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Citation for final published version:

Roos, Izanne, Sharmin, Sifat, Malpas, Charles, Ozakbas, Serkan, Lechner-Scott, Jeannette, Hodgkinson, Suzanne, Alroughani, Raed, Eichau Madueño, Sara, Boz, Cavit, van der Walt, Anneke, Butzkueven, Helmut, Buzzard, Katherine, Skibina, Olga, Foschi, Matteo, Grand?Maison, Francois, John, Nevin, Grammond, Pierre, Terzi, Murat, Prévost, Julie, Barnett, Michael, Laureys, Guy, Van Hijfte, Liesbeth, Luis Sanchez-Menoyo, Jose, Blanco, Yolanda, Oh, Jiwon, McCombe, Pamela, Ramo Tello, Cristina, Soysal, Aysun, Prat, Alexandre, Duquette, Pierre, Yamout, Bassem I., Khoury, Samia, van Pesch, Vincent, Macdonell, Richard, José Sá, Maria, Slee, Mark, Kuhle, Jens, Maimone, Davide, Spitaleri, Daniele L.A., Willekens, Barbara, Asmi, Abdallah Al, Tallantyre, Emma , Robertson, Neil P. , Coles, Alasdair, L Brown, J. William and Kalincik, Tomas 2024. Effectiveness of cladribine compared to fingolimod, natalizumab, ocrelizumab and alemtuzumab in relapsing-remitting multiple sclerosis. *Multiple Sclerosis Journal* 30 (9) , pp. 1163-1175.
10.1177/13524585241267211

Publishers page: <http://dx.doi.org/10.1177/13524585241267211>

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Effectiveness of cladribine compared to fingolimod, natalizumab, ocrelizumab and alemtuzumab in relapsing-remitting multiple sclerosis

Journal:	<i>Multiple Sclerosis Journal</i>
Manuscript ID	MSJ-24-0250.R1
Manuscript Type:	Original Research Paper
Date Submitted by the Author:	n/a
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Keywords:	Multiple sclerosis, Relapsing/remitting, Treatment Response, observational study, comparative effectiveness, cladribine
Abstract:	<p>Background: Comparisons between cladribine and other potent immunotherapies for multiple sclerosis are lacking.</p> <p>Objectives: To compare the effectiveness of cladribine against fingolimod, natalizumab, ocrelizumab and alemtuzumab in relapsing-remitting multiple sclerosis.</p> <p>Methods: Patients with relapsing-remitting multiple sclerosis treated with cladribine, fingolimod, natalizumab, ocrelizumab or alemtuzumab were identified in the global MSBase cohort and two additional UK centres. Patients were followed for $\geq 6/12$ and had ≥ 3 in-person disability assessments. Patients were matched using propensity score. Four</p>

pairwise analyses compared annualised relapse rates and disability outcomes.

Results:

The eligible cohorts consisted of 853(fingolimod), 464(natalizumab), 1131(ocrelizumab), 123 (alemtuzumab), or 493(cladribine) patients. Cladribine was associated with a lower ARR than fingolimod (0.07vs0.12, $p=0.006$), and a higher ARR than natalizumab (0.10vs0.06, $p=0.03$), ocrelizumab (0.09vs0.05, $p=0.008$), and alemtuzumab (0.17vs0.04, $p<0.001$). Compared to cladribine, the risk of disability worsening did not differ in patients treated with fingolimod (HR1.08, 95%CI 0.47-2.47) or alemtuzumab (0.73, 0.26-2.07), but was lower for patients treated with natalizumab (0.35, 0.13-0.94) and ocrelizumab (0.45, 0.26-0.78). There was no evidence for a difference in disability improvement.

Conclusion:

Cladribine is an effective therapy that can be viewed as a step-up in effectiveness from fingolimod, but is less effective than the most potent intravenous multiple sclerosis therapies.

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Manuscripts

Effectiveness of cladribine compared to fingolimod, natalizumab, ocrelizumab and alemtuzumab in relapsing-remitting multiple sclerosis

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41 **Keywords**

42 Cladribine; comparative effectiveness; observational studies; multiple sclerosis
43

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51
52 Word count: 2998

53 Tables: 1

54 Figure: 5
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ABSTRACT

Background:

Comparisons between cladribine and other potent immunotherapies for multiple sclerosis are lacking.

Objectives:

To compare the effectiveness of cladribine against fingolimod, natalizumab, ocrelizumab and alemtuzumab in relapsing-remitting multiple sclerosis.

Methods:

Patients with relapsing-remitting multiple sclerosis treated with cladribine, fingolimod, natalizumab, ocrelizumab or alemtuzumab were identified in the global MSBase cohort and two additional UK centres. Patients were followed for $\geq 6/12$ and had ≥ 3 in-person disability assessments. Patients were matched using propensity score. Four pairwise analyses compared annualised relapse rates and disability outcomes.

Results:

The eligible cohorts consisted of 853(fingolimod), 464(natalizumab), 1131(ocrelizumab), 123 (alemtuzumab), or 493(cladribine) patients. Cladribine was associated with a lower ARR than fingolimod (0.07vs0.12, $p=0.006$), and a higher ARR than natalizumab (0.10vs0.06, $p=0.03$), ocrelizumab (0.09vs0.05, $p=0.008$), and alemtuzumab (0.17vs0.04, $p<0.001$). Compared to cladribine, the risk of disability worsening did not differ in patients treated with fingolimod (HR1.08, 95%CI 0.47-2.47) or alemtuzumab (0.73, 0.26-2.07), but was lower for patients treated with natalizumab (0.35, 0.13-0.94) and ocrelizumab (0.45, 0.26-0.78). There was no evidence for a difference in disability improvement.

Conclusion:

Cladribine is an effective therapy that can be viewed as a step-up in effectiveness from fingolimod, but is less effective than the most potent intravenous multiple sclerosis therapies.

INTRODUCTION

Cladribine triggers lymphocyte apoptosis by inhibiting DNA synthesis and repair.¹ The superiority of cladribine over placebo in the treatment of relapsing-remitting multiple sclerosis (MS) was shown in the CLARITY randomised clinical trial, where 3.5mg/kg over two years reduced the frequency of relapses by 57%, and disability worsening by 33%.²

Since the CLARITY trial was placebo controlled, the comparative effectiveness of cladribine has not been studied in a randomised setting. In the absence of evidence from randomised trials, carefully designed observational studies can be used to compare the effectiveness of therapies, and subsequently guide treatment decisions.³ A recent study from the MSBase registry concluded that cladribine was superior to other oral MS therapies (fingolimod, dimethyl fumarate and teriflunomide) in reducing relapses, and in treatment persistence.⁴ A small number of head-to-head comparisons were of insufficient duration or power to evaluate disability outcomes, used merged data from registries and randomised trials, or did not compare cladribine to highly-effective therapies.⁵⁻⁷ In particular, no generalisable information exists about the effectiveness of cladribine compared with ocrelizumab or alemtuzumab. In practice, cladribine is viewed as a highly-effective therapy suitable for patients with highly active MS who are at risk of accumulating disability.⁸⁻¹⁰ Benchmarking cladribine against the most effective available therapies is therefore an unmet need essential for guiding evidence-based treatment selection.

In this study, we have emulated a trial comparing relapse activity, disability accumulation, and disability improvement among MS patients treated with cladribine and four other highly-

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3 effective and widely used MS therapies: fingolimod, natalizumab, ocrelizumab and
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5 alemtuzumab.
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10 **METHODS**

11 **Database and population**

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17 Longitudinal patient data were extracted from MSBase¹¹, an international observational MS
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19 registry, and from two non-MSBase centres in the United Kingdom (Cambridge and Cardiff).
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21 The study was approved by the Melbourne Health Human Research Ethics Committee and
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23 local ethics committees in all centers. Written informed consent was obtained from all
24
25 patients.
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32 Patients with relapsing-remitting MS¹²⁻¹⁴ who had been treated with cladribine, fingolimod,
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34 natalizumab, ocrelizumab or alemtuzumab between January 2018 and March 2023 were
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36 assessed for study inclusion. Inclusion criteria were: no prior treatment with haematopoietic
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38 stem cell transplantation, alemtuzumab or cladribine; no treatment with mitoxantrone in the
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40 preceding 3 years or anti-CD20 therapy in the preceding 12 months; minimum recorded
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42 follow-up (6-months before, and at least two disability scores ≥ 6 months apart after,
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44 treatment start); a minimum data set including sex, age, MS symptom onset, relapse dates,
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46 MS course and disability score at treatment start (within 6-months before and 1-month after
47
48 starting therapy). Only in-person disability assessments were included.
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51 For each pairwise treatment comparison, patients who received the comparator therapy
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53 before study inclusion were excluded.
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Procedures

Treatment protocols for cladribine (1.75mg/kg in year 1; 3.5mg/kg over two years), fingolimod (0.5mg daily), natalizumab (300mg monthly), ocrelizumab (600mg 6-monthly) and alemtuzumab (12–24 mg intravenous once per day for 5 days [cycle 1] or for 3 days [subsequent cycles]), are described elsewhere.^{2, 15-18} Baseline was the first commencement of a study therapy after January 2018. Patients were censored at the last recorded EDSS score, irrespective of change in treatment status (intention-to-treat contrast of interest).

