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Rituximab or cyclosporine in the treatment of membranous nephropathy

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et al.

ORIGINAL ARTICLE

Rituximab or Cyclosporine in the Treatment of Membranous Nephropathy

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ABSTRACT

BACKGROUND

B-cell anomalies play a role in the pathogenesis of membranous nephropathy. B-cell depletion with rituximab may therefore be noninferior to treatment with cyclosporine for inducing and maintaining a complete or partial remission of proteinuria in patients with this condition.

METHODS

We randomly assigned patients who had membranous nephropathy, proteinuria of at least 5 g per 24 hours, and a quantified creatinine clearance of at least 40 ml per minute per 1.73 m^2 of body-surface area and had been receiving angiotensin-system blockade for at least 3 months to receive intravenous rituximab (two infusions, 1000 mg each, administered 14 days apart; repeated at 6 months in case of partial response) or oral cyclosporine (starting at a dose of 3.5 mg per kilogram of body weight per day for 12 months). Patients were followed for 24 months. The primary outcome was a composite of complete or partial remission of proteinuria at 24 months. Laboratory variables and safety were also assessed.

RESULTS

A total of 130 patients underwent randomization. At 12 months, 39 of 65 patients (60%) in the rituximab group and 34 of 65 (52%) in the cyclosporine group had a complete or partial remission (risk difference, 8 percentage points; 95% confidence interval [CI], −9 to 25; P=0.004 for noninferiority). At 24 months, 39 patients (60%) in the rituximab group and 13 (20%) in the cyclosporine group had a complete or partial remission (risk difference, 40 percentage points; 95% CI, 25 to 55; P<0.001 for both noninferiority and superiority). Among patients in remission who tested positive for anti–phospholipase A_2 receptor (PLA2R) antibodies, the decline in autoantibodies to anti-PLA2R was faster and of greater magnitude and duration in the rituximab group than in the cyclosporine group. Serious adverse events occurred in 11 patients (17%) in the rituximab group and in 20 (31%) in the cyclosporine group (P=0.06).

CONCLUSIONS

Rituximab was noninferior to cyclosporine in inducing complete or partial remission of proteinuria at 12 months and was superior in maintaining proteinuria remission up to 24 months. (Funded by Genentech and the Fulk Family Foundation; MENTOR ClinicalTrials.gov number, NCT01180036.)

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Membranous nephropathy is the leading cause of nephrotic syndrome in white adults. Spontaneous remission occurs in approximately 30% of affected patients, and among patients who continue to have nephrotic syndrome, end-stage renal disease develops in 40 to 50% over a period of 10 years.[1] A total of 70 to 80% of patients with membranous nephropathy have circulating autoantibodies to the phospholipase A_2 receptor (PLA2R),[2] and 1 to 3% have circulating antibodies to thrombospondin type-1 domain-containing 7A (THSD7A).[3] In the remaining patients, the target antigen is unknown. In patients with anti-PLA2R antibodies, there is a tight correlation between antibody levels and disease activity, which suggests a causal relationship.[2,4-6]

Initial therapy for patients with membranous nephropathy is supportive[7]; immunosuppressive therapy is recommended for patients with persistent nephrotic syndrome.[7,8] A regimen of alternating glucocorticoids and cyclophosphamide[9-11] is effective in 60 to 70% of patients but has been associated with clinically significant toxic effects, including hyperglycemia, myelosuppression, infections, infertility, and cancer.[12-14] Calcineurin inhibitors, including cyclosporine, are effective and are the preferred treatment for membranous nephropathy in the United States and Canada.[15] However, these agents are associated with a high incidence of relapse after discontinuation and with frequent side effects, including hypertension and nephrotoxic effects.

B-cell dysfunction plays a role in the pathogenesis of membranous nephropathy.[16] Cyclophosphamide has a profound but unselective B-cell–depleting effect, leading to a reduced production of nephrotoxic antibodies.[17,18] More-selective B-cell depletion with rituximab, therefore, appears to be a promising approach.[19] Multiple uncontrolled studies with rituximab have shown a reduction in proteinuria of 60 to 80% in the majority of patients for as long as 24 months after the initiation of immunosuppressive treatment.[20-23] One randomized trial compared rituximab with supportive therapy in patients with membranous nephropathy. Although there was no advantage with rituximab with regard to the primary outcome at 6 months, follow-up over a period of 1 to 2 years showed more remissions with rituximab than with supportive therapy.[24] We designed the Membranous Nephropathy Trial of Rituximab (MENTOR) to investigate whether rituximab would be noninferior to cyclosporine in inducing and maintaining remission of proteinuria, regardless of patients' baseline anti-PLA2R status, for up to 24 months in patients with apparent primary membranous nephropathy.

METHODS

TRIAL DESIGN AND OVERSIGHT

This investigator-initiated, open-label, randomized, multicenter, noninferiority trial was conducted at 22 sites in North America. As described previously,[25] the trial was designed by the principal investigators and supported by Genentech and the Fulk Family Foundation. Genentech also donated rituximab; cyclosporine was purchased at the usual market price. The funders had no role in the trial design or conduct; the collection, management, analysis, or interpretation of the data; or in the preparation or review of the manuscript or the approval of the manuscript for submission. An independent data and safety monitoring board oversaw the trial (see the Supplementary Appendix, available with the full text of this article at NEJM.org). Appropriately authorized ethics committees approved the trial at all participating sites. The manuscript was drafted and written by the first and last authors, with input as appropriate from the statistical team and the investigators. The authors collected the data and vouch for the completeness and accuracy of the data and for the fidelity of the trial to the protocol (available at NEJM.org). The decision to submit the manuscript for publication was made by the authors.

