Rituximab versus ocrelizumab in relapsing-remitting multiple sclerosis

Subtitle: A non-inferiority observational study

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Word count: 3138

Date of revision: 13 February 2023

KEY POINTS

Question: Is treatment with rituximab non-inferior to ocrelizumab in preventing relapses and disability in patients with relapsing-remitting multiple sclerosis?

Findings: In this multicentre cohort study of 710 ocrelizumab and 186 rituximab-treated patients with multiple sclerosis, rituximab was not non-inferior to ocrelizumab, and rituximab treatment was associated with a higher rate and risk of relapse. There was no evidence for a difference in disability outcomes.

Meaning: Lack of a clinically relevant difference in the effectiveness between ocrelizumab and rituximab should not be assumed and is being further evaluated in clinical trials.

ABSTRACT

Importance: Ocrelizumab, a humanised monoclonal antibody targeted against CD20+ B cells, reduces the frequency of relapses by 46% and disability worsening by 40% compared to interferon-β 1a in relapsing-remitting multiple sclerosis (MS). Rituximab, a chimeric monoclonal anti-CD20 agent, is often prescribed as an off-label alternative to ocrelizumab.

Objective: To evaluate whether the effectiveness of rituximab is non-inferior to ocrelizumab in relapsing-remitting MS

Design: Observational cohort study conducted between 2015-2021. Patients were included in the treatment group for the duration of study therapy.

Setting: MSBase and Danish MS registry [DMSR]

Participants: Of 6027 patients with MS treated with ocrelizumab or rituximab, 1613 were included. Included patients had relapsing-remitting MS, minimum six-month follow-up, and sufficient data to calculate the propensity score. Patients with comparable baseline characteristics were 1-to-6 matched with propensity score on age, sex, MS duration, disability

(EDSS), prior relapse rate, prior therapy, disease activity (relapses, disability accumulation, or both), MRI lesion burden (missing values imputed), and country.

Exposure: Treatment with ocrelizumab or rituximab after 2015.

Main outcomes and Measures: Non-inferiority comparison of annualised rate of relapses (ARR), with a pre-specified non-inferiority margin of 1.63 rate ratio. Secondary endpoints were relapse and 6-month confirmed disability accumulation in pairwise-censored groups.

Results: 710 ocrelizumab-treated patients (414 MSBase, 296 DMSR) were matched with 186 rituximab-treated patients (110 MSBase, 76 DMSR). The mean age was 41 years, and 68% were female. Over a pairwise censored mean follow-up of 1.4 years, the ARR ratio was higher in rituximab-treated than OCR-treated patients (rate ratio 1.8 [95%CI 1.4-2.4]; ARR 0.20 vs 0.09, $p<0.001$). The cumulative hazard of relapses was higher among patients treated with rituximab than ocrelizumab (HR 2.1 [1.5-3.0]). No difference in the risk of disability accumulation was observed between groups. Results were confirmed in sensitivity analyses.

Conclusion: In this non-inferiority comparative effectiveness observational study, we did not show non-inferiority of treatment with rituximab compared to ocrelizumab. As administered in everyday practice, rituximab was associated with a higher risk of relapses than ocrelizumab. The efficacy of rituximab and ocrelizumab administered at uniform doses and intervals is being further evaluated in randomised non-inferiority clinical trials.

INTRODUCTION

Ocrelizumab (OCR), rituximab (RTX), ofatumumab, and ublituximab are monoclonal antibodies targeting CD20 cell surface proteins. B-cell depletion therapies are highly effective therapies for multiple sclerosis (MS) and have become an important part of the treatment armamentarium.

RTX is widely used in the treatment of haematological malignancies and rheumatological conditions and is listed in the WHO list of essential medicines for those indications.[1] Despite the successful phase II randomised controlled trial of RTX vs placebo in patients with relapsing-remitting MS (RRMS),[2] further clinical development of RTX was deferred in favour of OCR. In the pivotal phase III RRMS trial, OCR reduced the frequency of relapses by 46% and disability progression by 40% compared to interferon-beta, and subsequently became the first licensed B cell therapy for treatment of RRMS.[3] RTX is however frequently used as an off-label alternative to OCR. In June 2017, 53% of Swedish patients who started a DMT were prescribed RTX.[4] Accumulating evidence from observational studies, and a recent randomised controlled trial of RTX vs dimethyl fumarate, support the use of RTX as an effective and well tolerated treatment in patients with RRMS.[5-8] Ofatumumab and ublituximab are newer therapies with comparatively less real-world clinical experience.

Whereas RTX is a chimeric monoclonal antibody, OCR is humanised, with the proposed advantage of less immunogenicity and fewer indirect complement mediated effects.[2, 3] Whether RTX is unacceptably less clinically effective compared to OCR however remains unexplored. Data from large observational registries can be used to guide clinical decision-making by emulating a clinical trial.[9-11] In this study we used data from two MS registries to

147 evaluate the clinical non-inferiority of RTX compared to OCR in the treatment of patients
148 with relapsing-remitting MS.[12, 13]
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150 **METHODS**
151
152 **Setting**
153 The MSBase registry (ID ACTRN12605000455662) was approved by the Melbourne Health
154 Human Research Ethics Committee and local ethics committees in all centers. The study was
155 approved by the Danish Data Protection Agency through the joint notification of the Capital
156 Region of Denmark. In keeping with Danish law, studies consisting solely of registry data do
157 not require approval from The National Committee on Health Research Ethics. Written
158 informed consent was obtained from all included patients. STROBE reporting guidelines
159 were followed.
160
161 **Participants**
162 Patient data were obtained from two MS registries: MSBase, the largest international MS
163 registry,[14] and the nationwide population-based Danish Multiple Sclerosis Registry
164 (DMSR)[15]. Patients with relapsing-remitting MS (RRMS) who were treated with either OCR
165 or RTX for >= 6 months after 2015 were included in the study. Included patients required 6-
166 month pre-treatment follow up, a baseline visit 6 months before to 1 month after treatment
167 start, and two follow up visits at least 6 months apart. The baseline visit could not occur
168 within 30 days of the last relapse. Patients previously included in a randomised controlled
169 trial, previously treated with stem cell therapy or alemtuzumab, or treated with mitoxantrone
170 in the preceding 3 years, were excluded from the analysis.
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Procedures

Baseline was defined as the first date of OCR or RTX treatment after 2015. OCR was intravenously administered as two doses of 300mg 14 days apart, followed by 600mg 6monthly, as per previously reported trial protocols.[3] In most patients, RTX was intravenously administered as two doses of 1000mg 14 days apart, followed by 500-1000mg 6 monthly. Treatment protocols were at the discretion of each treating centre. RTX originator and biosimilar products were merged into one RTX group. Patients treated with the comparator therapy before 2015 were excluded (i.e., patients in the OCR treatment group who previously received RTX). Patients treated with a single course of OCR or RTX were presumed to be treated for 6 months. Consecutive OCR and RTX treatment entries were merged into a continuous entry, given there was no intervening therapy, and the gap between entries did not exceed 1 year. Patients were included in the treatment group for the duration of study therapy or until the last visit (whichever occurred first).

