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Comparative Effectiveness and Safety of Rituximab Versus Ocrelizumab in Relapsing–Remitting Multiple Sclerosis: A Finnish Population-Based Matched Cohort Study

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ABSTRACT

Background: B-cell–depleting anti-CD20 therapies are among the most effective disease-modifying treatments for relapsing–remitting multiple sclerosis (RRMS). Rituximab (RTX) is widely used off-label, while ocrelizumab (OCR) is approved for RRMS; yet comparative real-world evidence between the two remains limited.

Methods: We conducted a retrospective registry-based cohort study using the Finnish MS Registry, including adult RRMS patients treated with RTX or OCR between 2018 and 2024 at two university hospitals. Propensity score matching (1:1) was applied to balance baseline characteristics. Primary outcomes were annualized relapse rate (ARR) during follow-up and relapse-free survival. Secondary outcomes included MRI activity, disability progression, adverse events, and longitudinal plasma immunoglobulin G (IgG) levels.

Results: Of 636 screened patients, 191 met inclusion criteria and 112 patients (56 RTX, 56 OCR) were included after matching. Median follow-up was 3.1 years for RTX and 2.6 years for OCR. ARR was low and similar in both groups (mean 0.03), and relapse-free survival did not differ (log-rank $p = 0.95$; HR 0.95, 95% CI 0.21–4.33). MRI activity remained largely stable, with no significant differences in T2 lesion changes. Adverse events were infrequent and mild. IgG declined modestly in both groups (mean−13%), with values below the reference range in 4.5% of patients and no association with infections. No disease reactivation was observed among patients switching from OCR to RTX.

Conclusions: In this population-based Finnish real-world study, RTX and OCR demonstrated comparable effectiveness and safety in RRMS, supporting RTX as a rational alternative to OCR in routine clinical practice.

1 | Introduction

Multiple sclerosis (MS) is a chronic, immune-mediated disease of the central nervous system, in which both T and B cells contribute to tissue injury. Over the last two decades, converging evidence has underscored the role of B cells in MS pathogenesis and therapy [1]. The remarkable clinical efficacy of B-cell-depleting monoclonal antibodies in reducing relapses and new MRI activity has established B-cell depletion as one of the most potent therapeutic strategies in MS [2]. Currently, intravenous

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formulations include rituximab, ocrelizumab, and ublituximab, while ofatumumab is administered subcutaneously; subcutaneous formulations of ocrelizumab are under clinical investigation [3].

In the randomized, placebo-controlled HERMES trial, a single course of RTX, a chimeric anti-CD20, reduced clinical relapses and MRI activity in relapsing–remitting MS (RRMS) [4]. Subsequent observational cohorts, registry analyses, and a rater-blinded phase 3 randomized controlled trial comparing rituximab with dimethyl fumarate have replicated durable control of inflammatory activity with RTX and suggested potential benefits in progressive phenotypes [5–7]. These findings have been reinforced by the large Scandinavian COMBAT-MS population-based cohort, which demonstrated favorable long-term effectiveness and a consistent benefit–risk balance of RTX compared with other high-efficacy DMTs [8]. OCR, a humanized anti-CD20, is approved for both RRMS and primary progressive MS (PPMS) and has demonstrated robust efficacy in clinical trials [9, 10].

Head-to-head evidence for RTX compared with OCR is heterogeneous and limited. A large international MSBase analysis reported higher relapse activity among RTX-treated patients, with no difference in disability progression [11]. In contrast, two real-world RRMS cohorts outside Europe—an Egyptian propensity-balanced comparison and a Canadian propensity-matched study (non-peer-reviewed)—found no clinically meaningful differences in relapse rate, disability progression or MRI activity between RTX and OCR [12, 13]. For PPMS, a Spanish real-world study did not observe major differences between the two agents [14].

Finland offers a compelling environment for comparative effectiveness studies: MS is diagnosed exclusively in the public sector in Finland. All intravenous DMTs are likewise administered within the public healthcare system, enabling near-complete population-based registry capture of high-efficacy treatments and associated adverse events. During the study period, RTX off-label and OCR have been the two intravenous formulations of anti-CD20 DMTs widely available in Finland based on clinical judgment and hospital committee recommendations. Against this backdrop, we compared the real-world effectiveness and safety of RTX and OCR in RRMS in propensity-score matched cohorts using the Finnish MS Registry.

2 | Methods

2.1 | Study Design and Patient Selection Criteria

We performed a retrospective, registry-based cohort study using data from the Finnish MS Registry. Data were extracted from two university hospital districts: the Hospital District of Helsinki and Uusimaa (HUS) and the Turku University Hospital from the Wellbeing District of Southwest Finland (Varha). Finnish MS registry captures all patients with a diagnosis of MS (ICD-10 G35) in the electronic medical records of these hospital districts and is curated by treating neurologists to capture information on demographics, disease course, relapses, magnetic resonance imaging (MRI) findings, Expanded Disability Status Scale (EDSS) and key laboratory values.

Initially, all adult patients (≥ 18 years at treatment initiation) were identified with a registered diagnosis of multiple sclerosis (ICD-10 code G35) who had received rituximab or ocrelizumab ($n = 636$) between 2018 and 2024.