PARTICIPANTS

Patients with membranous nephropathy were eligible if their diagnosis was confirmed by renal biopsy, with the biopsy sample examined by light, immunofluorescence, and electron microscopy. Renal biopsy samples were centrally reviewed by the two principal investigators and two renal pathologists. Patients also had to be 18 to 80 years of age, have proteinuria of more than 5 g per 24 hours on average in two 24-hour urine samples obtained within 14 days, have a decline of less than 50% in proteinuria despite renin–angiotensin system blockade for at least 3 months before randomization, and have a stable quantified 24-hour creatinine clearance of at least 40 ml

per minute per 1.73 m^2 of body-surface area. Full eligibility criteria, including histologic results from kidney biopsy, are provided in the Supplementary Appendix.

All patients received best-practice supportive care that included blockers of the renin–angiotensin system, blood-pressure management targeting a value of less than 130/80 mm Hg, dietary sodium restriction to less than 4 g per day, and dietary protein restriction to 0.8 to 1 g of protein per kilogram of body weight per day during at least the previous 3 months before randomization. Patients who had not received best-practice supportive care as part of their routine treatment underwent a 3-month run-in phase. If proteinuria remained at a level of at least 5 g per 24 hours and the creatinine clearance was at least 40 ml per minute per 1.73 m^2, patients were randomly assigned in a 1:1 ratio to receive rituximab or cyclosporine. The randomization schedule was computer-generated, stratified according to site, blocked with randomly varied block sizes of two and four, and concealed with the use of a Web-based, locked central randomization system. All the patients provided written informed consent.

INTERVENTIONS

Patients who were assigned to the rituximab group received 1000 mg of intravenous medication (Rituxan, Genentech) on days 1 and 15. If proteinuria was reduced from baseline by at least 25% at 6 months but there was not complete remission, a second course of rituximab was administered regardless of the CD19+ B-cell count. If complete remission was observed at 6 months, no second course was given. If proteinuria was reduced by less than 25% by 6 months, the patient was considered to have treatment failure and no further rituximab was administered (Fig. S1 in the Supplementary Appendix).

Patients who were assigned to the cyclosporine group received dose-adjusted cyclosporine (Neoral, Novartis), starting at an oral dose of 3.5 mg per kilogram per day, divided into two equal doses given at 12-hour intervals. Target trough blood levels of cyclosporine were 125 to 175 ng per milliliter.[26] Blood levels were assessed every 2 weeks until the target trough level was reached. If complete remission was observed at 6 months, cyclosporine was tapered and discontinued over a 2-month period. If proteinuria was reduced from baseline by less than 25% at 6 months, the patient was considered to have treatment failure and cyclosporine was discontinued. If proteinuria was reduced by at least 25%, cyclosporine was continued for an additional 6 months. At the end of 12 months, cyclosporine was tapered by one third of the maintenance dose monthly and discontinued after 2 months. A persistent and otherwise unexplained increase in the serum creatinine level of more than 30% was managed by dose reduction as described previously.[25] If the creatinine level did not fall to baseline values despite dose reductions, cyclosporine was discontinued and the patient was considered to have treatment failure.

OUTCOMES AND FOLLOW-UP

The primary clinical outcome was the composite of complete or partial remission at 24 months. Secondary clinical outcomes included the composite of complete or partial remission at 6, 12, and 18 months; complete remission at 6, 12, 18, and 24 months; time to treatment failure up to 24 months; end-stage renal disease; and adverse events. Continuous secondary outcomes, including anti-PLA2R levels, quality of life as assessed with the modified Kidney Disease Quality of Life Short Form (KDQOL-SF), version 1.3,[27] proteinuria, and creatinine clearance, were systematically recorded only up to the occurrence of treatment failure.

Complete remission was defined as proteinuria of no more than 0.3 g per 24 hours and a serum albumin level of at least 3.5 g per deciliter. Partial remission was defined as a reduction in proteinuria of at least 50% from baseline plus final proteinuria between 0.3 g and 3.5 g per 24 hours regardless of creatinine clearance or the serum albumin level. We defined no response as no reduction in proteinuria of at least 25% from baseline. Relapse was defined as the development of proteinuria of more than 3.5 g per 24 hours after a complete or partial remission. End-stage renal disease was defined as a creatinine clearance of no more than 15 ml per minute, the initiation of dialysis, or renal transplantation. A list of outcomes and definitions is provided in the Supplementary Appendix.

The run-in phase included visits at −3 months and at week 0, when patients underwent randomization and treatment was initiated. Subsequent visits for patients who had undergone ran-

domization were scheduled at 1, 3, 6, 9, and 12 months (treatment period) and at 18 and 24 months (observation period). Proteinuria and creatinine clearance were estimated with the use of quantified 24-hour urine samples. Critical laboratory values, including 24-hour urinary protein and creatinine, serum creatinine, and anti-PLA2R antibody levels as measured by enzyme-linked immunosorbent assay (ELISA),[28] were assessed centrally (Section F in the Supplementary Appendix). Patients were considered to be anti-PLA2R–positive if the baseline antibody level was more than 40 U per milliliter.