Data were recorded as part of routine clinical practice, mostly in large tertiary MS centres. Data were entered into the MSBase data entry system or into COMPOS® (DMSR). All participating centres required Neurostatus certification. MRI information was included as reported by local radiologists based on local MRI protocols and reporting standards. A brain MRI performed within 12 months prior, and 1 month after, treatment initiation was considered the baseline MRI. Missing MRI data were handled through multiple imputation. Rigorous data quality assurance procedures were applied (eTable 1).[16]

Study Outcomes

The primary study endpoint was a non-inferiority comparison of annualised relapse rate (ARR). Secondary endpoints were cumulative hazards of relapse and 6-month confirmed

disability accumulation and improvement outcomes in pairwise-censored groups, and cumulative hazard of treatment discontinuation. Secondary endpoints were assessed for superiority.

Relapses were defined as new symptoms, or exacerbation of existing symptoms, for at least 24 hours in the absence of a concurrent illness or fever, and occurring >=30 days after the previous relapse.[17] Relapses were analysed as recorded by the treating physician, and did not require confirmation with a change in disability score. Disability accumulation was defined as an increase in Expanded Disability Status Scale (EDSS) by ≥1 step (1.5 step if EDSS 0, or 0.5 step if EDSS>5.5), confirmed over at least 6 months (in the absence of a relapse in the preceding 30 days), and sustained until the end of follow up. Disability improvement was defined as a decrease in EDSS by ≥1 step (1.5 steps if EDSS 1.5, or 0.5 step if EDSS>6) confirmed over at least 6 months.[18] Treatment discontinuation, and the reasons for treatment discontinuation (where available), were described as recorded by the treating clinician.

Statistical analysis

Propensity scores were calculated for each individual patient using a logistic regression model based on the following baseline variables: age, sex, MS duration (from MS onset), EDSS score, number of relapses in the previous 12 months, number of previous therapies, disease activity in the prior 12 months (relapse, disability accumulation, both or neither), MRI lesion burden (categorised as 1-2, 3-8 or >=9 lesions), presence/absence of contrast enhancing lesions on cerebral MRI at baseline, and country.[19]

If baseline MRI data were not available, multiple imputation with an expectation maximisation with bootstrapping algorithm was used to impute missing values.[20, 21] Multiple

imputation was based on patient ID, treatment group, age, MS duration, baseline EDSS, prebaseline disease activity, prebaseline therapy, and time since prebaseline therapy.

Patients were matched, without replacement, in a 6:1 variable ratio using nearest neighbour matching and a calliper of 0.1 standard deviations of the propensity score.[22] Covariate balance was assessed using standardised mean differences. Subsequent analyses were performed in paired models, weighted for matching ratio. Attrition bias was controlled by pairwise censoring in all analyses (i.e., on-treatment follow up was the shorter follow up within each patient pair), except for analysis of treatment persistence.

ARRs were calculated using a marginal weighted negative binomial model with cluster term per patient pair. Cumulative hazard of relapses and disability outcomes were analysed with weighted conditional proportional hazards models for recurrent events. Disability models were adjusted for visit density. The cumulative hazard of discontinuing therapy was assessed using weighted conditional proportional hazards models without pairwise censoring. The proportionality assumption was evaluated using Schoenfeld's global test. Time to event data were visualised using Kaplan-Meier plots. The minimum magnitude of unmeasured confounders required to change the conclusion of the analysis was calculated using Rosenbaum sensitivity test for Hodges-Lehmann Γ.[23]

The non-inferiority margin was identified based on the known efficacy of OCR, and as the smallest difference in effectiveness between OCR and RTX which was felt to be clinically relevant: 1 relapse every 10 patient-years.[24] This is in keeping with two presently ongoing trials of OCR vs RTX, which set their non-inferiority margins at 1 new/enlarging/enhancing cerebral lesion every 10 patient-years.[25, 26] The ARR of the OCR group in the Phase III pivotal trial of OCR vs interferon-beta was 0.16.[3] If the ARR in the trial comparator group

exceeded the OCR group by 1 relapse every 10 patient-years, this would equate to an absolute ARR of 0.16 vs 0.26. Therefore, the non-inferiority margin for the relative ARR ratio of OCR vs RTX was set as 1.63. Non-inferiority would be established if the upper bounds of the two-sided 95% confidence interval (95%CI) of ARR ratio did not exceed this pre-defined non-inferiority margin. A two-sided alpha of 0.05 was used for superiority testing of all secondary endpoints.

Five sensitivity analyses were performed: Using data from(i) DMSR only, (ii) MSBase only, (iii) applying an 'intention to treat' approach, where all subsequent events were analysed irrespective of changes in treatment status (to eliminate the potential effect of informative censoring), (iv) excluding the MRI variables from the estimation of the propensity score (to eliminate the effects of multiple imputation); (v) only including patients who started a study therapy after 2016, when both therapies were more widely available than in 2015 (to explore potential contribution of the positivity assumption); (vi) only including patients where the dose and frequency of study therapy was recorded, and patients received at least OCR 600mg 6-monthly or RTX 1g 6-monthly (to minimise the contribution of variable dosing practices).

RESULTS

Of 6027 patients (4128 MSBase, 1899 DMSR) with MS treated with either RTX or OCR, 1613 patients (898 MSBase, 715 DMSR) fulfilled the inclusion criteria and were included in the analysis (Fig 1). Patient disposition per contributing centre, and demographic features of patients treated with a study therapy who were excluded from the analysis are shown in eTables 2 and 3. The positivity assumption was not violated (eTable 4).

