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Efficacy and Safety of Obinutuzumab in Active Lupus Nephritis

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ABSTRACT

BACKGROUND

Obinutuzumab, a humanized type II anti-CD20 monoclonal antibody, provided significantly better renal responses than placebo in a phase 2 trial involving patients with lupus nephritis receiving standard therapy.

METHODS

In a phase 3, randomized, controlled trial, we assigned adults with biopsy-proven active lupus nephritis in a 1:1 ratio to receive obinutuzumab in one of two dose schedules (1000 mg on day 1 and at weeks 2, 24, 26, and 52, with or without a dose at week 50) or placebo. All patients received standard therapy with mycophenolate mofetil, along with oral prednisone at a target dose of 7.5 mg per day by week 12 and 5 mg per day by week 24. The primary end point was a complete renal response at week 76, defined by a urinary protein-to-creatinine ratio of less than 0.5 (with protein and creatinine both measured in milligrams), an estimated glomerular filtration rate of at least 85% of the baseline value, and no intercurrent event (i.e., rescue therapy, treatment failure, death, or early trial withdrawal). Key secondary end points at week 76 included a complete renal response with a prednisone dose of 7.5 mg per day or lower between weeks 64 and 76 and a urinary protein-to-creatinine ratio lower than 0.8 without an intercurrent event.

RESULTS

A total of 271 patients underwent randomization; 135 were assigned to the obinutuzumab group (combined dose schedules) and 136 to the placebo group. A complete renal response at week 76 was observed in 46.4% of the patients in the obinutuzumab group and 33.1% of those in the placebo group (adjusted difference, 13.4 percentage points; 95% confidence interval [CI], 2.0 to 24.8; P=0.02). A complete renal response at week 76 with a prednisone dose of 7.5 mg per day or lower between weeks 64 and 76 was observed in more patients in the obinutuzumab group than in the placebo group (42.7% vs. 30.9%; adjusted difference, 11.9 percentage points; 95% CI, 0.6 to 23.2; P=0.04), and a urinary protein-to-creatinine ratio lower than 0.8 without an intercurrent event was more common with obinutuzumab than with placebo (55.5% vs. 41.9%; adjusted difference, 13.7 percentage points; 95% CI, 2.0 to 25.4; P=0.02). No unexpected safety signals were identified. More serious adverse events, mainly infections and events related to coronavirus disease 2019, occurred with obinutuzumab than with placebo.

CONCLUSIONS

Among adults with active lupus nephritis, obinutuzumab plus standard therapy was more efficacious than standard therapy alone in providing a complete renal response. (Funded by F. Hoffmann–La Roche; REGENCY ClinicalTrials.gov number, NCT04221477.)

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CME

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Despite treatment advances in lupus nephritis, including regulatory approvals of belimumab and voclosporin,[1,2] the goal to sufficiently improve short- and long-term outcomes in patients with lupus nephritis remains unmet. Obinutuzumab, a humanized glycoengineered type II anti-CD20 monoclonal antibody that has been approved for the treatment of chronic lymphocytic leukemia and follicular lymphoma,[3,4] induces B-cell depletion that is superior to that with type I anti-CD20 monoclonal antibodies.[5,6] The phase 2, randomized, placebo-controlled NOBILITY trial compared obinutuzumab plus standard therapy (mycophenolate mofetil and glucocorticoids) with standard therapy alone in patients with lupus nephritis.[7] In that trial, obinutuzumab led to clinically meaningful improvements in the percentage of patients with a complete renal response at weeks 52, 76, and 104, as compared with placebo. Post hoc analyses showed that obinutuzumab delayed the time to a lupus nephritis flare and an unfavorable kidney outcome (a composite of treatment failure, doubling of the serum creatinine level, or death) and attenuated the decline of the estimated glomerular filtration rate (eGFR), as compared with placebo.[8] We performed the current trial to evaluate the efficacy and safety of obinutuzumab, as compared with placebo, when added to standard therapy (mycophenolate mofetil and glucocorticoids) in patients with active proliferative lupus nephritis.

Methods

Trial Design and Oversight

We conducted this phase 3, randomized, double-blind, placebo-controlled trial in 15 countries. The trial was performed according to the principles of the Declaration of Helsinki and the International Conference on Harmonisation guidelines for Good Clinical Practice. The trial protocol, available with the full text of this article at NEJM.org, was approved by the ethics committee or institutional review board at each participating center, and all trial participants provided written informed consent. The trial was reported according to the Consolidated Standards of Reporting Trials Guidelines.

The sponsor (F. Hoffmann–La Roche) designed the trial and participated in the collection, analysis, and interpretation of the data and in the preparation and submission of the manuscript for publication. The sponsor placed no restrictions on the publication of trial results by the academic authors. All the authors, including employees of the sponsor, approved the manuscript for submission and vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol. The first draft of the manuscript was written by the penultimate author, and Nucleus Global provided writing and editorial assistance (funded by the sponsor) on subsequent drafts, which were reviewed and agreed on by all the authors.

Entry Criteria

Eligible patients were 18 to 75 years of age, met the American College of Rheumatology classification criteria for systemic lupus erythematosus,[9] and had active class III or IV lupus nephritis, with or without concomitant class V disease (according to the classification of the International Society of Nephrology and the Renal Pathology Society[10]), as confirmed on kidney biopsy performed either during or within 6 months before screening. Enrollment criteria included a urinary protein-to-creatinine ratio of at least 1 (with protein and creatinine both measured in milligrams) based on 24-hour urine collection and antinuclear antibody (ANA) positivity (i.e., an ANA titer of ≥1:80 on HEp-2 cells or ≥1 equivalent positive ANA test). Key exclusion criteria were an eGFR lower than 30 ml per minute per 1.73 m^2 of body surface area or end-stage kidney disease necessitating dialysis or transplantation, evidence of active infection, receipt of anti-CD20 therapy during or within 9 months before screening, and receipt of cyclophosphamide, tacrolimus, cyclosporine, or voclosporin therapy during or within 2 months before screening.