Patients were excluded if the study treatment had been initiated before 2018, if prior treatment was not restricted to the pre-defined first-line disease-modifying therapies (interferon beta, glatiramer acetate, teriflunomide, dimethyl fumarate, or no prior DMT), if the recorded year of MS diagnosis was before 2010, or if discrepancies were identified in the recorded MS diagnosis date. Patients with insufficient baseline information for cohort classification or without evaluable follow-up were excluded. Patients whose disease course was classified as primary progressive MS (PPMS) or unspecified (UNS) were excluded. There were two patients in the OCR arm with a registry marking of secondary progressive MS (SPMS) at initiation of OCR but in expert neurologist evaluation (M.S. and S.M.L), the disease subtype was evaluated to be RRMS also for these two patients based on radiological activity (new lesions correlating to clinical findings) at the initiation of study DMT. Thus, only patients with RRMS at treatment initiation were included in the study.

After application of these criteria, the study population consisted of 191 patients who had RRMS at treatment initiation. Propensity score matching (1:1) was used thereafter to minimize treatment-selection bias.

Rituximab was administered as an initial total dose of 1000 mg (given as a single infusion or as two 500-mg infusions two weeks apart), followed by maintenance dosing of 500 mg every six months. Ocrelizumab was administered as two 300-mg infusions given two weeks apart, followed by maintenance doses of 600 mg every six months.

2.2 | Clinical Variables Collected

Baseline variables included sex, age at MS onset, age at study DMT initiation, disease duration, time from onset to diagnosis, prior DMT exposure, annualized relapse rate (ARR) before study DMT, EDSS score at baseline, and plasma immunoglobulin G (P-IgG) level. A neurologist (M.S.) performed chart review of all eligible subjects in both centers and confirmed and filled in the missing data.

2.3 | Outcome Measures

Primary effectiveness outcomes were ARR during follow-up and relapse-free survival, estimated with Kaplan–Meier analysis and compared using the log-rank test. Secondary outcomes included qualitative changes in MRI activity, categorized as increased, decreased, or unchanged T2 lesion load, and changes in EDSS where available.

MRI activity was assessed using neuroradiology reports from routine clinical practice recorded in the Finnish MS Registry;

source images were not re-evaluated for this study. The MRI outcome was defined as a qualitative T2 lesion burden trend ("increased", "unchanged", "decreased") as documented in the report. "Increased" was recorded if the report documented ≥1 new or enlarging T2 lesion compared with the preceding MRI scan; pre-treatment MRI was not used as a reference; "unchanged" if no change was reported; and "decreased" if fewer/smaller lesions were reported. To assess on-treatment disease activity, only re-baseline MRI scans and those taken thereafter during follow-up could serve as the reference, whichever was the immediately preceding scan for each MRI examination. Information on gadolinium-enhancing lesions was not systematically available in the registry and was therefore not analyzed.

Safety outcomes included all reported adverse events, hospital-treated infections, neutropenia alone and in context of febrile infections, allergic or infusion reactions, and hypogammaglobulinemia defined as P-IgG below the reference range. P-IgG trends were assessed longitudinally from baseline to last available follow-up.

2.4 | Ethical and Data Governance Approvals

The study was conducted in accordance with Finnish data protection legislation governing secondary use of health data. Permission for data use was granted by Findata (THL/941/14.02.00/2024). As a non-interventional registry-based study, no ethics committee approval or individual patient consent was required under Finnish law. All analyses were performed in the pseudonymized HUS Acamedic secure environment managed by Helsinki University Hospital. This study follows the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) guidelines.

2.5 | Statistical Analysis

Baseline demographic and clinical characteristics were summarized using descriptive statistics. For continuous variables, results are presented as means with standard deviations (SD) or medians with interquartile ranges (IQR), as appropriate. Categorical variables are summarized as counts and percentages based on non-missing observations. The proportion of missing data was also documented. Partial dates in the MS registry data were imputed as middle of the month or year, where applicable.

Propensity scores (PSM) were matched using nearest-neighbor matching with a 1:1 ratio and a caliper of 0.1 SDs controlling adequate pair similarities. Propensity scores were estimated via logistic regression including the following covariates: sex, ARR prior to study DMT initiation, prior DMT exposure (none