The probability of being treated with RTX vs OCR was calculated using a logistic regression model (eTable 5). RTX treated patients tended to have higher disability scores, more relapses and MRI activity in the prior 12 months, and received more prior MS therapies than patients treated with OCR. Table 1 shows patient characteristics before and after propensity score matching. 710 OCR-treated patients (414 MSBase, 296 DMSR) were matched with 186 RTX-treated patients (110 MSBase, 76 DMSR). Propensity score matching resulted in a 71% improvement in balance between the matched groups (eTable 6), with a standardised mean difference of 0.10 or less achieved for all variables. Clinocodempgraphic details of patients who were not propensity score matched resemble the included cohort before matching (eTable 7).

Effectiveness

The mean ARR was higher in patients treated with RTX than OCR (ARR 0.20 vs 0.09, $p<0.001$, Figure 2A). Similarly, the ARR ratio was higher in RTX- than OCR-treated patients (ARR ratio 1.8, 95%CI 1.4-2.4, Figure 2B). Both the estimate of the effect size, and the upper bounds of the 95%CI were higher than the pre-determined non-inferiority margin of 1.63. The difference was resistant to unmeasured confounders to a magnitude of 40% of the reported treatment effect. The cumulative hazard of relapses was higher in RTX-treated patients (HR 2.1, 95%CI 1.5-3.0, Figure 2C). No evidence of difference in disability accumulation (HR 1.51, 95%CI 0.86-2.64) or disability improvement (HR 0.80, 95%CI 0.49-1.31) was observed between study therapies over a mean 1.4 year pairwise-censored follow up (Figure 3).

Persistence

Patients were more likely to discontinue RTX than OCR (HR 3.11, 95%CI 2.36-4.11, Figure 4). While recording the reason for treatment discontinuation does not form part of the minimum dataset, data were available in 66% of OCR and 49% of RTX discontinuations (eTable 8). The most common reasons for RTX discontinuation were patient/clinician decision (33%) and other/unknown reasons (48%). 69% of patients who discontinued RTX were subsequently treated with OCR. It is therefore likely that many of these switches were prompted by the availability and regulatory approval of OCR. Very few patients discontinued OCR or RTX due to lack of tolerance (16 and 9 patients respectively). The available adverse event data were insufficient to allow comparison between therapies.

Sensitivity analyses

Further sensitivity analysis using (1) an 'intention to treat' approach, (2) excluding MRI variables from the estimation of the propensity score, (3) only including patients who commenced study therapy after 2016, (4) using data from MSBase only, and (5) only including patients who received at least OCR 600mg 6-monthly or RTX 1g 6-monthly (eTable 9), showed results consistent with the primary analysis. A sensitivity analysis using data from the DMSR only was inconclusive (ARR ratio 1.41, 95%CI 0.99-2.01), likely due to insufficient power.

DISCUSSION

Whether RTX is non-inferior to OCR is a clinically relevant question. While both therapies have similar mechanisms of action, the significantly lower cost of RTX may motivate its preferential use despite 'off-label' status. Whether these two therapies are interchangeable however remains an ongoing topic of debate.[27, 28] In this comparative effectiveness study

from the international MSBase and nationwide population-based Danish MS registries, we evaluated the noninferiority of treatment with RTX compared to OCR in patients with RRMS.

The effect of RTX on relapses was inferior to OCR with an ARR of 0.20 vs 0.09, translating into a difference of 1 relapse every 9 patient-years. The study did not find evidence for a difference in the probability of disability accumulation or improvement. Treatment discontinuation was more common in RTX-treated patients, for which OCR was the most frequent subsequent therapy.

Although the study was designed to assess non-inferiority of RTX compared to OCR, our findings demonstrated that patients treated with RTX experienced more relapses. To meet the pre-defined definition of non-inferiority, the upper bound of the 95%CI of the ARR must not exceed 1.63. The ARR ratio was calculated as 1.8, with a two-sided 95% CI of 1.4-2.4. Therefore, based on recommendations on the interpretation of non-inferiority studies [29, 30], our results suggest the inferiority of RTX over OCR on relapses. While it is still plausible that the true relative difference in ARR is less than the non-inferiority margin, relapse frequency was significantly higher when treated with RTX than with OCR. The magnitude of this difference exceeded the predefined clinically meaningful difference between the compared therapies. The probability that the frequency of relapses in RTX-treated patients exceeded that of OCR by more than 1 relapse every 10 patient-years was 80%.

The respective effects of OCR and RTX in RRMS have previously been studied in two randomised trials. In the HERMES phase II RTX trial, patients were treated with two doses of RTX 1g on days 1 and 14.[2] At week 24, the ARR in RTX-treated patients was 0.4 (95% CI 0.23-0.60). In the phase II OCR trial, patients were treated with OCR on days 1 and 15

(300mg per day), and at week 24 (600mg).[31] At week 24, the ARR in patients treated with 600mg OCR was 0.13 (95% CI 0.03-0.29). Although direct comparison of outcomes between these two studies should be avoided due to differences between the cohorts and the definition of relapse (objective worsening of neurological disability was required in the OCR trial), these findings suggest that the rate of relapse is higher in patients treated with RTX compared to OCR. Similarly, in our study using patients with comparable baseline characteristics and uniform definitions, we report higher rates of relapse in patients treated with RTX than OCR.

A head-to-head comparison of RTX vs OCR has not previously been performed, apart from an analysis in primary progressive MS, which did not account for baseline group differences.[32] Observational data have, however, been used to explore the effectiveness of both RTX and OCR in comparison with other disease modifying therapies. In two analyses from Sweden, patients treated with injectable therapies (interferon-beta and glatiramer acetate) had significantly higher risk of relapse than RTX-treated patients.[6, 7] After propensity score adjustment, there was no evidence of a difference in ARR between RTX-treated patients and patients receiving dimethyl fumarate, fingolimod, or natalizumab.[7] A study from the MSBase registry reported superior control of relapses under OCR compared to interferon-beta and fingolimod, but no evidence of a difference compared to natalizumab.[33] These findings may indirectly indicate a potential difference in effectiveness between OCR and RTX. Potential biological differences between OCR- and RTX-treated patients have been described, with more pronounced T-cell reduction in patients treated with OCR.[34] The clinical relevance of these findings remain uncertain. The present study is the first non-inferiority direct comparison of OCR and RTX, using rigorous methodology to mitigate group differences that allows direct comparison between therapies. Two randomised controlled trials exploring the non-inferiority of RTX vs OCR are presently under recruitment

in Norway and Denmark, with expected completion of recruitment in late 2022 and May 2023 respectively.[25, 26] Both trials are designed to primarily assess radiological outcomes, with a pre-specified non-inferiority margin of 1 new/enlarging/enhancing cerebral lesion every 10 patient-years.