Data were entered into the MSBase data entry system or local data entry systems as part of routine clinical practice and mostly at tertiary MS centres. The data entry procedures were consistent across both MSBase and non-MSBase centers. MRI data were included as reported by local radiologists based on local protocols. An MRI brain performed within 12 months before, and 1 month after, baseline was considered the baseline MRI. Missing baseline MRI data were addressed through multiple imputation.^{19, 20}

A rigorous data quality assurance procedure was followed (eTable 1).²¹

Study endpoints

The primary study outcome was annualised relapse rate (ARR); secondary study outcomes were cumulative hazards of relapses, disability accumulation events, and disability improvement events.

Relapses were defined as new symptoms, or exacerbation of existing symptoms, for at least 24 hours in the absence of a concurrent illness or fever, and occurring ≥ 30 days after a previous relapse.²²

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6 Disability was quantified using the Expanded Disability Status Scale (EDSS). Disability
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8 accumulation was defined as an increase in EDSS by ≥ 1 step (1.5 step if EDSS 0, or 0.5 step
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10 if EDSS >5.5), confirmed over ≥ 6 months (in the absence of a relapse in the preceding 30
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12 days), and sustained until the end of follow up. Disability improvement was defined as a
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14 decrease in EDSS by ≥ 1 step (1.5 steps if EDSS 1.5, or 0.5 step if EDSS >6) confirmed over
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16 at least 6 months.²³
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21 **Statistical analysis**

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23 Four separate matched analyses of cladribine versus fingolimod, natalizumab, ocrelizumab or
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25 alemtuzumab were performed. Individual patients were matched, at baseline, on their
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27 propensity of being treated with cladribine conditional on clinicodemographic characteristics.
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29 Propensity scores were calculated using a multivariable logistic regression model containing
30
31 the following baseline variables: age, sex, EDSS, MS duration from first symptom, number
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33 of relapses in the prior 12 months, disease activity in the prior year (relapses/ disability
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35 progression/both relapses and disability progression/no activity), number of prior MS
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37 immunotherapies, the most effective previously used treatment (categorised as high-efficacy
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39 [natalizumab, rituximab, ocrelizumab, ofatumumab, mitoxantrone], moderate-efficacy
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41 [fingolimod, dimethyl fumarate], low-efficacy [interferons β , glatiramer acetate,
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43 teriflunomide] or no therapy), presence/absence of new T2 or contrast-enhancing brain MRI
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45 lesions, MRI T2-lesion burden (1-2, 3-8, or ≥ 9 lesions), registry and country.²⁴
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54 In the absence of a baseline MRI brain, missing values were imputed using a multiple
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56 imputation with an expectation maximisation with bootstrapping algorithm based on
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58 treatment group, age, MS duration, EDSS, pre-baseline disease activity, pre-baseline therapy
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3 and time since preceding therapy.^{19, 25} A sensitivity analysis was conducted after loosening
4 the assumption of missingness-at-random. Normalised weights were used to estimate
5 inferences within the dataset assuming MRI missingness not at random.²⁶ The relationship
6 between clinical and demographic variables and the absence of MRI data was assessed using
7 multivariable logistic regression, with selection of δ guided by a published algorithm.²⁷
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17 Patients were matched, without replacement, in a variable (3:1 to 5:1) matching ratio by
18 nearest neighbour matching within 0.1 standard deviations of the propensity score.²⁸ The
19 matching ratio specifies the maximum allowed number of control units in each matched pair.
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Covariate balance was assessed using standardised mean differences. All subsequent analyses were performed using paired models, weighted to account for variable matching ratio. Within each matched patient pair, follow-up was censored at the shorter of the two follow-up periods (pairwise censoring) to mitigate differential treatment persistence and attrition bias. The last eligible timepoint for 6-month confirmed disability outcomes was 6-months before the censor date to ensure adequate follow-up for confirmation. ARRr were compared using a marginal negative binomial model with cluster term for matched patient set. Cumulative hazards of relapses, disability accumulation, and disability improvement events were analysed with weighted conditional proportional hazards models for recurrent events, adjusted for visit frequency for disability outcomes. Schoenfeld's global test was used to evaluate the proportionality assumption. The robustness of our findings to unidentified confounders was calculated using Rosenbaum sensitivity test for Hodges-Lehmann Γ .²⁹

A sensitivity analysis required \geq 18 months follow-up for all patients. In a further sensitivity analysis data were censored at treatment discontinuation, commencement of subsequent therapy, or the last recorded EDSS, whichever occurred first. For this analysis, the duration

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3 of treatment effect was presumed based on pharmacokinetics, or previous evidence:
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5 cladribine 4years, alemtuzumab 5years, ocrelizumab 270days, natalizumab 60days and
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7 fingolimod 30days. Treatment discontinuation was assessed using weighted conditional
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9 proportional hazards models without pairwise censoring. The analysis was also repeated
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11 using inverse probability of treatment weighting.
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17 Data were analysed using R, v4.2.1 (R CoreTeam).
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21 RESULTS

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26 Of 30142 patients with MS who were ever treated with a **studied** therapy, a total of 853
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28 (fingolimod), 464 (natalizumab), 1131 (ocrelizumab), 123 (alemtuzumab) and **up to 493**
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30 (cladribine) patients fulfilled inclusion criteria (Figure 1; eTable 2). The clinicodemographic
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32 details of the included population were similar to those of patients ever received **studied**
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34 therapy but were excluded from the analysis (eTable 3).
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40 Prior to matching, the four treatment groups differed in their baseline characteristics (eTable
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42 4). The probability of being treated with either therapy was calculated using a logistic
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44 regression model (eTable 5). Patients treated with cladribine were less likely to have received
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46 a high-efficacy therapy than patients treated with alemtuzumab, ocrelizumab or natalizumab,
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48 had lower EDSS scores than patients treated with alemtuzumab and ocrelizumab, and were
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50 older than patients treated with natalizumab.
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56 Table 1 shows the characteristics of the matched cohorts for all four pairwise primary
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58 analyses. Characteristics of patients who were excluded by the matching procedure are in
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eTable 6. Propensity score matching resulted in 86%-98% improvement in balance between the matched groups, with standardised mean differences of <10% (Table 1; eFigure 1; eFigure 2). Mean pairwise censored follow-up ranged from 1.8 to 2.1 years. Patient numbers allowed assessment of relapses for up to 3years for alemtuzumab, 3.5years for natalizumab, and 4years for fingolimod and ocrelizumab. Disability outcomes were evaluated for up to 2.5 years for fingolimod, natalizumab, and ocrelizumab, and 2years for alemtuzumab.

Effectiveness

Fingolimod vs cladribine

198 cladribine-treated patients were matched with 403 patients treated with fingolimod (Table 1). On average, patients received one prior MS therapy (low-efficacy in 48-52%), and a mean EDSS of 1.8. The mean ARR was higher in patients treated with fingolimod than cladribine (mean [SD], ARR 0.12[0.30] vs 0.07[0.23], Figure 2A). Similarly, the cumulative hazard of relapses was higher for fingolimod than cladribine (HR=1.71, 95%CI 1.12-2.63, Figure 2B). The difference was robust to unmeasured confounding to the magnitude of >100% of the cumulative effect of the measured confounding using Rosenbaum sensitivity test for Hodges-Lehmann Γ . There was no evidence for a difference in disability accumulation (HR=1.08, 0.47-2.47, Figure 2C) or disability improvement (HR=0.38, 0.13-1.1, Figure 2D) between groups.

Natalizumab vs cladribine

220 patients treated with cladribine were matched with 331 natalizumab patients. On average, patients received one prior MS therapy (moderate-efficacy in 45%), and had a mean EDSS of 2.1. The mean ARR was lower in patients treated with natalizumab than cladribine (ARR

0.06[0.22] vs 0.10[0.30], Figure 3A). Furthermore, both the cumulative hazard of relapses (HR=0.55, 0.33-0.93, Figure 3B) and disability accumulation (HR=0.35, 0.13-0.94, Figure 3C) were lower for natalizumab than cladribine. The difference in relapses was robust to the magnitude of 20% of the measured confounding (Hodges-Lehmann Γ). There was no evidence for a difference in disability improvement (HR=0.65, 0.36-1.17).

Ocrelizumab vs cladribine

380 cladribine-treated patients were matched with 667 ocrelizumab patients. The mean age was 42 years, EDSS 2.4, and patients had received 2 previous MS therapies (43% moderate-efficacy, 18% high-efficacy). The mean ARR was lower in patients treated with ocrelizumab than cladribine (ARR 0.05[0.18] vs 0.09[0.27], Figure 4A). Furthermore, both the cumulative hazards of relapses (HR=0.61, 0.42-0.88, Figure 4B), and disability accumulation (HR=0.45, 0.26-0.78, Figure 4C) were lower for ocrelizumab than cladribine. The difference in relapses was robust to unmeasured confounders to the magnitude of 40% of the measured confounding (Hodges-Lehmann Γ). There was no evidence for a difference in disability improvement (HR=0.8, 0.5-1.29, Figure 4D).

