Comparative efficacy of ofatumumab *versus* oral therapies for relapsing multiple sclerosis patients using propensity score analyses and simulated treatment comparisons

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Abstract

Background: Evidence from network meta-analyses (NMAs) and real-world propensity score (PS) analyses suggest monoclonal antibodies (mAbs) offer a therapeutic advantage over currently available oral therapies and, therefore, warrant consideration as a distinct group of high-efficacy disease-modifying therapies (DMTs) for patients with relapsing multiple sclerosis (RMS). This is counter to the current perception of these therapies by some stakeholders, including payers.

Objectives: A multifaceted indirect treatment comparison (ITC) approach was undertaken to clarify the relative efficacy of mAbs and oral therapies.

Design: Two ITC methods that use individual patient data (IPD) to adjust for between-trial differences, PS analyses and simulated treatment comparisons (STCs), were used to compare the mAb ofatumumab *versus* the oral therapies cladribine, fingolimod, and ozanimod.

Data sources and methods: As IPD were available for trials of ofatumumab and fingolimod, PS analyses were conducted. Given summary-level data were available for cladribine, fingolimod, and ozanimod trials, STCs were conducted between ofatumumab and each of these oral therapies. Three efficacy outcomes were compared: annualized relapse rate (ARR), 3-month confirmed disability progression (3mCDP), and 6-month CDP (6mCDP).

Results: The PS analyses demonstrated ofatumumab was statistically superior to fingolimod for ARR and time to 3mCDP but not time to 6mCDP. In STCs, ofatumumab was statistically superior in reducing ARR and decreasing the proportion of patients with 3mCDP compared with cladribine, fingolimod, and ozanimod and in decreasing the proportion with 6mCP compared with fingolimod and ozanimod. These findings were largely consistent with recently published NMAs that identified mAb therapies as the most efficacious DMTs for RMS.

Conclusion: Complementary ITC methods showed ofatumumab was superior to cladribine, fingolimod, and ozanimod in lowering relapse rates and delaying disability progression among patients with RMS. Our study supports the therapeutic superiority of mAbs over currently available oral DMTs for RMS and the delineation of mAbs as high-efficacy therapies.

Keywords: annualized relapse rate, confirmed disability progression, indirect treatment comparison, propensity score, relapsing multiple sclerosis, simulated treatment comparison

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Introduction

Multiple sclerosis (MS) is an autoimmune demyelinating disease of the central nervous system (CNS) that affects 2.8 million people worldwide.[1,2] Although the clinical course of MS can be a dynamic process, four MS clinical subtypes are generally recognized: clinically isolated syndrome, relapsing-remitting multiple sclerosis (RRMS), secondary progressive multiple sclerosis (SPMS), and primary progressive MS.[3] The term relapsing multiple sclerosis (RMS) has been used to describe both RRMS and SPMS with superimposed relapses.[4] More recently, MS has been described as a continuum from RMS to progressive disease without stratification.[5]

The current treatment strategy for MS focuses on alleviating CNS inflammation, slowing disease progression, and reducing the recurrence of relapses, with an overall goal of improving long-term outcomes.[6] Multiple disease-modifying therapies (DMTs) are available for the treatment of MS, representing an opportunity for personalized care. These therapies have been broadly sorted into moderate and high efficacy groups, though the groupings differ across jurisdictions and guidelines and are not consistently recognized.[7] Guidelines published by the American Academy of Neurology, a position statement from the Multiple Sclerosis Therapy Consensus Group, and Public Summary Documents (PSDs) from the Pharmaceutical Benefits Advisory Committee (PBAC) in Australia consider high-efficacy monoclonal antibodies (mAbs; e.g. alemtuzumab, natalizumab, ocrelizumab, and ofatumumab) to be interchangeable with some oral therapies (cladribine and S1P receptor modulators) in their ability to manage relapse and disease progression.[8–10] However, evidence from network meta-analyses (NMAs) using randomized control trial (RCT) data suggests that these particular high-efficacy mAbs (e.g. alemtuzumab, natalizumab, ocrelizumab, and ofatumumab) are therapeutically superior to the respective oral therapies (e.g. cladribine, fingolimod, and ozanimod) for treating RMS.[11–17] For example, two recently published NMAs for relapse and disability outcomes consistently ranked all included mAb therapies above oral therapies.[11,18] Propensity score (PS) analyses and other studies using real-world data have also provided evidence supporting the superiority of mAb therapies over oral therapies.[19–26] This distinction is reflected in treatment guidelines published by

the Association of British Neurologists, which identify mAbs as high-efficacy therapies and suggest their use for treating patients with frequent clinical relapses.[27]

