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Comparison between dimethyl fumarate, fingolimod, and ocrelizumab after natalizumab cessation

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Key Points

Question: Is there any difference in the effectiveness and treatment persistence between dimethyl fumarate, fingolimod, and ocrelizumab among patients with relapsing-remitting multiple sclerosis (RRMS) who switched from natalizumab?

Findings: In this observational study, including 1,386 patients with RRMS who ceased natalizumab, switch to ocrelizumab was associated with the lowest annualized relapse rate and discontinuation rates, and the longest time to first relapse compared to dimethyl fumarate and fingolimod.

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

Abstract

Importance: Natalizumab cessation is associated with a risk of rebound disease activity. It is important to identify the optimal switch disease-modifying therapy (DMT) strategy after natalizumab to limit the risk of severe relapses.

Objectives: To compare the effectiveness and persistence of dimethyl fumarate (DMF), fingolimod, and ocrelizumab among relapsing-remitting multiple sclerosis (RRMS) patients who discontinued natalizumab.

Design: In this observational cohort study, patient data were collected from the MSBase registry between June 15, 2010 and July 06, 2021. Data were analyzed from May 24, 2022, to Jan 9, 2023. The median follow-up was 2.7 years.

Setting: Multicenter.

Participants: Among 66,840 RRMS patients, 1,744 had used natalizumab for ≥6 months and then switched to DMF, fingolimod, or ocrelizumab within 3 months after natalizumab discontinuation. After excluding 358 patients without baseline data, 1386 were included in the analytic cohort.

Exposures: DMF, fingolimod, and ocrelizumab.

Main Outcomes and Measures: Primary outcomes were annualized relapse rate (ARR) and time to first relapse. Secondary outcomes were confirmed disability accumulation, disability improvement, and subsequent treatment discontinuation, with the comparisons for the first two limited to fingolimod and ocrelizumab due to the small number of DMF users. We analyzed the associations after balancing covariates using an inverse-probability-treatment-weighting method.

Results: Overall, 1386 patients (71% female, mean age: 41.3 [SD:10.6]) switched to DMF (n=138), fingolimod (n=823), or ocrelizumab (n=425) after natalizumab. The ARR for ocrelizumab was 0.06, fingolimod, 0.26, and DMF, 0.27. The ARR ratio (95% CI) of fingolimod to ocrelizumab was 4.33 (3.12-6.01) and of DMF to ocrelizumab was 4.50 (2.89-7.03). Compared to ocrelizumab, the hazard ratio (HR) of time to first relapse was 4.02 (2.83-5.70) for fingolimod, 3.70 (2.35-5.84) for DMF; the HR of treatment discontinuation was 2.57 (1.74-3.80) for fingolimod and 4.26 (2.65-6.84) for DMF. Fingolimod use was associated with a 49% higher risk for disability accumulation compared to ocrelizumab. There was no significant difference in disability improvement rates between fingolimod and ocrelizumab.

Conclusion and Relevance: Among RRMS patients who switched from natalizumab to DMF, fingolimod, or ocrelizumab, ocrelizumab use was associated with the lowest ARR and discontinuation rates, and the longest time to first relapse.

Introduction

Natalizumab is a monoclonal antibody against α_4 integrin that prevents the development of multiple sclerosis (MS) lesions by interfering with $\alpha_4\beta_1$ and $\alpha_4\beta_7$ integrin binding to the endothelial ligand vascular cell adhesion molecule-1 (VCAM-1).[1, 2] Three randomized trials have demonstrated the efficacy of natalizumab in controlling relapsing-remitting MS (RRMS).[3-5] However, the long-term use of natalizumab is of concern due to an increased risk of progressive multifocal leukoencephalopathy (PML),[6, 7] an opportunistic brain infection caused by the JC virus (JCV).[8, 9] Therefore, in patients who are, or become, anti-JCV antibody positive, natalizumab is often discontinued to mitigate PML risk.[10-12] Patients are usually switched to an alternative disease-modifying therapy (DMT) after natalizumab cessation because this group is intrinsically at high relapse risk. One special concern after natalizumab cessation is rebound disease activity, which can occur around 12 weeks after cessation due to its relatively rapid offset of efficacy.[13-15]

Fingolimod, a functional antagonist of sphingosine-1-phosphate receptors that is effective in reducing relapse rate and improving MRI outcomes in RRMS,[16, 17] is commonly used after natalizumab cessation.[10, 12, 18-21] Dimethyl fumarate[22-24] and ocrelizumab are two other options[25, 26]. Dimethyl fumarate is effective in downregulating the pro-inflammatory responses of T-cells, B-cells, and myeloid cells.[27, 28] Ocrelizumab is a B-cell depleting humanized monoclonal antibody, which has shown a significant efficacy in reducing disease activity and MRI progression compared to interferon-beta in two phase 3 trials.[29, 30] However, evidence has been inconsistent regarding the comparative efficacy of these three common DMTs after switching from natalizumab,[22, 23, 31, 32] and a direct comparison between them is lacking.

