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Original Research Paper

Comparative effectiveness of rituximab relative to IFN-β or glatiramer acetate in relapsing-remitting MS from the Swedish MS registry

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Abstract

Objective: To compare treatment effectiveness and persistence in relapsing-remitting multiple sclerosis patients who initiated rituximab versus glatiramer acetate (GA) or interferon-beta (IFN-β).

Methods: A total of 461 patients from the Swedish MS registry in the rituximab arm were propensity score matched on a 1:2 basis with 922 patients from the IFN-β/GA comparator, between April 2005 and November 2015. Annualised relapse rate (ARR) was compared using the Poisson method. A marginal Cox model was used to analyse time to first relapse, 3-month confirmed disability progression and treatment discontinuation in the matched sample. A signed-rank test was used to compare Expanded Disability Status Scale (EDSS) change from baseline.

Results: Rituximab was associated with a reduction in ARR (0.003; 95% confidence interval (CI) = 0.001, 0.009) relative to IFN-β/GA (0.026; 95% CI = 0.020, 0.033) ($p < 0.001$). Rituximab was associated with an 87% reduction in the relapse rate (hazard ratio (HR) = 0.13; 95% CI = 0.04, 0.41) and an 85% reduction in the discontinuation rate (HR = 0.15; 95% CI = 0.11, 0.20) relative to IFN-β/GA. EDSS regression from baseline was greater in the rituximab group at 12 and 24 months.

Conclusion: Rituximab appears to be superior to first-generation disease-modifying treatments (DMTs) with respect to relapse control and tolerability, whereas superiority on disability outcomes is less clear.

Keywords: Rituximab, relapse, disability progression, treatment persistence, propensity score matching

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Introduction

Rituximab is a monoclonal antibody that selectively targets CD20 positive B cells and used widely across a number of immunological or inflammatory conditions characterised by excessive or over-active B cells, including multiple sclerosis (MS).[1–4] The phase-II placebo-controlled HERMES trial of 104 relapsing-remitting MS (RRMS) patients observed that subjects assigned to rituximab had both a significantly lower frequency of relapse and a reduction in the total number of gadolinium-enhancing (Gd+) lesions relative to the placebo arm, with differences sustained for the full 48-week trial duration.[5] Relative to placebo, rituximab was associated with a 50% reduction in relapse rate over the observation period. These results support similar observations of early reductions in inflammatory lesions post-rituximab initiation reported in a predecessor open-label, phase-I study.[6] By comparison, these suggestions of an effectiveness advantage favouring rituximab have generally not been replicated in studies of progressive variants of MS.[7–9]

While rituximab itself is currently not being further developed specifically for MS in the setting of newer era anti-CD20 agents such as ocrelizumab and ofatumumab,[10,11] the use of rituximab in the clinical setting has enjoyed an upsurge in use within Sweden for managing RRMS, despite not being specifically listed for the purpose. Under existing Swedish free right to prescription provisions, the treating hospital, rather than the pharmaceutical company, assume responsibility and the liabilities associated with off-label rituximab use. This has led to a rapid escalation of

rituximab for managing RRMS, accounting presently for approximately 23% (2300 of 100,00) of currently treated MS patients,[12] secondary to both a perceived effectiveness advantage and a marked reduction in the overall costs of treatment, relative to platform interferon (IFN)-based products or newer era disease-modifying treatments (DMTs).

Due in part to recent patent expirations, there are no phase-III studies exploring the efficacy and safety of rituximab in RRMS patients. Data supporting the long-term, real-world comparative effectiveness of rituximab is particularly limited. The Swedish MS registry (SMSreg) is a longitudinal, observational MS outcomes database used across all neurology departments in Sweden.[13] It is thus uniquely positioned to quantify and analyse local treatment trends, particularly with regard to comparative effectiveness. The objectives of this study were to compare relapse rate, treatment persistence and disability progression in RRMS patients who initiated rituximab relative to a contemporaneous, propensity-matched cohort of patients treated with interferon-beta (IFN-β)/glatiramer acetate (GA).