While our large cohort from two non-overlapping MS registries provides this study with power, the observational nature of the data is the main limitation. Observational data are vulnerable to multiple forms of bias.[35] Rigorous attention has been paid to data quality, using an operationalised data quality process.[16] Propensity score matching was performed to control indication bias, with pairwise censoring to mitigate attrition bias. Additionally, our findings were confirmed in sensitivity analyses that address potential informative censoring, and the effects of the positivity assumption. Whereas OCR is a single commercial product, the RTX group contains both the originator and biosimilar products. Differential treatment effects can therefore not be excluded. As RTX is used off label, there is also potential variability in dosing and administration schedules. While it is possible that our findings may not be generalisable to all treatment schedules, the findings remained consistent in a sensitivity analysis only including patients who received RTX at a dose of at least 1g 6-monthly or OCR at 600mg 6-monthly. Our results should however be interpreted as the effectiveness of OCR and RTX as prescribed in routine practice, and not as the efficacy of these therapies under strictly controlled trial conditions. Our analyses were performed in propensity score-matched groups with a moderate degree of disability, mean MS duration of 11 years and previous treatment with 2-3 MS therapies. These findings may therefore not be generalisable to newly diagnosed patients, or patients who are commencing OCR or RTX as their first MS therapy. Our conclusions are based on a mean on-treatment follow up of 1.4 years, which is insufficient for the assessment of long-term outcomes such as disability.

Partial availability of MRI data, lack of biological data (such as CD19+ B cell counts) and adverse effects preclude the evaluation of these outcomes.[25, 26]

In this non-inferiority study, we did not show non-inferiority of treatment with RTX compared to OCR in routine clinical practice. In fact, relapse rate in patients treated with RTX was higher than in OCR. Treatment selection for the individual patient, however, remains a complex and highly personalised decision, which considers additional factors such as availability and affordability of therapy, and adverse effects. Nevertheless, lack of a clinically relevant difference in the effectiveness between these two therapies should not be assumed. The efficacy of RTX compared to OCR is being further explored in two randomised non-inferiority clinical trials.[25, 26]

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FIGURE LEGENDS

Figure 1:

Patients previously treated with the comparator therapy were treated with OCR or RTX after 2015, but had previously received the comparator therapy. Patients excluded due to insufficient on-treatment follow up did not have a baseline visit (with EDSS recorded) within a calliper of 180 days before or 30 days after commencement of therapy or had fewer than 2 post-baseline visits more than 6 months apart. Of patients with progressive MS, 393 had secondary progressive MS and 225 had primary progressive MS.

RTX – rituximab; OCR – ocrelizumab

Figure 2:

Comparison of relapse outcomes for rituximab vs ocrelizumab. (A) Annualised relapse rate (mean plus 95% confidence interval), (B) Annualised relapse rate ratio (mean plus 95% confidence interval) with non-inferiority margin indicated by the dashed line, (C) Cumulative hazard of relapses

Figure 3:

Comparison of disability outcomes for rituximab vs ocrelizumab. (A) Cumulative hazard of disability accumulation, (B) Cumulative hazard of disability improvement

Figure 4:

Persistence on study therapy

TABLES

Table 1: Clinicodemographic characteristics before and after propensity score matching

	Before Matching			After Matching		
	OCR	**RTX**	**d**	**OCR**	**RTX**	**d**
Patients, n (% female)	1354 (67)	259 (69)	0.03	710 (68)	186 (68)	0.002
Registry, n (%)						
MSBase	716 (53)	182 (70)		414 (58)	110 (59)	
DMSR	638 (47)	77 (30)		296 (42)	76 (41)	
Age, y, mean (SD)	42.2 (10.9)	40.8 (10.7)	0.14	41.3 (10.5)	41.8 (10.7)	0.05
Disease duration, y, mean (SD)	11.3 (8.0)	11.5 (8.0)	0.03	11.3 (7.9)	11.7 (8.3)	0.06
Disability, EDSS step, mean (SD)	3.0 (1.8)	3.5 (1.9)	0.25	3.4 (1.8)	3.5 (1.8)	0.02
No of relapses in 12 mo before baseline, mean (SD)	0.5 (0.7)	0.7 (1.0)	0.18	0.7 (0.9)	0.7 (0.9)	0.01
Recent disease activity, n (%)						
none	625 (46)	99 (38)		265 (37)	71 (38)	
progression	171 (12)	43 (16)		125 (18)	31 (17)	
relapse	350 (25)	75 (29)		201 (28)	53 (29)	
relapse and progression	208 (15)	42 (16)		119 (17)	31 (17)	
MRI Brain: T2 lesion, n (%)						
Imaging available at baseline	562 (42)	99 (38)		276 (38)	83 (44)	
1-2	18 (3)[a]	12 (12)[a]		22 (8)[a]	5 (6)[a]	
3-8	39 (7)[a]	8 (8)[a]		16 (6)[a]	8 (10)[a]	
9+	505 (89)[a]	79 (80)[a]		238 (86)[a]	70 (84)[a]	
MRI Brain: new or contrast enhancing lesions, n (%)						
Imaging available at baseline	950 (70)	173 (67)		473 (67)	124 (67)	
Absent	565 (59)[a]	117 (68)[a]		309 (65)[a]	82 (66)[a]	
Present	385 (41)[a]	56 (32)[a]		154 (35)[a]	42 (34)[a]	
Number of previous DMTs, median [quartiles]	2.0 [1.0, 3.0]	2.0 [2.0, 3.0]	0.20	2.0 [1.0, 4.0]	3.0 [2.0, 4.0]	0.001
Pre-baseline follow up, years, median [quartiles]	6.9 [1.2, 11.1]	6.0 [2.3, 10.5]	0.18	5.9 [2.6, 10.3]	5.0 [2.7, 9.7]	0.14
Pre-baseline proportion of time on treatment, years, median [quartiles]	0.6 [0.3, 0.8]	0.6 [0.4, 0.8]	0.10	0.6 [0.4, 0.8]	0.6 [0.3, 0.8]	0.08
Post-baseline follow-up, y, mean (SD)	2.0 (0.8)	2.2 (1.3)	0.18	1.4 (0.7) [b]	1.4 (0.7) [b]	0.00
Visit interval, months, mean (SD)	5.2 (2.3)	3.6 (2.5)	0.45	6.1 (2.6)	5.7 (3.7)	0.10

[a] Proportion of patients with available MRI

[b] Follow-up and persistence after pairwise censoring, as per the primary analysis

ACKNOWLEDGEMENTS

We thank the patients who have agreed to participate in the global MSBase cohort study and Danish MS Registry. The list of MSBase Study Group coinvestigators and contributors is given in the online supplement.