We, therefore, conducted a retrospective study to directly compare the treatment outcomes in participants treated with dimethyl fumarate, fingolimod, or ocrelizumab after natalizumab cessation using the MSBase registry dataset.[33] We evaluated relapse activity, disability accumulation and improvement, and persistence of the three therapies to inform the selection of the optimal DMT for RRMS patients who discontinue natalizumab.

Methods

Patient data were obtained from the MSBase registry, an international observational cohort study of MS.[33] Ethical approval for the MSBase registry was granted by the Alfred Health Human Research and Ethics

Committee and the local ethics committees in participating centers. All enrolled patients provided written or verbal consent under local regulations. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

Study Population

Patients were included if they were diagnosed with RRMS according to the McDonald criteria,[32] had taken natalizumab monotherapy for ⩾6 months before discontinuation, and switched to either dimethyl fumarate, fingolimod, or ocrelizumab with a minimum treatment persistence of 6 months. To minimize the loss of treatment effect and reduce the risk of contaminating the analysis with rebound relapse activity, we only included patients with a treatment gap ⩽3 months.[10] Participants were also required to have at least 2 subsequent visits with a minimum 6-month gap and with recorded Expanded Disability Status Scale (EDSS, a nonlinear ordinal disability scale with range 0–10) during the follow-up to allow for the ascertainment of disability accumulation or improvement. Patients were excluded if they had any missing data for sex, age, the date of starting and stopping natalizumab, and the date of starting and stopping a new treatment after natalizumab cessation. Patient data were recorded during routine clinic visits at participating centers via the locally installed iMed or MDS MSBase data entry systems and monitored through a series of procedures to maintain quality.[34]

Study endpoints

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

The study baseline was defined as the date of new treatment commencement after natalizumab cessation. The EDSS obtained within 6 months before or after baseline was chosen as the baseline EDSS. We defined relapse as having new or recurrent neurological symptoms lasting for 24 hours or more without fever or infection.[35] Treatment discontinuation was defined as starting a new treatment. The primary reason for discontinuation was documented by the treating neurologist using pre-defined terms, but these data fell outside the MSBase minimum dataset requirements and the percentage of missing data was high. Nonetheless, "scheduled stop" was the main selected reason for discontinuing natalizumab, accounting for 62% of discontinuations (eTable 1 in Supplement).

Disability accumulation was defined as the confirmed increase in EDSS of ⩾ 0.5 steps for patients with a baseline score > 5.5, or ⩾ 1.0 steps for those with a baseline score between 1.0 and 5.5, and ⩾ 1.5 steps if the baseline score was 0. Disability improvement was defined as a decrease in EDSS by 1 step for baseline EDSS scores of 2-5.5, or 1.5 steps if baseline EDSS was 1.5 and 0.5 steps if baseline EDSS was >5.5. EDSS scores obtained less than 30 days after the relapse onset date were excluded to mitigate the risk of early disease activity being labeled as baseline EDSS. Confirmed disability accumulation or improvement was defined as observed disability accumulation or improvement for 2 subsequent visits compared with baseline EDSS scores, with a minimum of 6 months between each assessment.

Statistical analysis

The baseline characteristics are reported in Table 1. The inverse-probability-of-treatment-weighting (IPTW) was used to minimize baseline differences between the three treatment groups and selection bias.[36] The weights were obtained by taking the inverse of the propensity scores (PS), representing the probability of receiving a treatment conditional on observed covariates.[37] A multinomial logistic regression model was used to estimate the PS for each individual, with the treatment groups as a dependent variable and the baseline covariates listed in Table 1 as independent variables. To mitigate the influence of the extreme weights on the treatment effect, we stabilized the weights by multiplying the unstabilized weights by the proportion observed as treated or untreated in the data, respectively.[38] An absolute standardized difference (ASD) was calculated to evaluate covariate balance, with ASD>0.1 indicating an imbalance.[39]

We used an IPTW-weighted negative binomial model to compare the ARRs between the treatment groups, with the natural logarithm of the follow-up time after the baseline as an offset term, the relapse count as a dependent variable, and the treatment groups as an independent variable. Hazard ratios (HRs) of time-to-event outcomes were estimated using IPTW-weighted Cox proportional-hazards regression model with robust standard errors. Kaplan-Meier cumulative hazard curves were used to show the cumulative risk for each individual outcome across treatment groups. The proportional-hazards assumption was checked by the Schoenfeld global test, and no violation was detected.[40]

190 We performed subgroup analyses by the variables in Table 1 and the number of relapses one year before
191 natalizumab commencement. Due to the small number of dimethyl fumarate users, dimethyl fumarate and
192 fingolimod were grouped together into the 'moderate-efficacy' category.
193
194 All statistical tests were 2-sided with a significance defined as $P < .05$. All analyses were performed in R,
195 version 4.1.1. (R Foundation for Statistical Computing).
196

