ORIGINAL ARTICLE

Rituximab versus Ocrelizumab in Newly Diagnosed Relapsing Multiple Sclerosis

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ABSTRACT

BACKGROUND

Anti-CD20 monoclonal antibodies are effective for relapsing multiple sclerosis. However, data from head-to-head trials are lacking.

METHODS

In this phase 3, multicenter, double-blind, noninferiority trial, we randomly assigned adults with newly diagnosed relapsing multiple sclerosis and recent disease activity in a 3:2 ratio to receive rituximab or ocrelizumab every 6 months for 24 months. The primary end point was the absence of new or enlarging lesions on T2-weighted magnetic resonance imaging (MRI) from month 6 to month 24. Noninferiority was defined as a lower limit of the 95% confidence interval for the risk difference (rituximab minus ocrelizumab) of greater than or equal to –10 percentage points. Secondary end points included efficacy and safety.

RESULTS

A total of 218 participants underwent randomization; 216 received treatment (132 assigned to the rituximab group and 84 assigned to the ocrelizumab group). Between months 6 and 24, the estimated probability of having no new or enlarging lesions detected on T2-weighted MRI was 92.2% with rituximab and 94.8% with ocrelizumab, corresponding to a risk difference of –2.6 percentage points (95% confidence interval, –9.4 to 4.3), which met the prespecified noninferiority criterion. Relapse rates, disability outcomes, and cognitive-performance profiles appeared to be similar in the two groups. Infections were more common in the rituximab group than in the ocrelizumab group (in 82% vs. 69% of participants), although the percentage of participants with serious adverse events was similar in the two groups (8% and 7%, respectively).

CONCLUSIONS

In participants with newly diagnosed relapsing multiple sclerosis and recent disease activity, rituximab was noninferior to ocrelizumab in suppressing disease activity as detected by MRI from 6 to 24 months, with a similar incidence of serious adverse events. (Funded by the Research Council of Norway and others; OVERLORD-MS ClinicalTrials.gov number, NCT04578639; EudraCT number, 2020-001205-23; EU Clinical Trials Register number, 2024-510716-71-00.)

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Imaging evidence of inflammatory activity in relapsing multiple sclerosis has been associated with subsequent disability, and observational studies suggest that early use of high-efficacy therapy may improve long-term outcomes.[1-5] Anti-CD20 monoclonal antibodies are among the most effective therapies for relapsing multiple sclerosis.[6-9] Rituximab showed efficacy in the phase 2 HERMES trial, with results similar to those in early studies of ocrelizumab.[6-8] In phase 3 trials, ocrelizumab showed superiority over interferon beta-1a, which led to regulatory approval for its use in relapsing multiple sclerosis.[9] After patent expiration, biosimilar versions of rituximab have facilitated widespread off-label use owing to lower costs.[10,11] However, comparative evidence between rituximab and ocrelizumab is limited to observational studies subject to residual confounding and heterogeneity in doses and monitoring.[12-18] We therefore conducted OVERLORD-MS, a randomized, double-blind, head-to-head, noninferiority trial comparing rituximab with ocrelizumab in persons with newly diagnosed relapsing multiple sclerosis.

Methods

Trial Design and Oversight

OVERLORD-MS was a phase 3, randomized, double-blind, multicenter, noninferiority trial conducted at 12 neurology departments in Norway and Sweden. Participants were randomly assigned in a 3:2 ratio to receive rituximab or ocrelizumab and were treated for 24 months, with an additional prespecified blinded follow-up visit at month 30 to evaluate confirmed changes in disability that were sustained for at least 6 months. All participating sites were required to have certified Expanded Disability Status Scale (EDSS) evaluators and magnetic resonance imaging (MRI) capability as specified in the trial protocol. The protocol (version 7.2) was approved by the national ethics committee and regulatory authorities. The statistical analysis plan (version 1.0; dated October 21, 2025) was approved and signed before database lock. The protocol and statistical analysis plan are available with the full text of this article at NEJM.org. The authors vouch for the accuracy and completeness of the data and for the adherence of the trial to the protocol. The trial was conducted in accordance with Good Clinical Practice guidelines and overseen by an independent data and safety monitoring board. There was no commercial involvement in this trial, and the sponsors had no role in the design or conduct of the trial; the collection, analysis, or interpretation of the data; or the preparation, review, or approval of the manuscript.