CONFLICTS OF INTEREST

Izanne Roos served on scientific advisory boards, received conference travel support and/or speaker honoraria from Roche, Novartis, Merck and Biogen. Izanne Roos is supported by MS Australia and the Trish Multiple Sclerosis Research Foundation.

Stella Hughes has received unrestricted educational grants or speaking honoraria from Biogen, Merck Serono, Novartis, Roche and Sanofi Genzyme.

Gavin McDonnell did not declare any competing interests.

Charles Malpas has received conference travel support from Merck, Novartis, and Biogen. He has received research support from the National Health and Medical Research Council, Multiple Sclerosis Research Australia, The University of Melbourne, The Royal Melbourne Hospital Neuroscience Foundation, and Dementia Australia.

Sifat Sharmin did not declare any competing interests.

Cavit Boz received conference travel support from Biogen, Novartis, Bayer-Schering, Merck and Teva; has participated in clinical trials by Sanofi Aventis, Roche and Novartis.

Raed Alroughani received honoraria as a speaker and for serving on scientific advisory boards from Bayer, Biogen, GSK, Merck, Novartis, Roche and Sanofi-Genzyme.

Serkan Ozakbas did not declare any competing interests.

Katherine Buzzard received honoraria and consulting fees from Biogen, Teva, Novartis, Genzyme-Sanofi, Roche, Merck, CSL and Grifols.

Olga Skibina has received honoraria and consulting fees from Bayer Schering , Novartis, Merck, Biogen and Genzyme companies.

Anneke van der Walt served on advisory boards and receives unrestricted research grants from Novartis, Biogen, Merck and Roche She has received speaker's honoraria and travel support from Novartis, Roche, and Merck. She receives grant support from the National Health and Medical Research Council of Australia and MS Research Australia.

Helmut Butzkueven received institutional (Monash University) funding from Biogen, F. Hoffmann-La Roche Ltd, Merck, Alexion, CSL, and Novartis; has carried out contracted research for Novartis, Merck, F. Hoffmann-La Roche Ltd and Biogen; has taken part in speakers' bureaus for Biogen, Genzyme, UCB, Novartis, F. Hoffmann-La Roche Ltd and Merck; has received personal compensation from Oxford Health Policy Forum for the Brain Health Steering Committee.

Jeannette Lechner-Scott travel compensation from Novartis, Biogen, Roche and Merck. Her institution receives the honoraria for talks and advisory board commitment as well as research grants from Biogen, Merck, Roche, TEVA and Novartis.

Jens Kuhle did not declare any competing interests.

Murat Terzi received travel grants from Novartis, Bayer-Schering, Merck and Teva; has participated in clinical trials by Sanofi Aventis, Roche and Novartis.

Guy Laureys received travel and/or consultancy compensation and/or research grants from Sanofi-Genzyme, Roche, Teva, Merck, Novartis, Celgene, Biogen, Bristol Myers Squibb.

Liesbeth Van Hijfte did not declare any competing interests.

Nevin Johnis a local principal investigator on commercial studies funded by Novartis, Biogen, Amicus and Sanofi.

595 Pierre Grammond has served in advisory boards for Novartis, EMD Serono, Roche, Biogen
596 idec, Sanofi Genzyme, Pendopharm and has received grant support from Genzyme and
597 Roche, has received research grants for his institution from Biogen idec, Sanofi Genzyme,
598 EMD Serono.
599 Francois Grand'Maison received honoraria or research funding from Biogen, Genzyme,
600 Novartis, Teva Neurosciences, and ATARA Pharmaceuticals.
601 Aysun Soysal did not declare any competing interests.
602 Ana Isabel Figueira Jensen,
603 Peter Vestergaard Rasmussen has served on scientific advisory boards for, served as
604 consultant for, received support for congress participation or received speaker honoraria from
605 Alexion, Biogen, Bristol Myers Squibb, Merck, Novartis, Roche and Sanofi Genzyme.
606 Kristina Bacher Svendsen did not declare any competing interests.
607 Ismael Barzinji did not declare any competing interests.
608 Helle Hvilsted Nielsen did not declare any competing interests.
609 Tobias Sejbæk did not declare any competing interests.
610 Sivagini Prakash did not declare any competing interests.
611 Morten Leif Munding Stilund has served on scientific advisory boards for Sanofi, received
612 support for congress participation or received speaker honoraria fromBiogen, Teva, Merck,
613 Roche and Sanofi. M. Stilund has received grants for his research from Novartis, and is
614 currently engaged in sponsor-initiated research projects by Bayer, Jansen, Shionogi and
615 Sanofi.
616 Arkadiusz Weglewski served on scientific advisory boards for Merck and Roche, received
617 conference travel support from Biogen, Merck, Roche and Sanofi and speaker honoraria from
618 Roche, Merck and Sanofi.
619 Nadia Mubder Issa did not declare any competing interests.

Matthias Kant did not declare any competing interests.

Finn Sellebjerg has served on scientific advisory boards, been on the steering committees of clinical trials, served as a consultant, received support for congress participation, received speaker honoraria, or received research support for his laboratory from Biogen, Merck, Novartis, Roche, Sanofi Genzyme and Teva.

Orla Gray received honoraria as consultant on scientific advisory boards for Genzyme, Biogen, Merck, Roche and Novartis; has received travel grants from Biogen, Merck, Roche and Novartis; has participated in clinical trials by Biogen and Merck; has received research grant support from Biogen.

Melinda Magyari has served on scientific advisory boards for Abbvie, Biogen, Merck, Novartis, Roche, Sanofi and Teva, has received honoraria for lecturing from Biogen, Genzyme, Merck, Novartis and Sanofi, support for congress participation from Biogen, Genzyme, Roche and Teva, and research grants from Merck, Novartis and Sanofi.