197 **Sensitivity analysis**

198 The robustness of the primary outcome results was tested with six sensitivity analyses. To assess the consistency
199 of our results, we first repeated the analysis using a doubly-robust standardization method.[41, 42] It combines the
200 IPTW with the G-computation[43] method to mitigate the risk of model misspecification and achieve the double
201 robustness property. Secondly, we repeated the analysis by adding baseline cerebral MRI information
202 (presence/absence of contrast-enhancing lesion and the number of hyperintense T2 lesions) into the model for
203 PS generation. MRI information was collected by practitioners in accordance with local MRI protocols and
204 policies. Baseline MRI was defined as the most recent MRI undertaken 12 months before or 6 months after the
205 start date of treatment. Multiple imputation method was used to deal with missing data (86% of patients missing
206 data on contrast-enhancing lesion and 76% on hyperintense T2 information). Twenty imputed datasets were
207 generated, and the estimates were computed separately and then combined using Rubin's rules.[44] We also
208 introduced the intention-to-treat analysis to check the result consistency in the situation with censoring at either
209 event occurrence or the end of the follow-up. We added country as a covariate to the PS model and redid the
210 analyses using newly generated weights. Moreover, we evaluated the influence of different baseline EDSS on
211 results by narrowing the time interval for obtaining baseline EDSS to 6 months before or 1 month after the new
212 treatment start. Lastly, we assessed potential bias introduced by the difference in disease activities between the
213 treatment groups prior to natalizumab start. We added the number of relapses one year before natalizumab start
214 as a covariate to the PS model and repeated the main analysis.
215

216 # Results

217 After fulfilling the selection criteria, 1,386 of 66,840 RRMS patients (between June 15th, 2010 and July 06th,
218 2021) from 26 countries and 79 centers were included in the analysis (Figure 1). Among them, 138 patients

219 were treated with dimethyl fumarate (median [IQR] follow-up: 2.0 [1.1-3.4] years), 823 were treated with
220 fingolimod (3.5 [1.7-5.3] years), and 425 were treated with ocrelizumab (2.1 [1.2-3.1] years).
221
222 Before weighting, the mean age of the three treatment groups differed significantly, with the dimethyl fumarate
223 group being the oldest, followed by the ocrelizumab group and the fingolimod group. Patients who had
224 experienced more relapses in the previous year were more likely to receive fingolimod, followed by
225 ocrelizumab and dimethyl fumarate (Table 1). After weighting, all variables were balanced (ASDs⩽0.1).
226 (eTable 2 in Supplement)
227

228 **Effectiveness**

229 The IPTW-weighted ARR (95% confidence interval [CI]) was 0.06 (0.04-0.08) for ocrelizumab users, 0.26
230 (0.12-0.48) for fingolimod users, and 0.27 (0.12-0.56) for dimethyl fumarate users. Ocrelizumab use was
231 associated with a significant reduction in ARR compared with fingolimod (fingolimod vs ocrelizumab IPTW-
232 weighted ARR ratio 4.33, 95% CI 3.12-6.01) and dimethyl fumarate (dimethyl fumarate vs ocrelizumab 4.50,
233 2.89-7.03). Similar results were found for the cumulative hazards of the first relapse. Fingolimod and dimethyl
234 fumarate users had a significantly higher risk of experiencing the first relapse than ocrelizumab users, with
235 IPTW-weighted HRs of 4.02 (95% CI, 2.83-5.70) and 3.70 (2.35-5.84), respectively (Figure 2). No significant
236 differences in any primary outcome were observed between fingolimod and dimethyl fumarate.
237
238 Due to the small number of patients who took dimethyl fumarate meeting confirmed EDSS progression criteria,
239 we only compared fingolimod users with ocrelizumab users. Compared with ocrelizumab, fingolimod was
240 associated with a significantly increased risk of confirmed disability accumulation (IPTW-weighted HR, 1.49;
241 95% CI, 1.07-2.07) (Figure 2). There was no difference in confirmed disability improvement rates (IPTW-
242 weighted HR, 1.01; 95% CI, 0.64-1.57).
243
244 Results in the defined subgroups were generally consistent with the results in the main analysis. Ocrelizumab
245 significantly interacted with baseline EDSS and the number of previous therapies on the primary outcomes
246 (P<.05 for interaction), with the greater association seen in patients with lower EDSS (<3) and those with
247 exposure to fewer DMTs (<2) before natalizumab (eTable 3 in supplement)
248

Persistence

The most commonly reported reason for treatment discontinuation with fingolimod and dimethyl fumarate were lack of efficacy (48% and 31%), and for ocrelizumab was adverse events (35%). The detailed reasons for treatment discontinuation were shown in Supplementary eTable 4. Compared to ocrelizumab, fingolimod and dimethyl fumarate were associated with a significant increase in treatment discontinuation rates over time, with IPTW-weighted HR of 2.57 (95% CI, 1.74-3.80) and 4.26 (2.65-6.84), respectively. Compared to dimethyl fumarate, fingolimod users were less likely to discontinue the treatment (IPTW-weighted HR, 0.60; 95% CI, 0.44-0.84). The Kaplan-Meier cumulative hazard curves are presented in Figure 3.

Results from all sensitivity analyses were consistent with the main analysis results (Supplementary eFigure 1-6). Details on the covariates balance after weighting between the treatment groups were reported along with the results.