Clarifying the relative efficacy of mAbs and oral DMTs is important to inform treatment guidelines and allow patients with RMS to receive the best treatment for their individual needs. Currently, there are no RCTs comparing mAbs head-to-head and only a few RCTs comparing mAbs with oral therapies in RMS. Therefore, indirect treatment comparisons (ITCs) can be used to estimate the comparative efficacy of therapies for which direct head-to-head evidence is not available. Previous ITCs of mAb and oral therapies have taken the form of NMAs, which permit the estimation of the relative efficacy between multiple therapies but rely on published summary-level trial data with the inherent assumption that the underlying populations are comparable.[14,16,17,28] However, cross-study differences in patient and study characteristics (e.g. outcome definitions) can impact the treatment effect and potentially introduce bias when indirectly comparing treatment efficacy. This can be addressed using ITC methods that use individual patient data (IPD) from RCTs to adjust for between-trial differences, such as PS analyses using inverse probability treatment weighting (IPTW) and simulated treatment comparisons (STCs).[16,29,30] These methods are used in different situations depending on the available data: PS analyses are used when IPD are available for trials for both therapies, whereas STCs are used when IPD are available from trials for one therapy and only summary-level data (SLD) are available for trials for the comparator therapy. Population-adjustment techniques such as STC are increasingly being used in health technology assessment (HTA) applications.[31]

In light of differing guideline recommendations and to ensure appropriate evaluation of DMTs by HTA authorities, the objective of this study was to take a multifaceted ITC approach to compare the efficacy of mAb therapies (with a focus on ofatumumab) with cladribine, fingolimod, and ozanimod (i.e. oral therapies considered by several organizations to be interchangeable with mAb therapies in their efficacy) in the treatment of patients with RMS. Given the findings of published NMAs and PS analyses for relapse and disability outcomes, we sought to test the hypothesis

that mAbs are more efficacious than oral therapies. Outcomes of interest were annualized relapse rate (ARR), 3-month confirmed disability progression (3mCDP), and 6-month confirmed disability progression (6mCDP).

Methods

Literature review

A recently published systematic literature review (SLR) with an integrated NMA in RMS was used to identify key RCTs of interest.[12] In brief, searches of biomedical databases, conference proceedings, and trial registries were conducted to identify RCTs for DMTs in RMS.[12] The RCTs were included in the NMA if they met the following criteria: population was ≥75% RMS; interventions and comparators included DMTs approved or being reviewed for RMS by the United States Food and Drug Administration and/or the European Medicines Agency; outcomes included at least one of ARR, 3mCDP, or 6mCDP; trial duration was ≥48 weeks; and a full-text pivotal trial publication was available.[12]

In 2007, natalizumab was the first DMT recognized by the PBAC to demonstrate cost-effectiveness compared with interferon beta-1b.[32] Subsequently, fingolimod was recommended for PBS listing in 2011 based on its cost-effective safety and efficacy compared with interferon beta-1a.[33] Since then, alemtuzumab,[34] ocrelizumab,[35] cladribine,[36] ozanimod,[37] and ofatumumab[9] have been recommended for, and subsequently listed on, the Australian Government's Pharmaceutical Benefits Scheme (PBS) for the treatment of RRMS *via* a series of cost-minimization PBAC submissions claiming non-inferior safety and efficacy compared with fingolimod and/or natalizumab. These DMTs form what is now considered by the PBAC to be the 'high-efficacy' group for RRMS treatment. For the purpose of the present objective, only pivotal RCTs including adults with RMS who were treated with one of the DMTs of interest (i.e. those considered by the PBAC to be 'high-efficacy') *versus* a comparator (placebo and/or active comparator) and reported at least one outcome of interest (i.e. ARR, time to or proportion with 3mCDP, and time to or proportion with 6mCDP) identified in the SLR were considered. The following RCTs were identified from the SLR and included in the present analyses: ASCLEPIOS I/ II[38] for ofatumumab; FREEDOMS,[39] FREEDOMS II,[40] and TRANSFORMS[41] for fingolimod; CLARITY[42] for cladribine; and RADIANCE-B[43] and SUNBEAM[44] for ozanimod. Whereas SLD were available for all trials, IPD were only available for the ofatumumab (ASCLEPIOS I/II) and fingolimod (FREEDOMS, FREEDOMS II, TRANSFORMS) trials. Trials of other mAbs (alemtuzumab, natalizumab, and ocrelizumab) were not included due to the unavailability of IPD to the authors for comparisons using PS analyses or STCs. The RCTs included in the present analyses are summarized in Supplemental Appendix A.

Feasibility assessment

To assess the feasibility of different ITC approaches and similarity of included studies of interest, we considered the type of data available for RCTs of interest, their connectivity in an evidence network based on the availability of common comparators, and the degree and potential impact of cross-trial heterogeneity. Elements of study design, patient eligibility criteria, baseline patient characteristics, and outcome definitions were qualitatively assessed to determine comparability between trials. Recent publications have used similar methods to evaluate the feasibility of ITCs.[45–47]

As the goal of the present study was to compare the relative efficacy of mAbs to currently available oral DMTs, an assessment of the feasibility of ITCs between different mAbs was considered out of scope. Where feasible, ITCs were conducted to evaluate the comparative efficacy of ofatumumab *versus* oral therapies for the treatment of MS using IPD from pivotal trials for these therapies. Methodological details for these ITC analyses are provided in the next section.