Alemtuzumab vs cladribine

173 cladribine-treated patients were matched with 68 alemtuzumab patients with a mean EDSS of 2.8, 2 previous MS therapies (48% moderate-efficacy, 27% high-efficacy), and recent disease activity in 60% of patients **indicative of active MS**. Both the mean ARR (ARR 0.04[0.19] vs 0.17[0.38], Figure 5A), and cumulative hazards of relapses (HR=0.25, 0.10-0.65, Figure 5B) were lower in patients treated with alemtuzumab than cladribine. The difference was robust to unmeasured confounders to the magnitude of 80% of the measured confounding (Hodges-Lehmann Γ). There was no evidence for a difference in disability

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3 accumulation (HR=0.73, 0.26-2.07, Figure 5C) or improvement (HR=1.3, 0.50-3.38, Figure
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5 5D). The analysis was sufficiently powered to detect a minimum difference of 79%
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7 cumulative hazard of disability accumulation, and 73% disability improvement (based on 200
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9 simulations at $1-\beta=0.8$).
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14 Sensitivity analyses

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16 Sensitivity analyses (i) where patients were censored at the discontinuation of **studied**
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18 therapy, and (ii) where all patients were followed for ≥ 18 months after baseline, largely
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20 confirmed the results of the primary analysis (eTable 7). Inverse probability of treatment
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22 weighting was not superior to matching and provided consistent results. In keeping with the
23
24 presumed duration of treatment effect, patients treated with cladribine were reported as more
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26 persistent on therapy than those treated with fingolimod, natalizumab or ocrelizumab, but not
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28 alemtuzumab (eFigure 3). All results were fully replicated with imputation of missing MRI
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30 data under the missing-not-at-random assumption.
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38 DISCUSSION

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42 In the expanding MS treatment landscape, understanding of the comparative effectiveness of
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44 available therapies is paramount to optimising patient outcomes. In this observational,
45
46 propensity-score matched analysis of the global observational MSBase registry and two
47
48 additional UK centres, we have studied the effectiveness of cladribine compared with four
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50 therapies commonly used in relapsing-remitting MS. Cladribine was superior to fingolimod,
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52 but inferior to natalizumab, ocrelizumab and alemtuzumab in reducing relapse activity. In
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54 addition, treatment with cladribine was associated with a greater probability of disability
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56 accumulation than natalizumab and ocrelizumab.
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6 A previous inverse probability of treatment-weighted analysis from MSBase including 445
7 ocrelizumab-treated and 76 cladribine-treated patients suggested lower relapse rates for
8 ocrelizumab than cladribine after cessation of fingolimod.⁷ Our present study expands on this
9 initial observation and generalises the conclusions to a broad range of clinical scenarios
10 representative of the prevalent MS population. This study supports treatment with
11 ocrelizumab as a step up in effectiveness compared to cladribine, with superior effect on both
12 relapses and disability accumulation. Furthermore, this study is the first to compare the
13 effectiveness of alemtuzumab and cladribine, describing superiority of alemtuzumab in
14 suppressing relapses. The lack of an observed difference in disability outcomes between these
15 two immune reconstitution therapies may be attributable to the characteristics of the matched
16 cohort, who had moderate baseline EDSS scores (2.8-2.9), a high proportion of patients with
17 a recent relapse/disability accumulation, and a modest follow-up period of 2 years.
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35 The clinical scenarios within which treatments are used can influence the observed
36 differences between compared therapies, and should therefore be carefully considered in
37 study design.³⁰ For example, patients in the cladribine vs alemtuzumab pairwise comparison
38 had the highest disease activity. The effectiveness of cladribine was compared to interferon-
39 beta, fingolimod and natalizumab in a small, non-overlapping pilot study from MSBase.⁵
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45 Patients in this early study received cladribine as part of the Australian Product
46 Familiarisation Program(2011), and outcomes were evaluated over a 1-year period.
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51 Cladribine was comparable to fingolimod and inferior to natalizumab in reducing relapses
52 and disability accumulation and was more frequently associated with disability improvement
53 than either fingolimod or natalizumab. Caution is advised in interpreting the pilot study
54 results due to small cohort size, exposure to a single cladribine cycle for many patients, and a
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3 follow-up duration too short to draw definitive conclusions about disability. A further study
4 from MSBase, using a more contemporary cohort, also suggested that cladribine is superior
5 to fingolimod in reducing relapse activity.⁴ A study that combined data from the Italian MS
6 registry and the CLARITY trial in treatment-naive patients with MS reported relapse
7 outcomes that seemed comparable between fingolimod and cladribine.⁶ However, whether
8 treatment groups from registries can be compared to those from randomised trials is unclear.
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12 Finally, our finding that natalizumab is superior to cladribine in reducing relapses concurs
13 with previous reports.⁵⁻⁷ Unlike the previous studies, however, our present study has found
14 evidence for superiority of natalizumab over cladribine by showing a 65% reduction in the
15 cumulative hazards of disability accumulation over 2.5-years.
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31 Network meta-analyses combine direct and indirect evidence from multiple studies, assuming
32 transitivity and consistency of observations.³¹ This offers an alternative analytical approach
33 for comparing treatments in the absence of randomised clinical trials. Our findings align with
34 a network meta-analysis comparing cladribine to various therapies across 41 studies, ranking
35 it fourth in effectiveness, behind alemtuzumab, ocrelizumab and natalizumab.³² The use of
36 different methodological approaches, each with their own limitations and assumptions, to
37 arrive at similar conclusions provides additional confidence in the findings.
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The most significant limitation of this study is its observational nature.³³ We have however
performed a carefully designed propensity score matched analysis to minimise treatment
indication and attrition bias, informative censoring and ensure that positivity assumption is
satisfied. While this approach reduces measured confounding, it doesn't eliminate it, leaving
observational studies vulnerable to potential unmeasured confounding. We have therefore

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3 demonstrated that all analyses were robust to unmeasured confounders of a magnitude of
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5 >20% of the cumulative measured confounding. We improved homogeneity of disability
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7 assessments by excluding telehealth assessments, and ensuring Neurostatus certification at all
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9 centres.³⁴ Despite accessing data from the largest MS registry and two additional centres, the
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11 comparison of disability outcomes for alemtuzumab lacked statistical power. We report the
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13 effectiveness of cladribine in groups of patients with comparable baseline characteristics
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15 treated in common clinical contexts. Results may however not be generalisable to all patient
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17 populations, such as patients who are treatment naïve. The current analysis used an
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19 ‘intention-to-treat’ approach to evaluate the effectiveness of 3.5mg/kg cladribine over the
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21 available subsequent follow-up. Results were consistent using an ‘as-treated’ approach, using
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23 a presumed 4-year duration of treatment effect. Rigorous evaluation of the duration of
24
25 treatment effect or the value of additional treatment doses would, be best pursued in a
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27 separate study. While treatment safety and patient comorbidities are important components of
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29 disease management, these data were not available for inclusion in the present study. Since
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31 information about pre-baseline MRI activity was only available for a subset of patients, we
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33 utilised multiple imputation. As previously described, this approach produces no difference in
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35 outcomes among patients with baseline MRI available.^{20, 35} Limited information about MRI
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37 activity however precluded the evaluation of radiological outcomes.
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47 Our findings support cladribine as an effective therapy for the treatment of relapsing-
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49 remitting MS. While we show a superior effectiveness of natalizumab and ocrelizumab on
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51 reducing relapses and disability accumulation compared to cladribine, the magnitude of this
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53 difference is small, and equates to a reduction by one relapse every 25 patient-years.

54 **Compared to cladribine, alemtuzumab reduced relapses by one relapse every eight patient-**
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56 **years.** On the contrary, the effectiveness of cladribine was clearly superior to fingolimod in
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3 preventing relapses (reduction by one relapse every 20 patient-years). Clinical application of
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5 these findings remains complex, and requires careful consideration of multiple factors,
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7 including cost, safety, and convenience. The results however help to place cladribine in the
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9 context of other MS therapies and suggest that cladribine can be viewed as a step-up in
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11 effectiveness from fingolimod, but less effective than the most potent intravenous therapies.
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16 **ACKNOWLEDGEMENTS**

17 We thank the patients who have agreed to participate in the global MSBase cohort study. The
18 list of MSBase Study Group coinvestigators and contributors is given in the online
19 supplement.
20

21 **DISCLOSURES**

22
23 I. Roos served on scientific advisory boards, received conference travel support and/or
24 speaker honoraria from Roche, Novartis, Merck and Biogen.

25 S. Sharmin reports no disclosures relevant to the manuscript.

26 C. Malpas has received speaker honoraria and consultancy fees from Biogen, Merck and
27 Novartis

28 S. Ozakbas reports no disclosures relevant to the manuscript.

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

32 S. Hodgkinson received honoraria and consulting fees from Novartis, Bayer Schering, Merck,
33 and Sanofi Genzyme, and travel grants from Novartis, Biogen Idec and Bayer Schering.

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

36 S. Eichau-Madueño received speaker honoraria and consultant fees from Biogen Idec,
37 Novartis, Merck, Bayer, Sanofi Genzyme, Roche and Teva.

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

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

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

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

52 O. Skibina received honoraria and consulting fees from Bayer Schering, Novartis, Merck,
53 Biogen and Genzyme

54 M. Foschi received travel and meeting attendance support from Novartis, Biogen, Roche,
55 Sanofi-Genzyme and Merck.
56
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1
2
3 F. Grand'Maison received honoraria or research funding from Biogen, Genzyme, Novartis,
4 Teva Neurosciences, and ATARA Pharmaceuticals.

5 N. John is primary investigator on MS trials sponsored by Novartis, Roche and Biogen.

6 P. Grammond has served in advisory boards for Novartis, EMD Serono, Roche, Biogen idec,
7 Sanofi Genzyme, Pendopharm and has received grant support from Genzyme and Roche, has
8 received research grants for his institution from Biogen idec, Sanofi Genzyme, EMD Serono.