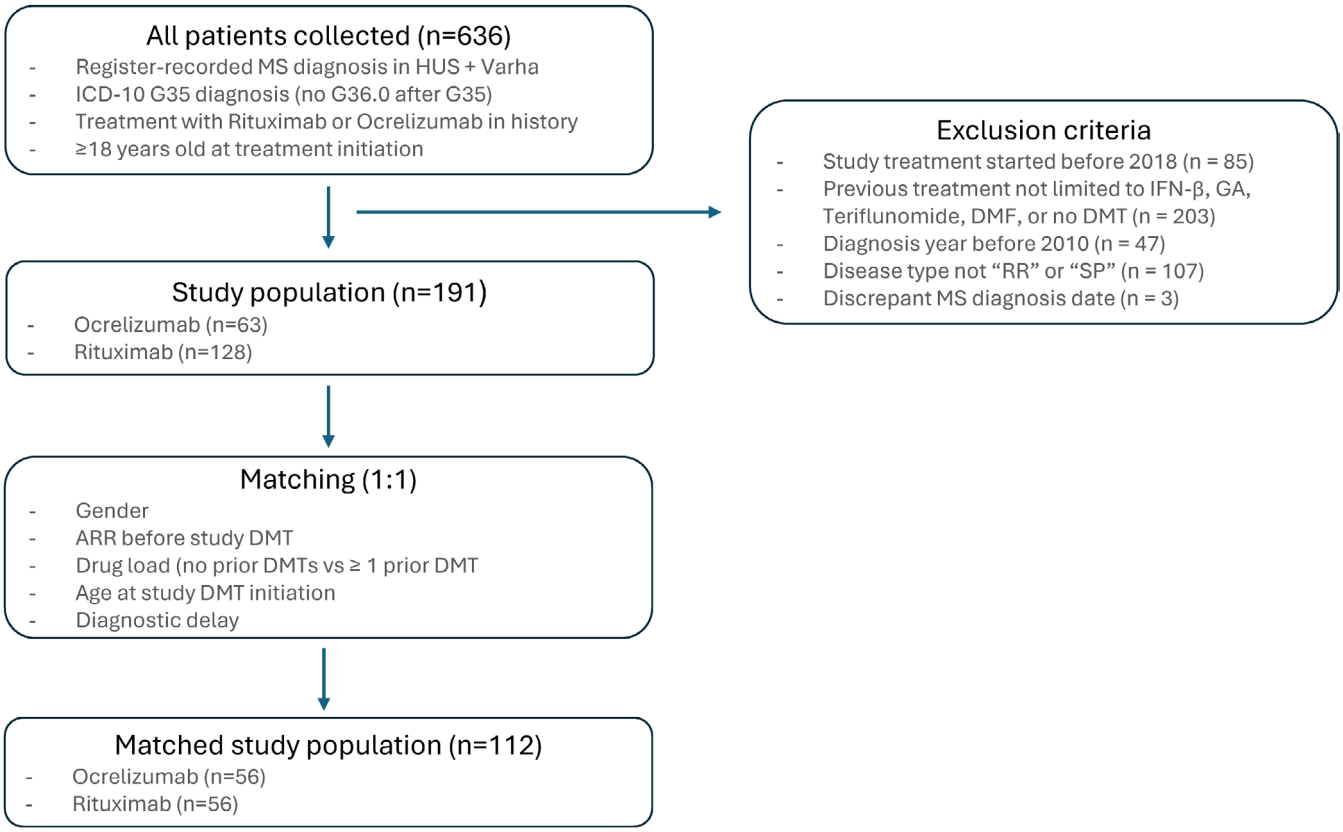

FIGURE 1 | Flowchart illustrating patient selection and matching process. All adult patients with a registry-confirmed MS diagnosis (ICD-10 G35) and treatment history with rituximab or ocrelizumab in the HUS and Varha regions were screened ($n = 636$). After applying exclusion criteria, 191 eligible patients remained (128 rituximab, 63 ocrelizumab). Propensity score matching (1:1) was performed based on gender, annualized relapse rate (ARR) before study treatment, prior DMT exposure, age at study DMT initiation, and diagnostic delay, resulting in a matched cohort of 112 patients (56 per group). ARR = annualized relapse rate; DMT = disease-modifying therapy; RR = relapsing–remitting; SP = secondary progressive; IFN-β = interferon beta; GA = glatiramer acetate; DMF = dimethyl fumarate.

TABLE 1 | Baseline demographics and clinical characteristics after propensity score matching for all patients in the study and divided by the two treatment groups.

	Rituximab ($n = 56$)	Ocrelizumab ($n = 56$)	SMD
Sex, female, *n* (%)	38 (67.9)	38 (67.9)	< 0.001
Age at MS onset, years			< 0.001
Mean (SD)	32.6 (8.05)	32.6 (9.20)	
Median (Q1–Q3)	31.0 (27.5–38.0)	30.0 (27.8–35.5)	
Age at MS diagnosis, years			0.058
Mean (SD)	34.5 (8.70)	35.0 (9.30)	
Median (Q1–Q3)	32.0 (28.0–40.0)	32.5 (29.0–39.2)	
Age at initial DMT start, years			0.034
Mean (SD)	35.2 (8.56)	35.6 (9.28)	
Median (Q1–Q3)	33.0 (28.8–41.0)	33.5 (29.0–40.2)	
Age at study DMT start, years			0.038
Mean (SD)	36.8 (8.76)	37.1 (9.30)	
Median (Q1–Q3)	36.0 (30.0–44.0)	37.5 (30.0–42.2)	
Time since onset to diagnosis, months			0.131
Mean (SD)	23.3 (34.80)	28.4 (43.14)	
Median (Q1–Q3)	7.2 (4.3–35.7)	11.3 (3.0–31.4)	
Time since onset to initial DMT start, months			0.087
Mean (SD)	31.3 (42.06)	35.1 (46.14)	
Median (Q1–Q3)	15.7 (7.1–37.9)	21.9 (5.3–40.4)	
Time since diagnosis to initial DMT start, months			0.066
Mean (SD)	8.0 (24.42)	6.7 (13.00)	
Median (Q1–Q3)	1.8 (1.0–3.2)	2.6 (1.4–5.0)	
Time since diagnosis to study DMT start, months			0.054
Mean (SD)	2.3 (3.30)	2.1 (3.31)	
Median (Q1–Q3)	1.0 (0.0–4.0)	0.0 (0.0–2.2)	
Initial DMT, *n* (%)			
Beta-interferons	6 (10.7)	7 (12.5)	
Dimethyl fumarate	8 (14.3)	5 (8.9)	
Glatiramer acetate	< 5	3 (5.4)	
Ocrelizumab	0 (0.0)	38 (67.9)	
Rituximab	36 (64.3)	0 (0.0)	
Teriflunomide	< 5	3 (5.4)	
DMT before study drug, *n* (%)			
None	36 (64.3)	38 (67.9)	
Beta-interferons	4 (7.1)	< 3	
Dimethyl fumarate	7 (12.5)	10 (17.9)	
Glatiramer acetate	3 (5.4)	< 3	