A Quick Take is available at NEJM.org

Participants

Eligible participants were between 18 and 60 years of age, had received a diagnosis of relapsing multiple sclerosis within the previous 12 months, showed evidence of recent inflammatory disease activity (defined by ≥1 clinical relapse or ≥1 new or enlarging lesion on MRI within the previous 12 months), and had an EDSS score of 0 to 4.0 (on a scale from 0 to 10, with higher scores indicating greater disability). The diagnosis of multiple sclerosis was established by treating neurologists at participating centers according to the McDonald criteria, on the basis of clinical and MRI findings.[19] Key exclusion criteria were a progressive form of multiple sclerosis, previous exposure to disease-modifying therapies, active infection, pregnancy or lactation, and contraindications to B-cell–depleting therapy or MRI examinations. Full eligibility criteria are provided in the Supplementary Appendix, available at NEJM.org. All the participants provided written informed consent.

Randomization and Blinding

Participants were randomly assigned to receive rituximab or ocrelizumab in a 3:2 ratio. Randomization was implemented within an electronic case-report system with the use of permuted blocks, stratified according to trial site. The initial allocation ratio was 2:1 (rituximab:ocrelizumab) with block sizes of 3 and 6; an implementation error at some sites led to reversal of the allocation sequence. After the error was identified, new site-specific allocation lists were generated for the remaining participants with the use of an adjusted allocation ratio (9:1), which resulted in the intended overall 3:2 allocation across the trial (see the Supplementary Appendix). To maintain blinding, trial medications were prepared by pharmacy personnel who were aware of the trial-group assignments and administered according to a standardized infusion protocol, with identical infusion setup and monitoring procedures in the two treatment groups. Premedication and

management of infusion-related reactions followed a prespecified protocol; all other trial personnel and participants remained unaware of the trial-group assignments.

INTERVENTIONS

Participants received intravenous rituximab (Rixathon, Sandoz) at a dose of 1000 mg at baseline, followed by 500 mg every 6 months, or intravenous ocrelizumab (Ocrevus, Roche) at a dose of 600 mg at baseline and every 6 months. Trial medications were supplied and funded by the participating hospitals as part of routine clinical procurement. Premedication included intravenous methylprednisolone (100 mg), oral antihistamine, and antipyretic agents. Concomitant treatments followed protocol guidelines; live vaccines were prohibited.

ASSESSMENTS

MRI scans were obtained at baseline and at months 6, 12, and 24. MRI acquisition followed protocol-defined sequences; scanner platforms varied across centers (see the Supplementary Appendix). MRI outcomes, including lesion counts on T2-weighted MRI, contrast-enhancing lesions, and brain volumes, were assessed at a blinded central reading center. Clinical assessments included relapse evaluations, disability scoring (EDSS), and cognitive scoring (Symbol Digit Modalities Test [SDMT]; scores range from 0 to 110, with higher scores indicating better performance). Disability assessments were performed by neurologists certified in Neurostatus examination procedures (Level B), a standardized method for EDSS assessment to ensure consistency across raters. All reported relapses were reviewed by a central adjudication committee whose members were unaware of the trial-group assignments, according to prespecified protocol definitions. Adverse events were collected systematically at each scheduled visit and coded according to the *Medical Dictionary for Regulatory Activities*, version 28.0.