Materials and methods

Data source

Swedish MS registry. All data were sourced from the Swedish MS registry (SMSreg). SMSreg was established in 2000 to capture and collate clinical data on MS patients.[13] While neurologist participation in the registry operates on an opt-in basis, SMSreg is currently used in all neurology departments across Sweden, capturing approximately 80% of the prevalent Swedish MS population. A minimum dataset of mandatory variables is required for data upload and includes patient demography, diagnostic criteria, clinical visit details, treatment and relapse parameters.

Study design

Patients. RRMS patients aged 18 years or older at baseline were included in the analysis. A minimum of 3-month persistence on the index DMT was also required. Baseline was defined as the start date of the index rituximab or IFN-β/GA. All patients eligible for matching were also required to report a full set of baseline data for all variables used in the derivation of the baseline score. A baseline Expanded Disability Status Scale (EDSS) recorded within 3 months of the index DMT start date was further required. The unmatched dataset included patients with baseline dates from April 2005 to November 2015. Patients were censored at either the date of the event (depending upon the outcome being analysed), else the discontinuation date of the index DMT, or where no discontinuation was recorded, the last observed visit.

Efficacy measures. The primary efficacy outcomes assessed were annualised relapse rate (ARR), time to first relapse on therapy and time to treatment discontinuation. Time to confirmed disability progression and EDSS change from baseline at 1 through 4 years of treatment were analysed as secondary outcomes. Baseline EDSS was defined as the nearest EDSS score reported within three months of the index DMT start date. Three-month confirmed disability progression events were defined as ⩾3-month confirmed increases of ⩾0.5 points for patients with a baseline EDSS score >5.5, ⩾1.0 point for those with a baseline EDSS score between 1.0 and 5.5, inclusive, and ⩾1.5 points for those with a baseline EDSS score of 0. EDSS scores recorded within 30 days after the onset of a relapse were excluded. A minimum of three visits (including baseline) at which an EDSS was formally recorded were, by definition, required to first observe and then confirm the disability progression event. Thus, the progression analysis was limited to patients with a minimum of three EDSS scores reported. The date of progression was taken as the date at which the progression event was first observed.

Statistical analyses. Categorical variables were summarised using frequency and percentage. Continuous variables were summarised using mean and standard deviation (SD), or median and inter-quartile range (IQR), as appropriate. Propensity scores, representing the theoretical probability of assignment to the rituximab group based on the distribution of baseline characteristics, was derived for each patient satisfying the inclusion criteria. A binomial logistic regression model was used to calculate the propensity score where receipt of rituximab was specified as the dependent outcome variable and age, sex, EDSS, disease duration at baseline, number of pre-baseline DMT start, the proportion of disease duration on treatment, the number of DMT starts as a proportion of disease duration, relapse activity in the 12 and 24 months pre-baseline and the index year of the DMT start specified as the independent explanatory variables. The final multivariate logistic regression was assessed for collinearity and interactions. A Hosmer–Lemeshow goodness-of-fit test was used to assess overall model fit. To control for differences in assessment frequency between the two treatment groups, visit density (defined as the number of assessments per year of follow-up) was included as an additional covariate in the derivation of the propensity score. Matching on

the resultant propensity score was conducted on a 2:1 basis using a 5-to-1 digit matching algorithm with a 0.01 calliper. Comparisons of baseline characteristics by treatment group in the unmatched sample and matched samples were assessed via the derivation of standardised differences. An absolute standardised difference of <20% was considered to represent acceptable balance between the rituximab group and IFN-β/GA comparator. Propensity score matching has previously been extensively applied to MS registry data to balance baseline confounding as previously described.[14–16]

ARR was derived and compared for each treatment group with confidence intervals (CIs) calculated from the Poisson likelihood. A marginal Cox model was used to analyse time to first relapse, time to first 3-month confirmed disability progression and time to treatment discontinuation, weighting for the 2:1 match. Hazard proportionality was assessed via the analysis of scaled Schoenfeld residuals. A Rosenbaum sensitivity analysis was used to test these models for the influence of unobserved confounding.[17] To adjust for differences in on-treatment follow-up time between the matched treatment arms, simultaneous censoring of the matched pairs was used in the time to first relapse modelling. Given the marked differences in treatment persistence by treatment group, a sensitivity analysis of the intention-to-treat (ITT) population was undertaken, censoring patients at the date of last recorded assessment rather than the date of treatment discontinuation. EDSS change from baseline was assessed using a Wilcoxon signed-rank test. For all analyses, $p < 0.05$ was considered significant. All analyses were conducted in Stata version 14 (StataCorp, College Station, Texas) and R (R Foundation for Statistical Computing, Vienna, Austria).

