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Authors

Meuth, Sven
Wolff, Stephanie
Mück, Anna
et al.

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Different Treatment Outcomes of Multiple Sclerosis Patients Receiving Ocrelizumab or Ofatumumab

Sven G. Meuth, MD, PhD,[1] Stephanie Wolff, MD,[2] Anna Mück, MD,[2] Alice Willison, MD,[1] Konstanze Kleinschnitz, PhD,[3] Saskia Räuber, MD,[1] Marc Pawlitzki, MD,[1] Franz Felix Konen, MD,[4] Thomas Skripuletz, MD,[4] Matthias Grothe, MD,[5] Tobias Ruck, MD,[1] Hagen B. Huttner, MD, PhD,[2] Christoph Kleinschnitz, MD,[3] Tobias Bopp, PhD,[6,7] Refik Pul, MD,[3] Bruce A. C. Cree, MD,[8] Hans-Peter Hartung, MD,[1] Kathrin Möllenhoff, PhD,[9,10] and Steffen Pfeuffer, MD[2]

Objective: B-cell–depletion via CD20 antibodies is a safe and effective treatment for active relapsing multiple sclerosis (RMS). Both ocrelizumab (OCR) and ofatumumab (OFA) have demonstrated efficacy in randomized controlled trials and are approved for treatment of RMS, yet nothing is known on their comparative effectiveness, especially in the real-world setting.
Methods: This prospective cohort study includes patients that were started on either OCR or OFA between September 2021 and December 2023. Patients were followed until June 2024 and recruited at 3 large tertiary centers in Germany (Duesseldorf, Essen, and Giessen). Propensity-score-matching was used to address baseline imbalances among patients. Clinical relapses, presence of new or enlarging MRI lesions and 6-month confirmed disability worsening were evaluated. Non-inferiority of OFA compared to OCR was evaluated through comparison of Kaplan–Meier-estimates.
Results: A total of 1,138 patients were initially enrolled in the cohort. Following patient selection and propensity-score-matching, 544 OCR and 417 OFA patients were included in the final analysis. In our primary analysis, OFA was non-inferior to OCR in terms of relapses, disability progression, and accrual of MRI lesions. Subgroup analyses confirmed findings in previously naïve and platform-treated patients. Potential differences between OFA and OCR were seen in patients switching from S1P receptor modulators or natalizumab.
Conclusion: We here provide comparative data on the effectiveness of OCR and OFA in patients with active RMS. OFA was non-inferior to OCR in the overall cohort. Potential differences observed in patients switching from S1P receptor modulators or natalizumab require further validation.

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Address correspondence to Dr med. Steffen Pfeuffer, Department of Neurology, University Hospital Giessen and Marburg, Justus-Liebig-University, Klinikstr. 33, D-35392, Giessen, Germany. E-mail: steffen.pfeuffer@neuro.med.uni-giessen.de,

From the [1]Department of Neurology, University Hospital Duesseldorf, Heinrich-Heine-University Duesseldorf, Duesseldorf, Germany; [2]Department of Neurology, University Hospital Giessen and Marburg, Justus-Liebig-University Giessen, Giessen, Germany; [3]Department of Neurology and Center for Translational Neuro- and Behavioral Sciences (C-TNBS), University Hospital Essen, University Duisburg-Essen, Duisburg, Germany; [4]Department of Neurology, Hannover Medical School, Hannover, Germany; [5]Department of Neurology, University Medicine Greifswald, Greifswald, Germany; [6]Institute of Immunology, University Medical Center Mainz, Mainz, Germany; [7]Research Center for Immunotherapy (FZI), University Medical Center Mainz, Mainz, Germany; [8]UCSF Weill institute for Neurosciences, Department of Neurology, University of California San Francisco, San Francisco, California, USA; [9]Institute of Medical Statistics and Computational Biology, Faculty of Medicine, University of Cologne, Cologne, Germany; and [10]Mathematical Institute, Heinrich-Heine-University Duesseldorf, Duesseldorf, Germany

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Depletion of B cells using monoclonal CD20 antibodies has been proven effective in active relapsing multiple sclerosis (RMS).[1] Although never officially approved for treatment of RMS, rituximab (RTX) demonstrated positive outcomes in a 2008 study,[2] which were confirmed by a phase 3 trial in 2022.[3] Ocrelizumab (OCR) was approved in 2017 and became the first on-label option for B-cell depletion in RMS.[4] More recently, ofatumumab (OFA) was introduced as a treatment option in 2021.[5]

While each of these antibody therapies induce a rapid and sustained depletion of circulating B cells by the targeted binding of CD20, they differ in various aspects of their pharmacodynamics and -kinetics.[4,6] RTX and OFA preferably induce complement-dependent cytotoxicity, while OCR also induces antibody-dependent cellular cytotoxicity.[7] OCR (and RTX) are approved for intravenous (IV) treatment and are administered semi-annually, although OCR has recently become available for subcutaneous (SC) administration as well. By contrast, OFA is administered SC and is given once a month.[1,5]

To date, very few studies have directly compared OCR and OFA. A single secondary analysis of the data from the phase 3 trials was carried out, and this study slightly favored OFA.[8] However, previous data comparing OCR and RTX indicated better outcomes following OCR compared to RTX and thus indicated that CD20 antibodies have distinct effectiveness profiles.[9] Based on the concentration and route of administration, the distribution of the CD20 antibodies in the lymphatic systems differs substantially.[10]

We therefore evaluated our large multicenter prospective real-world multicenter cohort to evaluate whether the more recently introduced OFA is non-inferior to OCR in terms of effectiveness in patients with active RMS.

Methods

Patients

Between September 2021 and December 2023, adult patients with RMS according to the 2017 revised McDonald criteria[11] eligible for treatment with OCR or OFA were enrolled in a multicenter prospective cohort recruiting at 3 tertiary centers in Germany (Giessen [GI], Duesseldorf [DUS], and Essen [ES]). Following treatment with CD20 antibodies, all patients were included and underwent standardized follow-up including standardized MRI assessment. All patients fulfilled on-label criteria for treatment, and the decision was made in accordance with current national guidelines and the most recent summary of product characteristics. Among the 3 centers, there was no specific policy regarding prescription of either drug, and all patients eligible for CD20 antibodies were offered both options within the framework of shared decision-making. The decision for either antibody was made independently from subsequent enrollment in the study cohort.

Patients who started treatment between September 2021 and December 2023 were enrolled in the study. Patients with previous exposure to any B-cell–depleting agent, alemtuzumab or cladribine and patients who fulfilled the Lorscheider criteria for progressive MS[12] at baseline were excluded.