Trial Procedures

Patients were randomly assigned in a 1:1 ratio to receive intravenous infusions of obinutuzumab or matching placebo. Randomization was performed by means of a centralized interactive voice- and Web-based response system (IxRS) with the use of a permuted block design, with stratification according to geographic region (United States or Canada, Latin America or the Caribbean, or other) and race (Black or other). Patients assigned to the obinutuzumab group were again randomly assigned in a 1:1 ratio to

receive obinutuzumab in one of two dose schedules (1000 mg on day 1 and at weeks 2, 24, 26, and 52, with or without an additional dose at week 50) (see the Supplementary Methods section and Fig. S1 in the Supplementary Appendix, available at NEJM.org). The rationale for including two dose schedules was exploratory and was aimed at gathering additional pharmacokinetic and pharmacodynamic data and exploring potential dose-related differences in efficacy to inform the selection of a dose regimen for long-term treatment (beyond week 76, which was used for the primary end point in this trial). Patients in both trial groups began receiving standard therapy with mycophenolate mofetil and prednisone at randomization (if not already receiving it). The target dose of prednisone was 7.5 mg per day by week 12 and 5 mg per day by week 24. Additional details on protocol-specified treatments and the oral prednisone tapering schedule are provided in the Supplementary Methods section and Table S1.

END POINTS

The primary end point was a complete renal response at week 76, which was defined by a urinary protein-to-creatinine ratio lower than 0.5 based on a timed 24-hour urine collection, an eGFR of at least 85% of the baseline value (calculated with the use of the 2009 Chronic Kidney Disease Epidemiology Collaboration equation[11]), and no occurrence of an intercurrent event (i.e., rescue therapy, treatment failure, death, or early trial withdrawal). Treatment failure was defined as end-stage kidney disease or the use of long-term dialysis or renal transplantation, receipt of rescue therapy (except for glucocorticoid-only rescue), or clinically significant and sustained worsening of the urinary protein-to-creatinine ratio or eGFR beyond week 24 that led the center investigator to conclude that the assigned regimen had failed.

Key secondary end points were a complete renal response at week 76 with a prednisone dose of 7.5 mg per day or lower between weeks 64 and 76; a urinary protein-to-creatinine ratio lower than 0.8 at week 76 with no intercurrent event; a change in the estimated GFR from baseline to week 76; death or a renal-related event through week 76; an overall renal response at week 50, which was defined as a complete renal response or a partial renal response; and a change in score on the Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-F) from baseline to week 76 (Table S2). A partial renal response was defined as the occurrence of all the following: at least a 50% reduction in the urinary protein-to-creatinine ratio from baseline, a urinary protein-to-creatinine ratio lower than 1 (or <3 if the baseline urinary protein-to-creatinine ratio was ≥3), an eGFR of at least 85% of the baseline value, and no occurrence of an intercurrent event. The FACIT-F is a 13-item measure that assesses patient-reported fatigue and its effect on daily activities and function; scores range from 0 to 52, with higher scores indicating less fatigue.

SAFETY ASSESSMENTS

Safety assessments included adverse events, serious adverse events, adverse events of special interest (see the Supplementary Methods section), vital signs, and laboratory assessments. Safety analyses were performed in the safety population, which included all the patients who received any infusion of obinutuzumab or placebo in a blinded manner. The patients in the safety population were grouped according to the infusion that was actually administered, regardless of the randomly assigned trial group. An independent data and safety monitoring committee provided ongoing safety review.

STATISTICAL ANALYSIS

Assuming that a complete renal response at week 76 would occur in 50% of the patients receiving obinutuzumab and 30% of those receiving placebo, we calculated that a sample of 252 patients randomly assigned in a 1:1 ratio to receive obinutuzumab or placebo would yield approximately 90% power to detect a between-group difference of 20 percentage points at a two-sided significance level of 0.05. Efficacy analyses were performed in the intention-to-treat population, with all randomly assigned patients grouped according to trial-group assignment. No difference in efficacy between the two obinutuzumab dose schedules was expected at week 76, and all primary and secondary comparisons were performed between the obinutuzumab group (pooled dose schedules) and the placebo group.

The percentages of patients with a complete renal response at week 76 in the two trial groups were compared with the use of a Cochran–Mantel–Haenszel test, with geographic region and race as stratification factors. Missing data were im-

puted by means of a multiple-imputation method that used fully conditional specification with predicted mean matching (100 imputed data sets) with the use of data from patients who did not have any intercurrent events. Data for the patients who had an intercurrent event were imputed as no response. The Cochran–Mantel–Haenszel test was performed with multiple imputations for the following key secondary end points: a complete renal response at week 76 with a prednisone dose of 7.5 mg per day or lower between weeks 64 and 76, a urinary protein-to-creatinine ratio lower than 0.8 at week 76 with no intercurrent event, death or renal-related event during the 76-week period, and overall renal response at week 50. Changes in the eGFR and FACIT-F score from baseline to week 76 were evaluated with the use of an analysis-of-covariance model, with adjustment for baseline values and stratification factors. For the primary end point, 11 subgroup analyses were prespecified to assess the consistency of the treatment effect, and the results are reported with adjusted differences in percentages and confidence intervals. A model-based multiple-imputation method was used for missing data, with estimates and standard errors obtained with the use of multiple-imputation combing rules. The numbers of the patients with missing end-point data that were subject to imputation are summarized in Table S12.