END POINTS

The primary end point was the absence of new or enlarging lesions on T2-weighted MRI between month 6 and month 24. Month 6 was used as the reference time point to allow for full treatment effect after initiation of B-cell–depleting therapy and to minimize the influence of preexisting inflammatory activity. Secondary end points were the absence of new or enlarging lesions on T2-weighted MRI from baseline to months 6 and 24; the occurrence of new contrast-enhancing lesions on the MRI scans; brain-volume change from month 6 to month 24; annualized relapse rate; freedom from relapse; confirmed disability progression and confirmed lessening of disability (disability improvement), as assessed by the change in the EDSS score from baseline to month 24 and confirmed at month 30; and worsening of the SDMT score. Predefined safety end points included serious adverse events, infusion-related reactions, infections, and cancers. All end points were prespecified in the protocol.

STATISTICAL ANALYSIS

The sample-size calculation was based on the primary end point and assumed a proportion of participants without new or enlarging lesions on T2-weighted MRI of 0.95,[9] a noninferiority margin of 10 percentage points, a two-sided significance level of 0.05, 90% power, and a dropout rate of 20%. With a 3:2 allocation ratio between rituximab and ocrelizumab and the assumption of no difference in treatment effect, the target sample size was 208 participants.

The primary end point was analyzed with the use of a logistic-regression model within the prespecified modified intention-to-treat population, which included all the participants who had received at least one dose of trial medication, with treatment group as a covariate. The prespecified noninferiority margin was –10 percentage points for the risk difference (rituximab minus ocrelizumab) in the percentage of participants without new or enlarging lesions on T2-weighted MRI from month 6 to month 24. Noninferiority would be concluded if the lower boundary of the two-sided 95% confidence interval was no less than –10 percentage points. The margin was chosen to preserve a substantial proportion of the established effect of anti-CD20 therapy on the suppression of lesions on MRI in previous phase 3 trials (see the Supplementary Appendix). Sensitivity analyses included the Newcombe hybrid score confidence interval in the modified intention-to-treat population and logistic regression in the per-protocol population. The per-protocol population comprised participants with evaluable MRI scans at months 6 and 24 who received all assigned infusions within protocol-defined intervals (see the Supplementary Appendix).

Missing data were handled with the use of multiple imputation by chained equations with 10 imputations, incorporating relevant baseline characteristics and jointly imputing secondary end points related to lesion activity on T2-weighted MRI and EDSS scores. Missingness was consistent with a missing-at-random assumption. Missing SDMT scores were imputed by means of a best-case approach, with participants classified as not having a worsened score.

Secondary end points with binary outcomes were analyzed with the use of logistic-regression models with trial site as a random intercept in the modified intention-to-treat population; the random effect was removed in models that failed to converge. Analyses of secondary end points were not adjusted for multiplicity; corresponding point estimates and 95% confidence intervals should not be interpreted as causal. The annualized relapse rate was analyzed with the use of a zero-inflated Poisson mixed-effects model with trial site as a random intercept and an offset to annualize follow-up time. New contrast-enhancing lesions and brain volume were analyzed descriptively because of missing data, without imputation (see the Supplementary Appendix).

RESULTS

PARTICIPANTS

Between November 2020 and November 2022, a total of 219 participants were screened, of whom

Table 1. Baseline Characteristics of the Participants.*

Characteristic	Rituximab (N=132)	Ocrelizumab (N=84)	Overall (N=216)
Age — yr	37.4±9.4	36.6±10.1	37.1±9.7
Female sex — no. (%)	95 (72)	57 (68)	152 (70)
Months since first clinical event	20.8±42.0	24.1±38.3	22.1±40.6
Months since diagnosis	0.6±2.0	0.4±0.5	0.5±1.6
EDSS score†	1.6±1.1	1.7±1.0	1.6±1.1
No. of relapses in past year	1.2±0.4	1.1±0.6	1.2±0.5
Total no. of relapses	1.5±0.7	1.8±1.0	1.6±0.8
Days since last relapse	120±218	131±310	124±257
Current smoker — no. (%)	13 (10)	7 (8)	20 (9)
Body-mass index‡	26.3±5.2	25.9±4.8	26.2±5.0
No. of lesions on T2-weighted MRI — no. (%)			
1–9	12 (9)	13 (15)	25 (12)
10–19	32 (24)	19 (23)	51 (24)
≥20	84 (64)	51 (61)	135 (62)
Missing	4 (3)	1 (1)	5 (2)
No. of contrast-enhancing lesions on T1-weighted MRI before inclusion — no. (%)			
0	70 (53)	48 (57)	118 (55)
1	21 (16)	9 (11)	30 (14)
≥2	35 (27)	25 (30)	60 (28)
Missing	6 (5)	2 (2)	8 (4)
Oligoclonal bands — no. (%)			
Yes	109 (83)	77 (92)	186 (86)
No	3 (2)	2 (2)	5 (2)
Not analyzed or missing	20 (15)	5 (6)	25 (12)