Outcome Measurements

Epidemiologic data at baseline were analyzed including "age," "sex," "disease duration since MS onset," "annualized relapse rate at baseline," "number of previous disease-modifying treatment (DMT)," and "last previous DMT" (injectable treatments, teriflunomide, and dimethyl fumarate were termed "platform treatments"; ozanimod, ponesimod, and fingolimod were termed "S1P receptor modulators (S1PRM)"). A baseline MRI was conducted no earlier than 6 weeks prior to the first dose of CD20 antibody and the number of T2-hyperintense lesions (T2L) and contrast-enhancing T1-weighted lesions (CEL) were quantified (these scans were conducted at the centers throughout as well as the follow-up scans). At baseline, the patients' Expanded Disability Status Scale (EDSS) scores were assessed. Washout duration from last previous DMT and reason for treatment switch were documented.

Follow-up was also standardized among centers. Patients were seen every 3 months and MRI was conducted semi-annually (±3 weeks were deemed acceptable for both follow-up visit and MRI), including assessment of neurologic status and EDSS. OFA patients were interviewed regarding drug administration and received new prescriptions. Relapses within the past 3 months were evaluated including date of onset, symptoms, and specific treatment (unless they were already evaluated during non-scheduled visits). Per protocol, a relapse required an increase of at least 1 function system score according to the EDSS scoring system to be deemed relevant, which is similar to the thresholds used in the pivotal phase 3 trials of OCR and OFA. Worsening of disability was considered relevant if the EDSS increased as follows: +1.5 points (baseline = 0.0), +1.0 point (baseline = 1.0–5.5), and +0.5 points (baseline ≥6.0) and this required confirmation 6 months later (6-months confirmed disability worsening [CDW]). Progression independent of relapse activity (PIRA) and relapse-associated worsening (RAW) were evaluated as described previously.[13]

Follow-up MRI scans were conducted at the respective centers using the recommended MAGNIMS-CMSC-NAIMS protocol at 3 T field strength.[14] Scans were evaluated by experienced neuroradiologists in a standardized manner.

$CD19^+$ B-cell measurements were obtained as a part of routine clinical practice using flow cytometry at the respective hospitals. Among all centers, relevant parameters such as gating strategy, thresholds, and analysis

volume were comparable, and all laboratories are accredited centers.

Statistical Analysis

Propensity-score-matching was performed to minimize the effect of possible confounding factors and to balance treatment groups. For each subject, a propensity score was estimated using a logistic regression model based on the following baseline variables: "age," "sex," "disease duration since MS onset," "number of MS relapses in the previous year," "EDSS at baseline," "number of T2L at baseline," "last previous DMT," and "center."

Patients were matched based on their propensity scores using nearest-neighbor matching without replacement, with a variable ratio of up to 5:1 and a caliper of 0.1 standard deviations (SDs) of the propensity score.[15] This is similar to previous studies comparing the effectiveness of different CD20 antibodies.[9] Covariate balance was assessed by standardized mean difference (SMD), where a difference of less than 0.1 was considered as an acceptable balance.

All of the following statistical analyses were based on the matched sample, and standard errors were computed using a cluster-robust standard error to account for the clustering within matched sets.[16] For all above-mentioned treatment outcomes, Kaplan–Meier estimates were calculated to visualize time-to-event data and adjusted log-rank tests were applied to assess treatment differences. Further, non-inferiority analyses were conducted in order to investigate the non-inferiority of OFA to OCR. Non-inferiority was assessed for each of the clinical endpoints previously evaluated using the Kaplan–Meier method separately to retain sensitivity of our analyses rather than using combined endpoints.[17]

Further analyses of categorical data were conducted using logistic regression models. Odds ratios (ORs) are given where appropriate including respective 95% confidence intervals (CIs).

Due to obvious violations of the proportional hazards assumption, these analyses could not be defined using the hazard ratio, but were based on a direct comparison of the Kaplan–Meier curves. Therefore, 2-sided (1-2α) CIs for the difference of the Kaplan–Meier curves were calculated for each time point. Non-inferiority was established if the upper bounds of these CIs did not exceed a prespecified non-inferiority margin.[18] Although pointwise CIs were used, which technically results in multiple tests at several time points, there is no need to correct for multiple comparisons. This is because the (overall) non-inferiority hypothesis, that is non-inferiority over the entire observation period, is an intersection of many "individual" alternative hypotheses, with non-inferiority being tested separately at each time point. As pointed out by several authors, performing such individual tests at a significance level of α result in an overall non-inferiority test of size α.[19–22]

There is no uniform guideline on selection of a margin, apart from bioequivalence studies, in which authorities accept a margin of log (1.25) translating into an acceptable exposure difference of 20%. For example, such margins were recently used in studies comparing SC vs. IV natalizumab (NTZ).[23]

Previous non-inferiority studies in MS substantially differ from our approach since these studies evaluated ratios of clinical endpoints and not differences of survival probabilities (such as in Ref.[24]). Meta-analyses for approaches similar to ours were conducted in oncology trials and indicate non-inferiority margins between $\Delta = 0.10$ and $\Delta = 0.15$.[25,26]

Of note, our approach remains generally independent from a pre-specified non-inferiority margin and allows the reader to directly interpret the graphical analysis using every possible margin. We included lines indicating $\Delta = 0.10$ (dashed lines) and $\Delta = 0.15$ (solid lines) as orientation. Our interpretation is based on a non-inferiority margin of $\Delta = 0.15$, allowing for a difference of 15% between the treatments, regarding probabilities of experiencing 1 of the treatment outcomes. This margin has also been used in studies with comparable design among RMS patients.[27,28]

Non-inferiority analyses were performed at a significance level α of 0.05. A *p*-value below 0.05 was considered statistically significant. All analyses were performed using R (R Core Team, 2023, version 4.3.1).

Standard Protocol Approvals, Registrations, and Patient Consents

Ethical approval was granted by local authorities (Institutional Review Board of Justus-Liebig-University Giessen [53/23], Institutional Review Board of Heinrich-Heine-University Dusseldorf, Germany [5951R, 2021-1475], and Institutional Review Board of University Duisburg-Essen [20-9510-BO]). All patients gave written consent for enrolment and data acquisition.

Results

Patients

Among 1,138 patients included in the cohort until December 2023, 76 patients were excluded from analysis: 26 retrospectively fulfilled Lorscheider criteria for secondary-progressive MS, and 50 were previously exposed to other B-cell–depleting therapies. Thus, 1,062 patients entered matching, and 961 patients were included in the analysis (Figure 1).