Indirect treatment comparisons

Variables for covariate adjustment. A previously published STC analysis between ofatumumab and ocrelizumab in RMS was used to identify important variables for adjustment.[48] Briefly, clinicians identified a subset of variables from a master list comprising the minimum number of variables required for adjustment to ensure clinical validity (hereafter referred to as Tier 1; the remaining variables are referred to as Tier 2). Fourteen variables were identified: six Tier 1 variables and eight Tier 2

variables. Tier 1 variables included age, body mass index, normalized brain volume, number of gadolinium-enhancing T1 lesions, and volume of T2 lesions. Although the number of T2 lesions was also identified as a Tier 1 variable, the number of T2 lesions was not available at baseline from ASCLEPIOS I/II and, therefore, could not be included. However, because the number and volume of T2 lesions are correlated with each other,[49] it was assumed one could serve as a proxy for the other.

Tier 2 variables included Expanded Disability Status Scale (EDSS) score at baseline, number of relapses in the past year, prior DMT experience, sex, race/ethnicity, and time since diagnosis. Additional Tier 2 variables that were identified included prior exposure to a high-efficacy therapy (i.e. alemtuzumab and natalizumab) and comorbidities. However, these variables were not included as they were not available from the RCTs. For example, prior experience with alemtuzumab was an exclusion criterion for ASCLEPIOS I/II but not the fingolimod or cladribine trials, and prior experience with either alemtuzumab or natalizumab was an exclusion criterion for the ozanimod trials. Only variables that were reported for the pairs of trials to be compared were adjusted for.

Standardized mean differences (SMDs) were used to assess imbalances between trials for each variable.[50] In the base case analysis for each outcome, Tier 1 and Tier 2 variables were collectively adjusted for in accordance with National Institute for Health and Care Excellence guidance.[51] An unadjusted analysis, referring to a comparison without adjusting for baseline characteristics (i.e. Tier 1 or Tier 2 variables) across populations, was also conducted for ITCs for each outcome.

The specific list of variables adjusted for in each ITC analysis is provided in Supplemental Appendix B.

Statistical analysis

Propensity score analyses using IPTW. PS analyses using IPTW were used to compare ofatumumab to fingolimod by balancing the trial populations through weighting. The PS analyses used pooled ASCLEPIOS I/II IPD for ofatumumab and pooled FREEDOMS, FREEDOMS II, and TRANSFORMS IPD for fingolimod. As time to 6mCDP was not reported for the TRANSFORMS trial, pooled IPD from FREEDOMS and FREEDOMS II for fingolimod were used instead to assess this outcome.

The PS is a balancing score defined by Rosenbaum and Rubin as the probability of treatment assignment conditional on observed baseline covariate.[52] IPTW uses the PS to remove the effects of measured confounding when estimating the effects of treatment on the outcome (i.e. balance baseline characteristics between patient populations).[53] PS scores were derived using a logistic regression with a binary treatment variable as the dependent variable and baseline covariates as explanatory variables.

The estimated PS values were then used to derive average treatment effect in the control (ATC) weights for each patient. In this case, ATC was the average treatment effect in the fingolimod population. Patients in the ofatumumab cohort were assigned a weight of $(1-p)/p$, where p is the PS predicting the inclusion in the ofatumumab cohort and patients in the fingolimod cohort were kept as observed (i.e. assigned a weight of one). That is, patients in the treated (ofatumumab) cohort were reweighted to become more similar to the control (fingolimod) population, where participants with similar characteristics received larger weights. The degree of balance achieved was assessed by calculating the SMD for each factor, where an SMD ≤0.2 was considered a small difference.[50] The effective sample size was calculated to assess the impact of weighting on the IPD.

Average treatment effect in the fingolimod population weighting allowed for the estimation of the relative treatment effect in a population similar to the comparator population. This approach aligns with STCs, which calculate the relative treatment effect in comparator population (see next section on STC analyses).

For ARR, a negative binomial regression model was used with log link to the number of relapses. The natural log of the time in study in years was used as an offset to annualize the relapse rate. Weights were applied for the adjusted comparison. Variance was estimated using a robust

sandwich variance estimator. Results were reported as a rate ratio (RR) with its respective 95% confidence interval (CI).