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding.
† Scores on the Expanded Disability Status Scale (EDSS) range from 0 to 10, with higher scores indicating greater disability.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.

218 underwent randomization; 216 received at least one infusion and were included in the modified intention-to-treat population (132 assigned to rituximab and 84 assigned to ocrelizumab). Overall, 201 of 216 participants (93%) completed the 30-month follow-up (Fig. S2 in the Supplementary Appendix). Baseline characteristics of the participants were similar in the two groups (Table 1) and were consistent with contemporary populations of patients with relapsing multiple sclerosis, except that all the participants were from Norway and Sweden (Table S7). The mean age was 37.4 years in the rituximab group and 36.6 years in the ocrelizumab group; women comprised 72% and 68%, respectively, of the participants. The mean EDSS score at baseline was 1.6 in the rituximab group and 1.7 in the ocrelizumab group. A substantial percentage of participants had contrast-enhancing lesions at baseline (42% in the rituximab group and 40% in the ocrelizumab group).

PRIMARY END POINT

The percentages of participants without new or enlarging lesions on T2-weighted MRI between month 6 and month 24 were 89% (117 of 132) in the rituximab group and 93% (78 of 84) in the ocrelizumab group, which corresponded to model-estimated probabilities of 92.2% and 94.8%, respectively (Table 2). The risk difference was –2.6 percentage points (95% confidence interval [CI], –9.4 to 4.3), which met the prespecified criterion

Table 2. Primary and Secondary End Points during the 2-Year Trial.*

End Point	Rituximab (N=132)	Ocrelizumab (N=84)
Primary end point		
No new or enlarging lesions on T2-weighted MRI from month 6 to month 24 — no. (%)	117 (89)	78 (93)
Estimated probability of no new or enlarging lesions on T2-weighted MRI (95% CI)	0.92 (0.88 to 0.97)	0.95 (0.90 to 1.00)
Risk difference: rituximab minus ocrelizumab (95% CI)	–0.03 (–0.09 to 0.04)	—
Secondary MRI end points		
No new or enlarging lesions on T2-weighted MRI from baseline to month 6 — no. (%)	98 (74)	65 (77)
Estimated probability of no new or enlarging lesions on T2-weighted MRI (95% CI)	0.78 (0.70 to 0.85)	0.79 (0.71 to 0.88)
No new or enlarging lesions on T2-weighted MRI from baseline to month 24 — no. (%)	94 (71)	61 (73)
Estimated probability of no new or enlarging lesions on T2-weighted MRI (95% CI)	0.80 (0.66 to 0.93)	0.79 (0.66 to 0.91)
Change in brain volume on MRI from baseline to month 24 — %†	–0.70±2.20	–1.75±2.12
Change in brain volume on MRI from month 6 to month 24 — %†	–0.42±1.77	–1.47±1.79
Secondary clinical end points		
Estimated annualized relapse rate over 24 months (95% CI)	0.09 (0.00 to 0.18)	0.04 (0.00 to 0.09)
Mean treatment difference: rituximab minus ocrelizumab (95% CI)	0.05 (–0.02 to 0.12)	—
Freedom from relapse over 24 months — no. (%)	121 (92)	79 (94)
Estimated probability of freedom from relapse (95% CI)	0.92 (0.85 to 0.99)	0.95 (0.89 to 1.00)
Disability progression at month 24, confirmed at month 30 — no. (%)‡	4 (3)	6 (7)
Estimated probability of confirmed disability progression (95% CI)	0.03 (0.00 to 0.07)	0.08 (0.02 to 0.14)
Disability improvement at month 24, confirmed at month 30 — no. (%)‡	38 (29)	20 (24)
Estimated probability of confirmed disability improvement (95% CI)	0.28 (0.16 to 0.40)	0.22 (0.11 to 0.33)
Worsening of SDMT score from baseline to month 24 — no. (%)§	3 (2)	3 (4)
Estimated probability of worsening of SDMT score (95% CI)	0.02 (0.00 to 0.06)	0.03 (0.00 to 0.09)