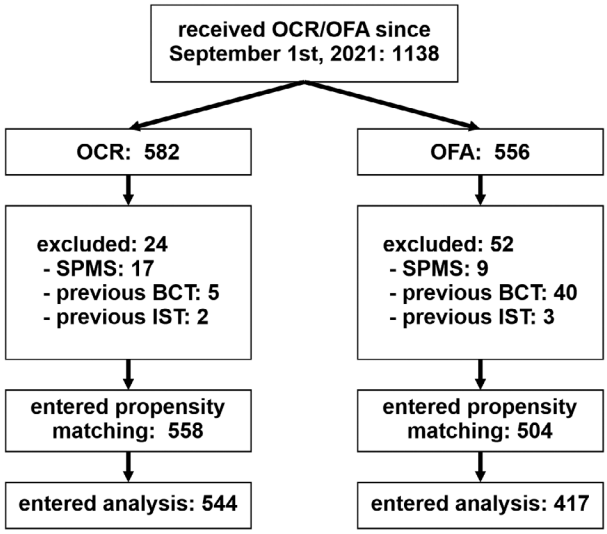

Figure 1: Flowchart depicting the composition of the study cohort. BCT, B-cell–depleting therapy; IRT, immune reconstitution therapy (alemtuzumab, cladribine); OCR, ocrelizumab; OFA, ofatumumab; SPMS, secondary progressive multiple sclerosis. Among patients with previous BCT, 5 patients switched from rituximab to OCR, whereas 40 patients switched from OCR to OFA. Among patients with previous exposure to IRT, 1 patient was previously treated with alemtuzumab, and 4 patients were previously treated with cladribine.

Analysis of SMDs among both treatment groups prior to propensity-score-matching indicated a substantial imbalance among groups. Specifically, this was seen with center distribution, baseline relapse rate, and number of previous DMT. Following propensity-score-matching, all covariates displayed satisfactory matching with a |SMD| < 0.1 (Table 1 & Supplemental Figure S1). The matched cohort consisted of patients with a mean age of 35.4 ± 9.2 years and a short mean disease course since MS onset (44.9 ± 32.9 months). RMS appeared active throughout with 0.8 ± 0.7 mean relapses within the past year and 19.1 ± 7.2 mean baseline T2L. The baseline epidemiologic parameters of the matched cohort are shown in Table 1 (for the unmatched cohort see Table S1). Baseline epidemiologic characteristics appeared evenly balanced among study centers (Table S2). The matched cohort accounts for a cumulative follow-up of 18,873 patient-months (OCR: 11,071 patient-months; OFA: 7,802 patient-months).

As already stated above, there was no specific policy for the prescription of either drug among consultants at the involved centers and the decision for a given treatment was made independently from participation in the cohort. However, we sought to identify further potential confounders/bias and thus evaluated baseline parameters among patients with different pre-treatments (Table 2; a detailed version including is shown in Table S3).

We found no significant differences among groups, which remained consistent even after the analysis of parameters not included in the propensity-score-matching process. While initiation of a high-efficacy DMT was requested among treatment-naïve patients across all centers, patients having previously received platform DMT were uniformly escalated to OCR/OFA due to disease activity.

Among patients having previously received S1PRM, fingolimod was most frequently used (149 patients), whereas ozanimod (12 patients) and ponesimod (4 patients) were prescribed less often. Within this group, comparable proportions among OCR and OFA patients were switched due to disease activity (OCR: 26.1% vs. OFA: 17.8%), whereas the remaining patients were clinically stable yet experienced adverse events.

The proportion of treatment-escalated patients that developed either relapses, new/enlarging T2L or a combination of both in the year before the treatment switch were comparable among OCR/OFA subgroups (Table S4). Adverse events resulting in switch among those 37 patients comprised lymphopenia (49%), infections (35%), skin irritation/rash (8%), syncope (5%), and increased intraocular pressure (3%). These patients were equally distributed to OCR/OFA in our cohort.

Increased risk for development of progressive multifocal leukoencephalopathy (PML) was the most common reason for CD20 antibodies among patients previously treated with NTZ (96.4% of previously NTZ-treated patients). However, 7 patients having subsequently received OCR experienced a relapse in the previous year compared to 2 patients that were switched to OFA.

Washout periods were comparable among all subgroups, apart from S1PRM patients. Here, we found that the washout duration among patients having received OCR was approximately 3 days longer. Of note, lymphopenia resolved toward >800 lymphocytes/mm^3 in all patients upon induction of OCR/OFA.

Among all subgroups, 31 patients experienced a clinical relapse during the washout period (OCR: 21 patients [6%] vs. OFA: 11 patients [4%]). Among subgroups with different previous DMT, fractions were comparable (platform: 3% vs. 1%; S1PRM: 5% vs. 5%; NTZ: 9% vs. 8%).

Treatment Outcomes

Following initiation of a CD20 antibody, 168 patients experienced a clinical relapse (OCR: 101; OFA: 67) translating to an annualized relapse rate of 0.11 in the overall cohort (baseline OCR: 0.76; baseline OFA: 0.92). Notably, relapse rates decreased within first 6 months following

Table 1. Baseline Parameters of the Matched Cohort

Matched cohort	OCR ($n = 544$)	OFA ($n = 417$)	SMD
Patients treated per center, no. (%)			
Duesseldorf	170 (31.3)	121 (29.0)	−0.0185
Essen	144 (26.5)	108 (25.9)	0.0479
Giessen	230 (42.3)	188 (45.1)	−0.0240
Age, years	35.2 ± 9.1	35.6 ± 9.4	0.0325
Females, no. (%)	365 (67.1)	290 (69.5)	−0.0034
Disease course since MS onset, months	44.8 ± 31.1	44.9 ± 35.0	0.0396
No. of MS relapses in the previous year	0.76 ± 0.66	0.92 ± 0.64	<0.0001
EDSS at baseline	2.1 ± 1.0	2.1 ± 1.0	0.0188
No. of T2L at baseline	19.2 ± 7.3	19.1 ± 7.1	0.0096
Last-previous DMT, no. (%)			
None	168 (30.9)	147 (35.3)	0.0050
Beta-interferon	36 (6.6)	34 (8.2)	0.0056
Glatiramer acetate	42 (7.7)	43 (10.3)	0.0346
Teriflunomide	19 (3.5)	21 (5.0)	−0.0371
Dimethyl fumarate	54 (9.9)	36 (8.6)	0.0394
S1P receptor modulator	92 (16.9)	73 (17.5)	−0.0184
Natalizumab	133 (24.4)	63 (15.1)	−0.0169

Note: Continuous variables are given as mean ± standard deviance.
Abbreviations: DMT, disease-modifying treatment; EDSS, expanded disability status scale; MS, multiple sclerosis; OCR, ocrelizumab; OFA, ofatumumab; SMD, standardized mean difference; T2L, T2-hyperintense MRI lesion.

induction of OCR/OFA and remained low throughout (Figure S2).