To control for overall type I error rate at a 5% significance level, the primary and key secondary end points were assessed with the use of a fixed-sequence testing approach with a fallback procedure adaptation. All reported P values are two-sided and unadjusted; therefore, comparisons were made against the prespecified significance level for each end point.

RESULTS

TRIAL POPULATION

From July 2020 through March 2023, a total of 513 patients underwent screening, and 271 were randomly assigned to receive obinutuzumab (135 patients) or placebo (136 patients) (Fig. S2). Baseline characteristics were generally balanced between the trial groups (Table 1 and Table S4). The mean (±SD) age of the patients was 33.0±10.5 years in the obinutuzumab group and 32.7±10.0 years in placebo group, and 114 patients (84.4%) and 115 patients (84.6%), respectively, were women. The enrolled population was deemed to be sufficiently diverse, including populations with a high prevalence of lupus nephritis and with a high risk of complications and death (e.g., Black or African American, Asian, and Hispanic or Latino patients, who composed 14.8% [40 patients], 5.9% [16 patients], and 57.6% [156 patients] of the trial population, respectively, according to patient-reported race or ethnic group). The representativeness of the trial population is shown in Table S3. Among the patients with previously diagnosed lupus nephritis (81 patients in the obinutuzumab group and 76 patients in the placebo group), as opposed to those with newly diagnosed lupus nephritis, the median duration since the first lupus nephritis diagnosis was 36.6 months (range, 0.4 to 330.4) in the obinutuzumab group and 34.3 months (range, 0.8 to 217.8) in the placebo group. The mean eGFR was 102.8±29.3 ml per minute per 1.73 m^2 in the obinutuzumab group and 101.9±32.2 ml per minute per 1.73 m^2 in the placebo group, and the mean urinary protein-to-creatinine ratio was 3.14±2.99 and 3.53±2.76, respectively.

PRIMARY AND KEY SECONDARY END POINTS

A complete renal response at week 76 (the primary end point) was observed in 46.4% of the patients in the obinutuzumab group and 33.1% of those in the placebo group (adjusted difference, 13.4 percentage points; 95% confidence interval [CI], 2.0 to 24.8; P=0.02) (Table 2). The percentages of patients with intercurrent events were numerically higher in the placebo group than in the obinutuzumab group (treatment failure in 17.6% vs. 3.7%; receipt of rescue therapy in 17.6% vs. 5.9%) (Table S5). A complete renal response at week 76 with a prednisone dose of 7.5 mg per day or lower between weeks 64 and 76 was observed in 42.7% of the patients in the obinutuzumab group and 30.9% of those in the placebo group (adjusted difference, 11.9 percentage points; 95% CI, 0.6 to 23.2; P=0.04).

The results of an exploratory analysis of the primary end point with death as the only intercurrent event were consistent with the those of the primary analysis (Table S6). The percentage of patients with a urinary protein-to-creatinine ratio lower than 0.8 at week 76 with no intercurrent event was 55.5% in the obinutuzumab group and 41.9% in the placebo group (adjusted difference, 13.7 percentage points; 95% CI, 2.0 to

Table 1. Baseline Demographic and Clinical Characteristics of the Patients in the Intention-to-Treat Population.*

Characteristic	Obinutuzumab (N=135)	Placebo (N=136)
Age — yr	33.0±10.5	32.7±10.0
Female sex — no. (%)	114 (84.4)	115 (84.6)
Race or ethnic group — no. (%)†		
American Indian or Alaska Native	25 (18.5)	26 (19.1)
Asian	9 (6.7)	7 (5.1)
Black or African American	20 (14.8)	20 (14.7)
White	65 (48.1)	64 (47.1)
Multiple	11 (8.1)	9 (6.6)
Unknown	4 (3.0)	6 (4.4)
Not reported	1 (0.7)	4 (2.9)
Race — no. (%)†		
Black	15 (11.1)	17 (12.5)
Other	120 (88.9)	119 (87.5)
Ethnic group — no. (%)†		
Hispanic or Latino	71 (52.6)	85 (62.5)
Not Hispanic or Latino	54 (40.0)	48 (35.3)
Not stated	9 (6.7)	1 (0.7)
Unknown	1 (0.7)	2 (1.5)
Median serum creatinine level (range) — mg/dl	0.79 (0.34 to 3.75)	0.74 (0.27 to 4.39)
Median eGFR (range) — ml/min/1.73 m^2	107 (15 to 164)	109 (13 to 166)
Median UPCR (range)‡	2.13 (0.2 to 21.6)	2.76 (0.1 to 13.3)
Anti-dsDNA positive at >120 IU/ml — no. (%)	57 (42.2)	61 (44.9)
C3 complement level <0.9 g/liter — no. (%)	77 (57.0)	76 (55.9)
C4 complement level <0.1 g/liter — no. (%)§	32 (23.7)	42 (31.1)
Median serum albumin (range) — g/liter	35 (16 to 46)	35 (15 to 46)
Previously diagnosed lupus nephritis — no. (%)	81 (60.0)	76 (55.9)
Median SLEDAI-2K score (range)¶	10 (4 to 83)	12 (2 to 35)

* Plus–minus values are means ±SD. The intention-to-treat population included all the patients who had undergone randomization. To convert serum creatinine to micromoles per liter, multiply by 88.4. The term dsDNA denotes double-stranded DNA, and eGFR estimated glomerular filtration rate.