* Plus–minus values are means ±SD.
† Changes in brain volume were analyzed descriptively only. Because of missing data, no formal between-group statistical comparisons were performed.
‡ Disability progression and lessening of disability (disability improvement) were assessed by the change in the EDSS score.
§ Scores on the Symbol Digit Modalities Test (SDMT) range from 0 to 110, with higher scores indicating better cognitive performance.

for noninferiority (two-sided P=0.03) (Fig. 1). Seven participants (3%) had missing primary-end-point data (5 in the rituximab group and 2 in the ocrelizumab group); missing values were handled with multiple imputations as prespecified in the statistical analysis plan. Results were consistent in prespecified sensitivity analyses (Newcombe hybrid risk difference, –2.6 percentage points; 95% CI, –9.3 to 5.6), in the per-protocol population (risk difference, 2.3 percentage points; 95% CI, –6.0 to 10.6), as well as in sensitivity analyses in the intention-to-treat and complete-case populations (Table S11).

SECONDARY IMAGING END POINTS

From baseline to month 6, the estimated probability of having no new or enlarging lesions detected on T2-weighted MRI was 0.78 in the rituximab group and 0.79 in the ocrelizumab group (risk difference, –0.02; 95% CI, –0.13 to 0.10) (Table 2 and Fig. 2A). From baseline to month 24, the probability of having no new or enlarging lesions detected on T2-weighted MRI was 0.80 in the rituximab group and 0.79 in the ocrelizumab group (risk difference, 0.01; 95% CI, –0.11 to 0.13). No new contrast-enhancing lesions were observed among participants with available MRI data at months 6, 12, or 24 (Fig. S3). Changes in brain volumes appeared similar in the two groups (Figs. S4 and S5).

SECONDARY CLINICAL END POINTS

Annualized Relapse Rate

The annualized relapse rate was low in both groups, 0.09 (95% CI, 0.0 to 0.2) with rituximab and 0.04 (95% CI, 0.0 to 0.1) with ocrelizumab, with a between-group difference of 0.05 relapses per year (95% CI, –0.02 to 0.12) (Fig. 2B). Similar findings were observed in the sensitivity analyses in the per-protocol population (between-group difference, 0.05 relapses per year; 95% CI, –0.05 to 0.10).

Relapse-free Status

From baseline to month 24, a total of 92% of the participants who received rituximab and 94% of those who received ocrelizumab remained relapse-free (risk difference with respect to estimated probability, –3.4 percentage points; 95% CI, –10.3 to 3.4) (Fig. 2C). Sensitivity analyses in the per-protocol population yielded similar results (risk difference, –2.5 percentage points; 95% CI, –10.6 to 5.6).

Disability and Cognitive End Points

Confirmed disability progression that was sustained for at least 6 months occurred in 3% of the participants who received rituximab and 7% of those who received ocrelizumab (risk difference with respect to estimated probability, –4.5 percentage points; 95% CI, –11.3 to 2.2). Confirmed disability improvement that was sustained for at least 6 months occurred in 29% of the participants who received rituximab and 24% of those who received ocrelizumab (risk difference, 6.0 percentage points; 95% CI, –6.1 to 18.2). Worsening of the SDMT score was infrequent, with no apparent between-group differences (Table 2 and Fig. 2D).