A total of 278 new or enlarging T2L were detected in 213 patients (OCR: 174 lesions/126 patients; OFA: 104 lesions/87 patients). The overall availability of MRI data was 1549/1593 scheduled scans (97.2%) among OCR patients and 1085/1117 (97.1%) among OFA patients. Frequencies of available/positive scans at 6-month intervals remained consistent (Figure S3). Given the potential difficulties in detection of enlarging lesions, we assessed their prevalence across centers and drug treatments, finding no significant differences (Figure S4).

Finally, 147/961 (15.6%) patients experienced CDW (OCR: 93 [17.1% of all OCR patients]; OFA: 54 [12.9% of all OFA patients]). Of these, 80 patients experienced RAW (OCR: 46 [8.4%]; OFA: 34 [8.2%]) and 67 patients experienced PIRA (OCR: 47 [8.6%]; OFA: 20 [4.8%]). Among patients with RAW, there was no significant difference regarding the proportion of patients having received IV corticosteroids for their relapse treatment between OCR and OFA patients (93% vs. 94%; $p = 0.885$, OR: 0.911; 95% CI: 0.258–3.214). Furthermore, the proportion of patients that developed RAW following a relapse was similar among OCR/OFA patients (45.5% vs. 50.7%; Figure S5). Interestingly, we found that, among treatment-naïve patients, RAW was less common than in patients who had previously received a DMT.

Among all patients with a clinical relapse, approximately 50% developed new or enlarging T2L in their subsequent MRI scan. Minor differences were found depending on the last previous DMT, with more MRI relapses among treatment-naïve OFA patients or platform-treated OCR patients, but no uniform trend became apparent. However, this analysis indicated that patients with development of new MRI lesions were more likely to develop RAW following a clinical relapse (Figure S6). In patients who developed PIRA, we found that most

Table 2. Baseline Parameters among Patients Stratified According to Their Last Previous DMT

	Naïve		Platform		S1PRM		NTZ	
	(*n* = 315)		(*n* = 285)		(*n* = 165)		(*n* = 196)	
	OCR	OFA	OCR	OFA	OCR	OFA	OCR	OFA
Parameter	(*n* = 168)	(*n* = 147)	(*n* = 151)	(*n* = 134)	(*n* = 92)	(*n* = 73)	(*n* = 133)	(*n* = 63)
Age, years	33.5 ± 9.3	33.4 ± 9.5	35.0 ± 9.0	36.3 ± 9.3	35.0 ± 7.9	36.6 ± 8.2	37.7 ± 9.2	37.7 ± 10.0
Females, no. (%)	115 (68.5)	99 (67.3)	100 (66.2)	96 (71.6)	60 (65.2)	52 (71.2)	90 (67.7)	43 (68.3)
Disease course since MS onset, months	16.0 ± 14.3	18.2 ± 19.9	46.8 ± 25.6	50.9 ± 28.3	57.0 ± 20.3	63.4 ± 32.9	70.8 ± 29.2	72.8 ± 37.0
No. of MS relapses in the previous year	1.2 ± 0.6	1.2 ± 0.5	0.9 ± 0.6	1.0 ± 0.6	0.8 ± 0.5	0.9 ± 0.6	0.1 ± 0.3	0.0 ± 0.2
Patients with new/enlarging T2L in the previous year	n/a	n/a	131 (86.8)	123 (91.8)	63 (68.5)	54 (74.0)	7 (5.3)	6 (9.5)
EDSS at baseline	1.9 ± 1.0	1.8 ± 0.9	2.1 ± 1.0	2.1 ± 1.0	2.2 ± 1.0	2.4 ± 1.0	2.3 ± 1.1	2.4 ± 1.0
No. of T2L at baseline	17.9 ± 6.1	17.7 ± 6.5	17.2 ± 6.4	17.1 ± 5.5	20.3 ± 7.2	22.6 ± 7.7	22.2 ± 8.4	22.5 ± 8.0
Patients with presence of CEL at baseline	30 (17.9)	28 (19.0)	26 (17.2)	20 (14.9)	13 (14.1)	15 (20.5)	24 (18.0)	18 (28.6)
No. of last previous DMT	n/a	n/a	1.6 ± 0.7	1.6 ± 0.8	2.1 ± 0.9	2.1 ± 0.8	2.2 ± 0.9	1.9 ± 0.9
Washout duration, days	n/a	n/a	13.1 ± 9.3	13.2 ± 9.6	49.9 ± 12.6	46.2 ± 11.2	58.0 ± 15.7	60.1 ± 14.5
Duration of last previous DMT, months	n/a	n/a	30.8 ± 19.1	33.6 ± 21.8	33.6 ± 18.2	36.4 ± 22.5	47.5 ± 21.2	48.0 ± 26.4
Reason for switch, no. (%)								
Initiation	168 (100)	147 (100)	0	0	0	0	0	0
Escalation	0	0	151 (100)	131 (100)	68 (73.9)	60 (82.2)	7 (5.3)	2 (3.2)
Adverse events	0	0	0	0	24 (26.1)	13 (17.8)	0	0
PML risk	0	0	0	0	0	0	126 (94.7)	61 (96.8)
Mean follow-up, months	19.7 ± 6.8	18.6 ± 6.3	21.0 ± 6.2	19.0 ± 6.0	20.2 ± 6.0	19.0 ± 6.5	20.6 ± 6.3	18.5 ± 6.5

Note: Continuous variables are given as mean ± standard deviation.

Abbreviations: CEL, contrast-enhancing MRI lesion; DMT, disease-modifying treatment; EDSS, expanded disability status scale; MS, multiple sclerosis; OCR, ocrelizumab; OFA, ofatumumab; PML, progressive multifocal leukoencephalopathy; T2L, T2-hyperintense MRI lesion.

patients did not exhibit new lesions in a scan subsequent to first disability progression (Figure S7). In this subgroup of patients with PIRA and positive findings in their next MRI scan, enlarging rather than new lesions were found (19 enlarging lesions vs. 3 new lesions).