† Race and ethnic group were determined on the basis of patient-reported data in the electronic case-report forms. At the time of enrollment, Black or other (a randomization stratification factor) were the only two randomization options for race in the IxRS system. One patient who was registered as Black in the IxRS system reported being multiracial in the case-report form, and nine patients who were registered as other in the IxRS system reported being Black or African American in the case-report form.

‡ The urinary protein-to-creatinine ratio (UPCR) was based on 24-hour urine collection, with protein and creatinine both measured in milligrams. Data were missing for one patient in the obinutuzumab group.

§ Data on C4 complement level were missing for one patient in the placebo group.

¶ Scores on the Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) range from 0 to 105, with higher scores indicating greater disease activity. Data were missing for three patients in the placebo group.

25.4; P=0.02) (Table 2). The adjusted mean (±SE) eGFR increased by 2.31±2.71 ml per minute per 1.73 m^2 from baseline to week 76 in the obinutuzumab group but decreased by 1.54±2.71 ml per minute per 1.73 m^2 in the placebo group (adjusted difference, 3.84 ml per minute per 1.73 m^2; 95% CI, –1.83 to 9.51). Death or a renal-related event through week 76 occurred in 18.9% of the patients in the obinutuzumab group and 35.6% of those in the placebo group (adjusted

Table 2. Primary and Secondary End Point Results in the Intention-to-Treat Population.*

End Point	Obinutuzumab (N=135)	Placebo (N=136)	Adjusted Difference (95% CI)†	P Value‡
Primary end point				
Complete renal response at wk 76 — % (95% CI)§¶‖	46.4 (38.0 to 54.9)	33.1 (25.2 to 41.0)	13.4 (2.0 to 24.8)	0.02
Key secondary end points				
Complete renal response at wk 76 with prednisone taper to ≤7.5 mg/day between wks 64 and 76 — % (95% CI)§¶‖**	42.7 (34.3 to 51.1)	30.9 (23.1 to 38.7)	11.9 (0.6 to 23.2)	0.04
UPCR <0.8 at week 76 with no intercurrent event — % (95% CI)¶‖††	55.5 (47.1 to 64.0)	41.9 (33.6 to 50.2)	13.7 (2.0 to 25.4)	0.02
Change in the eGFR from baseline to wk 76 — ml/min/1.73 m^2‡‡	2.31±2.71	−1.54±2.71	3.84 (−1.83 to 9.51)	
Death or renal-related event through wk 76 — % (95% CI)¶§§	18.9 (12.1 to 25.6)	35.6 (27.5 to 43.8)	−16.8 (−27.4 to −6.2)	
Overall renal response at wk 50 — % (95% CI)¶‖¶¶	59.1 (50.8 to 67.4)	50.7 (42.2 to 59.2)	8.4 (−3.4 to 20.1)	
Change in FACIT-F score from baseline to wk 76 — points‡‡	1.8±1.2	3.1±1.2	−1.4 (−3.9 to 1.2)	

* Plus–minus values are means ±SE. The percentages of patients with a response represent pooled response rates in each group from 100 missing data–imputed data sets generated with multiple imputation.

† The difference in the percentage of patients with a response or an event is given in percentage points. For response end points, the difference was adjusted for stratification factors (geographic region and race). For end points involving a change from baseline (eGFR and Functional Assessment of Chronic Illness Therapy–Fatigue [FACIT-F]), the difference was adjusted for stratification factors (geographic region and race) and baseline values.

‡ Testing for statistical significance of the primary and the key secondary end points was performed with the use of fixed-sequence testing with a fallback procedure adaptation to control the trialwide type I error rate at a 5% significance level. Multiple imputation was used for missing data. Missing data for the 24-hour UPCR were imputed with spot measurement of the UPCR when available at the corresponding trial week. In the analyses of responses, data for the patients who had an end point–specific intercurrent event (i.e., rescue therapy, treatment failure, death, and early trial withdrawal) were imputed as no response. In the analyses of the change from baseline, data for the patients who died were imputed as 0 for the week 76 values, and all other missing data were handled by multiple imputations. All estimates are based on 100 imputed data sets.

§ A complete renal response was defined by a UPCR lower than 0.5, an eGFR of at least 85% of the baseline value (calculated with the use of the 2009 Chronic Kidney Disease Epidemiology Collaboration equation), and no occurrence of an intercurrent event. Data for 5 patients with missing observed values for complete renal response, UPCR, or eGFR were imputed.

¶ A Cochran–Mantel–Haenszel test with the stratification factors of race and geographic region was performed to test the null hypothesis of equal response proportions. The adjusted differences (i.e., the common risk differences) were calculated with the use of Mantel–Haenszel weights. The 95% confidence intervals are based on the standard error obtained from the stratified Newcombe confidence interval with the use of Mantel–Haenszel weights.

‖ Patients who discontinued obinutuzumab or placebo were evaluated with the use of their observed data according to the treatment-policy strategy.

** Successful prednisone taper was defined as no receipt of prednisone at dose higher than 7.5 mg per day from week 64 through week 76.

†† Data for 5 patients with missing observed values were imputed.

‡‡ Analyses of the changes from baseline in the eGFR and the FACIT-F score were performed with the use of an analysis of covariance model with trial group, baseline value, and the stratification factors of race and geographic region included as independent variables. Patients who had an intercurrent event (e.g., rescue therapy, treatment failure, or early discontinuation of obinutuzumab or placebo) were evaluated with the use of their observed data according to the treatment-policy strategy. Data after the intercurrent event of death were imputed as 0. Data from only the patients who did not die were included in the imputation model. The FACIT-F is a 13-item measure that assesses patient-reported fatigue and its effect on daily activities and function; scores range from 0 to 52, with higher scores indicating less fatigue. Missing observed changes from baseline in the estimated GFR and FACIT-F score were imputed for 20 and 22 patients, respectively.

