C3 at week 52 was significantly correlated with renal response in the placebo group ($\rho = 0.54$, $P < 0.001$) but not in the rituximab group ($\rho = 0.12$, $P = 0.30$).

To further analyze the relationship between the anti-dsDNA response and the renal response, patients were stratified into anti-dsDNA responders and anti-dsDNA nonresponders. A response was defined as a reduction in an individual patient's anti-dsDNA level greater than the median reduction in the patient's treatment group; nonresponse was defined as a reduction lower than the median reduction in the treatment group. The median reduction in the UPC ratio was

Table 3. Adverse events reported through study week 78 in patients with lupus nephritis treated with rituximab or placebo plus MMF and corticosteroids (n = 144)*

	Placebo (n = 71)	Rituximab (n = 73)
Any AE	68 (95.8)	72 (98.6)
Grade 3 or higher AE	31 (43.7)	29 (39.7)
Study drug–related AE	24 (33.8)	25 (34.2)
Deaths	0	2 (2.7)
AE leading to discontinuation of study drug	3 (4.2)	1 (1.4)
Serious AE	29 (40.8)	24 (32.9)
Infection-related	14 (19.7)	14 (19.2)
Opportunistic infection†	1 (1.4)	3 (4.1)
Infusion-related	2 (2.8)	1 (1.4)
Any infection	64 (90.1)	62 (84.9)
Any grade 3 or higher infection	15 (21.1)	12 (16.4)
Most common infections		
Upper respiratory tract infection	23 (32.4)	21 (28.8)
Urinary tract infection	20 (28.2)	17 (23.3)
Herpes zoster	9 (12.7)	11 (15.1)
Infusion-related AE, no. of patients/no. of patients assessed (%)‡	29 (40.8)	25 (34.2)
1st infusion	18/72 (25.0)	16/72 (22.2)
2nd infusion	8/71 (11.3)	6/71 (8.5)
3rd infusion	5/56 (8.9)	8/67 (11.9)
4th infusion	2/54 (3.7)	6/66 (9.1)
Infusion-related AE attributed to study drug	6 (8.5)	12 (16.4)
Most common infusion-related AEs		
Hypertension	2 (2.8)	4 (5.5)
Dyspepsia	3 (4.2)	2 (2.7)
Nausea	3 (4.2)	2 (2.7)
Headache	2 (2.8)	2 (2.7)
Diarrhea	3 (4.2)	1 (1.4)
Dysgeusia	3 (4.2)	1 (1.4)

* Except where indicated otherwise, values are the number (%). One patient randomized to placebo inadvertently received 2 rituximab infusions during the second cycle and was included in the rituximab group for safety analyses. Multiple occurrences of the same event for a patient were counted once in the overall incidence. MMF = mycophenolate mofetil.
† The placebo-treated patient had cytomegaloviral pneumonitis; the 3 rituximab-treated patients had colitis, histoplasmosis, and cryptococcal pneumonia plus fungal sepsis, respectively.
‡ Defined as any adverse event (AE) occurring during or within 24 hours after an infusion of study drug.

greater and the median UPC ratio was lower in anti-dsDNA responders than in anti-dsDNA nonresponders in both treatment arms (Figures 2E and F). The differences in proteinuria outcomes manifested as early as week 8 and increased after week 24 (Figures 2E and F). A similar analysis for C3 revealed comparable results but only for the placebo arm (data not shown).

Safety. *Adverse events.* Safety data are summarized in Table 3. AEs, including those considered possibly study drug–related, occurred at similar frequencies in both treatment groups. Neutropenia, leukopenia, and hypotension were more frequent in the rituximab group. Infection-related AEs occurred with similar frequency in the placebo and rituximab arms through week 78 (90% and 85% of patients, respectively).

Deaths. Two deaths occurred; both occurred in the rituximab group, and both were considered to be unrelated to the study drug. One death was due to sepsis secondary to a *Staphylococcus aureus* infection in a 50-year-old woman who experienced a myocardial infarction 64 days after the first rituximab infusion. The second patient, a 26-year-old woman, died of alveolar hemorrhage 58 days after the first rituximab treatment.

Serious adverse events (SAEs) and hospitalizations. Serious adverse events were more frequent in placebo-treated patients than in rituximab-treated patients (74.3 [95% CI 58.9, 93.8] versus 42.9 [95% CI 31.9, 57.7] per 100 patient-years). The most common SAEs in the placebo and rituximab arms were anemia (4.2% versus 4.1%), renal failure (5.6% versus 1.4%), and neutropenia (1.4% versus 2.7%). Serious infections occurred in 14 patients from each group (19.9 per 100 patient-years and 16.6 per 100 patient-years in the placebo and rituximab arms, respectively), with similar hospitalization rates per 100 patient-years (18.8 versus 14.6). Non–infection-related hospitalizations occurred more often with placebo than with rituximab (48.1 [95% CI 36.1, 64.3] versus 17.6 [95% CI 11.1, 27.9] per 100 patient-years).