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

11 J. Prevost accepted travel compensation from Novartis, Biogen, Genzyme, Teva, and
12 speaking honoraria from Biogen, Novartis, Genzyme and Teva.

13 M. Barnett served on scientific advisory boards for Biogen, Novartis and Genzyme and has
14 received conference travel support from Biogen and Novartis. He serves on steering
15 committees for trials conducted by Novartis. His institution has received research support
16 from Biogen, Merck and Novartis.

17 G. Laureys received travel and/or consultancy compensation from Sanofi-Genzyme, Roche,
18 Teva, Merck, Novartis, Celgene, Biogen.

19 L. Van Hijfte received travel compensation from Merck

20 J.L. Sanchez-Menoyo accepted travel compensation from Novartis, Merck and Biogen,
21 speaking honoraria from Biogen, Novartis, Sanofi, Merck, Almirall, Bayer and Teva and has
22 participated in clinical trials by Biogen, Merck and Roche

23 Y. Blanco received speaker honoraria/consulting fees from Merck, Biogen, Roche, Bristol,
24 Novartis, Sanofi and Sandoz.

25 J. Oh has received research funding from the MS Society of Canada, National MS Society,
26 Brain Canada, Biogen, Roche, EMD Serono (an affiliate of Merck KGaA); and personal
27 compensation for consulting or speaking from Alexion, Biogen, Celgene (BMS), EMD
28 Serono (an affiliate of Merck KGaA), Novartis, Roche, and Sanofi-Genzyme.

29 P. McCombe received speakers fees and travel grants from Novartis, Biogen, Teva, Sanofi

30 C. Ramo-Tello received research funding, compensation for travel or speaker honoraria from
31 Biogen, Novartis, Merck, Roche, Almirall, Bristol, Sanofi

32 A. Soysal reports no disclosures relevant to the manuscript.

33 A. Prat reports no disclosures relevant to the manuscript.

34 P. Duquette served on editorial boards and has been supported to attend meetings by EMD,
35 Biogen, Novartis, Genzyme, and TEVA Neuroscience. He holds grants from the CIHR and
36 the MS Society of Canada and has received funding for investigator-initiated trials from
37 Biogen, Novartis, and Genzyme.

38 B.I. Yamout reports no disclosures relevant to the manuscript.

39 S. J. Khoury received compensation for scientific advisory board activity from Merck and
40 Roche, and received compensation for serving on the IDMC for Biogen.

41 V. van Pesch received travel grants from Merck Healthcare KGaA (Darmstadt, Germany),
42 Biogen, Sanofi, Bristol Meyer Squibb, Almirall, Alexion and Roche. His institution has
43 received research grants and consultancy fees from Roche, Biogen, Sanofi, Merck Healthcare
44 KGaA (Darmstadt, Germany), Bristol Meyer Squibb, Janssen, Almirall and Novartis Pharma

45 R. Macdonell or his institution have received remuneration for his speaking engagements,
46 advisory board memberships, research and travel from Biogen, Merck, Genzyme, Bayer,
47 Roche, Teva, Novartis, CSL, BMS, MedDay and NHMRC.

48 M.J. Sa received consulting fees, speaker honoraria, and/or travel expenses for scientific
49 meetings from Alexion, Bayer Healthcare, Biogen, Bristol Myers Squibb, Celgene, Janssen,
50 Merck-Serono, Novartis, Roche, Sanofi and Teva.

51 M. Slee has participated in, but not received honoraria for, advisory board activity for
52 Biogen, Merck, Bayer Schering, Sanofi Aventis and Novartis.

1
2
3 J. Kuhle received speaker fees, research support, travel support, and/or served on advisory
4 boards by Swiss MS Society, Swiss National Research Foundation (320030_189140/1),
5 University of Basel, Progressive MS Alliance, Bayer, Biogen, Bristol Myers Squibb,
6 Celgene, Merck, Novartis, Octave Bioscience, Roche, Sanofi.

7 D. Maimone received speaker honoraria for Advisory Board and travel grants from Almirall,
8 Biogen, Merck, Novartis, Roche, Sanofi-Genzyme, and Teva.

9 D.L.A. Spitaleri received honoraria as a consultant on scientific advisory boards by Bayer-
10 Schering, Novartis and Sanofi-Aventis and compensation for travel from Novartis, Biogen,
11 Sanofi Aventis, Teva and Merck.

12 B. Willekens received honoraria for acting as a member of Scientific Advisory
13 Boards/Consultancy for Almirall, Biogen, Celgene/BMS, Merck, Janssen, Novartis, Roche,
14 Sandoz, Sanofi-Genzyme and speaker honoraria and travel support from Biogen,
15 Celgene/BMS, Merck, Novartis, Roche, Sanofi-Genzyme; research and/or patient support
16 grants from Biogen, Janssen, Merck, Sanofi-Genzyme, Roche. Honoraria and grants were
17 paid to UZA/UZA Foundation. Further, B.W. received research funding from FWO-TBM,
18 Belgian Charcot Foundation, Start2Cure Foundation, Queen Elisabeth Medical Foundation
19 for Neurosciences and the National MS Society USA.

20 A. Al-Asmi reports no disclosures relevant to the manuscript.

21 E. Tallantyre reports no disclosures relevant to the manuscript.

22 N.P. Robertson reports no disclosures relevant to the manuscript.

23 A. Coles reports no disclosures relevant to the manuscript.

24 J.W.L Brown reports speaking honoraria from The Corpus, Biogen and Novartis; and
25 advisory board fees from Biogen and Intesso.

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

32 **FUNDING**

33 This study was supported by the NHMRC [1140766, 1129189, 1157717]. IR is supported by
34 a MS Australia postdoctoral fellowship grant. The MSBase Foundation is a not-for-profit
35 organization that receives support from Biogen, Novartis, Merck, Roche, Teva and
36 Sanofi Genzyme. Design and conduct of the study; collection, management, analysis, and
37 interpretation of the data; preparation, review, or approval of the manuscript; and decision to
38 submit the manuscript for publication were conducted separately and apart from the guidance
39 of the sponsors.

40 **DATA ACCESS, RESPONSIBILITY AND ANALYSIS**

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

43 **DATA AVAILABILITY**

44 The MSBase registry is a data processor and warehouses data from individual principal
45 investigators who agree to share their datasets on a project-by-project basis. External party
46 access to data from either the MSBase centres or two non-MSBase UK centers is subject to
47 reasonable requests and solely at the discretion of the principal investigators. Permission for
48 data access must be sought individually from the respective principal investigators.

REFERENCES

1. Beutler E. Cladribine (2-chlorodeoxyadenosine). *Lancet* 1992; 340: 952-956. DOI: 10.1016/0140-6736(92)92826-2.
2. 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: 416-426. research-article 20100120. DOI: 10.1056/NEJMoa0902533.
3. Hernán MA and Robins JM. Using Big Data to Emulate a Target Trial When a Randomized Trial Is Not Available. *Am J Epidemiol.* 2016, pp.758-764.
4. Spelman T, Ozakbas S, Alroughani R, et al. Comparative effectiveness of cladribine tablets versus other oral disease-modifying treatments for multiple sclerosis: Results from MSBase registry. *Mult Scler* 2023; 29: 221-235. 20221126. DOI: 10.1177/13524585221137502.
5. Kalincik T, Jokubaitis V, Spelman T, et al. Cladribine versus fingolimod, natalizumab and interferon beta for multiple sclerosis. *Mult Scler* 2018; 24: 1617-1626. 20170831. DOI: 10.1177/1352458517728812.
6. Signori A, Sacca F, Lanzillo R, et al. Cladribine vs other drugs in MS: Merging randomized trial with real-life data. *Neurol Neuroimmunol Neuroinflamm* 2020; 7 20200814. DOI: 10.1212/NXI.0000000000000878.
7. Zhu C, Zhou Z, Roos I, et al. Comparing switch to ocrelizumab, cladribine or natalizumab after fingolimod treatment cessation in multiple sclerosis. *J Neurol Neurosurg Psychiatry* 2022; 93: 1330-1337. 20221019. DOI: 10.1136/jnnp-2022-330104.
8. Magalashvili D, Mandel M, Dreyer-Alster S, et al. Cladribine treatment for highly active multiple sclerosis: Real-world clinical outcomes for years 3 and 4. *J Neuroimmunol* 2022; 372: 577966. 20220906. DOI: 10.1016/j.jneuroim.2022.577966.
9. Lublin FD, Häring DA, Ganjgahi H, et al. How patients with multiple sclerosis acquire disability. *Brain* 2022; 145: 3147-3161. DOI: 10.1093/brain/awac016.
10. Alonso R, Casas M, Lazaro L, et al. Achieving no evidence of disease activity-3 in highly active multiple sclerosis patients treated with cladribine and monoclonal antibodies. *Mult Scler J Exp Transl Clin* 2023; 9: 20552173231154712. 20230222. DOI: 10.1177/20552173231154712.
11. 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: 769-774. 2007/02/01. DOI: 10.1177/1352458506070775.
12. Polman CH, Reingold SC, Edan G, et al. Diagnostic criteria for multiple sclerosis: 2005 revisions to the "McDonald Criteria". *Ann Neurol* 2005; 58: 840-846. 2005/11/12. DOI: 10.1002/ana.20703.
13. Polman CH, Reingold SC, Banwell B, et al. Diagnostic criteria for multiple sclerosis: 2010 Revisions to the McDonald criteria. *Annals of Neurology* 2011; 69: 292-302. DOI: 10.1002/ana.22366.
14. Thompson AJ, Banwell BL, Barkhof F, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. *Lancet Neurol* 2018; 17: 162-173. 2017/12/26. DOI: 10.1016/S1474-4422(17)30470-2.
15. Kappos L, Radue EW, O'Connor P, et al. A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis. *N Engl J Med* 2010; 362: 387-401. research-article 2010/01/22. DOI: 10.1056/NEJMoa0909494.