In our main analysis, we now evaluated whether OFA was non-inferior to OCR. First, we used the Kaplan–Meier method to determine the proportion of patients without clinical relapses (REL), CDW, and T2L over time. Here, we found no relevant differences for the time to first clinical relapse (Figure 2A), time to first CDW (Figure 2B), and time to first new/enlarging T2L (Figure 2C).

The non-inferiority analysis based upon these Kaplan–Meier estimates indicated that the upper 95% CIs

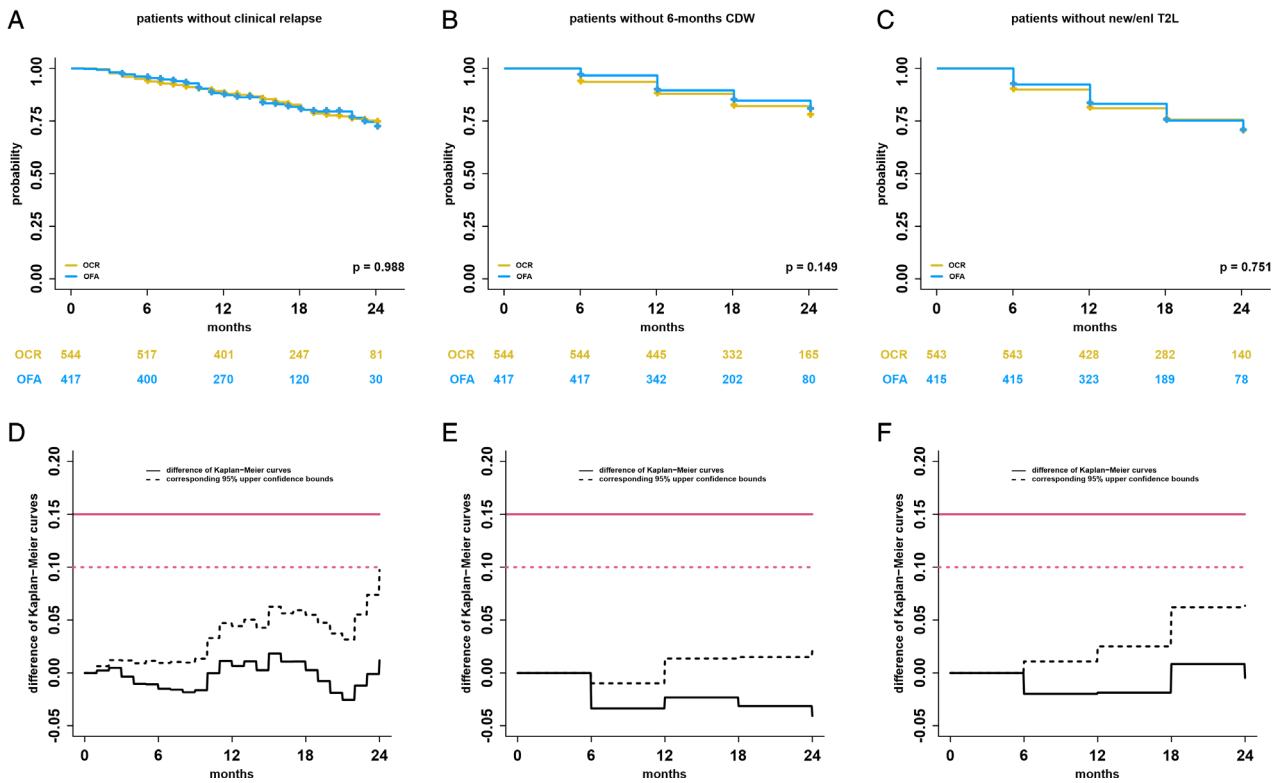

Figure 2: Treatment outcomes of ofatumumab (OFA) vs. ocrelizumab (OCR) patients. (A–C) Kaplan–Meier plots indicating proportion of patients without a clinical MS relapse (REL; A), new or enlarging T2-hyperintense MRI lesions (new/enl T2L; B), and 3-months confirmed worsening of disability (CDW; C). Patients at risk are indicated below the respective plots. (D–F) Non-inferiority analysis regarding the respective endpoints. Solid red lines indicate the non-inferiority margin of Δ = 0.15; dashed lines indicate Δ = 0.10. [Color figure can be viewed at www.annalsofneurology.org]

for the differences between the Kaplan–Meier curves remained below 0.15 for the time to first clinical relapse (Figure 2D), time to first CDW (Figure 2E), and time to first new/enlarging T2L (Figure 2F). Given these findings, OFA was non-inferior to OCR.

Following our main analysis, we stratified the cohort depending on the last previous DMT. In previously treatment-naïve patients, Kaplan–Meier plots demonstrated similar proportions of event-free patients over time regarding treatment outcomes (Figure 3A) and non-inferiority was also confirmed according (Figure 3B). Among patients escalating to CD20 therapy from platform treatment, we again found comparable disease outcomes using the Kaplan–Meier method (Figure 3C). Although OFA was formally not non-inferior in terms of relapses, non-inferiority was still shown for CDW and T2L (Figure 3D).

Within the cohort of patients switched from S1PRM, we observed 30 relapses in OCR patients (32.6%) compared to 7 relapses in patients receiving OFA (9.6%), and comparable observations were made in terms of development of new or enlarging T2L or CDW. Log-rank tests indicated significant differences of Kaplan–Meier curves for the respective outcome parameters (Figure 4A). Analyses showed that OFA was non-inferior to OCR in this subgroup (Figure 4B).

Following previous treatment with NTZ, 19 OFA patients (30.2%) experienced a clinical relapse compared to 19 OCR patients (14.3%). The log-rank test again indicated significant differences for each outcome parameter over time (Figure 4C). OFA was inferior to OCR in our analyses (Figure 4D).

Among all subgroups, MRI outcomes were robust to re-baselining (Figure S8). Given the impact of washout duration on relapses in patients switching from S1PRM or NTZ, we performed a sensitivity analysis by splitting subgroups based on the median washout duration and this analysis again showed no significant differences (Figure S9). Swimmer's lane plot-analysis including all patients meeting the respective endpoint were used to rule out that our findings depended on single individuals with longer washout durations (Figure S10).