§§ Death or renal-related event was defined as death, treatment failure, worsening proteinuria (i.e., a confirmed ≥50% increase in the UPCR to ≥3 from the previous visit), or worsening eGFR (i.e., a confirmed ≥30% decrease in the eGFR to <60 ml per minute per 1.73 m^2 of body-surface area). Early trial withdrawal due to lack of efficacy was considered to be a renal-related event.

¶¶ An overall renal response was defined as either a complete renal response or partial renal response, which was defined as the occurrence of all the following: at least a 50% reduction in the UPCR from baseline, a UPCR lower than 1 (or <3 if the baseline UPCR was ≥3), an eGFR of at least 85% of the baseline value, and no occurrence of an intercurrent event. Data for 28 patients with missing observed values were imputed.

difference, −16.8 percentage points; 95% CI, −27.4 to −6.2). The adjusted mean change in the FACIT-F score from baseline to week 76 was 1.8±1.2 points in the obinutuzumab group and 3.1±1.2 points in the placebo group (adjusted difference, −1.4 points; 95% CI, −3.9 to 1.2), a finding indicating that a mild reduction in fatigue occurred to a similar degree in both groups.

SUBGROUP ANALYSES

Results of prespecified subgroup analyses of complete renal response at week 76 were generally consistent across the subgroups, including patients with class IV lupus nephritis, patients with concomitant class V lupus nephritis, patients with a baseline urinary protein-to-creatinine ratio of 3 or higher, or patients with serologic activity (i.e., a low C3 or C4 complement level or a high level of antibodies against double-stranded DNA [dsDNA] at baseline) (Fig. 1). Differences in effect sizes with respect to a complete renal response were observed between men and women because of a high percentage of men in the placebo group who had a complete renal response (67% in a relatively small subgroup of 21 patients). The percentage of patients with a complete renal response at week 76 did not differ significantly between the two obinutuzumab dose schedules (Table S7).

PHARMACODYNAMICS, SEROLOGIC ANALYSIS, AND IMMUNOGENICITY

Adjusted mean changes in the levels of C3 complement, C4 complement, and antibodies against dsDNA from baseline to week 76 were greater in the obinutuzumab group than in the placebo group (Fig. 2A, 2B, and 2C and Table S11). The percentage of patients with complete depletion of peripheral CD19-positive B cells was greater in the obinutuzumab group than in the placebo group (Fig. 2D and Fig. S4). A longitudinal assessment of IgG levels is shown in Fig. S5.

SAFETY

The percentage of patients with adverse events was similar in the obinutuzumab group and the placebo group (Table 3). Serious adverse events occurred in 44 of 136 patients (32.4%) in the obinutuzumab group and 24 of 132 patients (18.2%) in the placebo group. The most frequent serious adverse events observed among the obinutuzumab-treated patients were infections, including coronavirus disease 2019 (Covid-19)–related events, urinary tract infection, pneumonia, and gastroenteritis. When confirmed or suspected Covid-19–related events were excluded, the incidence of serious infections decreased from 16.9% to 11.0% in the obinutuzumab group, with no change (7.6%) in the placebo group (Table S8). Serious Covid-19–related events occurred early in the trial (Fig. S3). Four patients died during the 76-week evaluation period — 3 in the obinutuzumab group (2 from Covid-19–related pneumonia and 1 from nephrotic syndrome) and 1 in the placebo group (from Covid-19) (Table S9). Protocol-defined adverse events of special interest (infusion-related reactions, grade ≥3 infections, and drug-related neutropenia) occurred in more patients in the obinutuzumab group than in the placebo group (Table 3). Except for one serious adverse event of weight loss and the four deaths, all serious adverse events in the patients who received obinutuzumab had resolved or were resolving by week 76. All drug-related neutropenic events had resolved or were resolving by week 76 (Table S10).

DISCUSSION

Given the importance of B cells in the pathogenesis of lupus nephritis, B-cell depletion is considered to be a scientifically sound therapeutic approach.[12,13] The Lupus Nephritis Assessment with Rituximab (LUNAR) trial did not show a significant increase in the percentage of patients who had a complete renal response when treated with rituximab, as compared with those who received placebo[14]; however, a post hoc analysis suggested that greater B-cell depletion correlated with a higher percentage of patients having a complete renal response.[15] The NOBILITY trial, which evaluated whether deeper B-cell depletion would enhance complete renal response rates, showed that patients with lupus nephritis who received obinutuzumab plus standard therapy had a complete renal response more frequently than those who received standard therapy alone.[7] The current phase 3 REGENCY trial confirmed this observation: obinutuzumab plus standard therapy resulted in a significantly greater increase in the percentage of patients who had a complete renal response than placebo plus standard therapy. Greater adjusted between-group differences in the percentages of patients who had a complete renal response were observed in subgroups with baseline features indicative of high disease activity (e.g., proteinuria with a urinary protein-to-creatinine ratio of >3, low C3 or C4 complement levels, a high level of antibodies against dsDNA, class IV lupus nephritis, or coexistent class V disease). These findings are consistent with the observations in the NOBILITY trial.[16]

The glycoengineered type II anti-CD20 configuration of obinutuzumab results in greater direct