STATISTICAL ANALYSIS

We calculated that a sample of 63 patients per group would provide the trial with 80% power to detect noninferiority regarding the primary outcome at a one-sided alpha of 0.025 (equivalent to a two-sided alpha of 0.05) and a noninferiority margin of 15 percentage points on an absolute risk-difference scale, assuming that 55% of the patients in the rituximab group and 45% of those in the cyclosporine group had a complete or partial remission at 24 months. The analysis of the primary composite outcome was performed in the intention-to-treat population with the use of a stepwise approach to control the family-wise type I error, first testing the noninferiority of rituximab and then testing the superiority of rituximab if the noninferiority test was significant. An additional, prespecified noninferiority analysis of the primary outcome was performed in the per-protocol population. In both the intention-to-treat analysis and the per-protocol analysis, noninferiority would be claimed if the lower limit of the two-sided 95% confidence interval for the risk difference was not below −15 percentage points. A noninferiority analysis of the secondary outcome of complete or partial remission at 12 months in the intention-to-treat population was prespecified in the statistical analysis plan. The analysis used a prespecified Bonferroni correction, which allowed for this outcome to be tested in addition to the primary outcome at a one-sided alpha level of 0.0125. One-sided P values for noninferiority were calculated from z tests against the noninferiority margin, with calculation of the standard error in a generalized linear model.

An extended description of the statistical methods, including subgroup analyses, is provided in the Supplementary Appendix. Since the widths of 95% confidence intervals for secondary outcomes were not adjusted for multiple comparisons, these intervals should not be used for inferences about treatment effects. All the analyses were performed with the use of Stata software, version 14.2 (StataCorp).

RESULTS

PATIENTS

From March 2012 through September 2015, a total of 182 patients were screened, 130 were enrolled, and 65 were randomly assigned to each group (Fig. S2 in the Supplementary Appendix). The mean age of the patients was 52 years, 100 patients (77%) were men, and 96 patients (74%) were anti-PLA2R–positive (Table 1). One patient who was randomly assigned to the rituximab group was anti-THSD7A–positive.

One patient who was assigned to the rituximab group withdrew consent after randomization and before treatment began; the remaining patients received at least one dose of the assigned intervention. A total of 2 patients (3%) in the rituximab group and 11 (17%) in the cyclosporine group discontinued the intervention (difference, 14 percentage points; 95% confidence interval [CI], 4 to 24). Patients who had a decrease in proteinuria of less than 25% and were classified as having treatment failure at 6 months tended to have higher anti-PLA2R levels at baseline and 6 months, were less likely to have an immunologic response, and had a lower serum albumin level at 6 months than patients who had a decrease in proteinuria of 25% or more (Tables S1 through S3 in the Supplementary Appendix). CD19+ B-cell counts in the rituximab group and serum trough cyclosporine levels in the cyclosporine group are shown in Figures S3 and S4, respectively, in the Supplementary Appendix. Follow-up was complete for 63 patients (97%) in the rituximab group and for 61 (94%) in the cyclosporine group.

CLINICAL OUTCOMES

A total of 39 patients (60%) in the rituximab group and 13 (20%) in the cyclosporine group had a primary composite outcome of complete or partial remission at 24 months (risk difference, 40 percentage points; 95% CI, 25 to 55) (Fig. 1). Tests for noninferiority in the intention-to-treat and per-protocol populations (Table S4 in the

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Rituximab (N=65)	Cyclosporine (N=65)
Age — yr	51.9±12.6	52.2±12.4
Male sex — no. (%)	47 (72)	53 (82)
Blood pressure — mm Hg		
Systolic	125.7±14.8	123.3±13.4
Diastolic	74.7±10.1	76.5±9.8
Height — m	1.7±0.1	1.7±0.1
Weight — kg	96±23	90±20
Body-mass index†	31.8±6.3	29.3±5.6
History of immunosuppressive therapy — no. (%)	19 (29)	20 (31)
Cholesterol — mg/dl		
Low-density lipoprotein	114.1±57.7	122.3±63.0
Total	145.1±61.6	144.8±69.8
Anti-PLA2R — U/ml		
Median	409	413
Interquartile range	163–834	206–961
Anti-PLA2R positive — no. (%)‡	50 (77)	46 (71)
Serum albumin — g/dl		
Median	2.5	2.5
Interquartile range	2.1–2.9	2.1–2.9
Serum creatinine — mg/dl	1.3±0.4	1.3±0.4
Urinary protein — g/24 hr		
Median	8.9	8.9
Interquartile range	6.8–12.3	6.7–12.9
Urinary creatinine — g/24 hr	1.7±0.5	1.8±0.6
Creatinine clearance — ml/min/1.73 m^2	84.9±29.8	87.4±34.4
Protein:creatinine§	6.2±2.6	6.2±3.3

* Plus–minus values are means ±SD. To convert values for cholesterol to millimoles per liter, multiply by 0.02586. To convert values for creatinine to micromoles per liter, multiply by 88.4. Anti-PLA2R denotes anti–phospholipase A_2 receptor autoantibody.
† The body-mass index is the weight in kilograms divided by the square of the height in meters.
‡ Patients were considered to be anti-PLA2R–positive if the value was more than 40 U per milliliter.
§ Protein and creatinine values were measured in milligrams.

