Original research

Comparing switch to ocrelizumab, cladribine or natalizumab after fingolimod treatment cessation in multiple sclerosis

Chao Zhu ,[1] Zhen Zhou,[2] Izanne Roos ,[3,4] Daniel Merlo,[1] Tomas Kalincik ,[3,4] Serkan Ozakbas,,[5] Olga Skibina,[1,6] Jens Kuhle,[7] Suzanne Hodgkinson,[8] Cavit Boz,[9] Raed Alroughani,[10] Jeannette Lechner-Scott,[11,12] Michael Barnett ,[13] Guillermo Izquierdo,[14] Alexandre Prat,[15] Dana Horakova,[16] Eva Kubala Havrdova,[16] Richard Macdonell,[17] Francesco Patti,[18,19] Samia Joseph Khoury ,[20] Mark Slee,[21] Rana Karabudak,[22] Marco Onofrj ,[23] Vincent Van Pesch,[24] Julie Prevost,[25] Mastura Monif,[1,6] Vilija Jokubaitis ,[1,6] Anneke van der Walt ,[1,6] Helmut Butzkueven,[1,6] on behalf of the MSBase Study Group

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/jnnp-2022-330104).

For numbered affiliations see end of article.

Correspondence to
Dr Chao Zhu, Department of Neuroscience, Central Clinical School, Monash University, Melbourne, VIC, Australia; Chao.Zhu@monash.edu

Received 3 August 2022
Accepted 26 September 2022

To cite: Zhu C, Zhou Z, Roos I, *et al*. *J Neurol Neurosurg Psychiatry* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/jnnp-2022-330104

ABSTRACT

Background To compare the effectiveness and treatment persistence of ocrelizumab, cladribine and natalizumab in patients with relapsing–remitting multiple sclerosis switching from fingolimod.

Methods Using data from MSBase registry, this multicentre cohort study included subjects who had used fingolimod for ≥6 months and then switched to ocrelizumab, cladribine or natalizumab within 3 months after fingolimod discontinuation. We analysed relapse and disability outcomes after balancing covariates using an inverse-probability-treatment-weighting method. Propensity scores for the three treatments were obtained using multinomial-logistic regression. Due to the smaller number of cladribine users, comparisons of disability outcomes were limited to natalizumab and ocrelizumab.

Results Overall, 1045 patients switched to ocrelizumab (n=445), cladribine (n=76) or natalizumab (n=524) after fingolimod. The annualised relapse rate (ARR) for ocrelizumab was 0.07, natalizumab 0.11 and cladribine 0.25. Compared with natalizumab, the ARR ratio (95% confidence interval [CI]) was 0.67 (0.47 to 0.96) for ocrelizumab and 2.31 (1.30 to 4.10) for cladribine; the hazard ratio (95% CI) for time to first relapse was 0.57 (0.40 to 0.83) for ocrelizumab and 1.18 (0.47 to 2.93) for cladribine. Ocrelizumab users had an 89% lower discontinuation rate (95% CI, 0.07 to 0.20) than natalizumab, but also a 51% lower probability of confirmed disability improvement (95% CI, 0.32 to 0.73). There was no difference in disability accumulation.

Conclusion After fingolimod cessation, ocrelizumab and natalizumab were more effective in reducing relapses than cladribine. Due to the low ARRs in all three treatment groups, additional observation time is required to determine if statistical difference in ARRs results in long-term disability differences.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ There is no clear consensus on the optimum treatment in the context of patients switching from fingolimod. Is there any difference in the effectiveness and treatment persistence between ocrelizumab, cladribine and natalizumab among patients with relapsing–remitting multiple sclerosis (RRMS) who switched from fingolimod?

WHAT THIS STUDY ADDS

⇒ In this observational study including 1045 patients with RRMS who ceased fingolimod, switch to ocrelizumab was associated with reduced annualised relapse rate compared with natalizumab and cladribine switches. Ocrelizumab was associated with a lower rate of disability improvement than natalizumab.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Using real-world data from the MSBase registry, this study provides a direct and clinically useful outcome comparison of three treatment choices after fingolimod cessation.

INTRODUCTION

Fingolimod is an effective disease-modifying therapy (DMT) for relapsing–remitting multiple sclerosis (RRMS), as demonstrated in two pivotal randomised placebo-controlled trials and one active comparator trial.[1–4] It is approved as a second-line therapy in Europe and first-line therapy in Australia, the USA, Canada and other countries.[5] However, it is common that patients discontinue fingolimod after a few years of treatment, mainly due to adverse events, relapse, MRI activity, disease progression or pregnancy planning.[6] Fingolimod cessation is associated with severe relapses resembling immune reconstitution inflammatory syndrome, therefore, the standard practice is to switch to another high-efficacy DMT with a short treatment gap, including natalizumab, ocrelizumab and cladribine.[7 8] Evidence is lacking for the relative

net clinical benefit between these treatment choices after fingolimod cessation.

Ocrelizumab is a humanised monoclonal antibody[9] that depletes CD20-expressing B cells with minimal impact on pre-existing humoral immunity.[10 11] Cladribine is a semi-selective immune reconstitution pulse therapy that temporarily depletes 80% of peripheral B cells and 50% of T cells.[12] It provides long-term (at least 4 years) benefits for patients with RRMS.[13–16] Natalizumab is the first monoclonal antibody used for multiple sclerosis (MS). The great efficacy of natalizumab in RRMS has been shown in three randomised control trials.[17–19] Several network meta-analyses have compared the effectiveness of these three treatments in reducing RRMS disease burden, but not in the specific scenario of the fingolimod switch.[20–22] However, no study to date has directly compared the relative efficacy of ocrelizumab, natalizumab and cladribine.

We, therefore, performed a retrospective analysis to compare treatment outcomes with ocrelizumab, cladribine and natalizumab after fingolimod cessation using the MSBase registry data set.[23] Outcomes of interest included time to first relapse, relapse rate, confirmed disability progression or improvement and DMT discontinuation.

PATIENTS AND METHODS

Standard protocol approvals, registrations and patient consents

The MSBase registry is an international observational cohort study of MS. It was established in 2004.[23] Written informed consent was obtained from all enrolled registry participants.