Subgroup	No. of Patients		Patients with Complete Renal Response		Adjusted Difference (95% CI)
	Obinutuzumab	Placebo	Obinutuzumab	Placebo	
			percent		*percentage points*
All patients	135	136	46	33	13.4 (2.0 to 24.8)
Sex					
Female	114	115	47	27	20.6 (8.4 to 32.7)
Male	21	21	43	67	−28.2 (−53.3 to 2.3)
Race					
Black	15	17	60	41	17.7 (−15.8 to 45.4)
Other	120	119	45	32	12.8 (0.7 to 24.9)
Geographic region					
Latin America or the Caribbean	77	77	39	30	9.2 (−5.5 to 23.9)
Other	38	39	60	36	23.7 (2.8 to 44.5)
United States or Canada	20	20	50	40	10.0 (−19.3 to 37.2)
24-Hr UPCR at baseline					
<3	82	74	52	46	7.8 (−7.7 to 23.3)
≥3	52	62	37	18	17.8 (1.6 to 33.9)
Anti-dsDNA antibody level at baseline					
≤120 IU/ml	78	75	42	32	10.8 (−4.2 to 25.8)
>120 IU/ml	57	61	52	34	18.3 (1.0 to 35.7)
C3 complement at baseline					
≥0.9 g/liter	58	60	38	32	10.2 (−7.3 to 26.9)
<0.9 g/liter	77	76	53	34	16.4 (1.0 to 31.8)
C4 complement at baseline					
≥0.1 g/liter	103	93	41	31	12.0 (−1.4 to 25.3)
<0.1 g/liter	32	42	63	36	26.2 (2.4 to 46.1)
Lupus nephritis class at baseline					
Class III	56	51	50	41	7.1 (−11.5 to 25.6)
Class IV	79	85	44	28	15.2 (0.8 to 29.5)
Concomitant class V disease at baseline					
No	88	98	45	37	8.8 (−5.2 to 22.8)
Yes	47	38	49	24	25.5 (6.3 to 44.7)
History of lupus nephritis at baseline					
Previously diagnosed	81	76	43	38	6.0 (−9.2 to 21.3)
Newly diagnosed	54	60	52	27	23.8 (5.7 to 39.8)
eGFR at baseline					
≥90 ml/min/1.73 m^2	96	96	49	39	10.9 (−3.0 to 24.9)
<90 ml/min/1.73 m^2	39	40	41	20	15.1 (−6.6 to 35.0)

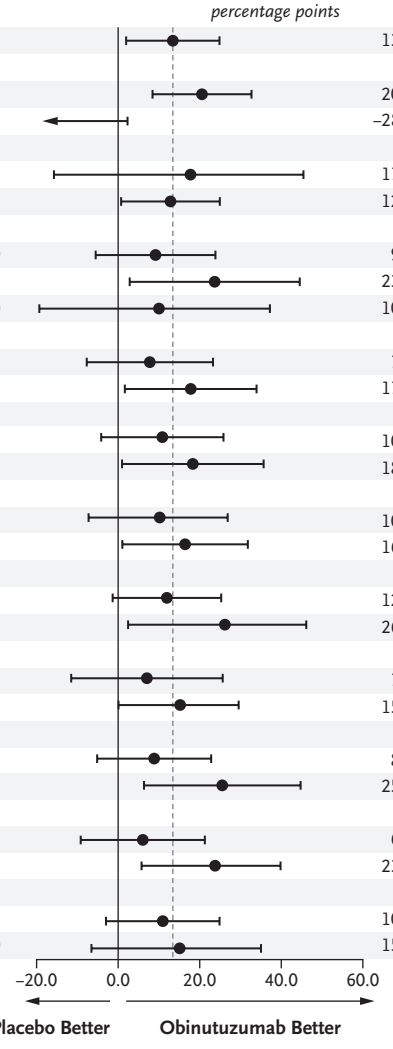

Figure 1. Subgroup Analysis of Complete Renal Response at Week 76 in the Intention-to-Treat Population.

The intention-to-treat population included all the patients who had undergone randomization. The difference in the percentage of patients who had a complete renal response at week 76 was adjusted for stratification factors (geographic region and race). For the subgroup categories with missing data, the 95% confidence intervals were constructed from the standard errors, which were derived from the stratified Newcombe confidence intervals with Mantel–Haenszel weight. Multiple imputation was used for missing data. The subgroups with missing data were female sex, geographic regions of Latin America or the Caribbean and other, 24-hour urinary protein-to-creatinine ratio (UPCR) at baseline of 3 or lower and of at least 3 (with protein and creatinine both measured in milligrams), anti–double-stranded DNA (dsDNA) antibody level at baseline of 120 IU per milliliter or lower and greater than 120 IU per milliliter, C3 complement at baseline lower than 0.9 g per liter, C4 complement at baseline of at least 0.1 g per liter, lupus nephritis class at baseline — both class III and class IV, concomitant class V disease at baseline — both no and yes, history of previously diagnosed lupus nephritis at baseline, and estimated glomerular filtration rate (eGFR) at baseline of at least 90 ml per minute per 1.73 m^2 of body-surface area. For the subgroup categories without missing data, the 95% confidence intervals were stratified Newcombe confidence intervals with Mantel–Haenszel weight. The two subgroups with lower-level eGFRs of 30 to lower than 60 and 60 to 90 ml per minute per 1.73 m^2 of body-surface area were combined post hoc owing to the small number of patients. The arrows indicate that the data point and the 95% confidence interval exceed the graphed area.