We evaluated the levels of peripheral $CD19^{+}$ B cells among our cohort as well. Following treatment with either CD20 antibody, patients exhibited profound reduction of B cells throughout. Among OCR patients, B cells showed a further decline beyond month 6 in a dose-dependent manner whereas OFA patients reached their steady-state

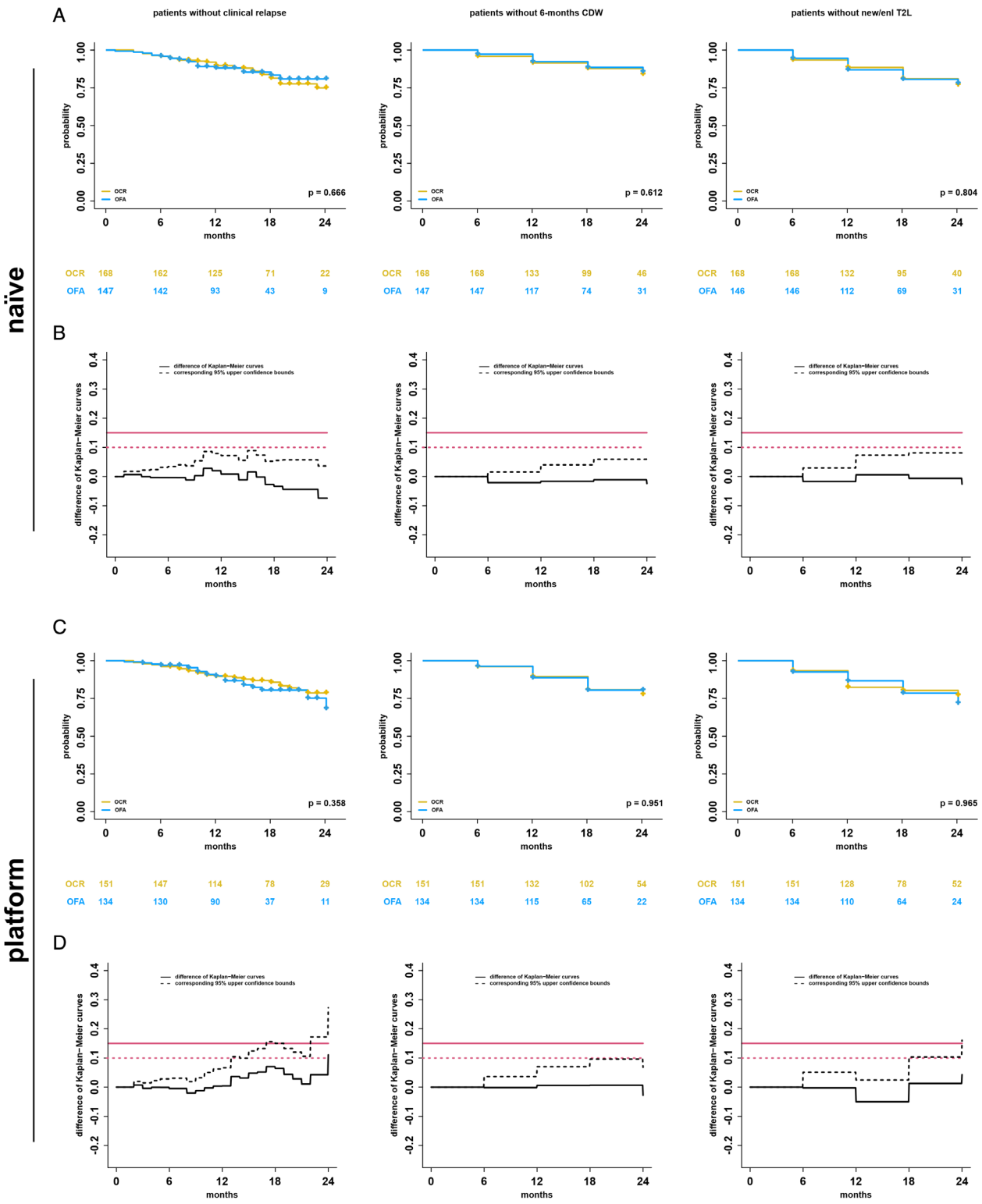

Figure 3: Treatment outcomes among ofatumumab (OFA) vs. ocrelizumab (OCR) patients who were either previously treatment-naïve or received platform treatment. (A) Kaplan–Meier-plots indicating proportion of previously naïve patients without a clinical MS relapse (REL), new or enlarging T2-hyperintense MRI lesions (new/enl T2L), and 3-months confirmed worsening of disability (CDW). Patients at risk are indicated below the respective plots. (B) Non-inferiority analysis regarding the respective endpoints. (C) Kaplan–Meier plots indicating the above-mentioned treatment outcomes among patients switching from platform treatment to OFA or OCR. (D) Non-inferiority analysis regarding the respective endpoints. Solid red lines indicate the non-inferiority margin of $\Delta = 0.15$; dashed lines indicate $\Delta = 0.10$ (B and D). [Color figure can be viewed at www.annalsofneurology.org]