SAFETY

Among the 216 participants exposed to trial medication, the median follow-up time was 30.2 months (interquartile range, 29.9 to 30.5) in the rituximab group and 30.2 months (interquartile range, 29.9 to 30.6) in the ocrelizumab group. At least one adverse event was reported in 113 of 132 participants (86%) who received rituximab

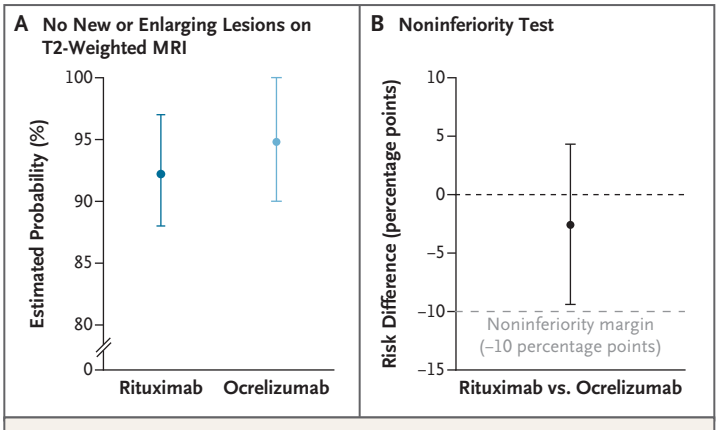

Figure 1. Primary End Point.

Panel A shows the model-estimated probability of having no new or enlarging lesions detected on T2-weighted MRI between month 6 and month 24 in the modified intention-to-treat population, which included all the participants who had received at least one dose of trial medication. Panel B shows the risk difference for rituximab as compared with ocrelizumab. The point estimate and two-sided 95% confidence interval are shown. The dashed horizontal line indicates the prespecified noninferiority margin of –10 percentage points. I bars represent two-sided 95% confidence intervals.

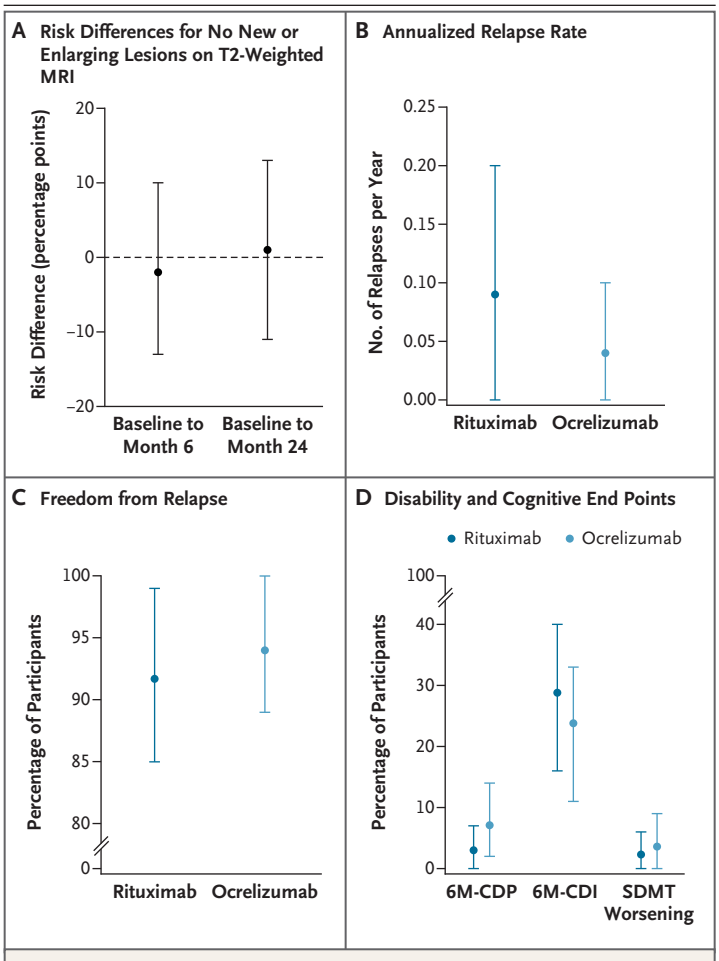

Figure 2. Secondary End Points.