Results

Patients

A total of 461 rituximab and 1960 IFN-β/GA patients from SMSreg satisfied the inclusion criteria. Prior to matching, patients in the rituximab group were significantly older, had a higher baseline EDSS, longer disease duration, greater exposure to pre-baseline treatment and less relapse activity relative to unmatched IFN-β/GA patients (Table 1). Following propensity score matching, treatment groups were well balanced with regard to all baseline prognostic used to derive the propensity score (Table 2). All 461 eligible rituximab patients were successfully matched on a 2:1 basis to 922 IFN-β/GA patients. Females accounted for 343 (74.4%) of the matched rituximab group and the median (IQR) age was 41.5 years (34.5, 48.5). Median (IQR) EDSS at baseline was 2 (1.5, 3) across both matched treatment groups, while the median (IQR) number of prior DMT treatments was 2 (1, 3) in both the matched rituximab and IFN-β/GA groups. Pre-baseline relapse activity was low with a mean 12- and 24-month count of 0.07 and 0.10, respectively, for both matched treatment groups. Mean (SD) on-treatment follow-up was 2.14 (1.42) years in the rituximab group and 2.80 (2.05) years in the matched IFN-β/GA group.

Relapse

Rituximab was associated with a very low on-treatment ARR across the observation period (ARR = 0.003; 95% CI = 0.001, 0.009) (Table 3). This represented a significant reduction relative to the IFN-β/GA comparator (ARR = 0.026; 95% CI = 0.020, 0.033) ($p < 0.0001$). Rituximab was associated with an 87% reduction in the rate of first on-treatment relapse relative to IFN-β/GA (hazard ratio (HR) = 0.13; 95% CI = 0.03, 0.56) (Figure 1) on simultaneous censoring of the matched pairs. A sensitivity analysis using non-simultaneous censoring of the matched pair returned similar results (Supplementary Figure 1). The ITT sensitivity analysis returned similar results. The rituximab ITT population was associated with a significant reduction in ARR (0.004; 95% CI = 0.001, 0.010) relative to their matched IFN-β/GA comparator (0.022; 95% CI = 0.018, 0.027) ($p = 0.0002$) (Supplementary Table 1). Similarly, the first relapse rate was markedly reduced in the rituximab ITT population (HR = 0.18: 95% CI = 0.06, 0.49; reference = IFN-β/GA) (Supplementary Figure 2).

EDSS regression and disability progression

Rituximab was associated with a significantly greater reduction in EDSS from baseline at both 12 and 24 months of treatment, relative to IFN-β/GA (Table 4). Rituximab was associated with a mean (SD) 0.12 (0.36) EDSS point decrease from baseline after 12 months of therapy compared to just a 0.02 (0.37) point decrease in IFN-β/GA ($p = 0.0415$). A similar difference was observed after 24 months of treatment with rituximab associated with a mean (SD) 0.15 (0.58) point decrease in EDSS compared to a 0.02 (0.49) point decrease in IFN-β/GA (p = 0.0382). There was no observed difference at either 3 or 4 years on treatment although this in part may be secondary to relative under-powering, given the smaller retained sample. There was no difference by treatment group in the rate of first 3-month confirmed disability

Table 1. Comparison of baseline characteristics by treatment arm – unmatched sample.

Baseline factor	Rituximab ($n=461$)	IFN/GA ($n=1960$)	Standardised difference
Female sex, *n* (%)	343 (74.4)	1466 (74.8)	−0.009
Age (years), median (IQR)	41.5 (34.5, 48.5)	37.2 (30.9, 44.7)	0.354
EDSS, median (IQR)	2 (1.5, 3)	1.5 (1, 2.5)	0.407
Disease duration (years), median (IQR)	10.6 (7.4, 15.0)	5.7 (2.0, 11.1)	0.682
Proportion of disease duration on treatment, mean (SD)	0.62 (0.27)	0.22 (0.29)	1.463
Number of disease modifying drug treatment starts, mean (SD)	2.6 (1.5)	0.9 (1.2)	1.257
Number of disease modifying drug treatment starts/disease duration, mean (SD)	0.27 (0.22)	0.17 (0.36)	0.353
Total relapse onsets last 12 months, mean (SD)	0.07 (0.29)	0.15 (0.47)	−0.218
Total relapse onsets last 24 months, mean (SD)	0.10 (0.39)	0.22 (0.61)	−0.232

IFN: interferon; GA: glatiramer acetate; IQR: inter-quartile range; EDSS: Expanded Disability Status Scale; SD: standard deviation.