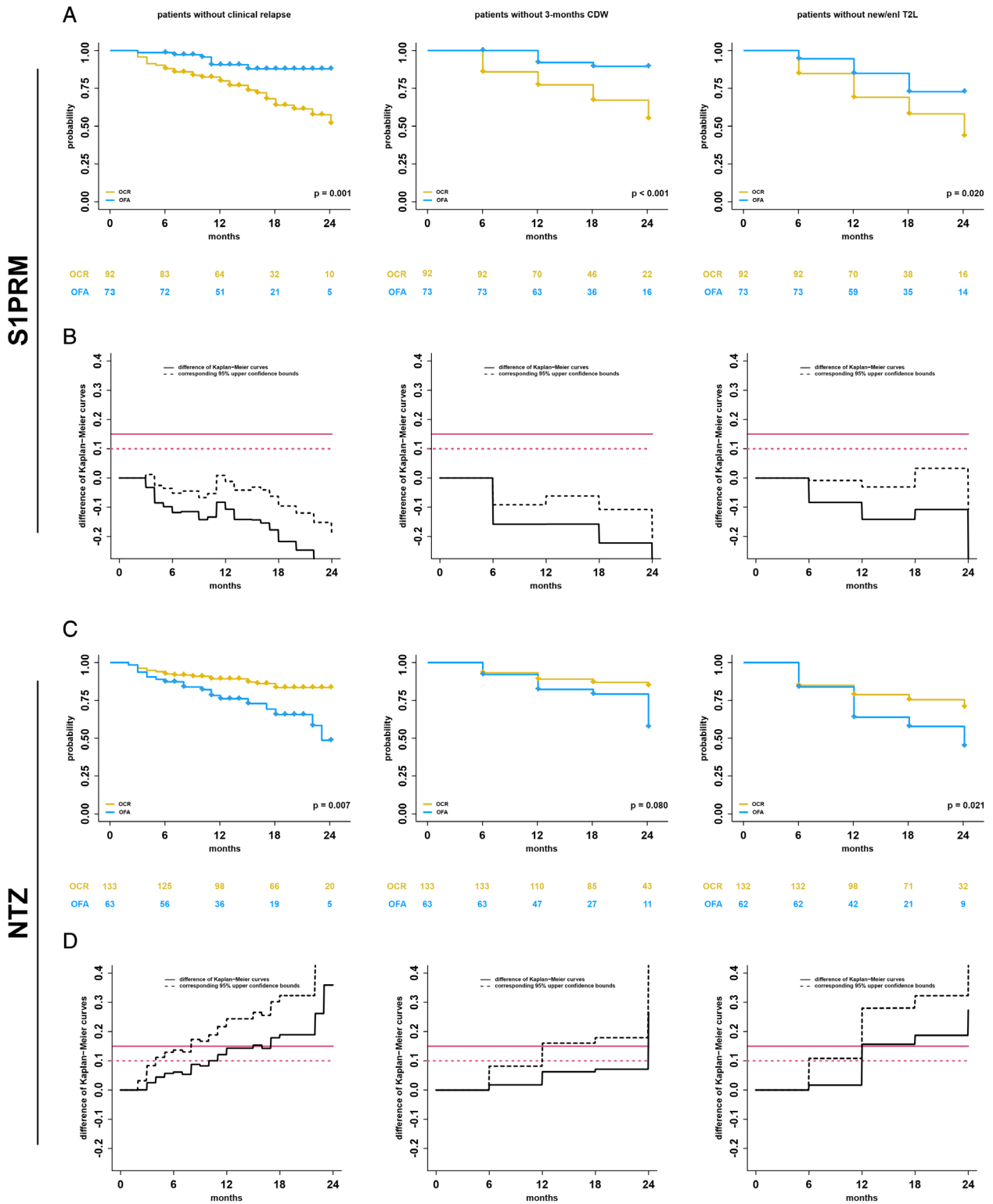

Figure 4: Treatment outcomes among ofatumumab (OFA) vs. ocrelizumab (OCR) among patients switching from S1P receptor modulators (S1PRM) or natalizumab (NTZ). (A) Kaplan–Meier plots indicating proportion of previously fingolimod-treated patients without a clinical MS relapse (REL), new or enlarging T2-hyperintense MRI lesions (T2L), and 3-months confirmed worsening of disability (CDW). Patients at risk are indicated below the respective plots. (B) Non-inferiority analysis regarding the respective endpoints. (C) Kaplan–Meier plots indicating the above-mentioned treatment outcomes among patients switching from NTZ treatment to OFA or OCR. (D) Non-inferiority analysis regarding the respective endpoints. Solid red lines indicate the non-inferiority margin of $\Delta = 0.15$; dashed lines indicate $\Delta = 0.10$ (B and D). NTZ, natalizumab; S1PRM, S1P receptor modulator. [Color figure can be viewed at www.annalsofneurology.org]

already at month 6 (Figure 5). Among subgroups, we observed well-described patterns of B cells at baseline with depressed levels in patients switching from S1PRM and increased levels in patients switching from NTZ. Following treatment, all subgroups showed a similar decline of peripheral B cells (Figure S11).

Discussion

The depletion of B cells using CD20 antibodies has been implemented in treatment of active RMS for many years now and provides us with well-tolerated and highly effective treatment opportunities.

Whereas one could have expected comparable effectiveness of both substances based upon the similar mechanism of action, a recent study indicated potential inferiority of RTX versus OCR.[9] Of course, these findings warrant cautious interpretation, yet they indicate potential differences among different CD20 antibodies. Besides structural differences of both antibodies, OFA and OCR also differ in their pharmacodynamic properties, route of administration, and dosing frequency.

Additionally, OFA and OCR differ in binding and depletion capacity. OFA induced a more profound depletion of immune cells in the lymph nodes in animal experiments, whereas the effect of OCR was more pronounced in blood and bone marrow.[10,29] While OCR is administered IV and thus rapidly peaks in the lymphoid tissues, OFA enters the lymphoid tissues slowly since capillary vessels remain almost impermeable for monoclonal antibodies and thus redistribution depends on lymphatic vessels.[30]

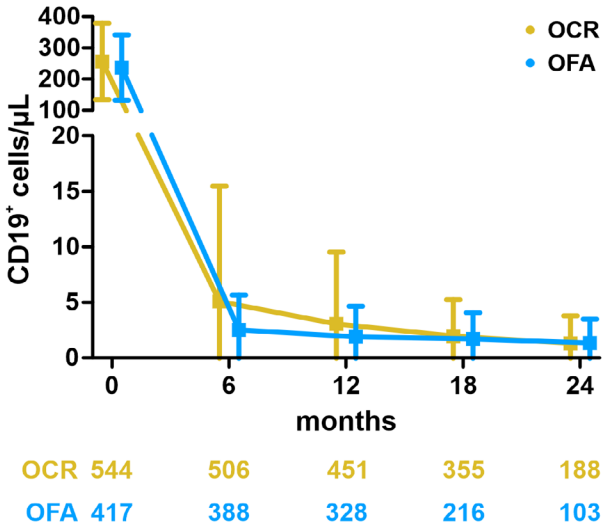

Figure 5: Evaluation of CD19$^+$ B cells in the peripheral blood. CD19$^+$ B cells prior to treatment initiation were assessed on the day of first treatment before first infusion/injection. Follow-up assessments were made prior to next scheduled drug administration. Numbers below the graph represent sample sizes. OCR, ocrelizumab; OFA, ofatumumab. [Color figure can be viewed at www.annalsofneurology.org]

Nonetheless, OFA also induces profound peripheral B-cell depletion as predicted in pharmacokinetic modeling studies and confirmed in the ASCLEPIOS trials.[5,31]

We thus sought to evaluate the comparative effectiveness of OFA and OCR in our large multicenter prospective real-world cohort of patients with active RMS.