16. 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. 2003/01/03. DOI: 10.1056/NEJMoa020696.
17. Hauser SL, Bar-Or A, Comi G, et al. Ocrelizumab versus Interferon Beta-1a in Relapsing Multiple Sclerosis. *N Engl J Med* 2017; 376: 221-234. research-article 20161221. DOI: 10.1056/NEJMoa1601277.
18. Coles AJ, Compston DA, Selmaj KW, et al. Alemtuzumab vs. interferon beta-1a in early multiple sclerosis. *N Engl J Med* 2008; 359: 1786-1801. 2008/10/24. DOI: 10.1056/NEJMoa0802670.
19. Ferro MA. Missing data in longitudinal studies: cross-sectional multiple imputation provides similar estimates to full-information maximum likelihood. *Ann Epidemiol* 2014; 24: 75-77. 20131018. DOI: 10.1016/j.annepidem.2013.10.007.
20. Kalincik T, Brown JW, Robertson N, et al. Treatment effectiveness of alemtuzumab compared with natalizumab, fingolimod, and interferon beta in relapsing-remitting multiple sclerosis: a cohort study. *Lancet Neurol* 2017; 16: 271-281. 20170211. DOI: 10.1016/S1474-4422(17)30007-8.
21. Kalincik T, Kuhle J, Pucci E, et al. Data quality evaluation for observational multiple sclerosis registries. *Mult Scler* 2017; 23: 647-655. 20160805. DOI: 10.1177/1352458516662728.
22. 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: 552-568. 1965/03/31. DOI: 10.1111/j.1749-6632.1965.tb20235.x.
23. Kalincik T, Cutter G, Spelman T, et al. Defining reliable disability outcomes in multiple sclerosis. *Brain* 2015; 138: 3287-3298. Article 20150910. DOI: 10.1093/brain/awv258.
24. Rosenbaum PR and Rubin DB. Reducing Bias in Observational Studies Using Subclassification on the Propensity Score. *Journal of the American Statistical Association* 1984; 79: 516-524. DOI: 10.1080/01621459.1984.10478078.
25. Chua AS, Egorova S, Anderson MC, et al. Using multiple imputation to efficiently correct cerebral MRI whole brain lesion and atrophy data in patients with multiple sclerosis. *Neuroimage* 2015; 119: 81-88. 20150618. DOI: 10.1016/j.neuroimage.2015.06.037.
26. Carpenter JR, Kenward MG and White IR. Sensitivity analysis after multiple imputation under missing at random: a weighting approach. *Statistical Methods in Medical Research* 2007; 16: 259-275. DOI: 10.1177/0962280206075303.
27. Heraud-Bousquet V, Larsen C, Carpenter J, et al. Practical considerations for sensitivity analysis after multiple imputation applied to epidemiological studies with incomplete data. *BMC Med Res Methodol* 2012; 12: 73. 20120608. DOI: 10.1186/1471-2288-12-73.
28. Austin PC. Optimal caliper widths for propensity-score matching when estimating differences in means and differences in proportions in observational studies. *Pharm Stat* 2011; 10: 150-161. 2010/10/07. DOI: 10.1002/pst.433.
29. Rosenbaum PR. Sensitivity Analysis in Observational Studies.
30. Sharmin S, Lefort M, Andersen JB, et al. Natalizumab Versus Fingolimod in Patients with Relapsing-Remitting Multiple Sclerosis: A Subgroup Analysis From Three International Cohorts. *CNS Drugs* 2021; 35: 1217-1232. 20210918. DOI: 10.1007/s40263-021-00860-7.
31. Salanti G. Indirect and mixed-treatment comparison, network, or multiple-treatments meta-analysis: many names, many benefits, many concerns for the next generation evidence synthesis tool. *Res Synth Methods* 2012; 3: 80-97. 20120611. DOI: 10.1002/jrsm.1037.

- 1
2
3 32. Siddiqui MK, Khurana IS, Budhia S, et al. Systematic literature review and network
4 meta-analysis of cladribine tablets versus alternative disease-modifying treatments for
5 relapsing-remitting multiple sclerosis. *Curr Med Res Opin* 2018; 34: 1361-1371. 20171128.
6 DOI: 10.1080/03007995.2017.1407303.
7
8 33. Kalincik T and Butzkueven H. Observational data: Understanding the real MS world.
9 *Mult Scler* 2016; 22: 1642-1648. Review 20160606. DOI: 10.1177/1352458516653667.
10
11 34. D'Souza M, Yaldizli O, John R, et al. Neurostatus e-Scoring improves consistency of
12 Expanded Disability Status Scale assessments: A proof of concept study. *Mult Scler* 2017;
13 23: 597-603. 2016/07/02. DOI: 10.1177/1352458516657439.
14
15 35. Kalincik T, Kubala Havrdova E, Horakova D, et al. Comparison of fingolimod,
16 dimethyl fumarate and teriflunomide for multiple sclerosis. *J Neurol Neurosurg Psychiatry*
17 2019; 90: 458-468. 20190113. DOI: 10.1136/jnnp-2018-319831.
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For Peer Review

TABLES

Table 1: Demographic, clinical and paraclinical characteristics of matched patients

	Clad- ribine	Fingo- limod	SMD	Clad- ribine	Natali- zumab	SMD	Clad- ribine	Ocreli- zumab	SMD	Clad- ribine	Alemtu- zumab	SMD
Number of patients	198	403		220	331		380	667		173	68	
Registry, n (%) ^a												
<i>Cambridge</i>	4.0 (2.0)	10.4 (2.6)		3.0 (1.4)	6.0 (1.8)		5.0 (1.3)	11.7 (1.8)		12.7 (7.4)	5.0 (7.4)	
<i>Cardiff</i>	3.0 (1.5)	6.8 (1.7)		3.0 (1.4)	4.3 (1.3)		2.0 (0.5)	1.8 (0.3)			1.0 (1.5)	
<i>MSBase</i>	191.0 (96.5)	385.8 (95.7)		214.0 (97.3)	320.7 (96.9)		373.0 (98.2)	653.5 (98.0)		152.6 (88.2)	62.0 (91.2)	
Female sex, n (%)	148 (75)	300 (74)	0.01	177 (79)	265 (80)	0.04	289 (76)	512 (77)	0.02	131 (75)	50 (74)	0.05
Age, y	39.4 (10.6)	39.3 (10.6)	0.01	38.3 (10.4)	39.1 (9.7)	0.08	42.3 (12.2)	42.3 (11.1)	<0.001	38.1 (9.9)	38.2 (10.9)	0.01
MS duration, y	9.8 (7.8)	10.0 (7.7)	0.03	8.9 (6.5)	9.0 (7.1)	0.02	10.6 (8.2)	10.2 (7.9)	0.05	9.9 (7.0)	10.5 (7.0)	0.08
Nr of relapses in prior 12 months	0.5 (0.7)	0.5 (0.7)	0.03	0.5 (0.7)	0.5 (0.7)	0.03	0.4 (0.6)	0.4 (0.6)	0.02	0.7 (0.8)	0.7 (0.8)	0.01
EDSS step	1.5 [1.0, 2.5]	1.5 [1.0, 2.5]	0.03	2.0 [1.0, 3.0]	2.0 [1.0, 3.0]	0.01	2.0 [1.0, 3.5]	2.0 [1.5, 4.0]	0.02	2.0 [1.5, 3.5]	2.5 [1.9, 4.1]	0.07
Disease activity over prior 12 months, n (%)												
<i>none</i>	98.0 (49.5)	210.8 (52.3)		107.0 (48.6)	159.5 (48.2)		218.0 (57.4)	391.4 (58.7)		67.1 (38.8)	31.0 (45.6)	
<i>progression</i>	22.0 (11.1)	37.0 (9.2)		22.0 (10.0)	26.6 (8.0)		30.0 (7.9)	50.3 (7.5)		18.1 (10.4)	6.0 (8.8)	
<i>relapse</i>	55.0 (27.8)	110.9 (27.5)		57.0 (25.9)	93.5 (28.3)		89.0 (23.4)	155.3 (23.3)		57.3 (33.1)	19.0 (27.9)	
<i>relapse & progression</i>	23.0 (11.6)	44.2 (11.0)		34.0 (15.5)	51.4 (15.5)		43.0 (11.3)	69.9 (10.5)		30.5 (17.6)	12.0 (17.6)	
MRI Brain: T2 lesion, n (%)												
<i>Imaging available</i>	65 (33)	123 (31)		65 (30)	71 (38)		90 (24)	153 (23)		50 (29)	27 (40)	
1-2	2.0 (1.0)	4.6 (1.2)		3.0 (1.4)	4.5 (1.4)		17.0 (4.4)	32.8 (4.9)		9.8 (5.7)	5.0 (7.4)	
3-8	5.0 (2.5)	12.5 (3.1)		23.0 (10.5)	37.9 (11.4)		25.0 (6.6)	49.1 (7.4)		12.2 (7.1)	4.0 (5.9)	
9+	191.0 (96.5)	385.8 (95.7)		194.0 (88.2)	288.6 (87.2)		338.0 (88.9)	585.1 (87.7)		151.0 (87.3)	59.0 (86.8)	
MRI Brain: new or contrast enhancing lesions, n (%)												
<i>Imaging available</i>	120 (60)	192 (48)		128 (58)	158 (48)		182 (49)	312 (47)		77 (45)	35 (51)	
<i>Absent</i>	88.0 (44.4)	184.9 (45.9)		90 (40.9)	139.7 (42.4)		201 (52.9)	353.7 (53.0)		57.8 (33.4)	25 (36.8)	
<i>Present</i>	110.0 (55.6)	218.1 (54.1)		130.0 (59.1)	191.3 (57.8)		179.0 (47.1)	313.3 (47.0)		115.2 (66.6)	43.0 (63.2)	
Nr of previous therapies	1 [1, 2]	1 [1, 2]	0.03	1 [1, 3]	1 [1, 2]	0.04	2 [1, 3]	2 [1, 3]	0.02	2 [1, 3]	2 [1, 3]	0.09
Top previous therapy category, n (%)												
<i>None</i>	20.0 (10.1)	39.8 (9.9)		30.0 (13.6)	50.2 (15.2)		42.0 (11.1)	73.7 (11.1)		27.4 (15.9)	6.0 (8.8)	