Study population

Patients continuously treated with fingolimod monotherapy ≥6 months before discontinuation were included if they had definite relapse-onset MS[24 25] and continued using ocrelizumab, natalizumab or cladribine ≥6 months after switching. They were also required to have at least two visits with a minimum 6-month gap and complete Expanded Disability Status Scale (EDSS, a non-linear ordinal disability scale with a range 0–10) assessment during follow-up to allow for the ascertainment of disability progression. Study inclusion also required complete information for sex, age, the date of starting and stopping fingolimod, the starting and stop date of the new treatments after fingolimod, EDSS assessments, and dates of relapses. To reflect current switch practice and minimise complete loss of treatment efficacy, including rebound risk, we only included patients with a treatment gap less than 3 months.[26]

Study inclusion criteria and definitions

Included patients were treated with fingolimod (0.5 mg orally daily) for at least 6 months and were categorised into three switch groups: ocrelizumab (600 mg, every 24 weeks),[11] cladribine (3.5 mg/kg total dose orally, initial treatment consisting of two courses completed at week 1 and week 5)[16] and natalizumab (300 mg intravenously every 4 weeks).[19] Patients were censored at either treatment discontinuation or the last recorded EDSS visit, whichever occurred first. The discontinuation was defined as starting a new treatment. In addition, the closest EDSS visit within 6 months before or after the switching date was chosen as the baseline EDSS visit.

Patient data were recorded as part of routine clinical visits at participating centres via the locally installed iMed or MDS MSBase data entry systems and monitored through a series of procedures to maintain quality.[26]

Study endpoints

The primary study outcomes were annualised relapse rate (ARR, calculated by dividing the total number of relapses by the total number of person-years at risk) and time to the first relapse. Secondary outcomes were disability accumulation events, disability improvement events and treatment discontinuation.

Relapse was defined as new symptom occurrence or exacerbation of existing symptoms for at least 24 hours, in the absence of concurrent illness or fever and occurring at least 30 days after a previous relapse.[27] Disability progression was defined as the confirmed increase in EDSS of ≥0.5 steps for patients with a baseline score >5.5, or ≥1.0 step for those with a baseline score between 1.0 and 5.5, and ≥1.5 steps if the baseline score was 0. Similarly, the confirmed disability improvement was defined as a decrease in EDSS by one step (1.5 steps if baseline EDSS was 0 and 0.5 steps if baseline EDSS was >5.5). Scores obtained <30 days after relapse were excluded. Six-month confirmed disability progression was defined as disability progression sustained over two subsequent visits relative to the baseline EDSS score, with a minimum of 6 months between each assessment. Treatment discontinuation event dates were always recorded. The treating neurologist recorded the primary reason for discontinuation using predefined terms, but these data are not part of the MSBase minimum data set, with relatively high missingness.

Statistical analysis

The demographic information and the baseline characteristics were reported as number and percentage for discrete variables and as mean (standard deviation [SD]) or median (interquartile range [IQR]) for continuous variables, as appropriate. To mitigate baseline differences between the groups and selection bias, we applied an inverse-probability-treatment-weighting (IPTW) approach based on propensity scores (PS) for three treatments groups to achieve covariate balance.[28 29] The PS represents the probability of receiving a treatment conditional on observed covariates. We calculated the PS using a multinomial-logistic regression model with treatment groups as a dependent variable and the baseline covariates listed in table 1 as independent variables.

The weights were obtained by taking the inverse of the probability of receiving the corresponding treatment. We truncated the weights at the 1st and 99th percentiles[30] and used the stabilised weights approach[31] to mitigate the influence of the extreme weights on the variability of the estimated treatment effect.[29] The covariate balance was evaluated using absolute standardised difference measure (ASD), where ASD≥0.1 indicates an imbalance.[32 33]

An IPTW-weighted negative binomial model was used to compare ARRs, with the relapse count as a dependent variable, the treatment group as an independent variable, and the natural logarithm of the follow-up time of the corresponding treatment after fingolimod discontinuation as an offset term. We used the IPTW-weighted Cox proportional-hazard regression model with robust standard errors and Kaplan-Meier cumulative hazard curves to assess and visualise treatment effect differences for the time-to-event outcomes. The proportional-hazard assumption was checked by the Schoenfeld global test, and no violation was detected.[34] All statistical tests were two-sided with a statistical significance defined as p≤0.05. All analyses were performed in R, V.4.1.1. (R Foundation for Statistical Computing).

Table 1 Characteristics of the study population by baseline treatment use

	Total (n=1045)	Cladribine (n=76)	Ocrelizumab (n=445)	Natalizumab (n=524)	ASD*	
					Before IPTW	After IPTW
Age, years	40.6±10.4	45.6±11.5	42.5±10.3	38.3±9.7	**0.69**	0.07
Female	780 (74.6)	61 (80.3)	300 (67.4)	419 (80.0)	**0.13**	0.06
Disease duration, years	10.2 (5.7–15.4)	14.6 (9.5–22.2)	11.8 (6.7–16.6)	8.8 (4.9–13.5)	**0.73**	0.04
Disability (EDSS)	3 (2–5)	2.5 (1.5–4.5)	3.5 (2–5.5)	3 (2–4.5)	**0.21**	0.09
Relapses 1-year prior to baseline	0.7±0.9	0.2±0.7	0.5±0.7	1.0±1.0	**0.91**	0.04
Relapses 2-year prior to baseline	1.1±1.3	0.4±0.9	0.8±1.0	1.5±1.4	**0.97**	0.06
Previous therapies (fingolimod excluded)	1 (1–2)	1 (0–2)	1 (1–2)	1 (0–2)	0.03	0.07
Gap period after fingolimod discontinuation†	29 (0–47)	40 (10–64)	27 (0–47)	29 (1–44)	**0.19**	0.05
Duration of fingolimod use, years†	2.6 (1.3–4.3)	4.3 (2.4–6.5)	3.4 (1.8–5.3)	1.8 (1.0–3.2)	**0.39**	<0.01

Values are median (IQR), n (%) or mean±SD.
*ASD is the absolute difference in means or proportions divided by the SE. An imbalance was defined as an ASD >0.10, indicated in bold.
†The gap period after fingolimod discontinuation and the duration of fingolimod were turned into binary by the corresponding median, respectively, when they were included in the propensity score model.
ASD, absolute standardised difference; EDSS, Expanded Disability Status Scale; IPTW, inverse-probability-treatment-weighting.