Infusion-related adverse events. Infusion-related AEs (defined as any AE occurring within 24 hours of study drug infusion) occurred with similar frequency in both treatment arms; those attributed to study drug were twice as frequent in the rituximab group (16.4%) than the placebo group (8.5%). Infusion-related AEs occurred most frequently following the first infusion and became less frequent with subsequent infusions. Serious infusion-related AEs were reported in 2 placebo-treated patients (generalized edema and anemia, not study drug–related) and 1 rituximab-treated HACA-positive patient (grade 3 urticaria, related to study drug).

Pharmacodynamics and immunogenicity. On day 28, after the first rituximab cycle, CD19+ cell counts were below the lower limit of normal (80 cells/μl) in all except 1 rituximab-treated patient. Median CD19+ cell counts over time are shown in Figure 3. At week 52, 79% and 89% of rituximab-treated patients had CD19+ counts of $<$20 cells/μl and less than the lower limit of normal, respectively. Pretreatment levels of CD19+ cells were not associated with the renal response at week 52. Using the median baseline CD19+ cell count of 156

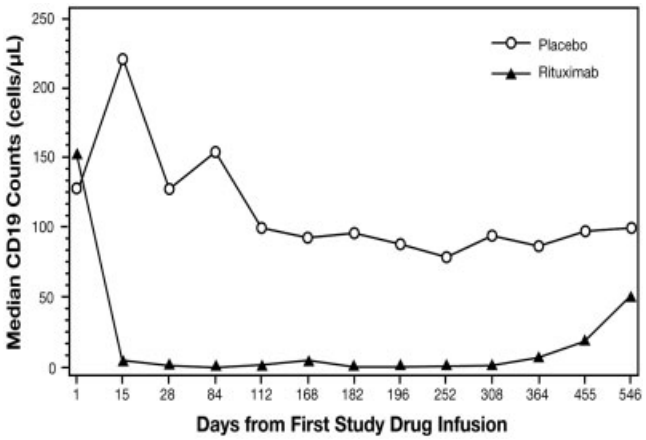

Figure 3. Median peripheral blood CD19+ cell counts in placebo-treated and rituximab-treated patients (n = 71 and n = 73, respectively). One patient randomized to placebo inadvertently received 2 rituximab infusions during the second cycle and was included in the rituximab group for safety analyses.

cells/μl in the rituximab group as a cutoff, the subsets of rituximab-treated patients with lower versus higher CD19+ cell counts at baseline had the same complete or partial renal response rates at week 52, while Spearman's correlation coefficient for the association between the overall renal response rate at week 52 and the baseline CD19+ count was −0.01. However, the data suggest that overall, at week 52, renal responders in the rituximab group experienced somewhat faster reconstitution of CD19+ cells than did nonresponders, particularly after the second treatment course. This difference was also apparent for the CD27+ and CD27− subsets (see Appendix Figure 3**,** available on the *Arthritis & Rheumatism* Web site at http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)1529-0131).

We assessed the association between baseline CD19 counts and baseline characteristics such as complement C3, C4, anti-dsDNA, and C-reactive protein (CRP) levels, the erythrocyte sedimentation rate, serum albumin and serum creatinine levels, and the UPC ratio. Of these parameters, the only ones that correlated with baseline CD19 counts ($\rho_o > 0.15$) were anti-dsDNA ($\rho_o = -0.38$, $P < 0.01$), and CRP ($\rho_o = -0.25$) (see Appendix Table 1**,** available on the *Arthritis & Rheumatism* Web site at http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)1529-0131). Although the small sample size did not allow for a full and valid evaluation of patient subgroups with respect to changes in CD19+ cell counts and response over time, we noted relationships between baseline anti-dsDNA levels relative to the median for each patient group, renal response, and degree of B cell depletion, as well as the time to cell repletion after the first treatment course. Among rituximab-treated patients with high baseline anti-dsDNA titers (>123 IU/ml), those who were renal responders at week 52 had a greater depletion of CD19+ cells compared with renal nonresponders (see Appendix Figure 3**,** available on the *Arthritis & Rheumatism* Web site at http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)1529-0131). Among rituximab-treated patients with anti-dsDNA antibody titers <123 IU/ml, B cell counts, particularly memory (CD19+CD27+) cell counts, appeared higher (i.e., less depleted) in patients who were renal responders at week 52 than in nonresponders. However, these differences were not statistically significant.

Six placebo-treated patients (8.5%) and 11 rituximab-treated patients (15.1%) were HACA positive at some point during the study (3 placebo patients became positive after their treating physicians withdrew from the study and administered off-label rituximab). HACA titers in the rituximab arm were 5.4–35,000 ng/ml (median 113 ng/ml). In the placebo arm, the HACA titer range was 6–442 ng/ml (the maximum titer of 442 ng/ml was seen in a placebo-treated patient without exposure to open-label rituximab). The rituximab-treated patient with the highest HACA titer experienced a severe infusion reaction (urticaria) during the fourth infusion.

Among HACA-positive patients, infusion-related events occurred in 5 (83%) of 6 placebo-treated patients and in 7 (64%) of 11 rituximab-treated patients. Infusion-related AEs were less frequent in HACA-negative patients (37% and 29%, respectively).