Supplementary Appendix) and the subsequent test for superiority in the intention-to-treat population were all significant at a P value of less than 0.001. The secondary noninferiority analysis of the composite of complete or partial remission at 12 months was significant (P=0.004). Table 2 presents data regarding the composite of complete or partial remission at time points from 6 months to 24 months.

The treatment effect of rituximab as compared with cyclosporine appeared to be consistent across subgroups defined according to age, proteinuria, anti-PLA2R antibody status, and history of immunosuppressive therapy at baseline. However, a test for interaction with sex indicated a more pronounced benefit of rituximab in women than in men (P<0.001 for interaction), which was probably due to baseline imbalances in anti-PLA2R levels (Fig. S5 and Table S5 in the Supplementary Appendix). The interaction disappeared after adjustment for anti-PLA2R levels at baseline (Table S6 in the Supplementary Appendix).

At 24 months, 23 patients (35%) in the rituximab group and none of the patients in the cyclosporine group had a complete remission (risk difference, 35 percentage points; 95% CI, 24 to 47) (Table S7 in the Supplementary Appendix). Of these patients, 18 were positive for anti-PLA2R antibodies at baseline and all were antibody-negative at 24 months.

A total of 26 patients (40%) in the rituximab group and 52 (80%) in the cyclosporine group had treatment failure by 24 months (hazard ratio, 0.34; 95% CI, 0.21 to 0.54) (Fig. 2). Figure S6 in the Supplementary Appendix shows time-to-event curves for complete or partial remission during the 12-month treatment period; patients in the cyclosporine group tended to have remission earlier, with a later catch-up in patients in the rituximab group. At the end of the treatment period, 39 patients (60%) in the rituximab group and 34 (52%) in the cyclosporine group had a complete or partial remission (hazard ratio for response, 0.85; 95% CI, 0.55 to 1.32). Figure S7 in the Supplementary Appendix presents time-to-event curves for treatment failure during the 12-month observation period among these 39 and 34 patients who were in remission at the end of treatment period. A total of 2 of the 39 patients (5%) in the rituximab group and 21 of the 34 patients (62%) in the cyclosporine group had treatment failure during this period (hazard ratio, 0.05; 95% CI, 0.01 to 0.23). Table S8 in the Supplementary Appendix shows the cumulative numbers of patients with treatment failure at months 6 to 24, with pronounced between-group differences at 18 months and 24 months.

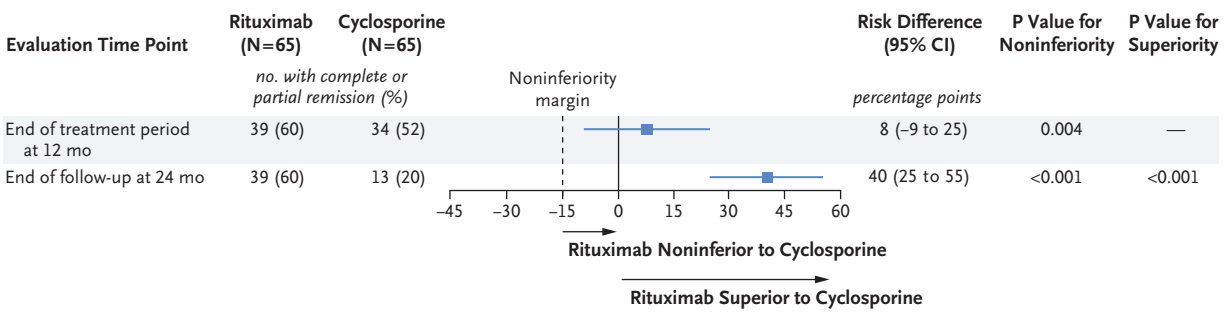


Figure 1. Composite Outcome of Complete or Partial Remission at 12 and 24 Months.

Point estimates and two-sided 95% confidence intervals are shown for the treatment effect, defined as the risk difference for complete or partial remission between groups in the intention-to-treat analysis. The noninferiority margin for rituximab as compared with cyclosporine was –15 percentage points. The lower end of the two-sided 95% confidence interval of the risk difference in the secondary composite of complete remission or partial remission at 12 months was above –15 percentage points, and the P value for noninferiority of 0.004 was significant, which met the prespecified alpha level of a P value of less than 0.0125 after Bonferroni correction. Per the statistical analysis plan, no test for superiority was performed for the secondary outcome of complete or partial remission at 12 months. The lower limit of the two-sided 95% confidence interval for the risk difference in the primary composite outcome of complete remission or partial remission at 24 months was above 0 percentage points; both the criterion for noninferiority and the criterion for superiority of rituximab were met at a P value of less than 0.001, which met the prespecified alpha levels specified for noninferiority (P<0.025) and superiority (P<0.05). P values for noninferiority are one-sided, and the P value for superiority is two-sided.