Sensitivity analyses

We performed seven sensitivity analyses to assess the robustness of our primary outcome results. First, the analyses were rerun using the doubly-robust approach,[35] adjusting the baseline covariates in the IPTW-weighted models to eliminate the potential risk of insufficient covariate balance. Second, we introduced the cerebral MRI information (number of hyperintense T2 lesions) at baseline to the PS model and repeated the analysis. MRI information was reported by the practicing neurologists according to the local MRI protocols and policies. Due to the sparse frequency of MRI, the baseline MRI was defined as the closest brain MRI taken within 12 months before, or 6 months after, the start date of treatment. The missing values were handled with multiple imputations. Overall, 20 imputed data sets were generated, and the estimates were computed separately and then combined using Rubin's rules.[36] Third, an intention-to-treat analysis was conducted with the start of study therapies and censoring at either event occurrence or the end of the follow-up. Fourth, the intention-to-treat analyses were repeated using patients with any duration of on-treatment follow-up (ie, not excluding patients who discontinued the switch therapy before 6 months.) Fifth, to eliminate possible confounding by country, we added country (Australia/others) to the PS model and reran the analysis with the newly generated weights. Sixth, to test the consistency of results across different baseline EDSS, we redefined baseline EDSS as obtained 6 months before or 1 month after the new treatment. Seventh, to mitigate the possible influence of different reasons for fingolimod discontinuation, we added it as a categorical variable to the PS model and repeated the analysis. Eighth, we also conducted an analysis with all patients censored at 1 year of follow-up to eliminate the possible effect in three treatment groups due to the different length of the follow-up. Ninth, to eliminate the potential effect of different approved dates, we conducted an analysis limiting to patients who started the study therapies after 1 January 2018.

RESULTS

Study population

We assessed the eligibility of a total of 62 100 patients with MS from MSBase (figure 1). Following the selection criteria fulfilment, we included 1045 patients from 26 countries and 64 centres who had discontinued fingolimod. Among them, 445 patients were treated with ocrelizumab (median [IQR] follow-up period: 1.8 [1.2–2.4] years), 76 were treated with cladribine (1.1 [0.9–1.8] years) and 524 were treated with natalizumab (3.6 [1.9–5.3] years) between 24 May 2010 and 13 November 2020.

Baseline characteristics of the original (non-weighted) study population are presented in table 1 and of the weighted study population were presented in online supplemental eTable 1. Before weighting, natalizumab users were more likely to be younger, have a shorter disease duration and a shorter period of fingolimod use compared with cladribine or ocrelizumab users. The baseline EDSS score and the number of previous treatments used were similar between the three groups. The main difference between the three treatment groups was the number of relapses in the 1 and 2 years prior to the treatment switch, with the highest relapse rate in the natalizumab group and the lowest rate in the cladribine group (table 1). After weighting, all baseline covariates were balanced (ASD<0.1).

Effectiveness

The mean ARR for ocrelizumab (IPTW-weighted ARR, 0.07; 95% CI, 0.04 to 0.13), cladribine (0.25; 95% CI, 0.12 to 0.57) and natalizumab (0.11; 95% CI, 0.09 to 0.14) were obtained using the negative binomial model. The IPTW-weighted ARR ratios between treatment groups were reported in figure 2. Ocrelizumab use was associated with a statistically significant reduction in ARR by 33% when compared with natalizumab; cladribine was less effective than natalizumab, with an ARR ratio of 2.31 (95% CI, 1.30 to 4.10). Consistent results were observed in the cumulative hazards of time to first relapse. The cumulative hazard of experiencing the first relapse in the ocrelizumab users was 43% lower than that in the natalizumab users over time (IPTW-weighted HR, 0.57; 95% CI, 0.40 to 0.83). In addition, the cumulative hazard curves for ocrelizumab and natalizumab were similar until about 5 months, after which the hazard of the first relapse was significantly increased in the natalizumab group compared with ocrelizumab (figure 3). There were no significant differences in the cumulative hazards of time to first relapse between cladribine and natalizumab users (IPTW-weighted HR, 1.18; 95% CI, 0.47 to 2.93).

Because the number of patients with cladribine was insufficient in the EDSS progression analyses, we only compared ocrelizumab with natalizumab. There was no significant difference in the cumulative hazard of disability accumulation between the ocrelizumab and natalizumab users (IPTW-weighted HR, 0.81;