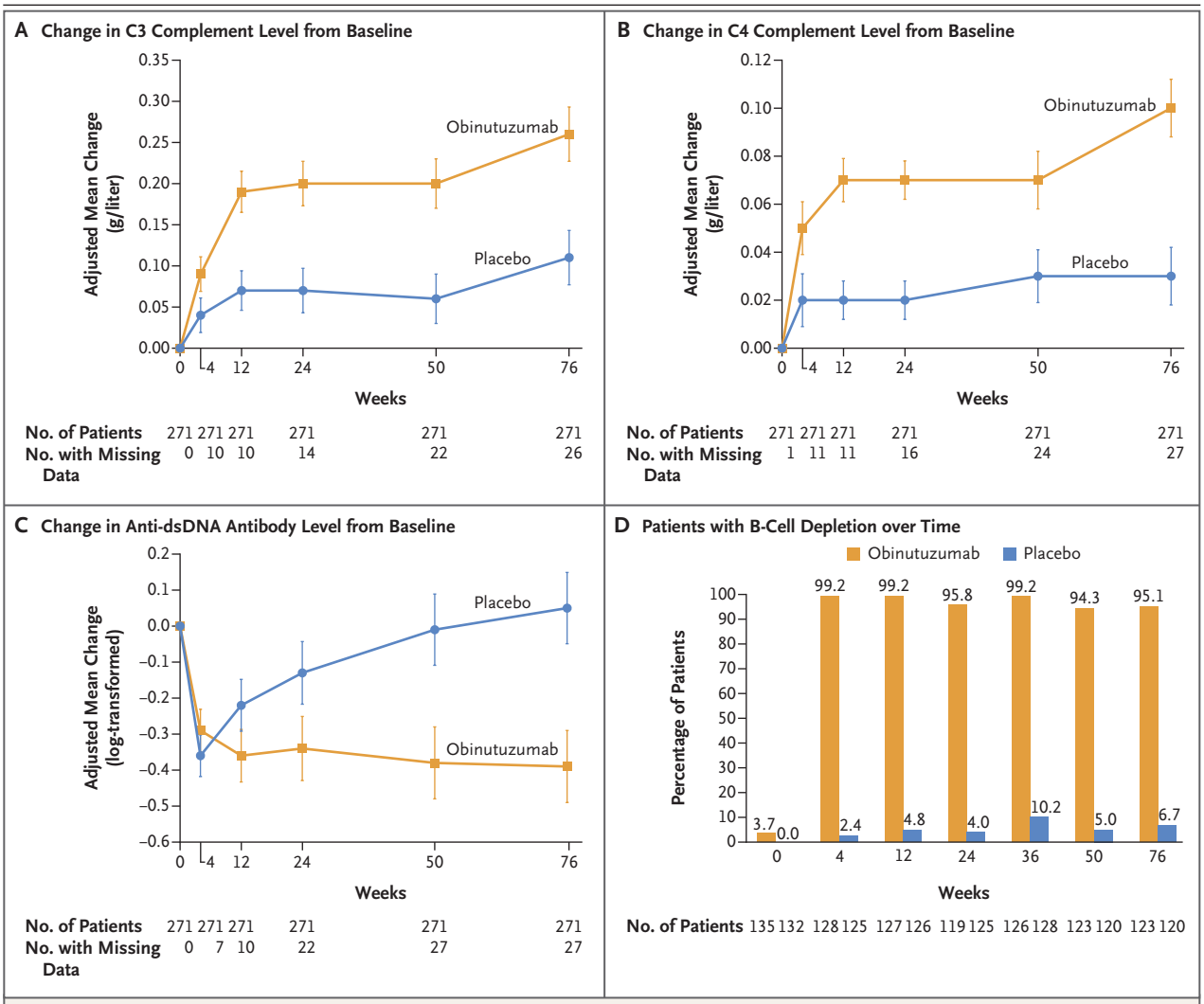

Figure 2. Serologic and Pharmacodynamic Analyses over Time.

Panel A shows the adjusted mean change in the C3 complement level from baseline in the intention-to-treat population. Panel B shows the adjusted mean change in the C4 complement level from baseline in the intention-to-treat population. Panel C shows the adjusted mean change in anti-dsDNA antibody level from baseline (log-transformed) in the intention-to-treat population. In Panels A, B, and C, an analysis-of-covariance model was used with multiple imputation for missing data; I bars indicate the standard error. Panel D shows the percentage of patients with B-cell depletion over time (T and B natural killer cells) in the safety population. B-cell depletion was defined by an absolute CD19-positive B-cell count lower than 10 cells per cubic millimeter.

cell death, enhanced Fc receptor–mediated antibody-dependent cellular cytotoxicity, and antibody-dependent cellular phagocytosis.[5,6,17-19] Besides increased elimination of B cells in peripheral blood, high-level depletion of tissue-resident B cells in nonhuman primates and humans has been shown after obinutuzumab administration.[5,20,21] In patients with B-cell malignant conditions, obinutuzumab resulted in superior B-cell depletion, as compared with rituximab, and the efficacy of obinutuzumab was superior to rituximab in patients with chronic lymphocytic leukemia.[20] Furthermore, the preliminary results of chimeric antigen receptor T-cell therapy suggest a potential benefit of deep B-cell depletion in patients with lupus nephritis.[22-24]

The incidence of serious adverse events, including infections, and the incidence of neutropenia