In our main analysis, disease outcomes were comparable demonstrating non-inferiority of OFA versus OCR. Thus, we support previously published retrospective data from an Italian multicenter cohort.[32] Furthermore, our findings confirm the efficacy data of both substances that were obtained in their respective randomized clinical trials. For example, the overall annualized relapse rate of 0.11 in our cohort closely resembles results from the OPERA and ASCLEPIOS studies.[4,5] Baseline demographics differed slightly between our cohort and respective trial populations. For example, baseline age, baseline disease duration, and baseline EDSS scores were lower in our cohort. On the other hand, our patients had higher previous DMT exposure including a far higher proportion of patients with exposure to high-efficacy DMT, thus expanding the evidence on the use of CD20 antibodies in active RMS.

We performed exploratory subgroup analyses of our cohort to evaluate the effectiveness of OFA and OCR depending on the last previous DMT.

The early use of high-efficacy DMT including CD20 antibodies was repeatedly associated with beneficial long-term outcomes in active RMS.[33,34] Our data indicate that, among previously naïve patients subjected to a "flipping the pyramid"-treatment approach,[35,36] both substances appear equally effective. This enables physicians to further tailoring of CD20 treatment to the individual patient's needs including preferred dosing interval or administration route. Similar observations were made in patients switching from platform treatment. Previous data indicate that, in those patients, a direct switch to a high-efficacy DMT is warranted once treatment goals are not achieved.[37] The presented results should hence encourage physicians to consider both CD20 antibodies in their early escalation strategy.

Besides treatment initiation or escalation from platform DMT, CD20 antibodies are widely used for lateral treatment switches among different high-efficacy DMT in active RMS. CD20 antibodies are widely used in patients stopping NTZ because of increased PML risk since positive evaluation of RTX in this subgroup.[38,39]

Generally, these patients have a high-risk of rebound disease activity following withdrawal since lymphocytes

are pooled in front of the blood–brain barrier.[40] In line, a relevant proportion of our patients developed new MRI lesions within first 6 months following switch from NTZ. However, we observed particular advantages for OCR compared to OFA even after re-baselining.

Switches from S1PRM are also common in active RMS for various reasons comprising adverse reactions and lack of effectiveness.[41] Several studies indicated that exposure to S1PRM might decrease effectiveness of subsequent high-efficacy DMT with first reports having been presented for alemtuzumab.[42] In terms of OCR, studies yielded conflicting results and indicated a potential role for length of washout duration.[43,44] Here, we found advantageous disease outcomes in patients having been switched to OFA compared to OCR. Effects were not restricted to a single S1PRM despite their different receptor subtype binding profile, half-life period, and dosing regimen.[45] Underlying mechanisms remain unclear, yet potentially include persistent sequestration of lymphocytes and thus their protection from depletion as well as qualitative changes in the immune network.[46,47]

Our study has important limitations. Patients were not randomized to treatment group, and we cannot exclude that unknown determinants for choosing 1 specific agent/drug exist directly influence the observed apparent differences in effectiveness. In general, propensity-score-matching is only effective for adjusting for known confounders. The matching was applied to the overall cohort given that this was the main object of the study. Thus, we refrained from performing matching for each subgroup analysis again. Consequently, some subgroups show slight differences in single parameters and this should underline the hypothesis-generating character of these analyses.

We generally observed in our cohort, that the mean follow-up duration was longer among OCR patients compared to their OFA counterparts. This appears reasonable since it reflects the increasing use of OFA over time compared to OCR and was seen before following introduction of new DMTs. However, we decided not to specifically adjust for this parameter because it would have further reduced the sample size.

Given that OFA was first made available in Germany in September 2021, future studies will become necessary to evaluate the long-term effectiveness and safety of both substances in the real-world setting.

Finally, our cohort is characterized by longer washout durations compared to other cohorts (eg, 48 days following S1PRM compared to 27 days in Ref. 44). This likely resulted from national guidelines recommending "resolution of treatment specific effects" such as lymphopenia following S1PRM treatment.[48] Prolonged washout periods pose a potential risk factor for disease reactivation.[49] We observed disease reactivation in some patients accompanied by the presence of contrast-enhancing lesions in the baseline MRI (especially following NTZ cessation). Although our MRI outcomes were robust to re-baselining, these observations prompt that treatment-free intervals should not be prolonged. The previous concept of a "washout" period should be reconsidered, and a rapid switch to a new DMT should be favored instead to minimize potential disease reactivation associated with prolonged treatment gaps.

Taken together, our data suggest that OFA and OCR treatments demonstrate similar effectiveness in most patients. We observed potential differences in patients switching from S1PRM and NTZ and these findings require further validation in future studies before treatment recommendations should be derived from our analyses.

Nonetheless, our findings underline distinct properties of different CD20 antibodies. Future studies incorporating further substances or formulations such as the recently approved SC formulation of OCR[50] appear warranted. Besides validation of effectiveness in the real-world setting, they also might enhance our understanding of the mechanisms of B-cell depletion in MS.

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Author Contributions

S.G.M. and S.P. contributed to the conception and design of the study. S.G.M., S.W., A.M., A.W., K.K., S.R., M.P., F.F.K., T.S., M.G., T.R., H.B.H., C.K., T.B., R.P., B.A.C., H.P.H., K.M., and S.P. contributed to the acquisition and analysis of data. S.G.M., K.M., and S.P. contributed to drafting the text or preparing the figures.

Potential Conflicts of Interest

Relevant entities are Roche (market authorization holder for ocrelizumab) and Novartis (ofatumumab). S.G.M.: honoraria for lecturing, travel expenses for attending meetings and financial research support from Novartis and Roche. S.W.: honoraria for lecturing and research grants from Novartis. S.R.: research grants from Novartis. M.P.: honoraria for lecturing and travel expenses for attending meetings from Novartis and Roche. F.K.: travel grants from Novartis. T.S.: honoraria for lecturing, travel expenses for attending meetings and financial research support from Novartis and Roche. M.G.: honoraria for

lecturing, travel expenses for attending meetings and financial research support from Novartis and Roche. T.R.: honoraria for lecturing and travel expenses for attending meetings and financial research from Roche. H.B.H.: financial research support from Novartis. C.K.: honoraria for lecturing, travel expenses for attending meetings and financial research support from Novartis and Roche. R.P.: honoraria for lecturing, travel expenses for attending meetings and financial research support from Novartis and Roche. H.P.H.: honoraria for lecturing and travel expenses for attending meetings from Novartis and Roche. B.A.C.: honoraria for lecturing and travel expenses for attending meetings from Novartis. S.P.: honoraria for lecturing, travel expenses for attending meetings and financial research support from Novartis and Roche. The remaining authors have nothing to report.

Data Availability

Anonymized data will be shared on reasonable request from qualified investigators.

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