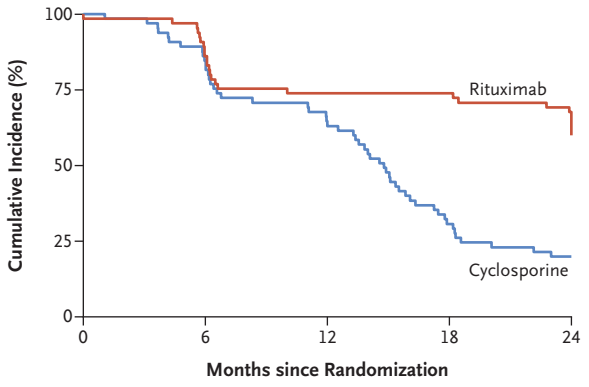
Table 2. Composite Outcome of Complete or Partial Remission at 6 to 24 Months.*

Time from Randomization	Rituximab	Cyclosporine	Risk Difference (95% CI)
	no. of patients with remission/total no. (%)		*percentage points*
Intention-to-treat population			
6 mo	23/65 (35)	32/65 (49)	–14 (–31 to 3)
12 mo	39/65 (60)	34/65 (52)	8 (–9 to 25)
18 mo	40/65 (62)	15/65 (23)	38 (23 to 54)
24 mo	39/65 (60)	13/65 (20)	40 (25 to 55)
Per-protocol population			
6 mo	22/63 (35)	32/63 (51)	–16 (–33 to 1)
12 mo	38/63 (60)	33/63 (52)	8 (–9 to 25)
18 mo	39/63 (62)	15/63 (24)	38 (22 to 54)
24 mo	39/63 (62)	13/63 (21)	41 (26 to 57)

* The intention-to-treat population included all the patients who underwent randomization, and the per-protocol population included all the patients who received a full course of trial medications, defined as at least one completed 6-month treatment cycle, according to the protocol. The primary outcome was the composite of complete or partial remission at 24 months. The primary noninferiority analysis and the superiority analysis of the primary outcome at 24 months were performed in the intention-to-treat population, and an additional noninferiority analysis of the primary outcome at 24 months was performed in the per-protocol population. Because the widths of the 95% confidence intervals for secondary outcomes were not adjusted for multiple comparisons, these intervals should not be used for inference about treatment effects.

LABORATORY OUTCOMES AND QUALITY OF LIFE

In the 39 patients who were in remission 24 months after the initiation of rituximab therapy, proteinuria had decreased from a geometric mean of 8.79 g per 24 hours at baseline to 0.30 g per 24 hours at 24 months, and in the 13 patients who were in remission 24 months after the initiation of cyclosporine therapy, proteinuria had decreased



No. at Risk					
Rituximab	65	59	48	48	44
Cyclosporine	65	56	42	20	13

Figure 2. Time to Treatment Failure.

Shown are Kaplan–Meier estimates of the time to treatment failure. Patients were considered to have treatment failure if they had reduction in proteinuria of less than 25% from baseline at 6 months, had a relapse, had a premature termination of the protocol-specified treatment schedule before 12 months because of disease activity or adverse event, used an immunosuppressive medication other than the trial medication for the treatment of membranous nephropathy before 12 months, used any immunosuppressive medication for the treatment of membranous nephropathy after 12 months and before 24 months, or did not meet the criteria for a complete or partial remission at 24 months. Patients who were lost to follow-up at 24 months were considered to have had treatment failure unless they were found to have had a complete or partial remission at their 18-month visit. A test of the proportional-hazards assumption based on Schoenfeld residuals showed a P value of 0.06. A time-by-treatment interaction that was based on a cutoff at 1 year to distinguish between the treatment period up to 12 months and the subsequent follow-up from month 13 through month 24 was positive (ratio of hazard ratios, 0.22; 95% CI, 0.09 to 0.55; P=0.001 for interaction), with hazard ratios of 0.68 (95% CI, 0.36 to 1.26) for the period up to 12 months and 0.15 (95% CI 0.07 to 0.30) for the period between 13 and 24 months. After the inclusion of the interaction term, the overall test of the proportional-hazards assumption was negative (P=0.17).

from 9.46 g per 24 hours to 1.02 g per 24 hours (between-group difference at 24 months, −0.72 g per 24 hours; 95% CI, −0.86 to −0.47). Blood pressure remained stable during treatment with rituximab but increased with cyclosporine treatment, with differences at 12 months of −10.7 mm Hg (95% CI, −17.2 to −4.1) in the systolic blood pressure and −6.6 mm Hg (95% CI, −10.4 to −2.7) in the diastolic blood pressure. There was little evidence of between-group differences at 18 and 24 months. The mean creatinine clearance in patients in remission was higher in the rituximab group than in the cyclosporine group at all time points, with between-group differences of 26 ml per minute per 1.73 m^2 (95% CI, 17 to 35) at 12 months and of 18 ml per minute per 1.73 m^2 (95% CI, 5 to 31) at 24 months. Details are provided in Figures S8 and S9 and Tables S9 and S10 in the Supplementary Appendix.

The decline in anti-PLA2R antibody levels was faster and of greater magnitude and duration in anti-PLA2R–positive patients in remission in the rituximab group than in those in the cyclosporine group and was accompanied by a greater decline in proteinuria. The anti-THSD7A–positive patient who had been assigned to the rituximab group was anti-THSD7A–negative from 3 months onward and then had a partial remission at 9 months and a complete remission at 12 months, which was maintained until 24 months. Details are provided in Figure S10 and Tables S11 through S13 in the Supplementary Appendix.

Table S14 in the Supplementary Appendix presents selected quality-of-life subscales in patients with remission of proteinuria at 6, 12, and 24 months. There was little evidence of between-group differences, except in the symptom or problem list at 6 months and the mental health composite at 12 months.