Discussion

This retrospective study compared the effectiveness and persistence between ocrelizumab, fingolimod, and dimethyl fumarate after natalizumab cessation in 1,386 RRMS patients. Compared to fingolimod and dimethyl fumarate, ocrelizumab use was associated with a significant reduction in ARR and time to first relapse. No significant difference in ARR and time to first relapse was found between fingolimod and dimethyl fumarate users. The discontinuation rate was significantly lower in ocrelizumab users, followed by fingolimod and dimethyl fumarate. Due to a minority of patients taking dimethyl fumarate, we could only compare the disability accumulation and improvement between ocrelizumab and fingolimod. Ocrelizumab use was associated with a lower rate of sustained disability accumulation than fingolimod, but there was no significant difference in disability improvement. Given that patients treated with natalizumab typically have high intrinsic relapse risk and natalizumab cessation is associated with risk of rebound as its biological effect declines quickly,[15] our study is not, therefore, generalizable to other treatment switch scenarios or first-line therapy.

A previous study reported that fingolimod reduced the risk of relapse occurrence by 64% in comparison to interferon-β and glatiramer acetate after natalizumab cessation.[45] Another cohort study found that fingolimod successfully controlled disease activity in patients who had stopped natalizumab, with an ARR of 0.38.

278 Although the frequency of relapses was moderately higher than that during natalizumab treatment (ARR 0.26),
279 it was significantly lower than that before natalizumab was used (ARR 1.54).[10] We also found a relatively low
280 relapse rate in patients treated with fingolimod after natalizumab discontinuation, with an ARR of 0.26. We,
281 however, found that ocrelizumab is a better choice of switch DMT after natalizumab cessation, with an ARR of
282 0.06. This observation might be explained by the intrinsic superiority of ocrelizumab over fingolimod in
283 controlling disease activity rather than faster immunosuppression action, as both drugs lead to a fast lymphocyte
284 depletion or redistribution.[46] Natalizumab and fingolimod have similar therapeutic mechanisms, preventing
285 immune cells from migrating to the central nervous system.[1, 16] However, ocrelizumab has a very different
286 mechanism of action, depleting the CD20-expressing B cells.[46] This superiority indicates that B-cell depletion
287 could be advantageous over lymphocyte sequestration in rapidly controlling rebound after natalizumab
288 discontinuation. In a recent observational study of 54 fingolimod patients and 48 ocrelizumab patients at 1 year
289 after natalizumab cessation, ocrelizumab users had a significantly lower ARR than fingolimod (ARR 0.12 vs
290 0.41), and the HR of relapse was 3.4 for fingolimod versus ocrelizumab.[32] These results were consistent with
291 ours.
292
293 Our results showed a lower discontinuation rate for fingolimod than dimethyl fumarate (IPTW-weighted HR,
294 0.60; 95% CI, 0.44-0.84). A retrospective study including 732 RRMS patients (409 on dimethyl fumarate and
295 323 on fingolimod) showed similar results regarding the discontinuation between dimethyl fumarate and
296 fingolimod (29.3% of patients discontinued dimethyl fumarate versus 20.7% in fingolimod, P=.008).[23]
297 However, they found that dimethyl fumarate was associated with an increased relapse risk compared to
298 fingolimod, with an HR of 1.9 (95% CI 1.4-2.6) and a higher relapse risk in dimethyl fumarate patients pre-
299 treated with natalizumab compared to those switching to fingolimod (HR 4.5, 95% CI 1.9-10.8). In our study,
300 no significant difference in ARR and time to first replase between fingolimod and dimethyl fumarate was
301 observed.
302
303 The superiority of ocrelizumab to dimethyl fumarate and fingolimod might be explained by the different
304 immunological mechanisms of action between the treatment classes. This includes the onset of treatment effect
305 and relative treatment effectiveness in patients at very high risk of relapse. However, in MSBase, we currently
306 do not have enough patient records to examine whether our findings are a class effect (e.g., other anti-CD20
307 DMTs such as rituximab or ofatumumab, other S1P inhibitors beyond fingolimod or diroximel fumarate).

308 Although our data is observational in nature, it is very unlikely that prospective randomized trials for specific
309 switch scenarios will be funded in the future. Observational data is increasingly important for refining approved
310 treatment indications and funding decisions of payers. Our results could be incorporated into specific switch
311 treatment guidelines and, together with other real-world observational studies, could provide an extended
312 evidence base for regulators and payers.
313