CDP was assessed as time to 3mCDP and time to 6mCDP. This was in alignment with best practices for PS analyses (i.e. using Cox regression for IPD–IPD comparisons). A Cox proportional hazards model (with weights applied for the adjusted comparison) was used to derive a hazard ratio (HR) and its respective 95% CI. The variance was estimated using a robust sandwich variance estimator. All analyses were performed using R (version 3.6.1).[54]

STC analyses. Unanchored STCs were conducted to compare ofatumumab to fingolimod, cladribine, and ozanimod by fitting a regression model to the outcome. The STCs used pooled ASCLEPIOS I/II IPD for ofatumumab and SLD for each individual RCT for fingolimod (FREEDOMS, FREEDOMS II, TRANSFORMS), cladribine (CLARITY), and ozanimod (pooled CDP data were used for the RADIANCE-B and SUNBEAM ozanimod trials because these data were not reported for SUNBEAM alone). As 6mCDP was not reported by TRANSFORMS, an STC for 6mCDP was not possible using this trial.

Multivariable regression models were specified using available baseline characteristics as covariates and were fit using IPD from ASCLEPIOS I/II. The models permitted outcomes to be estimated for the hypothetical situation where an average patient from the comparator trial received ofatumumab instead of the comparator (cladribine, fingolimod, and ozanimod) by predicting outcomes at the means of the covariates reported in the comparator trial. These predicted outcomes were then compared with published outcomes from the comparator trial to derive point estimates of ofatumumab relative to the comparator. Since the model can predict values outside of the reported ranges in the comparator trial, differences in eligibility criteria were adjusted by representing matching criteria as covariates in the model. To adjust for imbalances in baseline characteristics, the linear predictions for a typical patient from the comparator population were derived by substituting means and proportions of baseline characteristics from the comparator study into the fitted equation.

ARR was obtained by fitting a negative binomial regression model with log link function to the number of relapses. The natural log of the time-in-study was used as an offset to annualize the relapse rate. Results were reported as an RR with its respective 95% CI.

CDP was assessed as the proportion of patients with 3mCDP and proportion of patients with 6mCDP. This was in alignment with previously published STCs and NMAs of DMTs in RMS.[16,48] A binomial model with a complementary log–log (cloglog) link function was used to account for the variable treatment duration among ASCLEPIOS I/II patients. An offset was applied to adjust the hazard rate estimated for ASCLEPIOS I/II to the follow-up time of the comparator trial. Results were reported as an HR with its respective 95% CI.

Regression models were evaluated based on their model fit using common diagnostics such as the Akaike Information Criterion and the Bayesian Information Criterion. All analyses were performed using R (version 3.6.1).[54]

Sensitivity analyses. For each outcome for each ITC approach, two sensitivity analyses were conducted to assess the impact of variables included in the model. The first analysis adjusted for only Tier 1 variables, whereas the second analysis adjusted for only Tier 2 variables.

Results

Feasibility assessment

In general, all RCTs considered for the ITC analyses were comparable in terms of study design characteristics, patient eligibility criteria, baseline patient characteristics, and outcome definitions (Supplemental Appendix A). One or more trials for all therapies of interest reported ARR, 3mCDP, and 6mCDP, which meant ITCs were possible for these outcomes.

Considering the availability of IPD for both ofatumumab trials (ASCLEPIOS I/II) and all three fingolimod trials (FREEDOMS, FREEDOMS II, TRANSFORMS), a PS analysis was identified as an appropriate ITC method. Considering the availability of IPD for both ofatumumab trials

(ASCLEPIOS I/II) and SLD for each of the three fingolimod trials (FREEDOMS, FREEDOMS II, TRANSFORMS), cladribine trial (CLARITY), and ozanimod trial (RADIANCE-B and SUNBEAM), STCs were also considered to be appropriate. Specifically, unanchored STCs were required due to the lack of a common comparator between ASCLEPIOS I/II and the trials for cladribine, fingolimod, and ozanimod. The use of unanchored STCs between ofatumumab and each of fingolimod, cladribine, and ozanimod also offered consistency with a previously published STC evaluating efficacy outcomes between the mAb therapies ofatumumab and ocrelizumab.[48] The lack of IPD for alemtuzumab, natalizumab, and ocrelizumab RCTs meant that PS analyses were not possible between these mAbs and the three oral DMTs of interest, and STCs were not possible for comparisons with cladribine and ozanimod. Although IPD were available for fingolimod trials, given the lack of equivalent data for cladribine and ozanimod, we did not indirectly compare alemtuzumab, natalizumab, and ocrelizumab to fingolimod using STCs.

PS analyses using IPTW

Comparative efficacy estimates for ofatumumab *versus* fingolimod in the PS analysis using IPTW for each outcome of interest are summarized in Figure 1 and the results of covariate balancing for each outcome are summarized in Supplemental Appendix C.

Ofatumumab versus *fingolimod.* For ARR, ofatumumab was significantly favored with a 40% reduction in this outcome relative to fingolimod [RR: 0.60 (95% CI: 0.45–0.81)] after IPTW adjustment. For time to 3mCDP, ofatumumab was significantly favored with a 46% reduced risk of progression [HR: 0.54 (95% CI: 0.29–0.99)] after adjustment. For time to 6mCDP, ofatumumab had a 41% reduced risk of progression [HR: 0.59 (95% CI: 0.31–1.12)] after adjustment, but this was not statistically significant.