ADVERSE EVENTS

The incidence of adverse events was similar in the rituximab group and the cyclosporine group (71% and 78% of patients, respectively). The incidence of adverse events of grade 3 or higher was 52% in the rituximab group and 68% in the cyclosporine group, and the incidence of serious adverse events was 17% and 31%, respectively (Table 3). A total of seven patients (11%) discontinued cyclosporine because of adverse events (Table S15 in the Supplementary Appendix). Increased serum creatinine levels and gastrointestinal events were more common with cyclosporine, whereas pruritus and infusion-related reactions were more frequent with rituximab. End-stage renal disease developed in one patient in the cyclosporine group. No cancers or deaths occurred during the trial. Tables S16 through S32 and Figure S11 in the Supplementary Appendix present additional analyses of efficacy and safety outcomes.

DISCUSSION

We found that rituximab was noninferior to cyclosporine in inducing proteinuria remission at

Table 3. Adverse Events.

Event	Rituximab (N=65)		Cyclosporine (N=65)		P Value*
	Patients	Events	Patients	Events	
	no. (%)	*no. of events (rate per 100 patients)*	*no. (%)*	*no. of events (rate per 100 patients)*	
Any adverse event	46 (71)	179 (275)	51 (78)	218 (335)	0.31
Grade ≥3	11 (17)	14 (22)	23 (35)	27 (42)	0.02
Grade <3	44 (68)	165 (254)	45 (69)	191 (294)	0.85
Serious adverse event	11 (17)	13 (20)	20 (31)	22 (34)	0.06
Fatal	0	0	0	0	1.00
Nonfatal	11 (17)	13 (20)	20 (31)	22 (34)	0.06
Adverse event occurring in ≥4 patients					
Hypertension	0	0	5 (8)	6 (9)	0.06
Hyperkalemia	1 (2)	1 (2)	4 (6)	12 (18)	0.37
Gastrointestinal pain	1 (2)	2 (3)	9 (14)	9 (14)	0.02
Gingival event	1 (2)	1 (2)	4 (6)	4 (6)	0.37
Nausea or vomiting	2 (3)	4 (6)	9 (14)	15 (23)	0.03
Chills	1 (2)	1 (2)	5 (8)	5 (8)	0.21
Edema	4 (6)	5 (8)	5 (8)	6 (9)	1.00
Fatigue	5 (8)	6 (9)	8 (12)	8 (12)	0.38
Influenza-like symptoms	6 (9)	8 (12)	3 (5)	3 (5)	0.49
Infusion-related reaction	16 (25)	22 (34)	0	0	<0.001
Gastrointestinal infection	4 (6)	4 (6)	4 (6)	4 (6)	1.00
Pneumonia	1 (2)	1 (2)	6 (9)	6 (9)	0.12
Other respiratory tract infection	9 (14)	12 (18)	9 (14)	10 (15)	1.00
Skin infection	4 (6)	5 (8)	0	0	0.12
Muscle cramps	6 (9)	9 (14)	4 (6)	5 (8)	0.74
Myalgia	4 (6)	4 (6)	6 (9)	8 (12)	0.74
Pain	2 (3)	3 (5)	4 (6)	7 (11)	0.68
Dizziness	2 (3)	3 (5)	4 (6)	5 (8)	0.68
Headache	4 (6)	5 (8)	7 (11)	8 (12)	0.34
Paresthesia or dysesthesia	2 (3)	2 (3)	4 (6)	5 (8)	0.68
Anxiety or depression	1 (2)	1 (2)	4 (6)	6 (9)	0.37
Increased creatinine level†	4 (6)	5 (8)	15 (23)	17 (26)	0.01
Cough	7 (11)	9 (14)	2 (3)	4 (6)	0.16
Dyspnea	2 (3)	2 (3)	3 (5)	3 (5)	1.00
Pruritus	7 (11)	8 (12)	0	0	0.01

* P values are for the difference in proportions of patients having a specific type of event. P values were not adjusted for multiple comparisons.
† End-stage renal disease developed in one patient in the cyclosporine group.

12 months and was superior in maintaining long-term proteinuria remission up to 24 months in patients with membranous nephropathy who were at high risk for progressive disease.[7] The superiority of rituximab at 24 months appeared to be driven by the significantly lower incidence of relapse in the rituximab group than in the cyclosporine group during the observation peri-

od at months 13 to 24. The observed response at 24 months was close to the percentage that had been assumed in the power analysis for rituximab but was less than half the assumed percentage for cyclosporine. The lower-than-anticipated response in the cyclosporine group may be due to the inclusion of patients who had more severe proteinuria than did the patients in our previous trial.[13] The decline in proteinuria was more pronounced in patients who had a complete or partial remission with rituximab than in those in the cyclosporine group who had a complete or partial remission, and 23 patients treated with rituximab had a complete remission at 24 months, as compared with none of the patients treated with cyclosporine — a finding that suggests more frequent and more sustained remissions with rituximab than with cyclosporine. Remission of proteinuria is a recognized surrogate marker for long-term outcome in patients with membranous nephropathy.[29] A recent study involving patients with membranous nephropathy showed that the longer the remission, the greater the improvement in renal survival — a finding that emphasizes the value of partial remission and complete remission of proteinuria as surrogates for long-term outcome in patients with membranous nephropathy.[30]

Adverse events were common and similar in the two groups, but serious events were slightly less frequent with rituximab than with cyclosporine — findings that are consonant with recent data.[14] Renal function was worse after cyclosporine therapy than after rituximab therapy; the reduction in renal function after cyclosporine use was only partially explained by reversible hemodynamic effects during active treatment. Residual kidney dysfunction persisted after the discontinuation of cyclosporine therapy, which suggests that chronic cyclosporine nephrotoxicity, a known negative effect of cyclosporine, may have played a role.