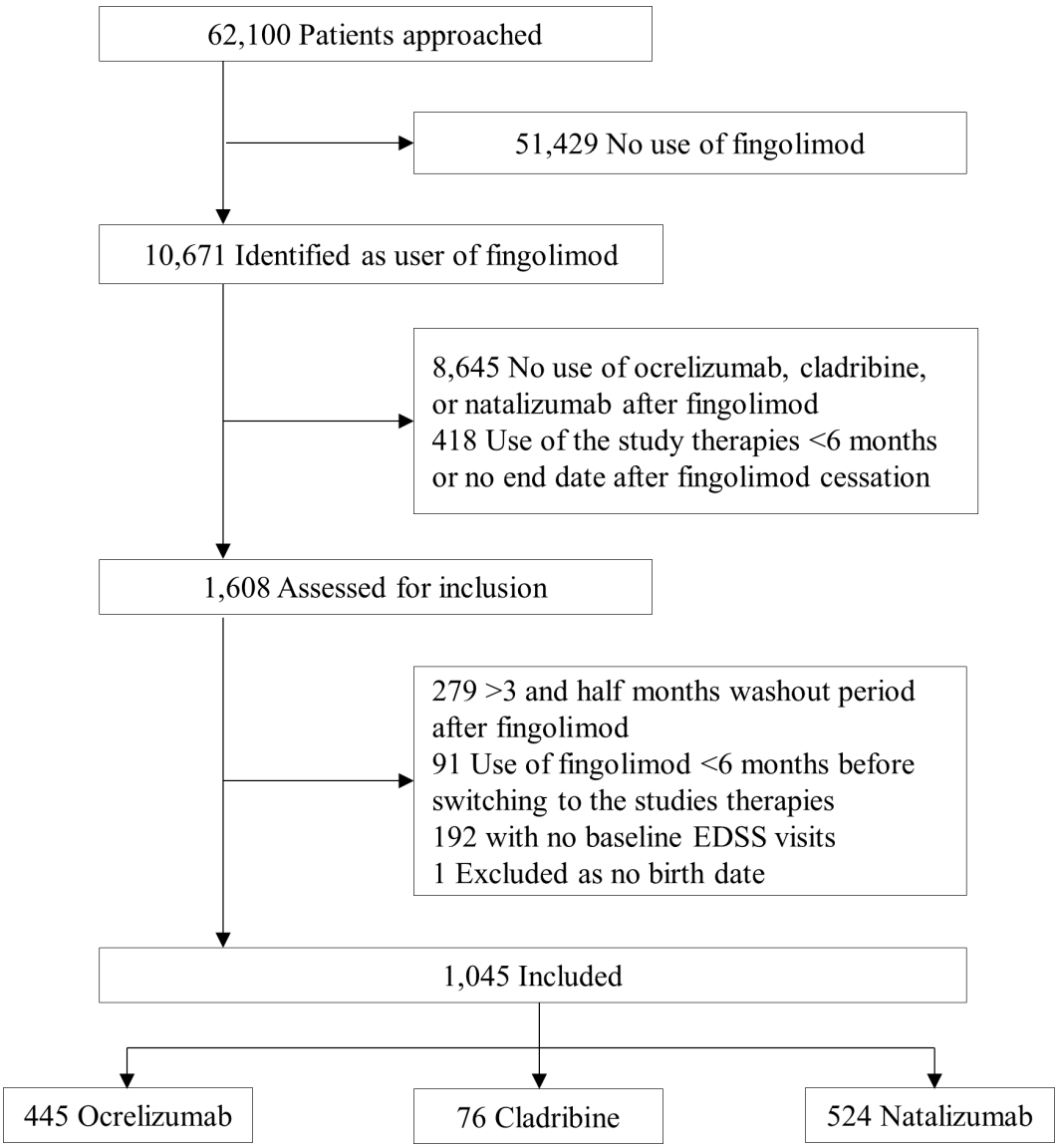

Figure 1 Flow chart of the patients inclusion/exclusion. EDSS, Expanded Disability Status Scale; MS, multiple sclerosis.

95% CI, 0.49 to 1.35). However, the probability of disability improvement in the ocrelizumab users was 51% lower than natalizumab users (IPTW-weighted HR, 0.49; 95% CI, 0.32 to 0.73) (figure 2). Of those who improved, 79% of patients in the natalizumab group maintained improvement until the end of follow-up, with a median follow-up of 1.6 years and 83% of patients in the ocrelizumab group maintained improvement, with a median follow-up of 1.1 years (online supplemental eTable 2).

Treatment discontinuation

There was no significant difference in treatment discontinuation between cladribine and natalizumab users (IPTW-weighted HR, 0.74; 95% CI, 0.26 to 2.10). In contrast, the hazard of treatment discontinuation was 89% lower in the ocrelizumab users compared with natalizumab users (IPTW-weighted HR, 0.11; 95% CI, 0.07 to 0.20). The Kaplan-Meier cumulative probability of discontinuation curves were shown in figure 3. The most reported reason for treatment discontinuation in the natalizumab and cladribine users was scheduled stop (36% and 50%) and in the ocrelizumab users was adverse events (18%) (online supplemental eTable 3). Of the three treatment groups, the most reported reason for fingolimod discontinuation was lack of efficacy (cladribine 35%, ocrelizumab 56% and natalizumab 64%) (online supplemental eTable 4).

Sensitivity analyses

We assessed the association between the primary outcome and the treatment groups using a doubly robust approach, and there was no evidence of substantial change in outcome (online supplemental eFigure 1). Consistency of the primary results was maintained in the remainder of the sensitivity analyses (online supplemental eFigure 2–8), except for a loss of statistical significance observed in the switch-date restricted analysis after 1 January 2018 due to the major loss of patients in the natalizumab group and, therefore, lack of power (online supplemental eFigure 9).

Primary outcome Annualized relapse rate	Number of events	Person-years	IPTW-weighted ARR (95% CI)	IPTW-weighted ARR ratio (95% CI)	p value
Ocrelizumab (n = 445)	55	763.58	0.07 (0.04, 0.13)	0.67 (0.47, 0.96)	0.03
Cladribine (n = 76)	14	94.05	0.25 (0.12, 0.57)	2.31 (1.30, 4.10)	<0.01
Natalizumab (n = 524)	147	1270.92	0.11 (0.09, 0.14)	1.00 (reference)	-
Time to first relapse				**HR (95% CI)**	
Ocrelizumab (n = 445)	47	-	-	0.57 (0.40, 0.83)	<0.01
Cladribine (n = 76)	9	-	-	1.18 (0.47, 2.93)	0.73
Natalizumab (n = 524)	110	-	-	1.00 (reference)	-
Secondary outcome					
Treatment discontinuation					
Ocrelizumab (n = 445)	17	-	-	0.11 (0.07, 0.20)	<0.01
Cladribine (n = 76)	6	-	-	0.74 (0.26, 2.10)	0.57
Natalizumab (n = 524)	206	-	-	1.00 (reference)	-
Disability accumulation					
Ocrelizumab (n = 322)	32	-	-	0.81 (0.49, 1.35)	0.42
Natalizumab (n = 374)	54	-	-	1.00 (reference)	-
Disability improvement					
Ocrelizumab (n = 322)	40	-	-	0.49 (0.32, 0.73)	<0.01
Natalizumab (n = 374)	96	-	-	1.00 (reference)	-

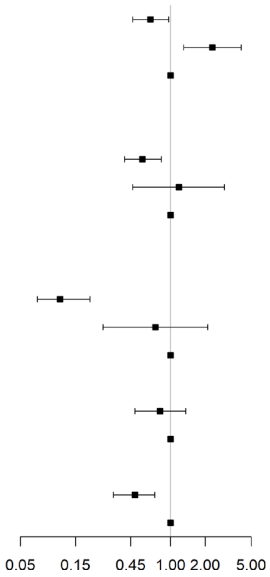

Figure 2 The annualised relapse rate and the hazards of study outcomes weighted using IPTW. ARR, annualised relapse rate; IPTW, inverse-probability-treatment-weighting.