Table 2. Comparison of baseline characteristics by treatment arm – propensity score matched sample.

Baseline factor	Rituximab ($n=461$)	IFN/GA ($n=922$)	Standardised difference
Female sex, *n* (%)	343 (74.4)	699 (75.8)	−0.033
Age (years), median (IQR)	41.5 (34.5, 48.5)	40.0 (33.1, 45.7)	0.128
EDSS, median (IQR)	2 (1.5, 3)	2 (1.5, 3)	0.092
Disease duration (years), median (IQR)	10.6 (7.4, 15.0)	9.9 (6.4, 12.8)	0.143
Proportion of disease duration on treatment, median (IQR)	0.6 (0.3, 0.7)	0.6 (0.2, 0.7)	0.183
Number of disease modifying drug treatment starts, median (IQR)	2 (1, 3)	2 (1, 3)	0.081
Number of disease modifying drug treatment starts/disease duration, median (IQR)	0.2 (0.1, 0.3)	0.2 (0.1, 0.3)	−0.138
Total relapse onsets last 12 months, mean (SD)	0.07 (0.29)	0.07 (0.28)	−0.004
Total relapse onsets last 24 months, mean (SD)	0.10 (0.39)	0.10 (0.38)	0.003

IFN: interferon; GA: glatiramer acetate; IQR: inter-quartile range; EDSS: Expanded Disability Status Scale; SD: standard deviation.

Table 3. Annualised relapse rate by treatment group.

Index DMD group	Number of on-treatment relapses	On-treatment follow-up years	ARR (95% CI)	*p*-value
Rituximab	3	986.33	0.0030 (0.0006, 0.0089)	<0.0001
IFN/GA	68	2584.42	0.0263 (0.0204, 0.0334)	

ARR: annualised relapse rate; CI: confidence interval; IFN: interferon; GA: glatiramer acetate.

progression (HR = 0.86; 95% CI = 0.52, 1.43; reference = IFN-β/GA) (Figure 2). Sensitivity analysis of the ITT population returned similar results with rituximab again associated with a significant reduction in EDSS from baseline at 1 and 2 years relative to IFN-β/GA (Supplementary Table 2).

Treatment persistence

A total of 684 (74.2%) of the IFN-β/GA group discontinued treatment during the observation period compared to just 37 (8.0%) of the matched rituximab group. Discontinuation of IFN-β/GA at 1, 2 and 5 years was 211 (22.9%), 374 (40.6%) and