Finally, between-group differences in complete or partial remission appeared to be more pronounced in women than in men — a finding that is probably explained by confounding due to baseline imbalances in anti-PLA2R levels. Antibody suppression occurred earlier and was more complete and sustained, persisting throughout the second year of the trial, in anti-PLA2R–positive patients who were treated with rituximab than in anti-PLA2R–positive patients who were treated with cyclosporine. The immunologic response to rituximab preceded the clinical response, a pattern that consistently emerges from the trials in membranous nephropathy that have shown the dynamics of anti-PLA2R antibody levels in relation to clinical variables.[4,6,20] Extensive immunologic damage requires prolonged podocyte remodeling before the architecture and function of the glomerular filtration barrier are restored, and such damage may explain the delay between immunologic response and decline in proteinuria.

The infrequent intravenous administration of rituximab, as compared with twice-daily oral cyclosporine, resulted in better adherence to therapy. Although the initial treatment costs are substantially higher with rituximab than with cyclosporine, this factor needs to be weighed against the prolonged benefits, higher quality of remission, better preservation of kidney function, and lower incidence of relapse with rituximab. A recent analysis of the cost-effectiveness of treating membranous nephropathy with alternating glucocorticoids and cyclophosphamide, as compared with rituximab, showed that despite initially higher costs of rituximab, the overall cost was lower because of the prolonged remission that was obtained with rituximab.[31] The limited overall incidence of remission of 50 to 60% may be an underestimation of the true effect of rituximab since, as shown in other studies involving patients who had a response to rituximab, proteinuria decline is gradual and the nadir may not be reached until 36 months after the initiation of treatment.[20]

Given the complex immunosuppressive treatment regimens and the cost involved, it did not seem feasible in our trial for patients and therapists to be unaware of the treatment assignments, which could have affected the treatment of the patient and the assessment of disease status. However, the definition of the primary outcome was based on objective laboratory values measured by personnel who were unaware of group assignments; thus, lack of blinding seems to be an unlikely explanation for the magnitude of the observed between-group difference at 24 months. We cannot rule out the possibility that longer treatment or follow-up of patients who did not have a decrease in proteinuria of at least 25% at

6 months might eventually have increased the percentage of patients with a response. However, in view of the symmetric pattern that was observed at 6 months in patients assigned to the rituximab group and those assigned to the cyclosporine group, we speculate that it is unlikely that a hypothetical change in protocol, with longer treatment and follow-up for patients with a decrease in proteinuria of less than 25% at 6 months, would have changed the overall conclusions.

Another limitation of our trial is that laboratory outcomes and quality of life were systematically recorded only up to the occurrence of treatment failure. Therefore, those outcomes were analyzed only in patients who had remission at each time point. Although that approach allowed comparisons of the quality of remission between groups, the design did not allow us to explore the effect of the originally assigned treatment strategy on laboratory outcomes and quality of life in the intention-to-treat population. It is possible that between-group differences in KDQOL-SF quality-of-life scores in the intention-to-treat population would have been considerably more pronounced, but studies involving patients with membranous nephropathy that could confirm or refute this hypothesis have been limited. The observed modest between-group differences in the KDQOL-SF mental health composite in patients who were in remission at 12 months, if confirmed, might relate to differences in perceived intrusiveness or effect of the two treatments on daily life, but their clinical relevance remains unclear.

Since the CD19+ B-cell counts remained low at 12 months, we cannot rule out a residual therapeutic effect of rituximab beyond this time period. However, in our two previous studies, CD19+ B-cell counts at 12 months showed no relation to proteinuria response.[21,22] We also acknowledge that using a lower cutoff value for the ELISA, performing Western blot, or detecting anti-PLA2R antibodies by means of serum immunofluorescence could have resulted in more patients who were considered to be PLA2R–positive.[32]

In conclusion, rituximab was noninferior to cyclosporine in inducing proteinuria remission at 12 months and was superior in maintaining long-term proteinuria remission up to 24 months in patients with membranous nephropathy who were at high risk for progressive disease.