DISCUSSION

This retrospective analysis of 1045 patients with MS compared the effectiveness of switch to ocrelizumab, natalizumab and cladribine following the discontinuation of fingolimod. Compared with natalizumab users, the ARR was statistically significantly lower in ocrelizumab users but higher in cladribine users. Consistently, the incidence of the time to first relapse and discontinuation rate were significantly lower in the ocrelizumab users compared with natalizumab users. Cladribine and natalizumab use were not significantly different for time to first relapse and discontinuation, acknowledging that this analysis was likely underpowered due to the relatively small sample size of cladribine users. Natalizumab was associated with a higher probability of sustained disability improvement than ocrelizumab. No significant difference in disability accumulation was found between the two groups.

In this cohort, natalizumab was associated with a higher ARR and shorter time to first relapse than ocrelizumab, yet natalizumab has a higher rate of sustained disability improvement than ocrelizumab. Our results comparing ocrelizumab to natalizumab appear to be inconsistent. However, we do not consider these results to be contradictory as EDSS improvement likely relates to the cessation of ongoing lesional central nervous system inflammation and enhanced remyelination whereas prevention of new relapses relates to new lesion formation. These mechanisms could easily be differentially affected by the different mechanisms of action of natalizumab and ocrelizumab.

It might also be unexpected that, in relation to relapse prevention, ocrelizumab was found to be more effective than natalizumab. This could relate to the particular patient population being studied, namely patients ceasing fingolimod due to recurrent disease activity. Perhaps in these patients, a drug mechanism interfering with lymphocyte migration (ie, fingolimod, natalizumab) could be less effective than one targeting B cell functions (ie, ocrelizumab). Our results are consistent with a prior comparative study of rituximab versus natalizumab. Like ocrelizumab, rituximab is also a monoclonal antibody targeting the B cell surface antigen CD20. A retrospective cohort study found that natalizumab use was associated with an increased relapse rate (HR 5.1; 95% CI, 1.20 to 22.20) and increased treatment discontinuation rate (HR, 13.90; 95% CI, 3.80 to 50.60) compared with rituximab.[37] Another retrospective observational study found that rituximab was superior to natalizumab in medication persistence (HR, 0.05; 95% CI, 0.01 to 0.38) but not in control of disease activity.[38] The authors stated that the latter result was possibly due to the small number of participants (n=48) in the rituximab group. An observational study of 740 patients showed no difference in the time to first relapse and EDSS worsening between anti-CD20 use (including ocrelizumab [n=59] and rituximab [n=278]) and natalizumab use (n=403), with an HR of 1.04 (95% CI, 0.74 to 1.46) and 1.13 (95% CI, 0.75 to 1.70) respectively.[39] Overall, their result of EDSS progression were consistent with ours. The result of time to first relapse in their study is inconsistent with ours and this may be explained by the different descriptions of relapse rate and analysis methodology used in the two studies.

Previous studies have compared the efficacy of ocrelizumab, cladribine and natalizumab separately. A PS-matched study comparing cladribine with natalizumab showed that the cladribine users were more likely to experience a relapse than the natalizumab users (HR, 1.80; 95% CI, 1.08 to 2.97).[40] A cohort study using data from two MS data sets reported that patients treated with cladribine had a significantly higher ARR than those treated with natalizumab (ARR ratio, 2.13; 95% CI, 1.17 to 3.88).[41] Both studies support our results. Two network meta-analyses reported no significant difference in the efficacy between cladribine, ocrelizumab and natalizumab (cladribine vs ocrelizumab ARR ratio 1.06, 95% CI, 0.78 to 1.45, and cladribine vs natalizumab 1.16, 95% CI, 0.89 to 1.53[21]; cladribine vs ocrelizumab ARR ratio 1.14, 95% CI, 0.81 to 1.60, and cladribine vs natalizumab 1.22, 95% CI, 0.89 to 1.68[42]), but the trend of these results was comparable with ours. However, the sample size of the cladribine group is small in our study, limiting the conclusions for this treatment. Future studies will be needed to confirm our findings.