(Continues)

TABLE 1 | (Continued)

	Rituximab ($n=56$)	Ocrelizumab ($n=56$)	SMD
Teriflunomide	6 (10.7)	6 (10.7)	
DMT after study drug, *n* (%)			
None	53 (94.6)	7 (12.5)	
Cladribine	< 3	3 (5.4)	
Mitoxantrone	0 (0.0)	< 3	
Natalizumab	< 3	< 3	
Ofatumumab	0 (0.0)	< 3	
Rituximab	0 (0.0)	40 (71.4)	
Teriflunomide	0 (0.0)	< 3	
ARR 1 year prior to MS diagnosis			0.025
Mean (SD)	0.9 (0.70)	0.9 (0.71)	
Median (Q1–Q3)	1.0 (0.8–1.0)	1.0 (0.0–1.0)	
ARR 1 year prior to study DMT			< 0.001
Mean (SD)	0.7 (0.69)	0.7 (0.61)	
Median (Q1–Q3)	1.0 (0.0–1.0)	1.0 (0.0–1.0)	
Baseline EDSS			0.543
Mean (SD)	1.9 (1.51)	2.7 (1.35)	
Median (Q1–Q3)	2.0 (1.0–2.2)	2.5 (2.0–3.5)	
Missing, *n* (%)	21 (37.5)	19 (33.9)	
Baseline P-IgG (g/L)			0.251
Mean (SD)	10.7 (2.27)	10.2 (2.00)	
Median (Q1–Q3)	10.7 (9.2–12.0)	10.1 (8.7–11.2)	
Missing, *n* (%)	13 (23.2)	6 (10.7)	
Diagnosis year, *n* (%)			
2010–2015	10 (17.9)	11 (19.6)	
> 2015	46 (82.1)	45 (80.4)	

Note: Propensity score matching was performed 1:1 based on sex, ARR prior to study DMT initiation, prior DMT exposure (none vs. ≥ 1), age at study DMT start, and diagnostic delay. To comply with data protection and anonymization requirements, patient counts below predefined, row-specific thresholds were suppressed and reported as "< 3" or "< 5".
Abbreviations: ARR, annualized relapse rate; DMT, disease-modifying therapy; EDSS, Expanded Disability Status Scale; IgG, immunoglobulin G; SMD, standardized mean difference.

vs. ≥ 1), age at study DMT start, and diagnostic delay. Covariate balance after matching was evaluated using standardized mean differences (SMD), with SMD < 0.2 considered indicative of acceptable balance between groups.

Comparisons between treatment groups were performed using the Student's *t*-test for normally distributed continuous variables and the Wilcoxon rank-sum test for non-normally distributed data. Fisher's exact test was applied to compare categorical variables.

Survival distributions were compared with log-rank test based on Kaplan–Meier analysis. Hazard ratio and its 95% confidence interval (CI) were estimated by Cox proportional hazards model with exact method for ties. Longitudinal changes in plasma immunoglobulin G (P-IgG) concentrations were described graphically, combining individual patient trajectories with group-level mean trends and 95% CIs, providing a repeated-measures visualization of within-patient variation over time.

All analyses and visualizations were performed on pseudonymized data using RStudio (version 2024.12.1 + 563). Two-tailed $p < 0.05$ were considered statistically significant.

Missing data are reported in the tables as counts and percentages of non-missing observations; no imputation was performed for MRI outcomes.

TABLE 2 | Outcome measures during follow-up for the two treatment groups.

	Rituximab ($n=56$)	Ocrelizumab ($n=56$)	p
ARR during follow-up			0.677
Mean (SD)	0.03 (0.12)	0.03 (0.14)	
Median (Q1–Q3)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	
No relapses, *n* (%)	52 (92.9)	53 (94.6)	0.99
MRI T2 lesion trend, *n* (%)			0.829
Same	32 (57.1)	26 (46.4)	
Increased	3 (5.4)	4 (7.1)	
Decreased	0 (0.0)	0 (0.0)	
Missing	21 (37.5)	26 (46.4)	
Follow-up time, years			0.009
Mean (SD)	3.6 (1.74)	2.6 (1.30)	
Median (Q1–Q3)	3.1 (1.9–5.1)	2.6 (1.6–3.4)	

Note: MRI lesion trends were categorized based on radiologist assessment: "same" = no change, "increased" = new or enlarging lesions, "decreased" = fewer or smaller lesions compared with the immediately preceding MRI taken after treatment initiation.
Abbreviations: Q1–Q3, first and third quartiles; ARR, annualized relapse rate; SD, standard deviation.

3 | Results

3.1 | Baseline Matching of the Compared Treatment Groups

A total of 636 registry-confirmed MS patients were screened, and 191 met the inclusion criteria (128 RTX, 63 OCR). After 1:1 propensity score matching, the final cohort comprised 112 patients (56 RTX, 56 OCR; Figure 1). Baseline demographic and clinical characteristics of the matched cohort are shown in Table 1.