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APPENDIX

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REFERENCES

1. Troyanov S, Wall CA, Miller JA, Scholey JW, Cattran DC. Idiopathic membranous nephropathy: definition and relevance of a partial remission. Kidney Int 2004;66:1199-205.
2. Beck LH Jr, Bonegio RG, Lambeau G, et al. M-type phospholipase A_2 receptor as target antigen in idiopathic membranous nephropathy. N Engl J Med 2009;361:11-21.
3. Tomas NM, Beck LH Jr, Meyer-Schwesinger C, et al. Thrombospondin type-1 domain-containing 7A in idiopathic membranous nephropathy. N Engl J Med 2014;371:2277-87.
4. Beck LH Jr, Fervenza FC, Beck DM, et al. Rituximab-induced depletion of anti-PLA2R autoantibodies predicts response in membranous nephropathy. J Am Soc Nephrol 2011;22:1543-50.
5. De Vriese AS, Glassock RJ, Nath KA, Sethi S, Fervenza FC. A proposal for a serology-based approach to membranous nephropathy. J Am Soc Nephrol 2017;28:421-30.
6. Ruggenenti P, Debiec H, Ruggiero B, et al. Anti-phospholipase A2 receptor antibody titer predicts post-rituximab outcome of membranous nephropathy. J Am Soc Nephrol 2015;26:2545-58.
7. Kidney Disease: Improving Global Outcomes (KDIGO) Glomerulonephritis Work Group. KDIGO clinical practice guideline for glomerulonephritis. Kidney Int 2012;2:Suppl 2:139-274.
8. Hofstra JM, Fervenza FC, Wetzels JF. Treatment of idiopathic membranous nephropathy. Nat Rev Nephrol 2013;9:443-58.
9. Ponticelli C, Zucchelli P, Imbasciati E, et al. Controlled trial of methylprednisolone and chlorambucil in idiopathic membranous nephropathy. N Engl J Med 1984;310:946-50.
10. Ponticelli C, Zucchelli P, Passerini P, Cesana B. Methylprednisolone plus chlorambucil as compared with methylprednisolone alone for the treatment of idiopathic membranous nephropathy. N Engl J Med 1992;327:599-603.
11. Jha V, Ganguli A, Saha TK, et al. A randomized, controlled trial of steroids and cyclophosphamide in adults with nephrotic syndrome caused by idiopathic membranous nephropathy. J Am Soc Nephrol 2007;18:1899-904.
12. Praga M, Barrio V, Juárez GF, Luño J. Tacrolimus monotherapy in membranous nephropathy: a randomized controlled trial. Kidney Int 2007;71:924-30.
13. Cattran DC, Appel GB, Hebert LA, et al. Cyclosporine in patients with steroid-resistant membranous nephropathy: a randomized trial. Kidney Int 2001;59:1484-90.
14. van den Brand JAJG, Ruggenenti P, Chianca A, et al. Safety of rituximab compared with steroids and cyclophosphamide for idiopathic membranous nephropathy. J Am Soc Nephrol 2017;28:2729-37.
15. Alfaadhel T, Cattran D. Management of membranous nephropathy in Western countries. Kidney Dis (Basel) 2015;1:126-37.
16. Biancone L, Andres G, Ahn H, DeMartino C, Stamenkovic I. Inhibition of the CD40-CD40ligand pathway prevents murine membranous glomerulonephritis. Kidney Int 1995;48:458-68.
17. Cupps TR, Edgar LC, Fauci AS. Suppression of human B lymphocyte function by cyclophosphamide. J Immunol 1982;128:2453-7.
18. Zhu LP, Cupps TR, Whalen G, Fauci AS. Selective effects of cyclophosphamide therapy on activation, proliferation, and differentiation of human B cells. J Clin Invest 1987;79:1082-90.
19. Ruggenenti P, Fervenza FC, Remuzzi G. Treatment of membranous nephropathy: time for a paradigm shift. Nat Rev Nephrol 2017;13:563-79.
20. Ruggenenti P, Cravedi P, Chianca A, et al. Rituximab in idiopathic membranous nephropathy. J Am Soc Nephrol 2012;23:1416-25.
21. Fervenza FC, Abraham RS, Erickson SB, et al. Rituximab therapy in idiopathic membranous nephropathy: a 2-year study. Clin J Am Soc Nephrol 2010;5:2188-98.
22. Fervenza FC, Cosio FG, Erickson SB, et al. Rituximab treatment of idiopathic membranous nephropathy. Kidney Int 2008;73:117-25.
23. Remuzzi G, Chiurchiu C, Abbate M, Brusegan V, Bontempelli M, Ruggenenti P. Rituximab for idiopathic membranous nephropathy. Lancet 2002;360:923-4.
24. Dahan K, Debiec H, Plaisier E, et al. Rituximab for severe membranous nephropathy: a 6-month trial with extended follow-up. J Am Soc Nephrol 2017;28:348-58.
25. Fervenza FC, Canetta PA, Barbour SJ, et al. A multicenter randomized controlled trial of rituximab versus cyclosporine in the treatment of idiopathic membranous nephropathy (MENTOR). Nephron 2015;130:159-68.
26. Cattran DC, Alexopoulos E, Heering P, et al. Cyclosporin in idiopathic glomerular disease associated with the nephrotic syndrome: workshop recommendations. Kidney Int 2007;72:1429-47.
27. Hays RD, Kallich JD, Mapes DL, Coons SJ, Carter WB. Development of the Kidney Disease Quality of Life (KDQOL) instrument. Qual Life Res 1994;3:329-38.
28. Kanigicherla D, Gummadova J, McKenzie EA, et al. Anti-PLA2R antibodies measured by ELISA predict long-term outcome in a prevalent population of patients with idiopathic membranous nephropathy. Kidney Int 2013;83:940-8.
29. Thompson A, Cattran DC, Blank M, Nachman PH. Complete and partial remission as surrogate end points in membranous nephropathy. J Am Soc Nephrol 2015;26:2930-7.
30. Cattran DC, Kim ED, Reich H, Hladunewich M, Kim SJ. Membranous nephropathy: quantifying remission duration on outcome. J Am Soc Nephrol 2017;28:995-1003.
31. Hamilton P, Kanigicherla D, Venning M, Brenchley P, Meads D. Rituximab versus the modified Ponticelli regimen in the treatment of primary membranous nephropathy: a health economic model. Nephrol Dial Transplant 2018;33:2145-55.
32. Bobart SA, De Vriese AS, Pawar AS, et al. Noninvasive diagnosis of primary membranous nephropathy using phospholipase A2 receptor antibodies. Kidney Int 2019;95:429-38.