	<i>Low-efficacy</i>	104.0	194.5	72.0	105.8	101.0	174.6	17.9	9.0 (13.2)
		(52.5)	(48.3)	(32.7)	(32.0)	(26.6)	(26.2)	(10.4)	
	<i>Moderate-efficacy</i>	60.0	120.4	98.0	152.0	166.0	287.0	85.4	31.0
		(30.3)	(29.9)	(44.5)	(45.9)	(43.7)	(43.0)	(49.4)	(45.6)
	<i>High-efficacy</i>	14.0	48.3	20.0	23.1	71.0	131.6	42.2	22.0
		(7.1)	(12.0)	(9.1)	(7.0)	(18.7)	(19.7)	(24.4)	(32.4)
	Pre-baseline follow up, y	5.0 [2.1,4.7	8.6] [2.3,0.06	4.5 [2.0,4.1	8.0] [1.7,0.06	4.7 [2.2,4.9	9.2] [2.0,0.03	5.0 [2.1,6.4	10.3] [2.7, 0.17
	Visit interval, m	6.9 [4.9,8.1	11.0] [6.0,0.28	6.3 [4.8,7.3	9.7] [5.7,0.22	7.2 [5.2,8.0	11.3] [6.1,0.22	6.3 [4.4,7.7	12.2] [6.1, 0.5
	Study follow-up, y	2.1	2.1	0.00	1.8	1.8	0.00	2.1	2.1
		(0.9)	(0.9)		(0.8)	(0.8)		(0.8)	(0.8)

Mean (SD) or median [quartiles] as appropriate

^a Weighted estimates yield decimals in the control group, reflecting the fractional weights assigned to individual units in 1-to-multiple propensity score matching

Top previous therapy category:

Low-efficacy: interferons, glatiramer acetate, teriflunomide; Moderate-efficacy: fingolimod, dimethyl fumarate, diroximel fumarate, daclizumab; High-efficacy: natalizumab, alemtuzumab, rituximab, ocrelizumab, mitoxantrone

Follow-up after pairwise censoring, as per the primary analysis

SMD – standardised mean difference

FIGURE LEGENDS

Figure 1: Patient disposition

MS, multiple sclerosis

Figure 2: Comparison of treatment outcomes for fingolimod vs cladribine

- A. Annualised relapse rate
 - B. Cumulative hazard of relapses
 - C. Cumulative hazard of disability accumulation
 - D. Cumulative hazard of disability improvement
- HR, hazard ratio; CI, confidence interval

Figure 3: Comparison of treatment outcomes for natalizumab vs cladribine

- A. Annualised relapse rate
 - B. Cumulative hazard of relapses
 - C. Cumulative hazard of disability accumulation
 - D. Cumulative hazard of disability improvement
- HR, hazard ratio; CI, confidence interval

Figure 4: Comparison of treatment outcomes for ocrelizumab vs cladribine

- A. Annualised relapse rate
 - B. Cumulative hazard of relapses
 - C. Cumulative hazard of disability accumulation
 - D. Cumulative hazard of disability improvement
- HR, hazard ratio; CI, confidence interval

Figure 5: Comparison of treatment outcomes for alemtuzumab vs cladribine

- A. Annualised relapse rate
 - B. Cumulative hazard of relapses
 - C. Cumulative hazard of disability accumulation
 - D. Cumulative hazard of disability improvement
- HR, hazard ratio; CI, confidence interval

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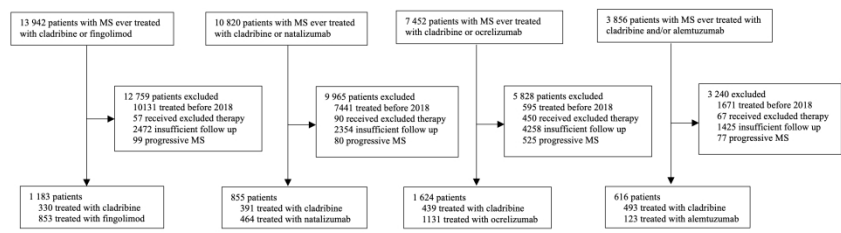


Figure 1: Patient disposition
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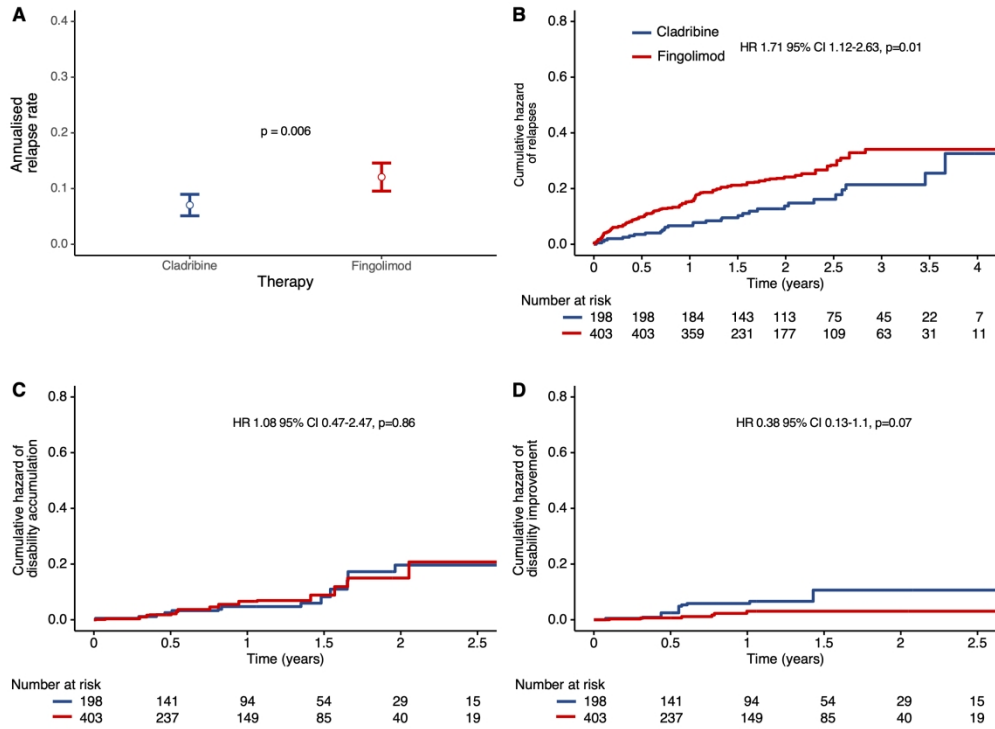


Figure 2: Comparison of treatment outcomes for fingolimod vs cladribine

A. Annualised relapse rate

B. Cumulative hazard of relapses

C. Cumulative hazard of disability accumulation

D. Cumulative hazard of disability improvement

HR, hazard ratio; CI, confidence interval

1058x793mm (72 x 72 DPI)