Panel A shows the risk differences between treatment groups in the percentage of participants without new or enlarging lesions on T2-weighted MRI from baseline to month 6 and from baseline to month 24; risk differences are calculated as rituximab minus ocrelizumab, and the dashed horizontal line at 0 indicates no difference between groups. Panel B shows the estimated annualized relapse rate over 24 months in the modified intention-to-treat population. Panel C shows the estimated probability of remaining relapse-free from baseline to month 24. Panel D shows the estimated probabilities of confirmed disability progression that was sustained for at least 6 months (6M-CDP), disability improvement that was sustained for at least 6 months (6M-CDI), and worsening of the Symbol Digit Modalities Test (SDMT) score regarding cognitive performance from baseline to month 24, with confirmation at month 30 for disability outcomes. I bars indicate two-sided 95% confidence intervals.

and 67 of 84 participants (80%) who received ocrelizumab. Serious adverse events occurred in 10 of 132 participants (8%; 12 events) in the rituximab group and in 6 of 84 participants (7%; 6 events) in the ocrelizumab group. Adverse events leading to treatment discontinuation occurred in 2 participants (2%) receiving rituximab and in 1 participant (1%) receiving ocrelizumab. There were no deaths (Table 3).

Infections occurred in 108 participants (82%) receiving rituximab and in 58 participants (69%) receiving ocrelizumab. Most infections were mild upper respiratory tract infections. Serious infections were rare, occurring in 4 participants in each treatment group. No opportunistic infections were observed during the trial.

Infusion-related reactions were reported in 31 of 132 participants (23%) receiving rituximab and in 21 of 84 participants (25%) receiving ocrelizumab. Most reactions were mild to moderate in severity. There were no anaphylactic reactions or severe delayed reactions. There was one infusion-related treatment discontinuation in each group. Hypogammaglobulinemia (defined as an IgG level of <4 g per liter) was not observed in any participants receiving rituximab and in 2 participants (2%) receiving ocrelizumab. No association between reduced immunoglobulin levels and serious infections was observed.

No neoplasms were reported in the rituximab group. One malignant melanoma occurred in the ocrelizumab group.

DISCUSSION

In this randomized, double-blind, noninferiority trial, rituximab was noninferior to ocrelizumab in suppressing disease activity on T2-weighted MRI between months 6 and 24, on the basis of a noninferiority margin of 10 percentage points. Results for other MRI, clinical, and cognitive end points appeared to be similar in the two groups, although the trial was not powered to detect differences in these end points. Safety profiles were similar in the two groups; however, there was a greater likelihood of infections in the rituximab group and one malignant melanoma in the ocrelizumab group.

The low incidence of MRI and clinical disease activity in both groups is consistent with the findings of previous studies of rituximab and ocrelizumab.[6,7,20,21] Relapse rates were low, in keeping with a potential floor effect described in recent analyses.[22] No contrast-enhancing lesions were observed during follow-up, which is consis-

tent with the limited sensitivity of this measure in participants receiving high-efficacy therapy. In contrast, new or enlarging lesions on T2-weighted MRI capture cumulative inflammatory activity over time and formed the basis for the primary end point and power calculations.

Observational analyses comparing rituximab and ocrelizumab have yielded mixed findings on comparative efficacy and safety, with the largest study showing higher annualized relapse rates with rituximab than with ocrelizumab.[12-14] Such estimates may be affected by residual confounding. The present trial addresses these limitations by providing randomized, double-blind comparative evidence in a uniform, previously untreated population of patients with early multiple sclerosis. However, the trial addressed noninferiority only; larger studies are needed to assess superiority.