STC analyses

Comparative efficacy estimates for ofatumumab *versus* cladribine, fingolimod, and ozanimod for each outcome of interest are summarized in Figure 1.

Ofatumumab versus *cladribine.* For ARR, the RR for ofatumumab *versus* cladribine was 0.74 (95% CI: 0.56–1.00) after multivariate adjustment, significantly favoring ofatumumab (the upper 95% CI value to three decimal places was 0.996). For the proportion with 3mCDP, the HR for ofatumumab *versus* cladribine was 0.61 (95% CI: 0.40–0.92) after adjustment, significantly favoring ofatumumab. For the proportion with 6mCDP, the HR for ofatumumab *versus* cladribine was 0.75 (95% CI: 0.44–1.26) after adjustment.

Ofatumumab versus *fingolimod.* For ARR using the FREEDOMS trial, the RR for ofatumumab *versus* fingolimod was 0.58 (95% CI: 0.41–0.82) after multivariate adjustment, significantly favoring ofatumumab. Using the FREEDOMS II trial, the RR for ofatumumab *versus* fingolimod was 0.51 (95% CI: 0.34–0.76) after adjustment, significantly favoring ofatumumab. Using the TRANSFORMS trial, the RR between ofatumumab and fingolimod was 0.66 (95% CI: 0.44–0.98) after adjustment, significantly favoring ofatumumab.

For the proportion with 3mCDP using the FREEDOMS trial, the HR between ofatumumab and fingolimod was 0.39 (95% CI: 0.24–0.63) after multivariate adjustment, significantly favoring ofatumumab. Using the FREEDOMS II trial, the HR between ofatumumab and fingolimod was 0.29 (95% CI: 0.17–0.49) after adjustment, significantly favoring ofatumumab. Using the TRANSFORMS trial, the HR between ofatumumab and fingolimod was 0.63 (95% CI: 0.35–1.12) after adjustment.

For the proportion with 6mCDP using the FREEDOMS trial, the HR between ofatumumab and fingolimod was 0.45 (95% CI: 0.27–0.75) after multivariate adjustment, significantly favoring ofatumumab. Using the FREEDOMS II trial, the HR between ofatumumab and fingolimod was 0.49 (95% CI: 0.28–0.84) after adjustment, significantly favoring ofatumumab. The 6mCDP outcome was not reported in the TRANSFORMS trial.

Ofatumumab versus *ozanimod.* Comparative ARR efficacy estimates for ofatumumab and ozanimod were calculated with unanchored STCs using each of the two ozanimod trials (RADIANCE-B and SUNBEAM) separately. Using the

RADIANCE-B trial, the RR between ofatumumab and ozanimod was 0.57 (95% CI: 0.42–0.78) after multivariate adjustment, significantly favoring ofatumumab. Using the SUNBEAM trial, the RR between ofatumumab and ozanimod was 0.54 (95% CI: 0.38–0.78) after adjustment, significantly favoring ofatumumab.

Comparative 3mCDP and 6mCDP efficacy estimates for ofatumumab and ozanimod were calculated with unanchored STCs using the pooled data reported for ozanimod from the RADIANCE-B and SUNBEAM trials. For the proportion with 3mCDP, the HR between ofatumumab and ozanimod was 0.56 (95% CI: 0.37–0.85) after multivariate adjustment, significantly favoring ofatumumab. For the proportion with 6mCDP, the HR between ofatumumab and ozanimod was 0.54 (95% CI: 0.33–0.90) after adjustment, significantly favoring ofatumumab.