314 **Limitations**

315 This study has several limitations. Although we applied the PS-based IPTW approach to balance baseline
316 covariates and our study findings were robust in sensitivity analyses, potential bias caused by unmeasured and
317 unobserved factors cannot be completely ruled out. Because the number of patients in the fingolimod and
318 dimethyl fumarate groups declined dramatically since 2018 (the approximate year of release of ocrelizumab),
319 we did not have sufficient patient numbers to assess data consistency for true contemporaneous use of the three
320 treatments. Also, because DMT approval dates vary from country to country, it may not be possible to have a
321 choice of all three treatments in all sites and for all study dates. Both issues may lead to the failure of fulfilling
322 the positivity assumption required by the PS method and introduce bias. To assess the impact of this bias, we
323 repeated the analysis using a doubly-robust standardization method, given that the doubly-robust estimators are
324 consistent when the positivity assumption holds or fails.[42, 47, 48] Furthermore, we did not include MRI data in the
325 primary PS model because only 34% of participants had this information. However, we performed a sensitivity
326 analysis using MRI information utilizing the multiple imputation method, and the results were consistent.
327 Moreover, previous studies have demonstrated that MRI activity prior to natalizumab start is a strong predictor
328 of future disease activity after natalizumab discontinuation.[49] In our study, only 12.2% (n=201) of patients had a
329 record of prior MRI activity. Thus, we were unable to verify this in our cohort. Future studies are needed to
330 provide useful evidence in this regard to guide personalized clinical decisions. Drug safety data are also
331 important to adequately assess the risk-benefit profiles of different DMTs, especially when used over the long
332 term. Currently, the safety data in the MSbase registry are largely missing, but we are engaged in improving the
333 collection of this data through a specific program.
334

335 # Conclusion

336 Among RRMS patients who had discontinued natalizumab, ocrelizumab was associated with a significant
337 reduction in the annualized relapse rate and the hazard of the time to first relapse, and a lower discontinuation

rate compared to fingolimod and dimethyl fumarate. In addition, switch to ocrelizumab was associated with a lower rate of confirmed disability progression events than switch to fingolimod. Stopping natalizumab for PML risk management is common. Our findings can help inform subsequent DMT selection for these patients.

Author Declaration

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Data Access, Responsibility, and Analysis: C. Zhu had full access to all of the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis.

Conflicts of Interest Disclosure:

C. Zhu, O. Skibina, J. Kuhle, E. Butler, A. Prat, A. Prat, R. Macdonell, B. Weinstock-Guttman, S. Ozakbas, M. Jose Sa, O. Gerlach, L. Van Hijfte, J. Garber, B. Yamout, and Z. Zhou report no disclosures. S. J. Khoury received compensation for scientific advisory board activity from Merck and Roche. V.G. Jokubaitis 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. T. Kalincik served on scientific advisory boards for BMS, Roche, Janssen, Sanofi Genzyme, Novartis, Merck and Biogen, steering committee for Brain Atrophy Initiative by Sanofi Genzyme. He also 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. D. Horakova 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 [project Progres Q27/LF1]. K. Buzzard received honoraria and consulting fees from Biogen, Teva, Novartis, Genzyme-Sanofi, Roche, Merck, CSL and Grifols. R. Alroughani received honoraria as a speaker and for serving on scientific advisory boards from Bayer, Biogen, GSK, Merck, Novartis, Roche and Sanofi-Genzyme. A. van der Walt served on advisory boards and receives unrestricted research grants from Novartis, Biogen, Merck and Roche She has received speaker's honoraria and travel support from Novartis, Roche, and Merck. She also received grant support from the National Health and Medical Research Council of Australia and MS Research Australia. H. Butzkueven 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

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Table 1 Characteristics of the Study Population by Baseline Switch DMT

	Total (n = 1,386)	Dimethyl fumarate (n = 138)	Fingolimod (n = 823)	Ocrelizumab (n = 425)	ASD* Before IPTW	ASD* After IPTW
Age, yrs	41.3 ± 10.6	44.0 ± 11.4	40.1 ± 10.0	42.8 ± 11.2	**0.35**	0.02
Female	990 (71)	103 (75)	581 (71)	306 (72)	0.04	0.02
Disease duration, yrs	10.6 (6.2 – 16.1)	10.0 (5.5 – 16.6)	11.0 (6.4 – 16.1)	10.1 (5.6 – 16.0)	0.02	0.03
Disability (EDSS)	3.0 (1.5 – 4.5)	3.0 (1.5 – 4.5)	3.0 (1.5 – 4.5)	3.0 (1.5 – 5.0)	0.05	0.02
Relapses one-year prior to baseline	0.2 ± 0.6	0.1 ± 0.4	0.3 ± 0.6	0.2 ± 0.5	**0.27**	0.03
Relapses two-year prior to baseline	0.6 ± 1.0	0.5 ± 0.8	0.6 ± 1.0	0.5 ± 0.9	**0.17**	0.03
Previous therapies (natalizumab excluded)	1 (1 – 2)	1 (1 – 2)	1 (1 – 2)	1 (0 – 2)	**0.12**	0.04
Washout period after natalizumab discontinuation	28 (0 – 49)	0 (0 – 50)	24 (0 – 55)	32 (0 – 47)	**0.18**	0.09
Duration of natalizumab use, yrs	2.6 (1.6 – 4.0)	2.5 (1.7 – 4.4)	2.6 (1.8 – 3.8)	2.4 (1.3 – 4.4)	0.10	0.03