Groups were well balanced for age, sex, ARR prior to study treatment, and prior DMT exposure, but EDSS at therapy initiation was higher for the OCR group (mean 1.9 for RTX vs. mean 2.7 for OCR group).

3.2 | Efficacy Analysis

The median follow-up from treatment initiation to the end of observation was 3.1 years (Q1-3 1.9–5.1) in the RTX group and 2.6 years (Q1-3 1.6–3.4) in the OCR group (Table 2). ARR was low and similar between the groups (mean 0.03 for both groups; difference −0.001; 95% CI −0.02 to 0.02). 52 patients in the RTX group (92.9%) and 53 patients in the OCR group (94.6%) did not experience a relapse during the follow-up. Relapse-free survival in time did not differ (log-rank $p=0.95$; HR 0.95, 95% CI 0.21–4.33) (Figure 2).

MRI activity, measured as change in T2 lesion burden, remained low in both groups. T2 lesion burden was unchanged for 32 patients (57.1%) in the RTX group and for 26 patients (46.4%) in the OCR group. T2 lesion burden increased for 3 patients (5.4%) in the RTX group and for 4 patients (7.1%) in the OCR group, while no decrease was observed in either group. These distributions of change did not differ between the groups ($p=0.83$).

3.3 | Safety Analysis

Adverse events were infrequent (Table 3). No serious adverse events or severe infections occurred. Transient IgG reductions and mild respiratory infections were the most common adverse events. Longitudinal trends of IgG decline are shown in Figure 3. IgG declined modestly in both groups (overall mean−13.0%). Values below the reference range occurred in 4.5% of patients (RTX 5.4%; OCR 3.6%) without an association to infection risk. To increase the capture of adverse events, unmatched cohorts (RTX $n=128$, OCR $n=63$) were also compared but no marked differences were seen (Table S1).

3.4 | Switching From OCR to RTX

Among patients who switched from OCR to RTX ($n=40$, 71%), median time to switch was 30 months from OCR initiation (Q1-Q3 17.8–40.8). IgG levels remained stable following the switch (mean change −12%; Table 4). There was no post-switch increase in relapses and MRI activity remained stable.

4 | Discussion

In this retrospective propensity-score matched study, RTX and OCR achieved similar clinical control of RRMS. Relapse-free survival curves were overlapping (log-rank $p=0.95$), follow-up ARR remained low (overall mean 0.03), and MRI activity was largely stable. Plasma IgG declined modestly (mean change −13%) without a clear clinical signal and values below the reference range were uncommon (detected in a total of 4.5% of patients). Adverse events were infrequent in both groups, and no serious adverse events were recorded. To our knowledge, this is the first study to document systematic switch between the two agents, with no evidence of subsequent disease re-activation or increased side effects.

Our results align with prior European real-world cohorts demonstrating low relapse risk with RTX, including large Swedish datasets [15] and Southern Swiss observational experience [16]. Previous head-to-head comparisons are few but our results are consistent with the Egyptian RRMS cohort ($n=126$) [12] and recent Canadian propensity-score matched RRMS study (266 pairs; ARR 0.04 for RTX vs. 0.03 for OCR); available as a conference abstract (not peer-reviewed) [13]. By contrast, the MSBase analysis, also containing data from