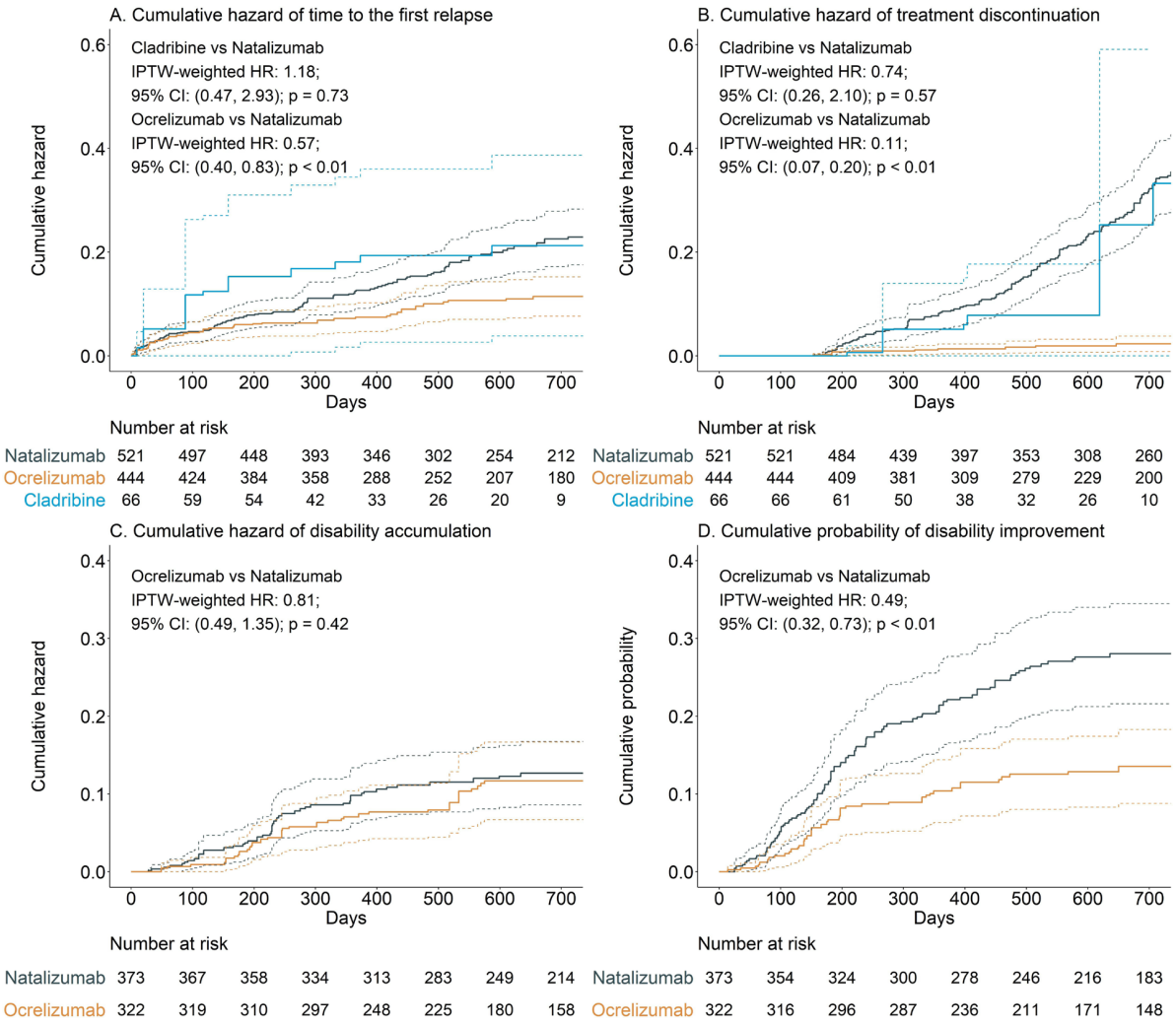

Figure 3 IPTW-weighted cumulative hazard of primary and secondary outcomes. Weighted Kaplan-Meier failure function was applied to present cumulative hazard of the (A) time to the first relapse in cladribine users (blue line), natalizumab users (black line) and ocrelizumab users (khaki line), and (B) treatment discontinuation, respectively. For (C) disability accumulation and (D) disability improvement, the plots were drawn from the weighted cumulative hazard models on the basis of separate propensity score models. Cladribine was not included due to the insufficient number of participants. IPTW, inverse-probability- treatment-weighting.

In addition, to our knowledge, a three-way comparison of efficacy and persistence among the three treatments is novel and necessary, as all are reasonable choices for subsequent DMT after fingolimod cessation.

Limitations

First, this study is an observational study and treatment indication bias is inevitable. To address this question, We used an IPTW approach that has been shown to be superior to the conventional adjustment approach in mitigating treatment indication bias. It allows observational studies to be designed similar to randomised experiments and estimates the causal effect based on all eligible participants.[29] Second, the sample size of cladribine users is still relatively small, as cladribine has only been approved in the last 2–3 years in most parts of the world. However, it is important to perform this analysis as the relevant treatment decisions are current. Overall, 70% of the cladribine users were from Australian centres, where cladribine is a popular treatment choice. The potential confounding influence due to country was assessed in a sensitivity analysis, and the results were consistent. Furthermore, we did not incorporate the MRI data in the primary PS model in our main analyses as only 38% of study participants had this information. However, we conducted a sensitivity analysis using MRI information, in combination with the data obtained by multiple imputations, and the results were consistent. Drug safety is an important part for comparing the net clinical benefit of different DMTs, especially in long-term. The collection of safety data from patients involved in the MSBase is currently underway.

CONCLUSION

In patients with RRMS who discontinue fingolimod and commence another disease-modifying treatment within 3 months, ocrelizumab was associated with a significant reduction in ARRs, longer time to first relapse and a lower discontinuation rate compared with cladribine and natalizumab. Natalizumab was associated with better sustained disability improvement compared with ocrelizumab. The relapse rates in all treatment groups were relatively low, suggesting that all these three DMTs are feasible and reasonable treatment options.

Author affiliations
[1]Department of Neuroscience, Central Clinical School, Monash University, Melbourne, Victoria, Australia
[2]Menzies Institute for Medical Research, University of Tasmania, Hobart, Tasmania, Australia
[3]Clinical Outcomes Research Unit, Department of Medicine, The University of Melbourne, Melbourne, Victoria, Australia
[4]Department of Neurology, Royal Melbourne Hospital, Melbourne, Victoria, Australia
[5]Dokuz Eylul University, İzmir, Turkey
[6]Department of Neurology, Alfred Hospital, Melbourne, Victoria, Australia
[7]Neurologic Clinic and Policlinic, Departments of Medicine and Clinical Research, University Hospital and University of Basel, Basel, Switzerland
[8]Departments of Nephrology and Neurology, Liverpool Hospital, Sydney, New South Wales, Australia
[9]KTU Medical Faculty Farabi Hospital, Trabzon, Turkey
[10]Division of Neurology, Amiri Hospital, Sharq, Kuwait
[11]Department of Neurology, John Hunter Hospital, Newcastle, New South Wales, Australia
[12]School of Medicine and Public Health, University Newcastle, Newcastle, New South Wales, Australia
[13]Brain and Mind Centre, University of Sydney, Sydney, New South Wales, Australia
[14]Hospital Universitario Virgen Macarena, Sevilla, Spain
[15]Hôpital Notre Dame, CHUM and Universite de Montreal, Montreal, Québec, Canada
[16]Department of Neurology and Center of Clinical Neuroscience, First Faculty of Medicine, Charles University in Prague and General University Hospital, Prague, Czech Republic
[17]Austin Health, Melbourne, Victoria, Australia
[18]Department of Medical and Surgical Sciences and Advanced Technologies, GF Ingrassia, Catania, Italy
[19]Multiple Sclerosis Center, University of Catania, Catania, Italy
[20]Nehme and Therese Tohme Multiple Sclerosis Center, American University of Beirut Medical Center, Beirut, Lebanon
[21]Flinders University, Adelaide, South Australia, Australia
[22]Department of Neurology, Faculty of Medicine, Hacettepe University, Ankara, Turkey
[23]Department of Neuroscience, Imaging, and Clinical Sciences, University G. d'Annunzio, Chieti, Italy
[24]Cliniques Universitaires Saint-Luc, Brussels, Belgium
[25]Centre integre de sante et de services sociaux des Laurentides point de service de Saint-Jerome, Saint-Jerome, Quebec, Canada

Acknowledgements We wish to thank all of the patients and their caregivers who participated in this study and contributed data to the MSBase registry.