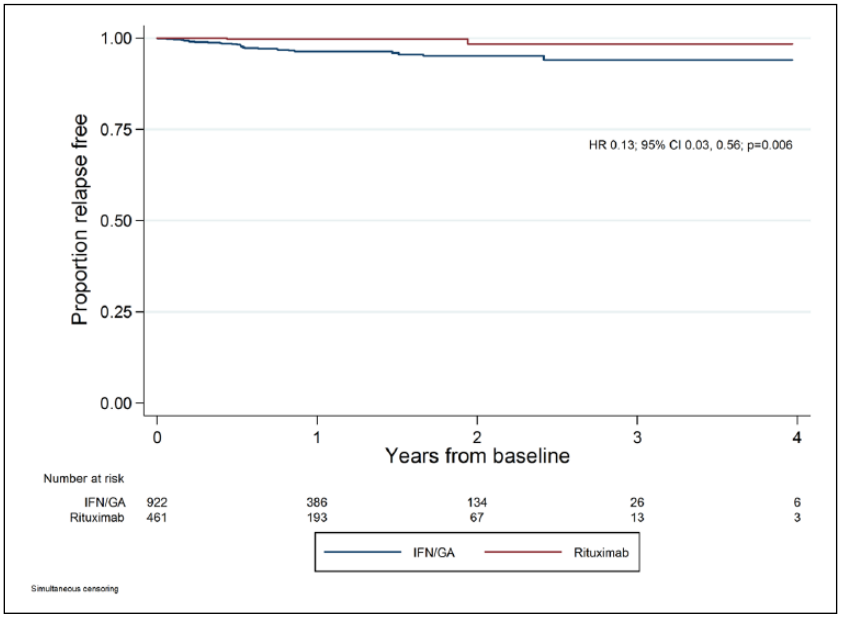

Figure 1. First on-treatment relapse by treatment group: Kaplan–Meier curve.

Table 4. EDSS change from baseline by treatment group.

Year(s) on treatment	Patient count		Mean (SD) EDSS change from baseline		*p*-value
	Rituximab	IFN/GA	Rituximab	IFN/GA	
1	351	688	−0.12 (0.36)	−0.02 (0.37)	0.0415
2	206	493	−0.15 (0.58)	−0.02 (0.49)	0.0382
3	118	368	−0.15 (0.78)	−0.02 (0.72)	0.1526
4	55	262	−0.15 (0.95)	−0.01 (0.92)	0.3488

EDSS: Expanded Disability Status Scale; SD: standard deviation; IFN: interferon; GA: glatiramer acetate.

592 (64.2%), respectively, compared with 14 (3.0%), 25 (5.4%) and 35 (7.6%) of rituximab patients. Rituximab was associated with an 85% reduction in the rate of discontinuation relative to IFN-β/GA (HR = 0.15; 95% CI = 0.11, 0.20) (Figure 3).

Rosenbaum sensitivity analysis for unmeasured confounding

A Rosenbaum sensitivity analyses of the propensity-matched relapse, progression and discontinuation models estimated that an unobserved confounder would need to impart a minimum 2.09-, 1.89- and 2.13-fold increase in the rate of relapse, confirmed disability progression and discontinuation, respectively, in order to reject the inference of a treatment effect in favour of selection effects and indication confounding. These represent improbably large differences in the context of the observed point estimates and associated CIs. This suggests that the effects of unmeasured confounding on the observed associations between treatment arm and studied outcomes were not sufficiently large enough to significantly change the inferences made herein.

Discussion

The recent growth in popularity of rituximab for the treatment of RRMS in Swedish clinical practice is likely driven in part by a perceived gain in effectiveness and tolerability over approved DMTs, in addition to cost considerations. However, data and formal analyses supporting these differences are lacking. Our study of a large national population-based sample showed a clear advantage favouring rituximab with regard to both ARR and time to first on-treatment relapse, relative to a propensity-matched cohort of comparable patients treated with platform IFN-β or glatiramer.

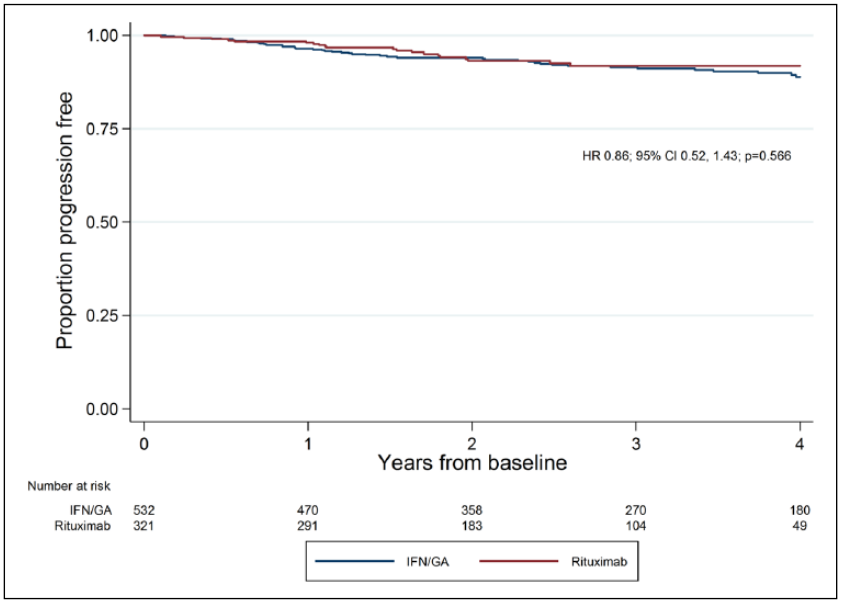

Figure 2. Three-month confirmed disability progression by treatment group: Kaplan–Meier curve.