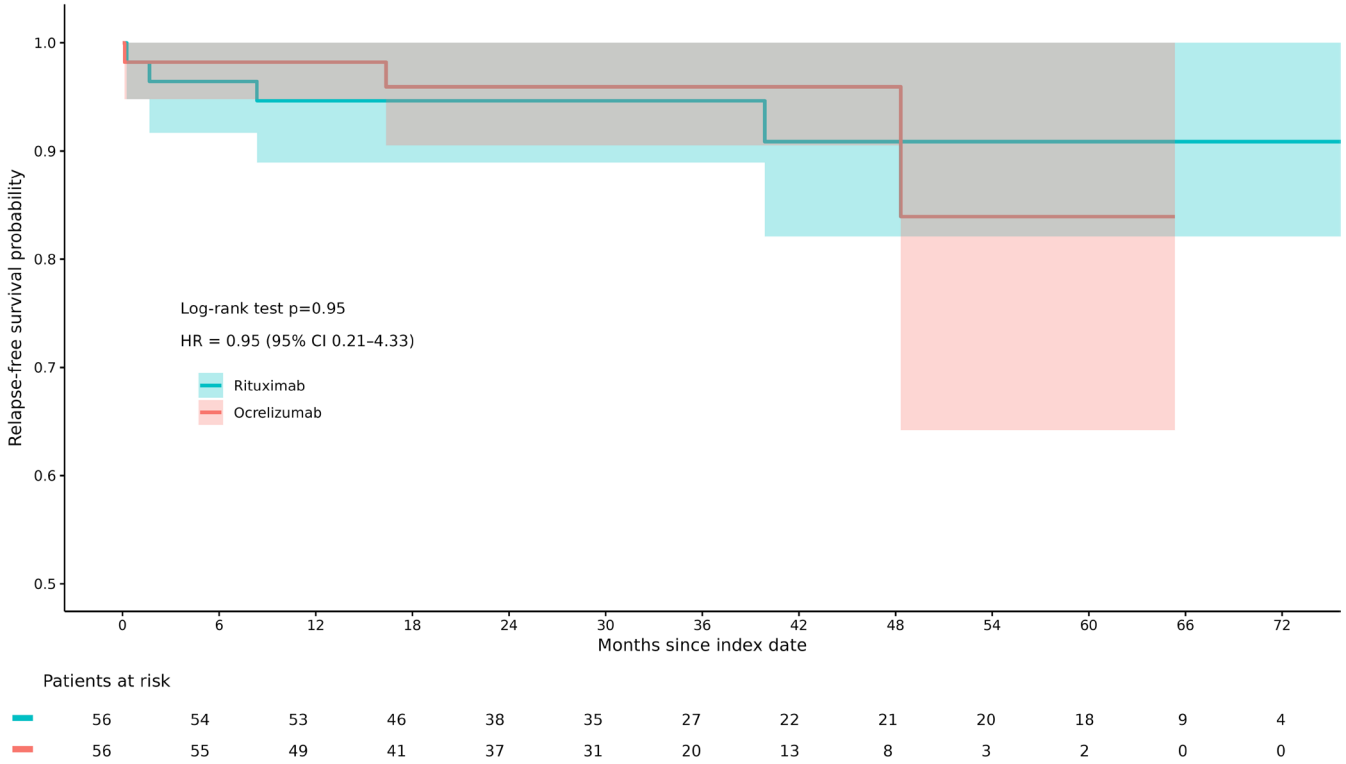

FIGURE 2 | Relapse-free survival in patients treated with rituximab or ocrelizumab. Kaplan–Meier analysis of relapse-free survival in the matched cohort ($n = 112$; 56 per group). The probability of remaining relapse-free was similarly high in both treatment groups throughout the follow-up period, with no significant difference between rituximab and ocrelizumab (log-rank $p = 0.95$). Most relapses occurred early during follow-up, and both treatments maintained stable relapse-free survival rates thereafter. RTX = rituximab; OCR = ocrelizumab. Shaded areas represent 95% confidence intervals.

TABLE 3 | Reported adverse events and decrease in immunoglobulin G in the two treatment groups.

Adverse effect	Rituximab ($n = 56$)	Ocrelizumab ($n = 56$)
Allergic reactions, *n*	< 3	< 3
Eczema	0	< 3
Pruritus	< 3	0
Swelling	0	< 3
Infections, *n*	< 3	4
Gastroenteritis	< 3	0
Influenza	0	< 3
Other respiratory infection	0	3
Neutropenia, *n*	< 3	< 3
Neutropenia	0	< 3
Febrile neutropenia	< 3	0
Decreased IgG, *n**	< 3	< 3
IgG change (%), mean (SD)	−14.2 (11.91)	−11.6 (10.79)
Median (Q1–Q3)	−10.9 (−16.9 – −5.4)	−10.1 (−13.9 to −4.1)
IgG below reference range during follow-up, *n* (%)	3	< 3

*As reported by the treating neurologist as an adverse event in the MS registry. IgG = immunoglobulin G. IgG change (%) refers to the relative change in serum IgG concentration from baseline to the most recent follow-up measurement. IgG value under reference range during follow-up indicates patients whose IgG values fell below the laboratory reference range. No serious adverse events were observed. To comply with data protection and anonymization requirements, patient counts of 1–2 are reported as "< 3".