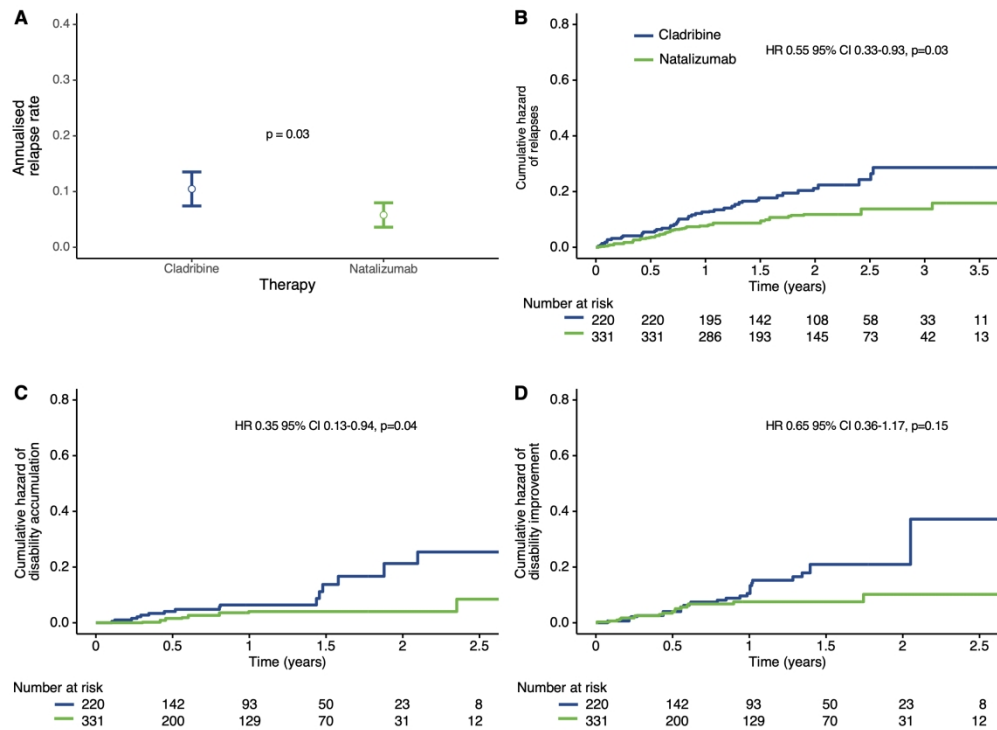


Figure 3: Comparison of treatment outcomes for natalizumab vs cladribine

- A. Annualised relapse rate
 - B. Cumulative hazard of relapses
 - C. Cumulative hazard of disability accumulation
 - D. Cumulative hazard of disability improvement
- HR, hazard ratio; CI, confidence interval

1058x793mm (72 x 72 DPI)

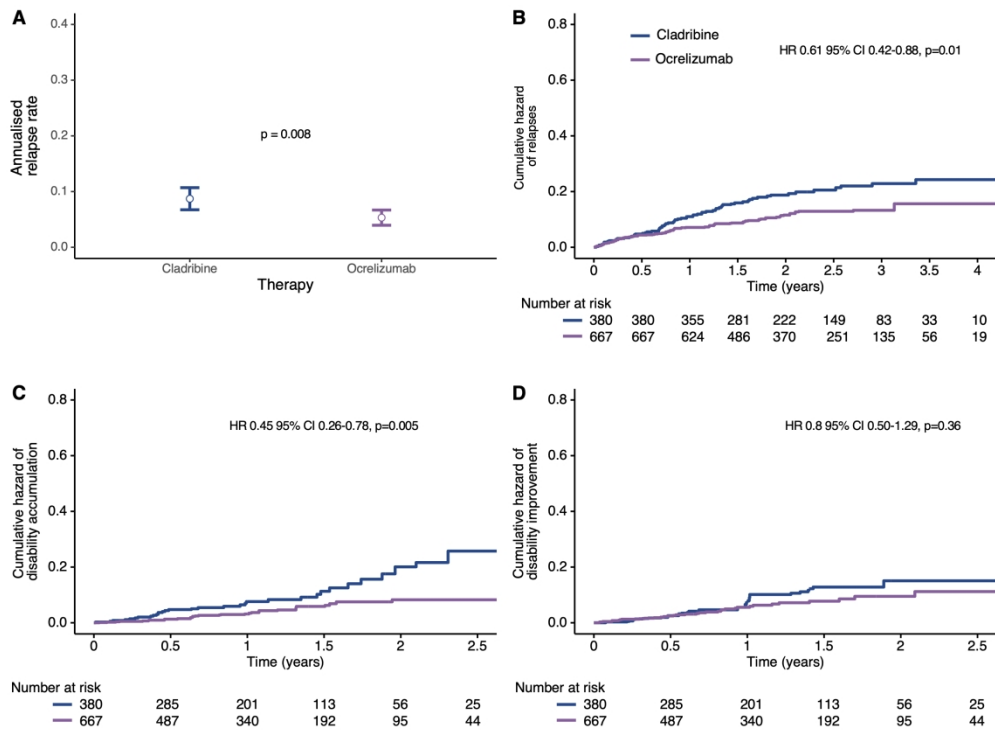


Figure 4: Comparison of treatment outcomes for ocrelizumab vs cladribine

- A. Annualised relapse rate
 - B. Cumulative hazard of relapses
 - C. Cumulative hazard of disability accumulation
 - D. Cumulative hazard of disability improvement
- HR, hazard ratio; CI, confidence interval

1058x793mm (72 x 72 DPI)

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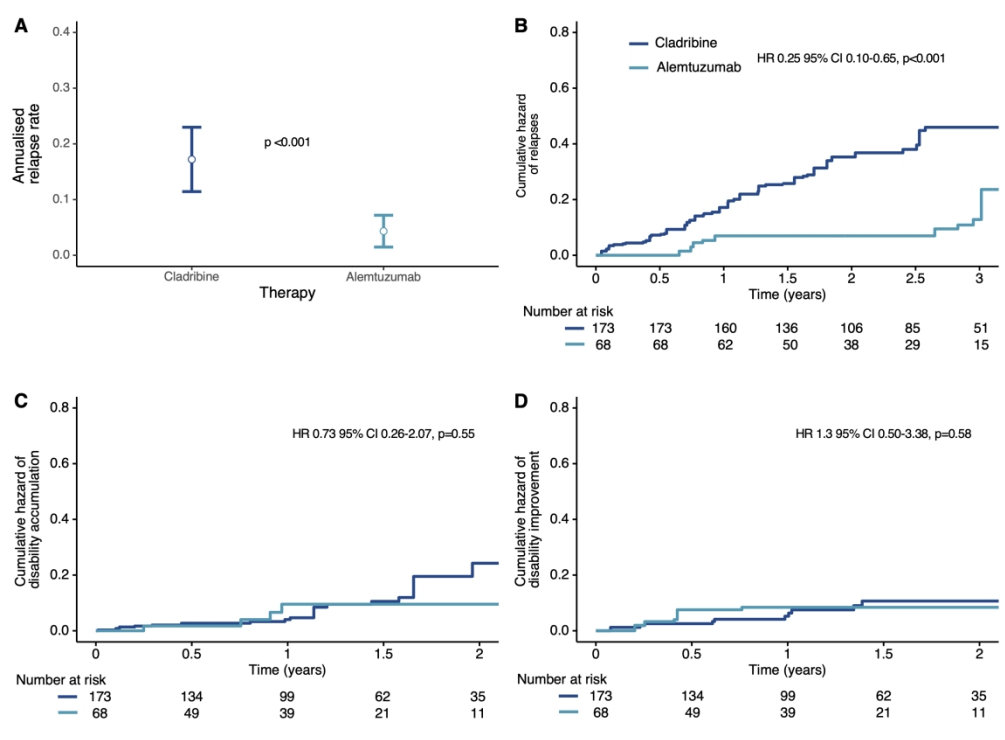


Figure 5: Comparison of treatment outcomes for alemtuzumab vs cladribine
 A. Annualised relapse rate
 B. Cumulative hazard of relapses
 C. Cumulative hazard of disability accumulation
 D. Cumulative hazard of disability improvement
 HR, hazard ratio; CI, confidence interval

1058x793mm (72 x 72 DPI)

Supplementary Appendix

List of contributors

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eTable 2: Number of matched patients by country

eTable 3: Disposition of patients treated with a study therapy, but who were excluded from the analysis

eTable 4: Characteristics of included patients at baseline (pre-match)

eTable 5: Logistic regression model used to estimate propensity scores

eTable 6: Disposition of patients who fulfilled inclusion criteria, but were not propensity score matched

eFigure 1: Propensity scores

eFigure 2: Love plots

eTable 7: Results from sensitivity analyses

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eTable 1: Data quality procedure

- Duplicate patient records were removed.
- Centres with <10 patient records were excluded.
- Patients with missing date of birth were excluded.
- MS onset dates after the data extract date were removed.
- Patients with missing date of the first clinical presentation of MS were excluded.
- The dates of MS onset and the first recorded MS course were aligned.
- Patients with the age at onset outside the 0-100 range were excluded.
- A logical sequence of the MS courses (e.g. clinically isolated syndrome, relapsing-remitting MS, secondary progressive MS) was assured.
- Entries with the initiation of progressive MS prior to its clinical onset of MS were excluded.
- Visits with missing visit date or the recorded date before the clinical MS onset or after the date of data extract were removed.
- EDSS scores outside the range of possible EDSS values were removed.
- Duplicate visits were merged.
- MS relapses with missing visit date or the recorded date after the date of MSBase data extract were removed.
- Duplicate MS relapses were merged.
- Relapses occurring within 30 days of each other were merged.
- Visits preceded by relapses were identified and time from the last relapse was calculated for each visit.
- Therapies were labelled as discontinued or continuing.
- Therapies with erroneous date entries were removed (e.g. commencement date > termination date, commencement after the MSBase data extract date, commencement of disease modifying therapy before the year 1980).
- MS disease modifying therapies were identified and labelled.
- Duplicate treatment entries were removed.
- Where multiple disease modifying therapies were recorded simultaneously, treatment end date of the previous therapy was imputed as the commencement date of the following therapy.

eTable 2: Patient disposition per country and treatment (only matched patients)