Sensitivity analyses
For both the PS and STC analyses, the results of sensitivity analyses adjusting for Tier 1 variables only or Tier 2 variables only were consistent with the results of the base case (Supplemental Appendices C and D).
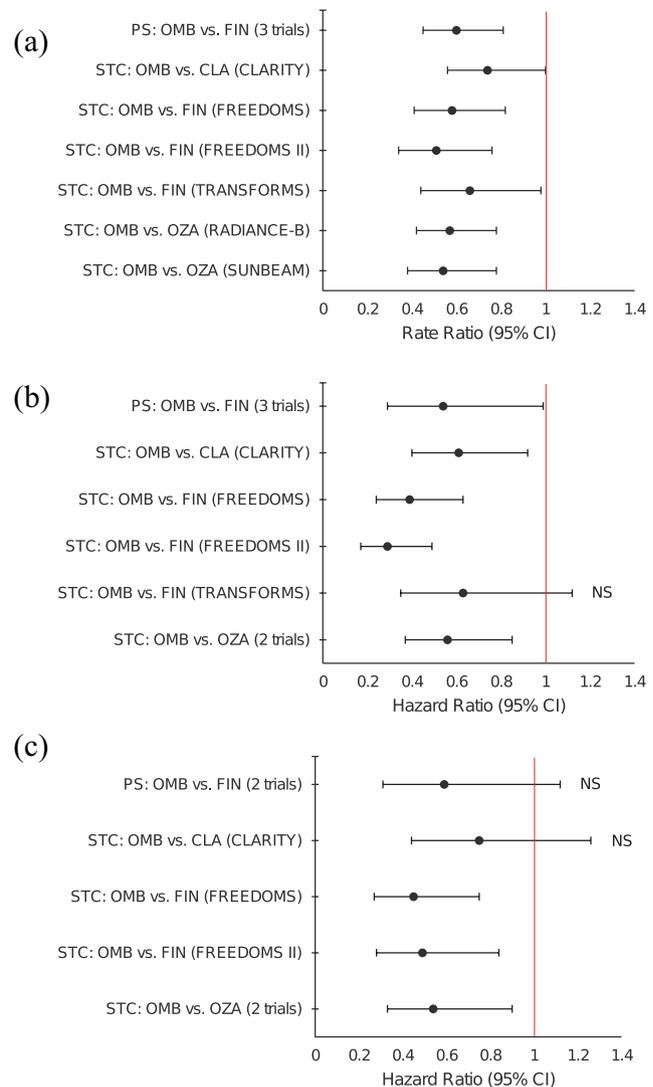
Summary of ITC results
The base case results of the PS analyses using IPTW and the unanchored STC analyses are summarized in Table 1. This table also included results from a recently published NMA[12] that was identified as part of the ITC feasibility assessment that reported comparative efficacy estimates between mAbs other than ofatumumab and the oral DMTs of interest where PS and STC analyses were not feasible.

Reporting guidelines
The STROBE checklist was used for reporting this study (Supplemental Appendix E).

Discussion
Treatment guidelines[27] and findings from NMAs[11–17] and real-world evidence studies[19–26] suggest that the currently available mAbs offer a therapeutic advantage over oral therapies and, therefore, warrant consideration as a distinct group of DMTs for patients with RMS. However,

Figure 1. Summary of base case results of PS (using IPTW) and STC analyses for ofatumumab *versus* oral therapies of interest for (a) ARR, (b) 3mCDP, and (c) 6mCDP.
An RR or HR below 1.0 indicates an improved outcome for ofatumumab relative to comparator. Time to 6mCDP was not reported for TRANSFORMS. Only pooled RADIANCE-B and SUNBEAM ozanimod trial data were available for 3mCDP and 6mCDP.
ARR, annualized relapse rate; 3mCDP, 3-month confirmed disability progression; 6mCDP, 6-month confirmed disability progression; CI, confidence interval; CLA, cladribine; FIN, fingolimod; HR, hazard ratio; IPD, individual patient data; IPTW, inverse probability of treatment weighting; NS, not significant; OMB, ofatumumab; OZA, ozanimod; PS, propensity score; RR, rate ratio; STC, simulated treatment comparison.

some jurisdictions, payers, and guidelines do not currently differentiate DMTs by their relative efficacy. There is a paucity of head-to-head trials for mAbs and oral therapies in RMS. Since it is impractical to assess all these DMTs in a single RCT, robust statistical methods are required to compare the relative efficacy of these therapies.

Table 1. Summary of ITC results.

Outcome	Ofatumumab *versus* cladribine		Ofatumumab *versus* fingolimod			Ofatumumab *versus* ozanimod	
	STC (base case)	Published NMA[12]	PS analysis (base case)	STC (base case)	Published NMA[12]	STC (base case)	Published NMA[12]
ARR [RR (95% CI/CrI)]	Ofatumumab is statistically superior CLARITY: 0.74 (0.56–1.00[a])	Non-significant 0.70 (0.45–1.12)	Ofatumumab is statistically superior 0.60 (0.45–0.81)	Ofatumumab is statistically superior FREEDOMS: 0.58 (0.41–0.82) FREEDOMS II: 0.51 (0.34–0.76) TRANSFORMS: 0.66 (0.44–0.98)	Non-significant 0.70 (0.51–1.03)	Ofatumumab is statistically superior RADIANCE-B: 0.57 (0.42–0.78) SUNBEAM: 0.54 (0.38–0.78)	Non-significant 0.69 (0.47–1.07)
3mCDP [HR (95% CI/CrI)]	Ofatumumab is statistically superior CLARITY: 0.61 (0.40–0.92)	Non-significant 0.67 (0.38–1.19)	Ofatumumab is statistically superior 0.54 (0.29–0.99)	Ofatumumab is statistically superior FREEDOMS: 0.39 (0.24–0.63) FREEDOMS II: 0.29 (0.17–0.49) TRANSFORMS: 0.63 (0.35–1.12)	Ofatumumab is statistically superior 0.62 (0.38–1.00)	Ofatumumab is statistically superior RADIANCE-B + SUNBEAM: 0.56 (0.37–0.85)	Non-significant 0.59 (0.32–1.09)
6mCDP [HR (95% CI/CrI)]	Non-significant CLARITY: 0.75 (0.44–1.26)	No difference 0.99 (0.50–1.97)	Non-significant 0.59 (0.31–1.12)	Ofatumumab is statistically superior FREEDOMS: 0.45 (0.27–0.75) FREEDOMS II: 0.49 (0.28–0.84)	Non-significant 0.79 (0.45–1.45)	Ofatumumab is statistically superior RADIANCE-B + SUNBEAM: 0.54 (0.33–0.90)	Non-significant 0.52 (0.25–1.14)