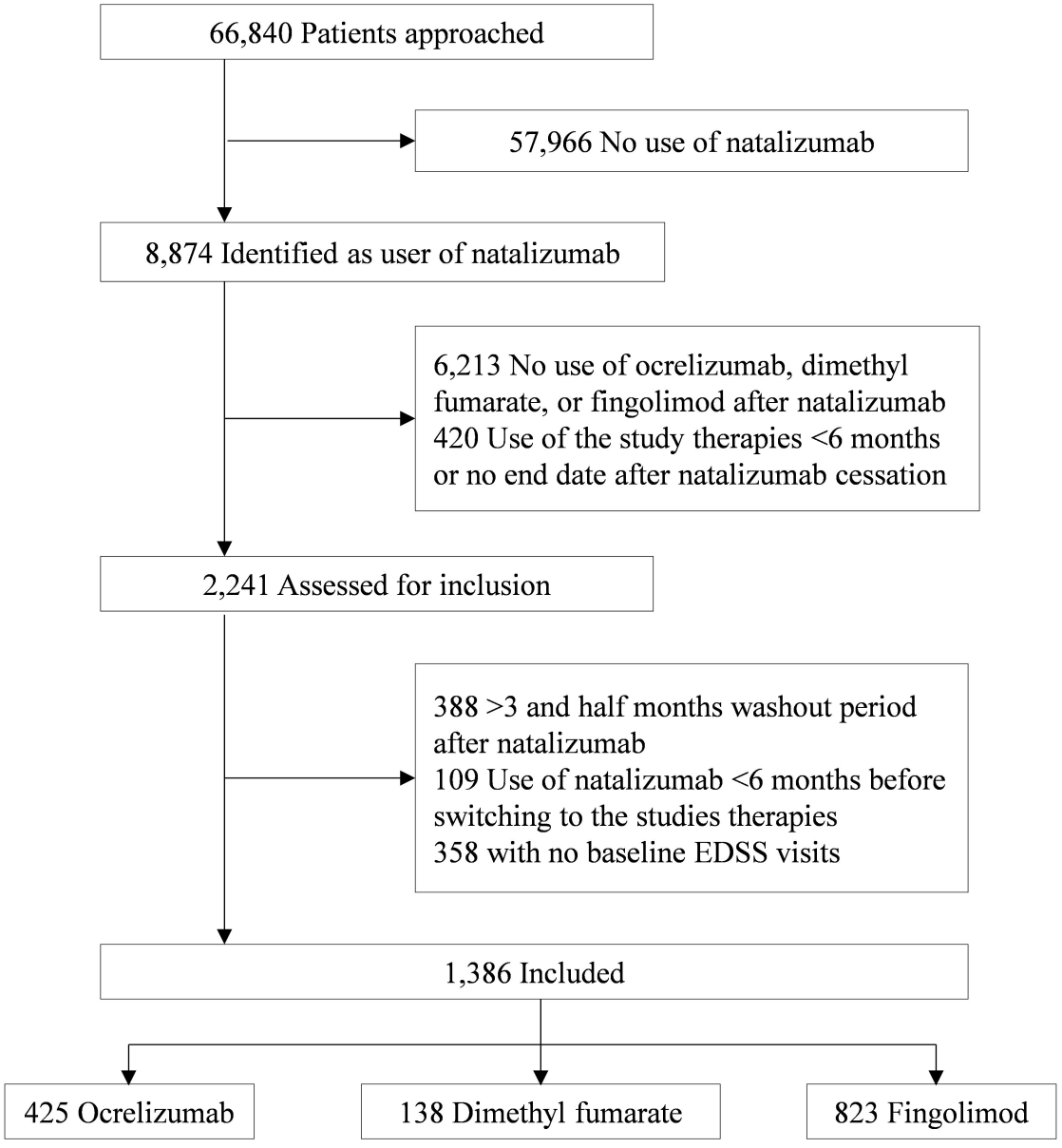
Values are median (interquartile range), n (%), or mean ± SD.
*ASD is the absolute difference in means or proportions divided by the standard error. An imbalance was defined as an ASD>0.10, indicated in bold.
ASD = absolute standardized difference; IPTW = inverse probability of treatment weighting; EDSS = Expanded Disability Status Scale.

581 **Figure 1. Flow chart of the Patients Inclusion/Exclusion**
582 EDSS = Expanded Disability Status Scale; MS = multiple sclerosis.
583
584