Table 3. Adverse Events through Week 76 in the Safety Population.*

Event	Obinutuzumab (N=136)	Placebo (N=132)	Total (N=268)
Any adverse event — no. (%)	126 (92.6)	117 (88.6)	243 (90.7)
Total no. of adverse events	748	665	1413
Any serious adverse event — no. (%)	44 (32.4)	24 (18.2)	68 (25.4)
Total no. of serious adverse events	68	35	103
Deaths — no. (%)†	3 (2.2)	1 (0.8)	4 (1.5)
Adverse event leading to trial withdrawal — no. (%)	0	0	0
Serious adverse events occurring in ≥5 patients — no. (%)			
Covid-19–related pneumonia	7 (5.1)	0	7 (2.6)
Pneumonia	4 (2.9)	3 (2.3)	7 (2.6)
Urinary tract infection	4 (2.9)	2 (1.5)	6 (2.2)
Covid-19	4 (2.9)	1 (0.8)	5 (1.9)
Gastroenteritis	3 (2.2)	2 (1.5)	5 (1.9)
Acute kidney injury	3 (2.2)	2 (1.5)	5 (1.9)
Adverse events occurring in ≥1 patient — no. (%)			
Grade ≥3 adverse event	44 (32.4)	22 (16.7)	66 (24.6)
Infection	98 (72.1)	81 (61.4)	179 (66.8)
Adverse event leading to discontinuation of obinutuzumab or placebo	10 (7.4)	5 (3.8)	15 (5.6)
Adverse event with fatal outcome	3 (2.2)	2† (1.5)	5 (1.9)
Infection as a serious adverse event	23 (16.9)	10 (7.6)	33 (12.3)
Serious adverse event leading to discontinuation of obinutuzumab or placebo	8 (5.9)	4 (3.0)	12 (4.5)
Adverse events of special interest — no. (%)			
Infusion-related reaction	21 (15.4)	15 (11.4)	36 (13.4)
Grade ≥3 infection	21 (15.4)	9 (6.8)	30 (11.2)
Any hepatitis B reactivation or progressive multifocal leukoencephalopathy	0	0	0
Drug-related neutropenia	17 (12.5)	5 (3.8)	22 (8.2)
Drug-related thrombocytopenia	1 (0.7)	0	1 (0.4)
Gastrointestinal perforation	0	0	0
Worsening of preexisting cardiac condition	0	2 (1.5)	2 (0.7)
Potential drug-induced liver failure meeting Hy's law criteria	0	0	0
Suspected transmission of an infectious agent by obinutuzumab or placebo	0	0	0

* The safety population included all the patients who received any infusion of obinutuzumab or placebo in a blinded manner; the patients were grouped according to the infusion that was actually administered, regardless of the randomly assigned trial group. Covid-19 denotes coronavirus disease 2019.

† One patient in the placebo group died after the data cutoff at week 76, but this adverse event that led to a fatal outcome had started before the data cutoff date.

were higher among the patients who received obinutuzumab than among those who received placebo in the current trial. No new types of adverse events were observed. These risks, and the safety profile of obinutuzumab more broadly, must be considered when deciding whether to initiate treatment. The imbalance related to infectious serious adverse events appeared to

be driven, in part, by Covid-19–related events; however, other infectious serious adverse events were also observed. With respect to Covid-19, the current trial initiated enrollment 4 months after the pandemic declaration by the World Health Organization, and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection–related serious adverse events occurred early in this trial before the availability of robust vaccination and antiviral therapy. In fact, no Covid-19–related serious adverse events occurred during the latter half of the current trial. Furthermore, global enrollment included areas with high rates of Covid-19–related infections and deaths.[25] In the phase 2 NOBILITY trial, which was conducted before the Covid-19 pandemic, obinutuzumab was associated with fewer serious adverse events, serious infections, and deaths than placebo; however, the overall obinutuzumab dose was lower than that used in the current phase 3 trial.[7] Vaccination against SARS-CoV-2 infection should be considered in patients receiving mycophenolate mofetil and anti-CD20 therapy.[26] Vaccinated patients with multiple sclerosis receiving anti-CD20 therapies had a lower incidence of severe infections than unvaccinated patients,[27] and vaccination mitigated Covid-19–related adverse outcomes in patients with follicular lymphoma treated with obinutuzumab.[28] Therefore, we believe that appropriate vaccinations in patients with systemic lupus erythematosus will probably reduce the incidence of infection-associated adverse outcomes with obinutuzumab treatment. Mycophenolate mofetil reduces both humoral and cellular responses to Covid-19 vaccination,[29] whereas B-cell depletion with anti-CD20 therapy mainly attenuates antibody responses, with T-cell–mediated responses remaining intact in patients with hematologic malignant conditions[30] and multiple sclerosis.[31] Nonetheless, obinutuzumab, when added to mycophenolate mofetil therapy, was associated with an increased risk of Covid-19 in the current trial, and this risk must be considered in treatment decision making.

The percentage of patients who received placebo and had a complete renal response was approximately 40 percentage points higher among men than among women; this difference may have been due to the relatively small number of men in the trial. In contrast to the findings of significant attenuation of the eGFR in the NOBILITY trial, attenuation of the eGFR from baseline to week 76 was not significant in the current trial. Findings regarding the eGFR end point at week 104 are not yet available.

Therapy with obinutuzumab was associated with a higher incidence of infections, principally respiratory tract infections, than receipt of placebo. The patients in the obinutuzumab group were more likely to have complete renal response at week 76 with a lower daily dose of prednisone than those in the placebo group. A significant reduction in proteinuria, a surrogate for enhanced long-term kidney survival, was observed at week 76 in those who received obinutuzumab.[32-39] These findings, and those from the NOBILITY trial, support the hypothesis that deep B-cell depletion with obinutuzumab is an effective treatment for patients with lupus nephritis.

In this trial involving adults with biopsy-proven active lupus nephritis, the addition of obinutuzumab to standard therapy led to a significantly greater percentage of patients with a complete renal response at week 76 than standard therapy alone.

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