Tomas Kalincik served on scientific advisory boards for MS International Federation and World Health Organisation, BMS, Roche, Sanofi Genzyme, Novartis, Merck and Biogen, steering committee for Brain Atrophy Initiative by Sanofi Genzyme, received conference travel support and/or speaker honoraria from WebMD Global, Novartis, Biogen, Sanofi-Genzyme, Teva, BioCSL and Merck and received research or educational event support from Biogen, Novartis, Genzyme, Roche, Celgene and Merck.

FUNDING

This study was supported by the NHMRC [1140766, 1129189, 1157717]. IR is supported by a MS Australia postdoctoral fellowship grant. The MSBase Foundation is a not-for-profit organization that receives support from Biogen, Novartis, Merck, Roche, Teva and

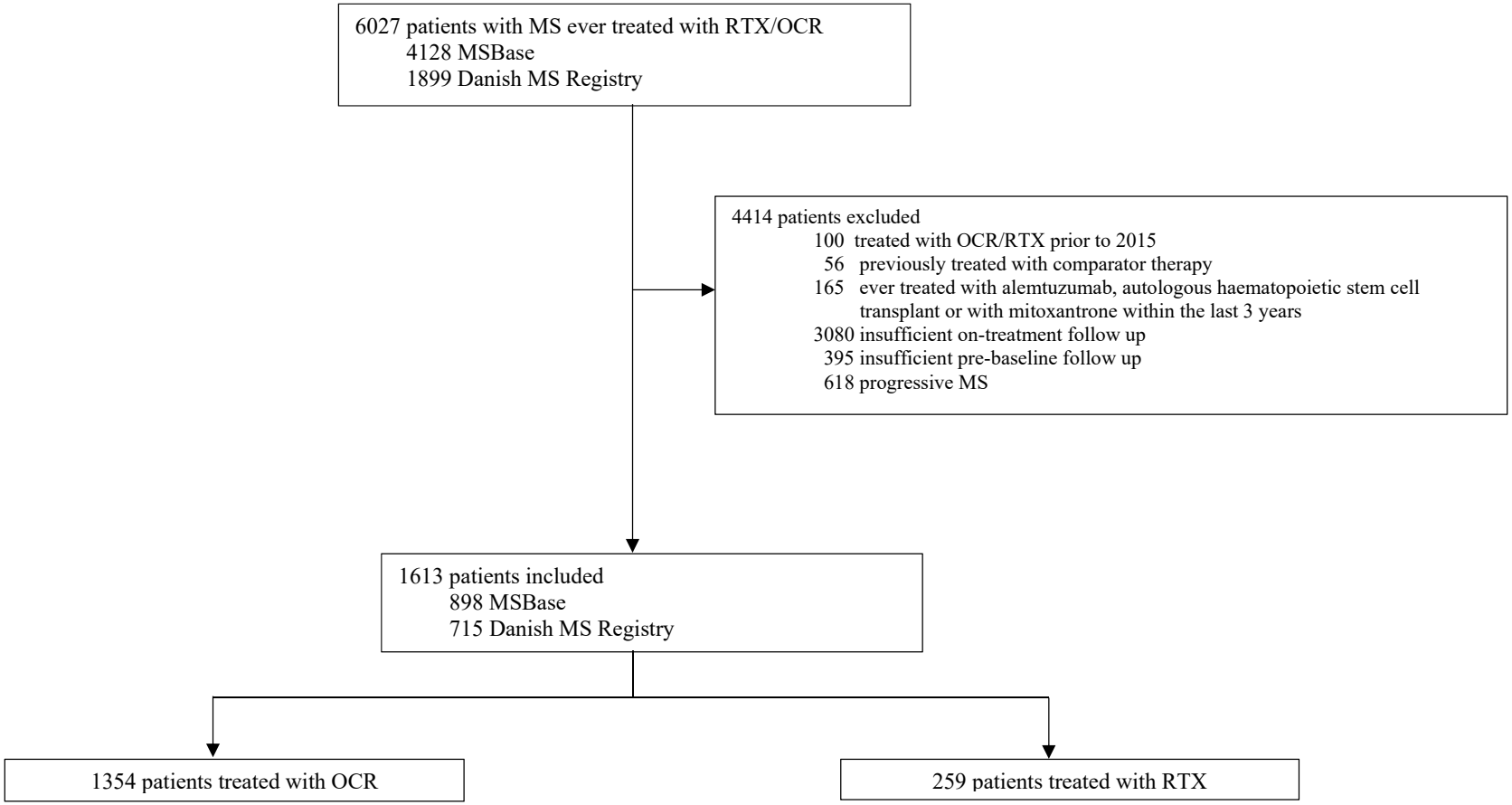
Sanofi Genzyme. Design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication were conducted separately and apart from the guidance of the sponsors.