Treatment costs for multiple sclerosis have risen substantially.[23] Rituximab currently is considerably less costly than ocrelizumab and is included on the World Health Organization Model List of Essential Medicines,[11] which potentially improves access to high-efficacy therapy in resource-limited settings.[18]

Some limitations warrant consideration. First, although the trial was powered for the prespecified noninferiority comparison of the primary MRI end point, the low number of MRI and clinical events limited the precision of secondary analyses and precluded meaningful subgroup analyses; accordingly, secondary clinical end points, including relapse-free status and disability progression, showed no clear differences between the two groups, with wide confidence intervals. The trial was also not powered to detect differences in safety outcomes or rare adverse events. Second, the trial used lesion activity on T2-weighted MRI as the primary end point. Although relapse rate has historically been used as a primary outcome in trials involving patients with relapsing multiple sclerosis, lesion activity on MRI is more sensitive to inflammatory activity, correlates with relapse occurrence (although not with disability), and has been widely used in clinical trials.[24-28]

Follow-up was limited to 30 months, which is sufficient to assess short-term MRI and clinical outcomes but does not rule out potential longer-term differences. Approximately half the participants were enrolled at a single high-volume center, which may limit generalizability despite stratified randomization and centralized outcome assessment. The trial population was predominantly of Northern European ancestry and was enrolled largely from a publicly funded health care

Table 3. Adverse Events and Serious Adverse Events.*

Event	Rituximab (N=132)	Ocrelizumab (N=84)
	no. of participants (%)	
Any adverse event	113 (86)	67 (80)
Adverse event leading to treatment discontinuation†	2 (2)	1 (1)
Serious adverse event	10 (8)	6 (7)
Infections‡	108 (82)	58 (69)
Covid-19	63 (48)	43 (51)
Nasopharyngitis	59 (45)	28 (33)
Influenza	24 (18)	10 (12)
Upper respiratory tract infection	10 (8)	7 (8)
Urinary tract infection	11 (8)	6 (7)
Viral gastroenteritis	8 (6)	4 (5)
Pneumonia	3 (2)	3 (4)
Serious infection§	4 (3)	4 (5)
Infusion-related reaction¶	31 (23)	21 (25)
Hypogammaglobulinemia‖	0	2 (2)
Neoplasm**	0	1 (1)
Death	0	0

* Safety data are shown for the double-blind, controlled treatment period and include all the participants who received at least one dose of trial medication. Covid-19 denotes coronavirus disease 2019.

† Adverse events leading to treatment discontinuation in the rituximab group were colitis and an infusion reaction; the adverse event leading to treatment discontinuation in the ocrelizumab group was an infusion reaction.

‡ Selected infections occurring in at least 5% of participants overall are shown; pneumonia is included because of clinical relevance. Infections were reported by the participants and were mostly classified as mild. Additional infection categories are provided in the Supplementary Appendix.

§ Serious infections in the rituximab group were Covid-19, herpes zoster, otitis externa, and pyelonephritis; serious infections in the ocrelizumab group were appendicitis, two cases of Covid-19, and a pilonidal cyst.

¶ Infusion-related reactions were defined as events within the *Medical Dictionary for Regulatory Activities*, version 28.0, system organ class of general disorders and administration-site conditions. Infusion reactions were predominantly mild to moderate in both groups, with no qualitative differences in severity or pattern observed.

‖ Hypogammaglobulinemia was defined as an IgG level below 4 g per liter at any time point.

** One malignant melanoma occurred in the ocrelizumab group.

system, which may limit generalizability to more ethnically diverse or resource-constrained settings. In addition, because the trial involved previously untreated participants, generalizability to longer disease duration remains uncertain. Ongoing controlled trials will address comparative efficacy and safety in more heterogeneous clinical settings.[29]

In this trial, rituximab was noninferior to ocrelizumab, on the basis of a 10-percentage-point noninferiority margin, in preventing new disease activity on MRI from 6 to 24 months after the start of treatment in newly diagnosed relapsing multiple sclerosis. Results for clinical and safety end points were similar in the two groups.

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