[a]Value to three decimal places is 0.996.
NMA results are for the main analysis (random effects model), with CrIs used instead of CIs because the NMA employed a Bayesian framework.
ARR, annualized relapse rate; 3mCDP, 3-month confirmed disability progression; 6mCDP, 6-month confirmed disability progression; CI, confidence interval; CrI, credible interval; HR, hazard ratio; IPTW, inverse probability of treatment weighting; ITC, indirect treatment comparison; NMA, network meta-analysis; PS, propensity score; RR, rate ratio; STC, stimulated treatment comparison.

We conducted PS and STC analyses to generate comparative efficacy data for DMTs of interest, which were then contextualized to the results of a recently published NMA.[12] Our analyses suggested that the mAb ofatumumab was superior to the oral therapies cladribine, fingolimod, and ozanimod in lowering ARR and delaying both 3mCDP and 6mCDP in patients with RMS, based on both PS and STC analyses.

The unavailability of IPD to the authors for alemtuzumab, natalizumab, and ocrelizumab RCTs meant that advanced pairwise ITC methods, such as PS or STC analyses were not possible between these mAbs and all three oral DMTs of interest. As such, using a recently published NMA[12] that included all mAb and oral therapies of interest and analyzed ARR, 3mCDP, and 6mCDP was pre-emptively identified *via* an ITC feasibility assessment as the most suitable ITC approach for these comparisons. This NMA[12] and several others[11,13,16,18] demonstrated the superior efficacy of ofatumumab over oral therapies, albeit not always at a statistically significant level. Further, these NMAs demonstrated that the most efficacious DMTs for RMS were ofatumumab and other mAb therapies, not oral therapies. These published findings aligned with the results of our study. Unlike the PS and STC analyses, an NMA does not adjust for cross-trial differences in baseline patient characteristics. Although an NMA is considered a robust analysis because it can use

trial data for multiple treatments to inform indirect comparisons, this also increases the level of uncertainty associated with comparisons, particularly when analyses are based on sparse networks and therapies being compared are distantly connected in a network. Specific limitations of NMAs for therapies in RMS have been described previously.[12] Reflecting the greater uncertainty, the NMA results had wider credible intervals compared to the CIs for the STCs, and point estimates did not always align. Overall, the results of the recently published NMA numerically (albeit non-significantly) favored mAbs over oral therapies, and ofatumumab was statistically superior to fingolimod in the time to 3mCDP analysis.[12] This NMA and several others also showed that treatment with mAb therapies was associated with the greatest reduction in ARR and delay of 3mCDP and 6mCDP. For example, analyses by Chen *et al.*[18] and the Institute for Clinical and Economic Review found that all included mAb therapies were ranked above oral therapies in NMAs for ARR and CDP outcomes.[11] Collectively, across multiple analytical approaches, ITC evidence suggests that mAbs have a therapeutic advantage over oral therapies in the treatment of patients with RMS and should be considered as a distinct group of high-efficacy DMTs.

PS analyses are used when IPD are available for trials for both treatments, with or without a common comparator.[55] They improve the validity of inferences compared to methods that rely on SLD (e.g. NMA), provide intuitive diagnostics for assessing the similarity of patient populations, and allow adjustment for a single scalar (i.e. the PS) rather than a full set of covariates. Weighting is commonly used in causal inference; unlike certain forms of matching, weighting uses the full patient population, with individual patients contributing variable information to the estimated treatment effect depending on their similarity or dissimilarity to the target population. IPTW creates weights for each patient, allowing for all patients to be included in the analysis, preventing selection bias that can happen with PS matching. As with other adjustment methods, IPTW is dependent on adequate adjustment for factors that differ across trials. Notably, for the PS analyses in this study, several patient characteristics varied slightly (i.e. had SMDs ~0.15–0.20) between the ofatumumab and fingolimod patient populations, even after adjusting for Tier 1 and Tier 2 variables. Specifically, the ofatumumab

population had a higher T2 lesion volume, lower normalized brain volume, and higher number of relapses in the past year compared with the fingolimod population, suggesting the ITCs could be biased against ofatumumab. Regardless, the PS analyses showed that ofatumumab is superior to fingolimod for the outcomes of ARR, 3mCDP, and 6mCDP.