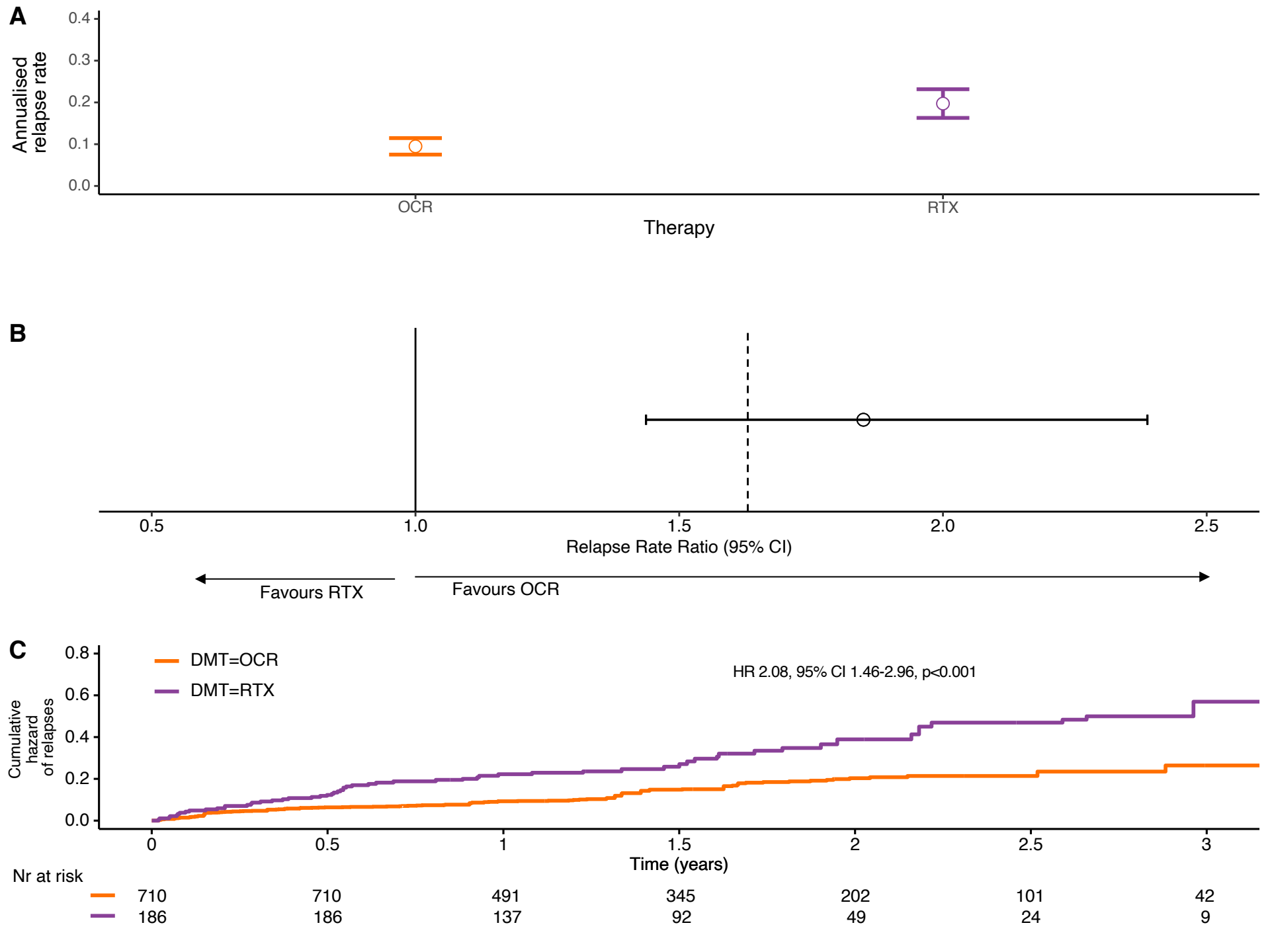
DATA ACCESS, RESPONSIBILITY AND ANALYSIS

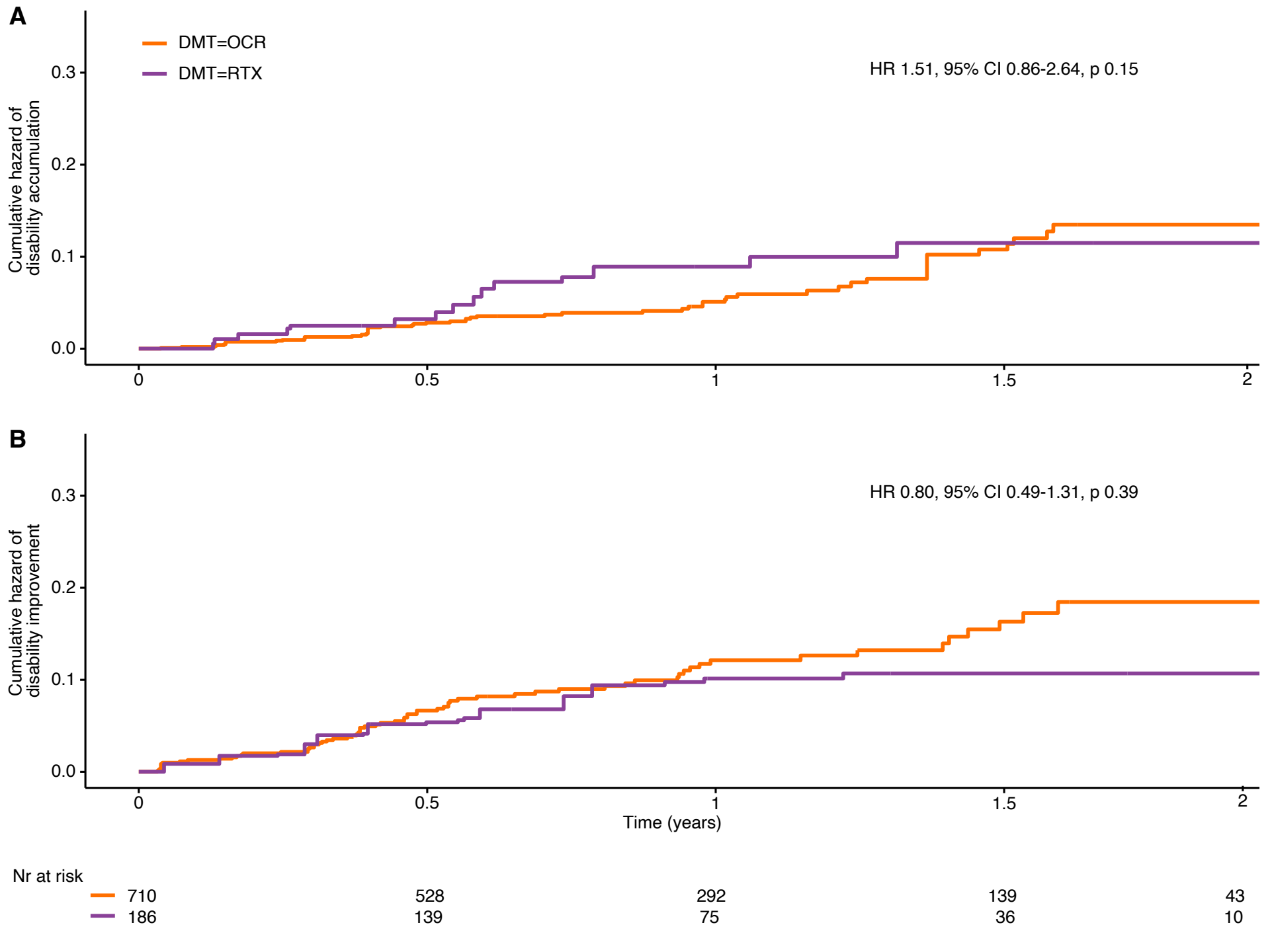
IR and TK had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis