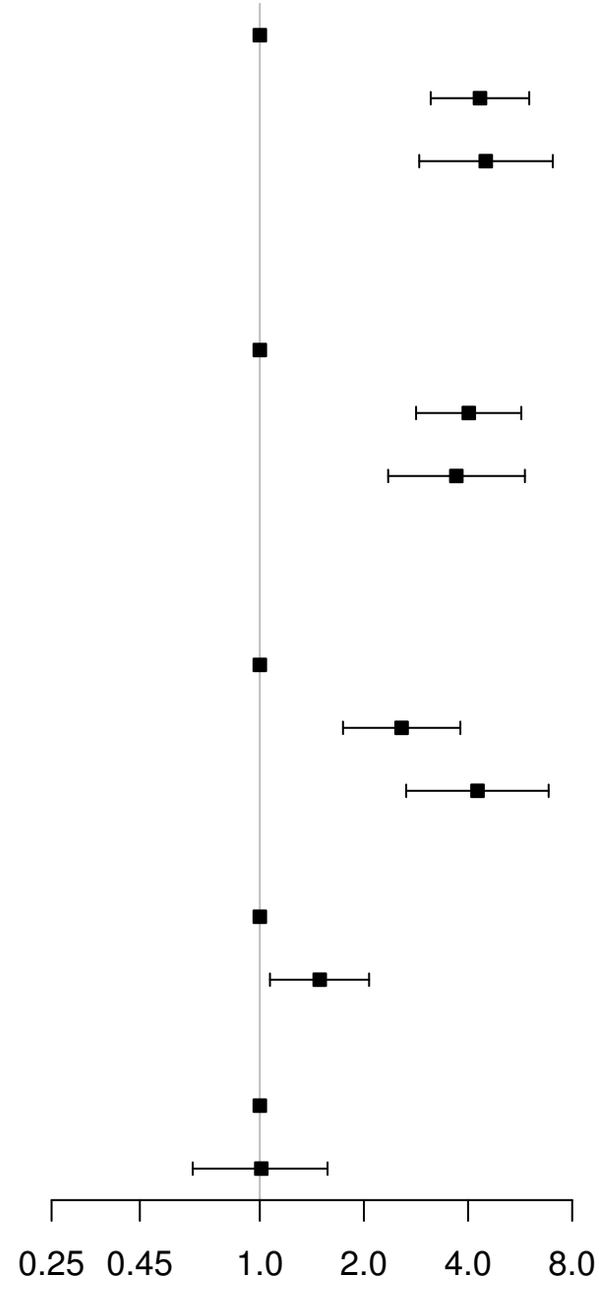
585 **Figure 2. The annualized relapse rate and the hazards of study outcomes weighted using IPTW**
586 CI = confidence interval; HR = hazard ratio; IPTW = inverse probability of treatment weighting.
587
588

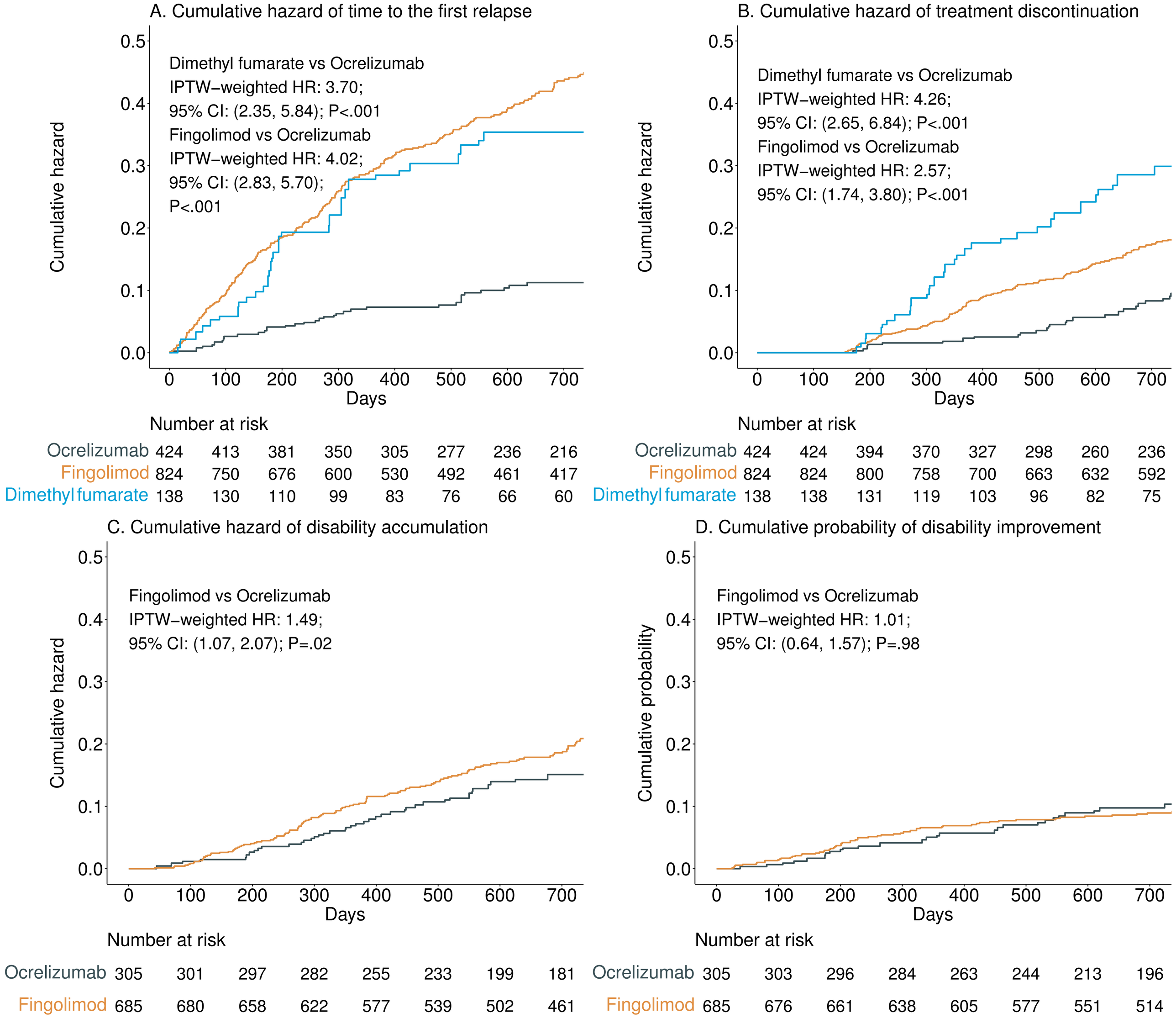
589 **Figure 3. IPTW-weighted cumulative hazard of Primary and Secondary Outcomes**