Contributors Guarantor: CZ. Concept and design: CZ, AvdW and HB. Acquisition, analysis or interpretation of data: CZ, ZZ, AvdW and HB. Drafting of the manuscript: CZ. Critical revision of the manuscript for important intellectual content: All authors. Statistical analysis: CZ and ZZ. Administrative, technical or material support: AvdW and HB. Supervision: AvdW and HB.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests CZ, OS, RM, AP, JK, MO, RK, SO, DM, IR and ZZ report no disclosures. VJ received conference travel support from Merck and Roche and speaker's honoraria from Biogen and Roche outside of the submitted work. She receives research support from the Australian National Health and Medical Research Grant and MS Research Australia. MB received conference travel support from Biogen and Novartis. His institution has received research support from Biogen, Merck and Novartis. TK received conference travel support and/or speaker honoraria from WebMD Global, Eisai, Novartis, Biogen, Sanofi-Genzyme, Teva, BioCSL and Merck and received research or educational event support from Biogen, Novartis, Genzyme, Roche, Celgene and Merck. JL-S received travel compensation from Novartis, Biogen, Roche and Merck. Her institution receives the honoraria for talks and advisory board commitment and research grants from Biogen, Merck, Roche, TEVA and Novartis. SJK received compensation for scientific advisory board activity from Merck and Roche. SH received honoraria and consulting fees from Novartis, Bayer Schering and Sanofi, and travel grants from Novartis, Biogen Idec and Bayer Schering. MS participated in, but not received honoraria for, advisory board activity for Biogen, Merck, Bayer Schering, Sanofi Aventis and Novartis. AvdW 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 also received grant support from the National Health and Medical Research Council of Australia and MS Research Australia. VVP has received travel grants from Merck Healthcare KGaA (Darmstadt, Germany), Biogen, Sanofi, Bristol Meyer Squibb, Almirall and Roche. His institution has received research grants and consultancy fees from Roche, Biogen, Sanofi, Merck Healthcare KGaA (Darmstadt, Germany), Bristol Meyer Squibb, Janssen, Almirall and Novartis Pharma. JP received travel compensation from Novartis, Biogen, Genzyme and Teva, and speaking honoraria from Biogen, Novartis, Genzyme and Teva. DH received speaker honoraria and consulting fees from Biogen, Merck, Teva, Roche, Sanofi Genzyme and Novartis, as well as support for research activities from Biogen and Czech Ministry of Education. EKH received honoraria/research support from Biogen, Merck Serono, Novartis, Roche and Teva. GI received speaking honoraria from Biogen, Novartis, Sanofi, Merck, Roche, Almirall and Teva. FP received speaker honoraria and advisory board fees from Almirall, Bayer, Biogen, Celgene, Merck, Novartis, Roche, Sanofi-Genzyme and TEVA. He received research funding from Biogen, Merck, FISM (Fondazione Italiana Sclerosi Multipla), Reload Onlus Association and University of Catania. RA received honoraria as a speaker and for serving on scientific advisory boards from Bayer, Biogen, GSK, Merck, Novartis, Roche and Sanofi-Genzyme. CB received conference travel support from Biogen, Novartis, Bayer-Schering, Merck and Teva; he participated in Sanofi Aventis, Roche and Novartis clinical trials. MM has served on advisory board for Merck, has received speaker honoraria from Merck and Biogen. Her institution receives funding from Merck, Australian National Health Medical Research Council, Brain Foundation, Charles and Sylvia Viertel Foundation, Bethlehem Griffith Foundation and MS Research Australia. HB has 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.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by The Alfred Health Human Research and Ethic Committee No 528/12, Version: 7, Dated 7 May 2020. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. In principle, patient-level data sharing is possible. However, permission from each contributing data controller is required.

ORCID iDs
Chao Zhu http://orcid.org/0000-0003-3951-7501
Izanne Roos http://orcid.org/0000-0003-0371-3666
Tomas Kalincik http://orcid.org/0000-0003-3778-1376
Michael Barnett http://orcid.org/0000-0002-2156-8864
Samia Joseph Khoury http://orcid.org/0000-0003-3198-6063
Marco Onofrj http://orcid.org/0000-0002-0480-2495
Vilija Jokubaitis http://orcid.org/0000-0002-3942-4340
Anneke van der Walt http://orcid.org/0000-0002-4278-7003

REFERENCES

1 Kappos L, Radue E-W, O'Connor P, *et al*. A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis. *N Engl J Med* 2010;362:387–401.
2 Khatri B, Barkhof F, Comi G, *et al*. Comparison of fingolimod with interferon beta-1a in relapsing-remitting multiple sclerosis: a randomised extension of the transforms study. *Lancet Neurol* 2011;10:520–9.
3 Devonshire V, Havrdova E, Radue EW, *et al*. Relapse and disability outcomes in patients with multiple sclerosis treated with fingolimod: subgroup analyses of the double-blind, randomised, placebo-controlled freedoms study. *Lancet Neurol* 2012;11:420–8.
4 Calabresi PA, Radue E-W, Goodin D, *et al*. Safety and efficacy of fingolimod in patients with relapsing-remitting multiple sclerosis (freedoms II): a double-blind, randomised, placebo-controlled, phase 3 trial. *Lancet Neurol* 2014;13:545–56.
5 Sorensen PS. New management algorithms in multiple sclerosis. *Curr Opin Neurol* 2014;27:246–59.
6 Merkel B, Butzkueven H, Traboulsee AL, *et al*. Timing of high-efficacy therapy in relapsing-remitting multiple sclerosis: a systematic review. *Autoimmun Rev* 2017;16:658–65.
7 Berger B, Baumgartner A, Rauer S, *et al*. Severe disease reactivation in four patients with relapsing-remitting multiple sclerosis after fingolimod cessation. *J Neuroimmunol* 2015;282:118–22.
8 Hatcher SE, Waubant E, Nourbakhsh B, *et al*. Rebound syndrome in patients with multiple sclerosis after cessation of fingolimod treatment. *JAMA Neurol* 2016;73:790–4.