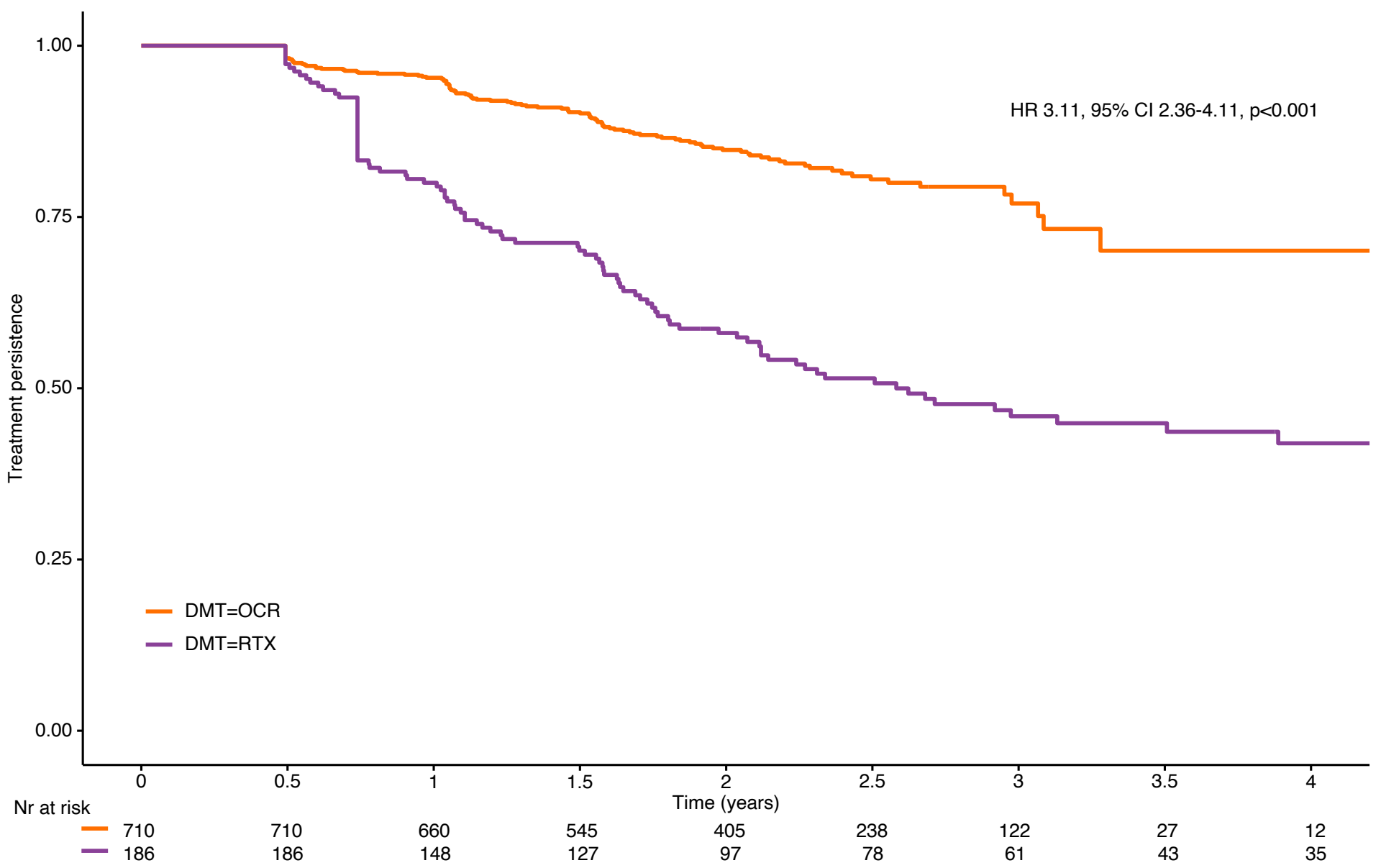
DATA SHARING STATEMENT

The MSBase registry is a data processor and warehouses data from individual principal investigators who agree to share their datasets on a project-by-project basis. Data access to external parties can be granted on reasonable request at the sole discretion of the principal investigators, who will need to be approached individually for permission. Data from the Danish MS Registry is accessible to authorised researchers after application to the Danish Health Data Authority and the board of the Danish Multiple Sclerosis Registry.


6027 patients with MS ever treated with RTX/OCR
4128 MSBase
1899 Danish MS Registry
4414 patients excluded
100 treated with OCR/RTX prior to 2015
56 previously treated with comparator therapy
165 ever treated with alemtuzumab, autologous haematopoietic stem cell transplant or with mitoxantrone within the last 3 years
3080 insufficient on-treatment follow up
395 insufficient pre-baseline follow up
618 progressive MS
1613 patients included
898 MSBase
715 Danish MS Registry
1354 patients treated with OCR
259 patients treated with RTX


A
Annualised relapse rate
0.4
0.3
0.2
0.1
0.0
OCR
RTX
Therapy
B
0.5
1.0
1.5
2.0
2.5
Relapse Rate Ratio (95% CI)
Favours RTX
Favours OCR
C
DMT=OCR
DMT=RTX
HR 2.08, 95% CI 1.46-2.96, p<0.001
Cumulative hazard of relapses
0.8
0.6
0.4
0.2
0.0
0
0.5
1
1.5
2
2.5
3
Time (years)
Nr at risk
710 710 491 345 202 101 42
186 186 137 92 49 24 9


A
DMT=OCR
DMT=RTX
HR 1.51, 95% CI 0.86-2.64, p 0.15
Cumulative hazard of disability accumulation
0.0
0.1
0.2
0.3
0
0.5
1
1.5
2
B
HR 0.80, 95% CI 0.49-1.31, p 0.39
Cumulative hazard of disability improvement
0.0
0.1
0.2
0.3
0
0.5
1
1.5
2
Time (years)
Nr at risk
710 528 292 139 43
186 139 75 36 10


1.00
0.75
0.50
0.25
0.00
Treatment persistence
HR 3.11, 95% CI 2.36-4.11, p<0.001
DMT=OCR
DMT=RTX
0
0.5
1
1.5
2
2.5
3
3.5
4
Time (years)
Nr at risk
710 710 660 545 405 238 122 27 12
186 186 148 127 97 78 61 43 35