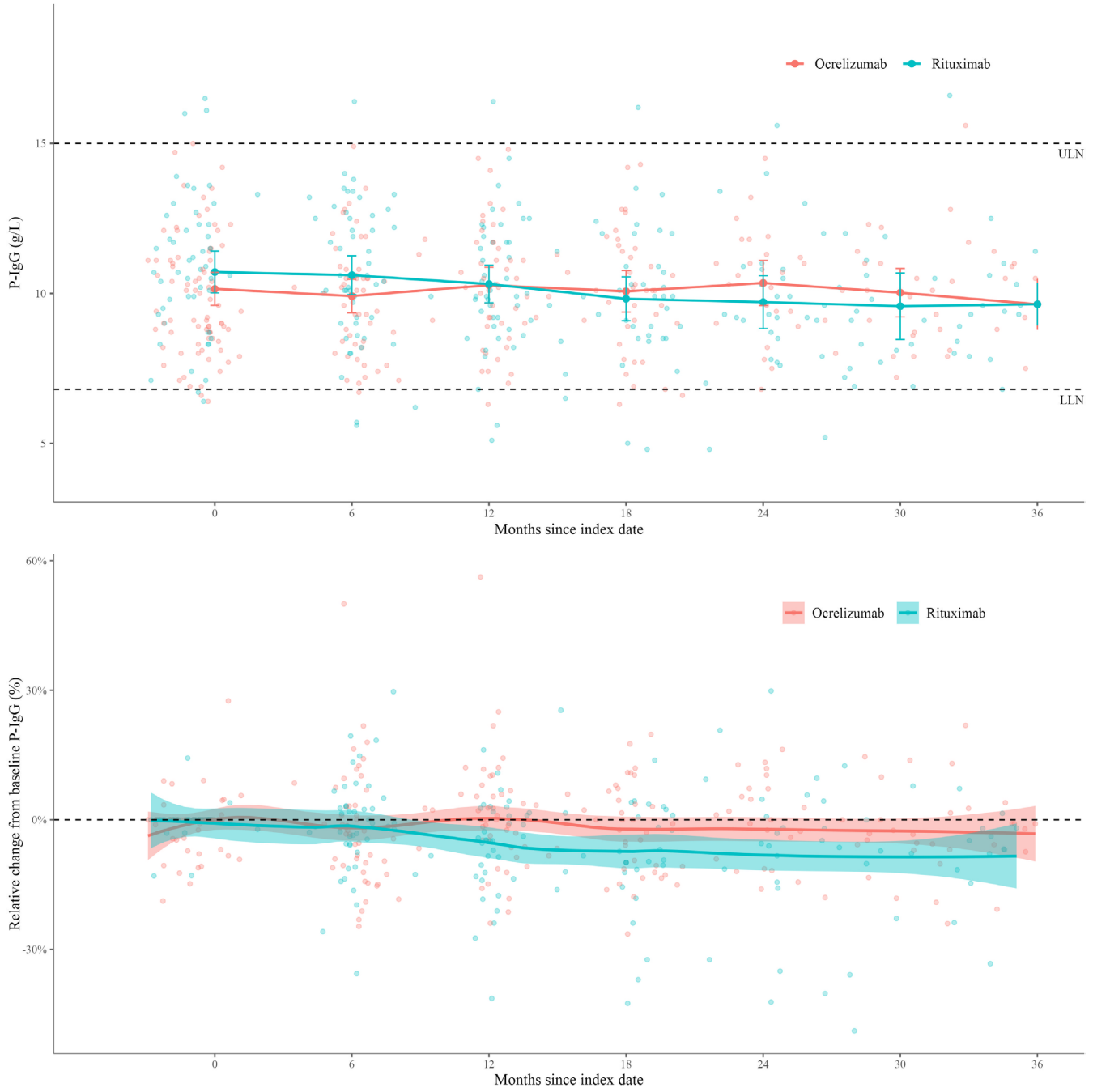

FIGURE 3 | Plasma immunoglobulin G (P-IgG) levels during follow-up in patients treated with rituximab or ocrelizumab. The upper panel shows individual P-IgG measurements (dots) and mean values with 95% confidence intervals across the follow-up period. The dashed lines indicate the upper (ULN) and lower (LLN) limits of the reference range. The lower panel illustrates the relative change from baseline in P-IgG levels over time, with shaded areas representing 95% confidence intervals. Both treatment groups showed a mild, comparable decline in IgG levels, with no significant difference between rituximab and ocrelizumab. P-IgG = plasma immunoglobulin G; ULN = upper limit of normal; LLN = lower limit of normal; OCR = ocrelizumab; RTX = rituximab.

Denmark, observed higher relapse activity among RTX-treated patients [11]. Differences in national recommendations and treatment selection likely contributed: in Denmark, OCR has been the preferred anti-CD20 therapy, whereas RTX has been reserved for exceptional use. Patients receiving RTX in that setting may therefore have differed systematically, for example by comorbid rheumatologic disease, which would likely introduce residual confounding.

In a recent Italian real-world study including 396 RRMS patients, OCR and ofatumumab showed comparable short-term effectiveness and safety (ARR 0.06 vs. 0.04; no evidence of disease activity in 92% vs. 94%, respectively). Mild post-dose reactions were more frequent with ofatumumab, while infection rates were similar. These findings further suggest that the efficacy of anti-CD20 is not dependent on epitope binding site or composition of the antibody [17].

TABLE 4 | Baseline and follow-up characteristics of patients switching from ocrelizumab to rituximab ($n = 40$).

	Ocrelizumab phase	Rituximab phase
Sex – female, *n* (%)	28 (70.0)	—
Age at MS onset, years – mean (SD)	32.6 (9.81)	—
Age at MS diagnosis, years – mean (SD)	35.2 (9.79)	—
Age at initial DMT start, years – mean (SD)	35.8 (9.83)	—
Age at OCR start, years – mean (SD)	37.0 (9.54)	—
Time since onset to diagnosis, months – mean (SD)	30.2 (48.49)	—
Time since onset to initial DMT start, months – mean (SD)	37.2 (51.98)	—
Time since diagnosis to initial DMT start, months – mean (SD)	7.0 (14.78)	—
Time since diagnosis to study DMT start, months – mean (SD)	1.8 (3.15)	—
Time from OCR start to RTX start, months – mean (SD)	30.1 (15.14)	—
ARR 1 year prior to OCR/RTX start – mean (SD)	0.7 (0.60)	0.1 (0.27)
Baseline EDSS – mean (SD)	2.4 (1.38)	2.0 (1.52)
Baseline P-IgG (g/L) – mean (SD)	10.2 (1.90)	10.0 (2.42)
Follow-up time, years – mean (SD)	2.5 (1.27)	1.4 (0.83)
IgG change (%) – mean (SD)	−12.1 (11.61)	−12.0 (9.63)
MRI T2 lesion trend – *n* (%)		
Same	20 (50.0)	5 (12.5)
Increased	3 (7.5)	0 (0.0)
Decreased	0 (0.0)	0 (0.0)
Missing	17 (42.5)	35 (87.5)

Note: T2 lesion trend refers to radiological assessment categorized as same, increased, or decreased compared with the immediately preceding MRI examination during treatment follow-up. Pre-treatment initiation MRI was not used as a reference.
Abbreviations: ARR, annualized relapse rate; DMT, disease-modifying therapy; EDSS, Expanded Disability Status Scale; IgG, immunoglobulin; OCR, ocrelizumab; RTX, rituximab.