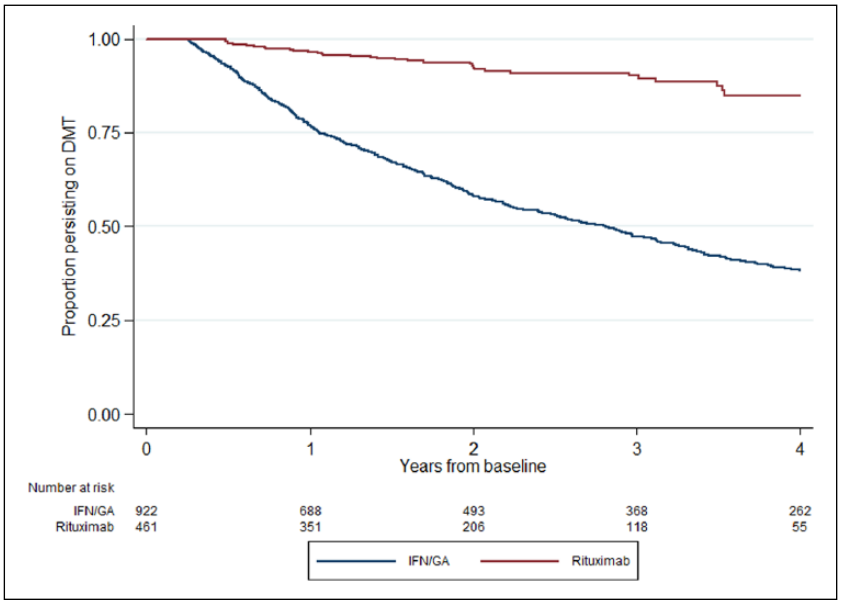

Figure 3. Treatment discontinuation by treatment group: Kaplan–Meier curve.

While rituximab has previously been studied as an add-on therapy to first-line DMT for RRMS in the phase-II setting, the trial was powered to detect changes in magnetic resonance imaging (MRI) lesion counts only and not relapse or EDSS-based endpoints.[18] Furthermore, direct effectiveness comparisons of rituximab against established DMTs for RRMS are limited. Across both relapse-based outcomes considered in our analysis (ARR and time to first on-treatment relapse), reported relapses on rituximab were a considerably rare event. This is consistent with a recent study also based on patient data sourced from SMSreg combined with relapse data sourced from chart review that observed a similarly marked reduction in the rate of clinical relapse on rituximab in a cohort of RRMS patients switching from natalizumab, relative to patients switching to fingolimod, although the absolute number of relapses observed was higher than our study.[19] Patients switching from natalizumab to rituximab secondary to JC

(John Cunningham) virus antibody positivity were associated with a 90% reduction in the rate of relapse (HR = 0.10; 95% CI = 0.02, 0.43), relative to fingolimod. This effect is broadly consistent with the equivalent association observed in our study favouring propensity-matched rituximab (HR = 0.13; 95% CI = 0.03, 0.56), although the disease characteristics and treatment pathways of patients in these two studies were not directly comparable. Furthermore, this observed difference in ARR exceeds the equivalent effect size recently reported by the phase-3 OPERA I and II clinical trials, which observed a 46% and 47% reduction in 2-year ARR favouring ocrelizumab over subcutaneous IFN-β-1a.[20]

While these markedly low rates may reflect the fact that such events on rituximab are indeed infrequent, this is likely to be in part secondary to under-reporting of relapses in the Swedish registry. There is no evidence available to suggest the presence of systematic differences in the pattern of relapse under-reporting between different DMTs. Thus, while the *absolute* relapse counts and their associated ARRs presented here are very likely to be under-estimates, the *relative* differences between rituximab and the matched platforms comparator are likely to be genuine. Thus, the strength of the relative signals here remains suggestive of a considerable effectiveness advantage favouring rituximab over platforms, corroborating the recent experience in Swedish clinical practice.