DISCUSSION

LUNAR is the largest randomized, placebo-controlled study to evaluate the effect of adding rituximab to initial therapy for proliferative LN. This study did not demonstrate a statistically significant difference between the responses of patients treated with rituximab and those of patients treated with placebo, although more partial responses occurred in the rituximab group. As noted previously, the study was powered to detect a difference mainly in complete response rates and was underpowered to detect a difference in partial responses such as that observed in LUNAR. The impetus for adding rituximab to MMF and corticosteroids was to improve the outcomes of patients with LN, because renal response rates, especially complete remissions,

continue to be unacceptably low despite the use of aggressive initial therapies. Furthermore, a number of smaller studies of LN have shown favorable responses to rituximab, including a recent study that demonstrated efficacy leading to a reduction or complete withdrawal of corticosteroids in some patients with LN (40).

There may be several reasons for the disparate outcome between LUNAR and other studies of rituximab in LN. Perhaps the most important difference is that LUNAR is a randomized, controlled trial, while other studies of rituximab were nonrandomized and were not controlled. However, it is also important to note that these investigations mainly studied LN patients who had been previously treated with cyclophosphamide and/or MMF and in whom disease was considered refractory to these standard therapies (23,34,41–48). LUNAR did not recruit such patients; rather, approximately half of the patients who were enrolled had experienced only a first episode of LN. Although it may seem paradoxical that rituximab would be effective in treatment-refractory disease and not in nascent disease, it is conceivable that those in whom conventional therapies failed are more responsive to drugs that act through different pathways.

Because LUNAR was designed to evaluate rituximab as add-on therapy to standard induction therapy, it was not possible to consider improved safety as an outcome. However, no new or unexpected safety signals were observed; the safety findings in this study are consistent with observations regarding the use of rituximab in rheumatoid arthritis (14). Overall, the incidence of AEs and SAEs was no higher with rituximab than with placebo, confirming the favorable safety profile of rituximab combined with highly immunosuppressive therapies (MMF and corticosteroids) in patients with LN.

In a prespecified, though underpowered, subgroup analysis, a higher proportion of black patients (versus patients of other races/ethnicities) achieved a renal response at week 52 with rituximab compared with placebo. This difference was not statistically significant, and the improved response was due to partial rather than complete remissions. Interestingly, this finding parallels, to some extent, the observation that black patients had a better response to MMF than the response to intravenous cyclophosphamide observed in the ALMS trial (32,49). Because black patients with LN often have severe disease that may be difficult to control, these data could be used to justify a randomized, controlled trial of rituximab in a cohort of black patients with LN.

The secondary clinical end points of the LUNAR trial also did not achieve statistical significance; however, when compared with placebo-treated patients, rituximab-treated patients showed a tendency toward superior responses for many of the parameters examined. These included a reduction in proteinuria, improvement in renal function, and need for rescue therapy. Additionally, differences between rituximab-treated and placebo-treated patients for some parameters (e.g., $>50\%$ reduction in proteinuria) persisted through 78 weeks, raising the possibility that a longer duration of observation may be necessary to understand the full impact of rituximab therapy.

In contrast to the effect of rituximab in terms of the clinical end points, rituximab significantly improved anti-dsDNA and complement levels as serologic markers of disease activity. Although these changes were not associated with improved renal responses, they correlated with reductions in proteinuria. Independent of treatment assignment, larger reductions in anti-dsDNA levels at week 52 were associated with greater improvements in both absolute and relative levels of proteinuria. In other studies, similar serologic effects correlated with favorable clinical outcomes (50) or with a reduced risk of flare (51). Although the small number of rituximab-treated patients in this study precludes conclusions on the relationship between the pharmacodynamic effect and clinical response, the observation that responders at week 52 appeared to replenish CD19+ cells faster than nonresponders is intriguing.

In summary, the LUNAR study failed to demonstrate the superiority of rituximab added to MMF plus corticosteroids over MMF plus corticosteroids alone in achieving either combined complete and partial responses or complete responses alone. However, several potentially clinically relevant effects occurred more often with rituximab treatment. Furthermore, rituximab elicited a stronger response in black patients. These favorable trends, along with the results of a large number of smaller open-label studies with positive results in patients with treatment-refractory LN, indicate a need to further examine the potential role for rituximab in certain subsets of patients with LN. Although noninferiority trials for LN are difficult to conduct and do not have a clear regulatory approval pathway (52), the results of the LUNAR study do not exclude the possibility that rituximab, alone or in combination with corticosteroids, could be as effective as commonly used initial therapies such as MMF or cyclophosphamide.

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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 published. Dr. Rovin 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.

Study conception and design. Rovin, Furie, Latinis, Looney, Zhang, Garg, Brunetta, Appel.

Acquisition of data. Rovin, Furie, Looney, Fervenza, Sanchez-Guerrero, Garg, Brunetta, Appel.

Analysis and interpretation of data. Rovin, Furie, Latinis, Fervenza, Sanchez-Guerrero, Maciuca, Zhang, Garg, Brunetta, Appel.

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