Recent large-scale comparative data have provided partly divergent safety signals. A real-world analysis from the University of California Health System found higher all-cause hospitalization and infection-related admission rates, as well as more frequent hypogammaglobulinemia, among RTX-treated patients compared to OCR [18]. These findings suggest that, in some settings, RTX may carry a greater risk of infections linked to lower IgG levels or cumulative exposure. However, the authors noted that healthcare-system factors and patient selection likely contributed to these differences. In our registry-based cohort, adverse events were infrequent and largely mild, and no severe infections occurred despite modest IgG declines. This aligns with prior Scandinavian experience reporting low rates of clinically significant infections on anti-CD20 therapy [19].

Overall, our data suggest that modest IgG reductions are common with both RTX and OCR but rarely translate into clinically relevant hypogammaglobulinemia during medium-term follow-up, highlighting the importance of continued laboratory monitoring to detect individuals at risk during prolonged B-cell depletion. Extended-interval dosing has lately emerged as a strategy to limit cumulative exposure, which may in turn help attenuate IgG decline without compromising efficacy [20]. Differences in infection risk between RTX and OCR observed in pharmacovigilance datasets, where OCR has been associated with more frequently reported infections than RTX, further underscore the need for long-term surveillance of immunoglobulin levels and infectious complications in patients receiving anti-CD20 therapies [21].

Most OCR-initiating patients in our study subsequently switched to RTX (71%) at a median of 30 months. This switch predominantly reflected hospital-level treatment policy decisions, given the emerging evidence on low rate of disease activation during RTX and safety benefits associated with extended-interval dosing investigated using RTX [22, 23]. This phase of treatment change, systematically captured within the Finnish MS Registry, provides a unique real-world perspective on the comparative effectiveness of the two anti-CD20 therapies. No increase in relapses or MRI activity was detected, and no major adverse events were observed after the switch.

Strengths of the present study include population-based capture of intravenous DMTs within the public sector, quality-assured registry data from two university hospitals, and propensity score matching on key confounders. The Finnish MS Registry covers approximately 80% of the national MS population, and the HUS

and Varha districts included here represent nearly half of all Finnish MS cases, ensuring broad geographic and demographic coverage [24].

Limitations of the study merit emphasis. EDSS could not be included in the matching model because of the limited number of complete observations, resulting in residual imbalance. This imbalance raises the possibility that pre-treatment disease activity differed between groups; the higher baseline EDSS in the OCR cohort may reflect more severe relapses prior to treatment initiation. Also, the power to detect rare safety signals was limited in the study, and follow-up was slightly shorter in the OCR group.

Several randomized non-inferiority trials are underway to directly compare RTX and OCR in RRMS, including the OVERLORD-MS and DanNORMS trials, which together with two additional randomized controlled trials (Noisy Rebels and TRIO) form the ROC-MS collaboration. This individual-participant prospective meta-analysis is planned to pool data from 1109 RRMS patients and provide high-quality evidence on potential differences in efficacy and safety by 2028 [25].

5 | Conclusions

In this Finnish real-world population-based study, RTX and OCR demonstrated comparable effectiveness and safety in RRMS. Both therapies achieved low relapse rates and stable IgG profiles, with few adverse events. These findings support RTX as a rational and clinically non-inferior alternative to OCR in routine clinical practice.

Author Contributions

Merja Soilu-Hänninen: conceptualization, methodology, data curation, writing – review and editing, investigation. **Matias Viitala:** methodology, formal analysis, visualization, writing – review and editing. **Henriikka Nurmi:** writing – review and editing, visualization, formal analysis, methodology. **Sini M. Laakso:** conceptualization, investigation, resources, methodology, supervision, project administration, writing – review and editing, visualization. **Maiju Savolainen:** methodology, data curation, investigation, writing – original draft, project administration, visualization, writing – review and editing. **Sari Atula:** conceptualization, methodology, writing – review and editing, investigation. **Pentti Tienari:** writing – review and editing.

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Ethics Statement

Secondary use of health data was authorized by Findata (THL/941/14.02.00/2024). No ethics committee approval or informed consent was required under Finnish law for non-interventional registry research. Data were pseudonymized and analyzed in HUS Acamedic secure environment. The study follows the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) guidelines.

Conflicts of Interest

Maiju Savolainen: support for congress and travel expenses Sanofi, Merck, Novartis. Merja Soilu-Hänninen has served as an adviser or speaker for Argenx, Biogen, Merck, Novartis, Roche, Sanofi, and Teva and received support for congress participation from Biogen, Celgene, Merck, Novartis, and Sanofi. Henriikka Nurmi: reports no disclosures. Matias Viitala reports no disclosures. Pentti Tienari: congress expenses Biogen, Novartis, Merck, Teva; fees for lectures Biogen, Roche, Novartis, Sanofi-Genzyme, Merck, Teva, Orion, Santen, Alexion. Sari Atula: Travel expenses: none. Fees for lectures: Amgen, Argenx, Novartis, UCB Pharma. Advisory boards: Amgen, Roche, Sanofi. Sini M. Laakso: fees for lectures Alexion, Argenx, Janssen, Lundbeck, Merck, Novartis, Sanofi, Teva; congress and travel expenses Merck, Novartis, UCB Pharma; advisory fees Argenx, Johnson & Johnson, Novartis, Sanofi, UCB Pharma.

Data Availability Statement

Due to Finnish data protection regulations and Findata permit conditions, individual-level data used to generate the results cannot be shared.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Table S1:** Adverse events in unmatched cohorts ($n = 191$). Summary of all reported adverse events among rituximab- and ocrelizumab-treated patients prior to matching.