While there was no observed difference in confirmed disability progression, rituximab was associated with a significant *regression* in EDSS, at least over the first 2 years of treatment for which patient numbers were sufficient and explanatory power adequate. By comparison, the confirmed disability progression analysis is more sample-intensive than the change from baseline EDSS analysis, the former requiring a minimum of three longitudinal EDSS assessments to first observe and then confirm a progression event, thus the lack of a progression signal favouring either matched treatment arm may be in part limited by under-powering and a larger sample with longer follow-up would be required to better isolate the relative effect of rituximab, should one exist. This further applies to a formal analysis of confirmed regression events. Both the EDSS progression and regression event analyses were further limited by their relative instability over the observation period.

Beyond effectiveness, rituximab was associated with a considerable increase in treatment persistence. Rituximab-treated patients were associated with a remarkable 85% reduction in the discontinuation rate relative to the platform DMT comparator group. The fact that the treatment arms were further matched on index year means that the groups were contemporaneous and this finding is thus unlikely to be a historical artefact. This suggests that rituximab is generally acceptable to patients in addition to clinicians and hospitals. As per the relapse analysis, these results are again quite consistent with Alping et al.'s[19] SMSreg-based comparison of rituximab and fingolimod, which demonstrated a 93% reduction in the rate of discontinuation (HR = 0.07; 95% CI = 0.01, 0.30) favouring rituximab relative to the fingolimod comparator on adjusted Cox proportional hazard regression. While these differences in treatment persistence were certainly marked, a sensitivity analysis of the ITT population returned similar results favouring rituximab in terms of ARR, first relapse and EDSS change, suggesting a limited impact of any ascertainment differential secondary to these very different discontinuation profiles. What these results do not account for is differences in discontinuation rules and dynamics between rituximab and the platform comparators. While the minimum persistence inclusion criterion may offset this to a degree, additional analysis of post-rituximab treatment course may better isolate the true persistence effect.

This study has a number of limitations beyond the suspected under-reporting of relapses previously discussed. While the propensity score matching ensured that the comparator groups were well balanced at baseline for key prognostic confounders and correlates of the study end-points, we cannot claim such balance for potential confounders *not* included in the derivation of the propensity score. The most notable omission being baseline MRI metrics, secondary to inadequate data availability. However, the Rosenbaum sensitivity analysis suggested that all three time-to-event models (first relapse, confirmed disability progression and treatment discontinuation) were all relatively robust to the effects of unmeasured confounding. As described above, the confirmed disability progression analysis was likely under-powered and would require a large sample with longer patient-level follow-up to characterise more accurately. Finally, data around safety outcomes, another important determinant of treatment choice, was insufficient to formally analyse in this particular study.

From this study, we conclude that rituximab also appears to be superior to first-generation DMTs with respect to relapse control and tolerability, whereas superiority on disability outcomes is less clear. Although rituximab is not labelled for use in RRMS,

it may well be a feasible treatment alternative for this group of MS patients.

Author contribution

T.S. conceptualised and designed the study, conducted and interpreted the analysis, and drafted, revised and approved the manuscript; T.F. and F.P. conceptualised the study, interpreted the analysis, and revised and approved the manuscript; J.H. conceptualised and designed the study, interpreted the analysis, and revised and approved the manuscript.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship and/or publication of this article: T.S. received compensation for serving on scientific advisory boards, honoraria for consultancy, funding for travel from Biogen Inc. and speaker honoraria from Novartis. T.F. declared no competing interests. F.P. received unrestricted academic research grants from Biogen, Genzyme and Novartis, and his department has received travel support and/or compensation for lectures and/or participation in advisory boards from Biogen, Genzyme, Merck Serono, Novartis, Roche and Teva, which have been exclusively used for the support of research activities. J.H. (Dr Hillert) has received honoraria for serving on advisory boards for Biogen, Sanofi-Genzyme and Novartis, and speaker's fees from Biogen, Novartis, Merck Serono, Bayer-Schering, Teva and Sanofi-Genzyme. He has served as P.I. for projects, or received unrestricted research support from, Biogen Idec, Merck Serono, Teva, Sanofi-Genzyme and Bayer-Schering. His MS research is funded by the Swedish Research Council and the Swedish Brain foundation.

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