An important strength of this study was the use of complementary ITC methods to evaluate the relative efficacy of mAb therapies *versus* oral therapies, which included the use of IPD for multiple trials in both ofatumumab (a mAb) and fingolimod (an oral therapy). These data were used to inform PS and STC analyses, which adjusted for differences in patient characteristics between trials. Many baseline patient characteristics were available for adjustment in these analyses. For the STCs, the cloglog link function was used to account for the variable treatment duration among ASCLEPIOS I/II patients, helping to align treatment duration between trials being compared. Although an NMA can be used to compare multiple therapies simultaneously, it is more susceptible to bias introduced by variability across the patient populations of trials informing the analysis. Notably, relative efficacy estimates for ofatumumab *versus* fingolimod could be compared across three ITC approaches; PS and STC analyses were reported here, and a recent NMA that included this treatment comparison was also considered.[12]

As with any study, our analyses had some limitations. Although many baseline characteristics were adjusted for in the PS and STC analyses, these analyses were limited in that some characteristics (e.g. number of T2 lesions, prior experience with a high efficacy therapy, comorbidities, and race) were not consistently available for the trials of therapies being compared. Consequently, it was not possible to adjust for these covariates. More broadly, RCTs are preferable to ITCs given the potential for between-trial differences to bias indirect comparisons. However, RCTs comparing ofatumumab with cladribine, fingolimod, and ozanimod were not available at the time of this study, necessitating the use of ITCs. Second, for 3mCDP and 6mCDP outcomes, time-to-event data were used for the PS analyses and previously published NMAs, whereas the proportion of patients with CDP was used for the STCs. Although this approach aligns with best practices

for PS analyses (i.e. using Cox regression for IPD–IPD comparisons) and with previously published STCs[48] and NMAs[12,14,16,17] of DMTs in RMS, comparisons across ITCs may be influenced by the difference in outcome measure. Third, the RCTs for cladribine and fingolimod used for the ITC analyses were published roughly a decade prior to the RCTs for ofatumumab, and there is evidence that ARR has been decreasing in RCTs over time.[56,57] Finally, although STCs allow for inclusion of all patients in fitting the regression models, diagnostic assessments of post-adjustment improvements are not available. Additionally, STCs rely on mutually available patient characteristics across RCTs to balance patient populations which may result in certain characteristics unadjusted if not available in both cohorts. Results of an unanchored STC are also susceptible to residual confounding if patient characteristics are unbalanced across trials with respect to unmeasured prognostic factors and treatment effect modifiers. Since unanchored STCs are a population-adjustment technique, there is also an assumption of conditional constancy of absolute effects, which assumes that all relevant prognostic factors and treatment effect modifiers are known and that treatment effects are constant at any level of prognostic factors and effect modifiers. Nevertheless, unanchored STCs are valuable in that, unlike an NMA, they permit adjustment for available prognostic factors and treatment effect modifiers and are not constrained by the limitations of a sparse extended network of treatments.

Treatment goals of DMTs for RMS include alleviating CNS inflammation, preventing and/or reducing relapses, and slowing disease progression. However, multiple factors must be considered when choosing a therapy for RMS, including safety and tolerability, convenience, preferred method of administration, likelihood of adherence, and access. Although ofatumumab and other mAbs showed superior efficacy for the three efficacy outcomes assessed in this study, comparisons based on other outcomes may help to further clarify the delineation between mAbs and other DMTs. As additional RCTs are conducted, their results can be incorporated into future ITCs to better understand the changing landscape of RMS treatments. Although NMAs continue to be an important source of data to inform decision making by healthcare stakeholders, population-adjusted ITC methods that use IPD, such as PS and STC analyses, can also continue to contribute to the totality of comparative evidence for DMTs in RMS.[51]

Conclusion

In conclusion, the introduction of mAbs has revolutionized the treatment landscape of MS by offering a targeted mechanism, potent efficacy, and a manageable safety profile (which is also quite favorable for anti-CD20 therapies). As new mAbs and other treatment options continue to emerge for patients with RMS, there will be a growing need for comparisons of relative efficacy to ensure patients and clinicians can make well-informed treatment decisions. In our study, the mAb ofatumumab showed superiority to the oral therapies cladribine, fingolimod, and ozanimod in reducing relapse rates and delaying disability progression among patients with RMS. Our study adds to a growing body of literature confirming that mAb therapies are the most efficacious DMTs for ARR, 3mCDP, and 6mCDP and challenges the notion that oral therapies achieve similar efficacy to mAbs.

Declarations

Author contributions
Nicholas Riley: Conceptualization; Methodology; Writing – review & editing.

Christopher Drudge: Investigation; Methodology; Project administration; Writing – original draft; Writing – review & editing.

Morag Nelson: Conceptualization; Methodology; Writing – original draft; Writing – review & editing.

Anja Haltner: Formal analysis; Investigation; Methodology; Writing – original draft; Writing – review & editing.

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Supplemental material
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