9 Genovese MC, Kaine JL, Lowenstein MB, *et al*. Ocrelizumab, a humanized anti-CD20 monoclonal antibody, in the treatment of patients with rheumatoid arthritis: a phase I/II randomized, blinded, placebo-controlled, dose-ranging study. *Arthritis Rheum* 2008;58:2652–61.
10 DiLillo DJ, Hamaguchi Y, Ueda Y, *et al*. Maintenance of long-lived plasma cells and serological memory despite mature and memory B cell depletion during CD20 immunotherapy in mice. *J Immunol* 2008;180:361–71.
11 Montalban X, Hauser SL, Kappos L, *et al*. Ocrelizumab versus placebo in primary progressive multiple sclerosis. *N Engl J Med* 2017;376:209–20.
12 Baker D, Herrod SS, Alvarez-Gonzalez C, *et al*. Both cladribine and alemtuzumab may effect MS via B-cell depletion. *Neurol Neuroimmunol Neuroinflamm* 2017;4:e360.
13 Giovannoni G. Cladribine to treat relapsing forms of multiple sclerosis. *Neurotherapeutics* 2017;14:874–87.
14 Giovannoni G, Soelberg Sorensen P, Cook S, *et al*. Safety and efficacy of cladribine tablets in patients with relapsing-remitting multiple sclerosis: results from the randomized extension trial of the clarity study. *Mult Scler* 2018;24:1594–604.
15 Baker D, Pryce G, Herrod SS, *et al*. Potential mechanisms of action related to the efficacy and safety of cladribine. *Mult Scler Relat Disord* 2019;30:176–86.
16 Giovannoni G, Comi G, Cook S, *et al*. A placebo-controlled trial of oral cladribine for relapsing multiple sclerosis. *N Engl J Med* 2010;362:416–26.
17 Miller DH, Khan OA, Sheremata WA, *et al*. A controlled trial of natalizumab for relapsing multiple sclerosis. *N Engl J Med* 2003;348:15–23.
18 Polman CH, O'Connor PW, Havrdova E, *et al*. A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. *N Engl J Med* 2006;354:899–910.
19 Rudick RA, Stuart WH, Calabresi PA, *et al*. Natalizumab plus interferon beta-1a for relapsing multiple sclerosis. *N Engl J Med* 2006;354:911–23.
20 Alroughani R, Inshasi JS, Deleu D, *et al*. An overview of high-efficacy drugs for multiple sclerosis: Gulf region expert opinion. *Neurol Ther* 2019;8:13–23.
21 Berardi A, Siddiqui MK, Treharne C, *et al*. Estimating the comparative efficacy of cladribine tablets versus alternative disease modifying treatments in active relapsing-remitting multiple sclerosis: adjusting for patient characteristics using meta-regression and matching-adjusted indirect treatment comparison approaches. *Curr Med Res Opin* 2019;35:1371–8.
22 McCool R, Wilson K, Arber M, *et al*. Systematic review and network meta-analysis comparing ocrelizumab with other treatments for relapsing multiple sclerosis. *Mult Scler Relat Disord* 2019;29:55–61.
23 Butzkueven H, Chapman J, Cristiano E, *et al*. MSBase: an international, online registry and platform for collaborative outcomes research in multiple sclerosis. *Mult Scler* 2006;12:769–74.
24 Polman CH, Reingold SC, Edan G, *et al*. Diagnostic criteria for multiple sclerosis: 2005 revisions to the "McDonald Criteria". *Ann Neurol* 2005;58:840–6.
25 Polman CH, Reingold SC, Banwell B, *et al*. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. *Ann Neurol* 2011;69:292–302.
26 Kalincik T, Kuhle J, Pucci E, *et al*. Data quality evaluation for observational multiple sclerosis registries. *Mult Scler* 2017;23:647–55.
27 Schumacher GA, Beebe G, Kibler RF, *et al*. Problems of experimental trials of therapy in multiple sclerosis: report by the panel on the evaluation of experimental trials of therapy in multiple sclerosis. *Ann N Y Acad Sci* 1965;122:552–68.
28 Imbens G. The role of the propensity score in estimating dose-response functions. *Biometrika* 2000;87:706–10.
29 Austin PC, Stuart EA. Moving towards best practice when using inverse probability of treatment weighting (IPTW) using the propensity score to estimate causal treatment effects in observational studies. *Stat Med* 2015;34:3661–79.
30 Lee BK, Lessler J, Stuart EA. Weight trimming and propensity score weighting. *PLoS One* 2011;6:e18174.
31 Xu S, Ross C, Raebel MA, *et al*. Use of stabilized inverse propensity scores as weights to directly estimate relative risk and its confidence intervals. *Value Health* 2010;13:273–7.
32 Austin PC. An introduction to propensity score methods for reducing the effects of confounding in observational studies. *Multivariate Behav Res* 2011;46:399–424.
33 Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. *Stat Med* 2009;28:3083–107.
34 Schoenfeld D. Chi-squared goodness-of-fit tests for the proportional hazards regression model. *Biometrika* 1980;67:145–53.
35 Funk MJ, Westreich D, Wiesen C, *et al*. Doubly robust estimation of causal effects. *Am J Epidemiol* 2011;173:761–7.
36 Rubin DB. *Multiple imputation for survey nonresponse*. New York: Wiley, 1987.
37 Granqvist M, Boremalm M, Poorghobad A, *et al*. Comparative effectiveness of rituximab and other initial treatment choices for multiple sclerosis. *JAMA Neurol* 2018;75:320–7.
38 Boremalm M, Juto A, Axelsson M, *et al*. Natalizumab, rituximab and fingolimod as escalation therapy in multiple sclerosis. *Eur J Neurol* 2019;26:1060–7.
39 Rollot F, Couturier J, Casey R, *et al*. Comparative effectiveness of natalizumab versus anti-CD20 in highly active relapsing-remitting multiple sclerosis after fingolimod withdrawal. *Neurotherapeutics* 2022;19:476–90.
40 Kalincik T, Jokubaitis V, Spelman T, *et al*. Cladribine versus fingolimod, natalizumab and interferon β for multiple sclerosis. *Mult Scler* 2018;24:1617–26.
41 Signori A, Saccà F, Lanzillo R, *et al*. Cladribine vs other drugs in MS: merging randomized trial with real-life data. *Neurol Neuroimmunol Neuroinflamm* 2020;7. doi:10.1212/NXI.0000000000000878. [Epub ahead of print: 14 08 2020].
42 Siddiqui MK, Khurana IS, Budhia S, *et al*. Systematic literature review and network meta-analysis of cladribine tablets versus alternative disease-modifying treatments for relapsing-remitting multiple sclerosis. *Curr Med Res Opin* 2018;34:1361–71.