590 Weighted Kaplan-Meier failure function was applied to present cumulative hazard of the (a) time to the first relapse in dimethyl fumarate
591 users (blue line), fingolimod users (khaki line), and ocrelizumab users (black line), and (b) treatment discontinuation, respectively. For (c)
592 disability accumulation and (d) disability improvement, the plots were drawn from the weighted cumulative hazard models on the basis of
593 separate propensity score models. And, dimethyl fumarate was not included due to the insufficient number of participants.
594


66,840 Patients approached
57,966 No use of natalizumab
8,874 Identified as user of natalizumab
6,213 No use of ocrelizumab, dimethyl fumarate, or fingolimod after natalizumab
420 Use of the study therapies <6 months or no end date after natalizumab cessation
2,241 Assessed for inclusion
388 >3 and half months washout period after natalizumab
109 Use of natalizumab <6 months before switching to the studies therapies
358 with no baseline EDSS visits
1,386 Included
425 Ocrelizumab
138 Dimethyl fumarate
823 Fingolimod

Primary outcome			IPTW–weighted	
Annualized relapse rate	**Number of events**	**Person–years**	**ARR ratio (95% CI)**	**P values**
Ocrelizumab (n = 425)	45	930.89	1.00 (reference)	–
Fingolimod (n = 823)	649	3095.02	4.33 (3.12, 6.01)	<.001
Dimethyl fumarate (n = 138)	65	343.46	4.50 (2.89, 7.03)	<.001
Time to first relapse			**HR (95% CI)**	
Ocrelizumab (n = 425)	37	–	1.00 (reference)	–
Fingolimod (n = 823)	354	–	4.02 (2.83, 5.70)	<.001
Dimethyl fumarate (n = 138)	43	–	3.70 (2.35, 5.84)	<.001
Secondary outcome				
Treatment discontinuation				
Ocrelizumab (n = 425)	31	–	1.00 (reference)	–
Fingolimod (n = 823)	285	–	2.57 (1.74, 3.80)	<.001
Dimethyl fumarate (n = 138)	51	–	4.26 (2.65, 6.84)	<.001
Disability accumulation				
Ocrelizumab (n = 306)	48	–	1.00 (reference)	–
Fingolimod (n = 686)	184	–	1.49 (1.07, 2.07)	.02
Disability improvement				
Ocrelizumab (n = 306)	28	–	1.00 (reference)	–
Fingolimod (n = 686)	75	–	1.01 (0.64, 1.57)	.98




A. Cumulative hazard of time to the first relapse
Dimethyl fumarate vs Ocrelizumab
IPTW−weighted HR: 3.70;
95% CI: (2.35, 5.84); P<.001
Fingolimod vs Ocrelizumab
IPTW−weighted HR: 4.02;
95% CI: (2.83, 5.70);
P<.001
Cumulative hazard
Days
Number at risk
Ocrelizumab 424 413 381 350 305 277 236 216
Fingolimod 824 750 676 600 530 492 461 417
Dimethyl fumarate 138 130 110 99 83 76 66 60
B. Cumulative hazard of treatment discontinuation
Dimethyl fumarate vs Ocrelizumab
IPTW−weighted HR: 4.26;
95% CI: (2.65, 6.84); P<.001
Fingolimod vs Ocrelizumab
IPTW−weighted HR: 2.57;
95% CI: (1.74, 3.80); P<.001
Cumulative hazard
Days
Number at risk
Ocrelizumab 424 424 394 370 327 298 260 236
Fingolimod 824 824 800 758 700 663 632 592
Dimethyl fumarate 138 138 131 119 103 96 82 75
C. Cumulative hazard of disability accumulation
Fingolimod vs Ocrelizumab
IPTW−weighted HR: 1.49;
95% CI: (1.07, 2.07); P=.02
Cumulative hazard
Days
Number at risk
Ocrelizumab 305 301 297 282 255 233 199 181
Fingolimod 685 680 658 622 577 539 502 461
D. Cumulative probability of disability improvement
Fingolimod vs Ocrelizumab
IPTW−weighted HR: 1.01;
95% CI: (0.64, 1.57); P=.98
Cumulative probability
Days
Number at risk
Ocrelizumab 305 303 296 284 263 244 213 196
Fingolimod 685 676 661 638 605 577 551 514
0.0
0.1
0.2
0.3
0.4
0.5
0
100
200
300
400
500
600
700