	Cladribine vs fingolimod		Cladribine vs natalizumab		Cladribine vs ocrelizumab		Cladribine vs alemtuzumab	
	Cladribine	Fingolimod	Cladribine	Natalizumab	Cladribine	Ocrelizumab	Cladribine	Alemtuzumab
<i>Australia</i>	35	96	90	139	191	360	22	9
<i>Belgium</i>	6	9	9	12	13	24	12	5
<i>Canada</i>	45	85	16	35	52	90	17	8
<i>Switzerland</i>	0	0	31	41	0	0	0	0
<i>Spain</i>	42	71	0	0	44	69	58	24
<i>Great Britain</i>	7	17	6	10	7	14	20	6
<i>Italy</i>	23	42	20	28	21	41	15	5
<i>Kuwait</i>	5	10	9	13	9	12	16	3
<i>Lebanon</i>	1	2	1	2	1	2	0	0
<i>Netherlands</i>	1	2	0	0	1	2	1	1
<i>Oman</i>	2	6	2	2	2	2	0	0
<i>Portugal</i>	2	6	2	4	4	4	2	1
<i>Turkey</i>	29	58	34	44	35	48	10	6

eTable 3: Disposition of patients treated with a study therapy, but who were excluded from the analysis

	Clad- ribine	Fingo- limod	Clad- ribine	Natali- zumab	Clad- ribine	Ocreli- zumab	Clad- ribine	Alemtu- zumab
Nr of patients (% female)	1114 (75)	11645 (71)	1182 (74)	8783 (73)	1374 (75)	4452 (65)	1834 (72)	1406 (74)
Registry, n (%)								
<i>Cambridge</i>	14 (1.3)	92 (0.8)	13 (1.1)	89 (1.0)	16 (1.2)	85 (1.9)	381 (20.8)	16 (1.1)
<i>Cardiff</i>	22 (2.0)	125 (1.1)	22 (1.9)	154 (1.8)	23 (1.7)	132 (2.9)	193 (10.5)	23 (1.6)
<i>MSBase</i>	1078 (96.8)	981 (8.1)	1147 (97.0)	8540 (97.2)	1335 (97.2)	4235 (95.2)	1260 (68.7)	1367 (97.2)
Age, y	42.8 (12.1)	38.4 (10.6)	42.9 (12.0)	37.3 (10.5)	43.5 (11.9)	43.1 (11.7)	36.0 (9.3)	43.7 (12.0)
MS duration, y	10.3 (9.3)	9.2 (7.5)	10.7 (9.3)	8.3 (7.3)	11.5 (9.5)	10.6 (8.6)	7.4 (6.7)	11.6 (9.5)
Nr of relapses in prior 12 months	0.4 (0.7)	0.6 (0.8)	0.4 (0.7)	0.9 (1.0)	0.4 (0.7)	0.3 (0.7)	1.0 (1.1)	0.4 (0.7)
EDSS step	2.5 (2.1)	2.7 (1.8)	2.3 (1.9)	3.3 (1.9)	2.6 (2.1)	3.8 (2.2)	3.1 (2.0)	2.7 (2.2)

Note: Patients in the excluded group are patients with multiple sclerosis who were treated with cladribine or the comparator therapy, but were excluded from the analysis based on insufficient treatment duration, inadequate follow-up, progressive MS or previous exposure to an excluded therapy. Baseline characteristics of the excluded patients are reported at the visit closest to the date of commencement of therapy.

eTable 4: Demographic, clinical and paraclinical characteristics of included patients before propensity score matching

	Clad- ribine	Fingo- limod	SMD	Clad- ribine	Natali- zumab	SMD	Clad- ribine	Ocreli- zumab	SMD	Clad- ribine	Alemtu- zumab	SMD
Nr of patients	330	853		391	464		439	1131		493	123	
Registry (%)												
<i>Cambridge</i>	20 (2.3)	4 (1.2)		4 (1.0)	4 (0.9)		5 (1.1)	13 (1.1)		5 (1.0)	12 (9.8)	
<i>Cardiff</i>	12 (1.4)	3 (0.9)		3 (0.8)	12 (2.6)		2 (0.5)	55 (4.9)		3 (0.6)	11 (8.9)	
<i>MSBase</i>	821 (96.2)	323 (97.9)		384 (98.2)	448 (96.6)		432 (98.4)	1063 (94.0)		485 (98.4)	100 (81.3)	
Female sex (%)	640 (75)	242 (73)		295 (75)	378 (81)		339 (77)	796 (70)		382 (77)	88 (72)	
Age, y	41.7 (11.9)	38.0 (10.5)	0.3	42.6 (12.0)	36.3 (9.6)	0.6	42.6 (12.1)	42.3 (11.2)	0.02	42.9 (11.9)	37.1 (8.9)	0.5
MS duration, y	9.9 (8.2)	9.3 (7.1)	0.1	10.7 (8.0)	8.6 (6.6)	0.2	10.8 (8.1)	11.2 (8.3)	0.05	11.1 (8.2)	9.8 (7.3)	0.2
Nr of relapses in prior 12 months	0.5 (0.7)	0.5 (0.7)	0.01	0.5 (0.7)	0.7 (0.8)	0.3	0.4 (0.7)	0.5 (0.7)	0.06	0.4 (0.7)	0.8 (0.9)	0.5
EDSS step	2.2 (1.7)	1.6 (1.5)	0.4	2.2 (1.7)	2.2 (1.7)	0.02	2.3 (1.7)	3.1 (1.9)	0.4	2.4 (1.8)	3.1 (1.9)	0.4
Disease activity over prior 12 months, n (%)												
<i>none</i>	179 (54.2)	446 (52.3)		215 (55)	179 (39)		256 (58.3)	559 (49.4)		293 (59.4)	46 (37.4)	
<i>progression</i>	22 (6.7)	56 (6.6)		31 (8)	44 (10)		31 (7.1)	146 (12.9)		36 (7.3)	11 (8.9)	
<i>relapse</i>	89 (27.0)	224 (26.3)		98 (25)	134 (29)		104 (23.7)	289 (25.6)		114 (23.1)	47 (38.2)	
<i>relapse & progression</i>	40 (12.1)	127 (14.9)		47 (12)	107 (23)		48 (10.9)	137 (12.1)		50 (10.1)	19 (15.4)	
MRI Brain: T2 lesion, n (%)												
<i>Imaging available</i>	79 (24)	517 (60)		91 (23)	231 (50)		100 (23)	400 (35)		106 (22)	45 (37)	
1-2	3 (1)	10 (2)		3 (3)	14 (6)		4 (4)	21 (5)		4 (4)	5 (11)	
3-8	10 (13)	22 (4)		10 (11)	21 (9)		12 (12)	29 (7)		14 (13)	1 (2)	
9+	66 (84)	447 (86)		78 (86)	196 (85)		84 (84)	351 (88)		88 (83)	39 (87)	
MRI Brain: new or contrast enhancing lesions, n (%)												
<i>Imaging available</i>	168 (51)	517 (60)		198 (49)	256 (39)		212 (48)	569 (50)		233 (47)	51 (41)	
<i>Absent^a</i>	76 (45)	299 (57)		97 (51)	157 (61)		101 (48)	350 (62)		119 (51)	19 (37)	
<i>Present^a</i>	92 (54)	218 (42)		101 (51)	157 (61)		111 (52)	219 (38)		114 (49)	32 (63)	
Nr of previous therapies	1 [1, 2]	1 [1, 2]	0.02	1 [1, 2]	2 [1, 3]	0.1	2 [1, 2]	2 [1, 3]	0.1	2 [1, 3]	2 [1, 3]	0.03
Top previous therapy category, n (%)												

None	48 (14.5)44 (5.2)	48 (12.3)59 (12.7)	48 (10.9)140 (12.4)	49 (9.9) 25 (20.3)
Low-efficacy	146 (44.2) 596 (69.9)	146 (37.3) 124 (26.7)	146 (33.3) 196 (17.3)	149 (30.2) 11 (8.9)
Moderate-efficacy	72 (21.8)163 (19.1)	174 (44.5) 207 (44.6)	174 (39.6) 404 (35.7)	181 (36.7) 48 (39.0)
High-efficacy	64 (19.4)50 (5.9)	23 (5.9) 74 (15.9)	71 (16.2)391 (34.6)	114 (23.1) 39 (31.7)
Prebaseline follow up, y	4.0 [1.8, 4.7 [2.3, 0.04 8.0] 8.1]	4.8 [2.3, 4.2 [1.9, 0.2 8.9] 7.6]	4.8 [2.2, 5.2 [2.1, 0.02 8.8] 9.3]	4.8 [2.4, 4.8 [1.2, 0.06 8.8] 8.9]
Visit density (per year)	1.7 [1.2, 1.9 [1.4, 0.2 2.4] 2.6]	1.7 [1.2, 1.9 [1.3, 0.3 2.3] 2.5]	1.6 [1.2, 1.8 [1.2, 0.08 2.3] 2.3]	1.7 [1.2, 1.5 [1.0, 0.2 2.4] 2.0]
Study follow-up, y	2.4 (1.0) 2.6 (1.1) 0.24	2.4 (1.0) 2.6 (1.1) 0.1	2.5 (1.0) 2.8 (1.1) 0.3	2.5 (0.9) 3.2 (1.0) 0.8

^a Proportion of patients with available MRI

Top previous therapy category:

Low-efficacy: interferons, glatiramer acetate, teriflunomide; Moderate-efficacy: fingolimod, dimethyl fumarate, diroximel fumarate, daclizumab; High-efficacy: natalizumab, alemtuzumab, rituximab, ocrelizumab, mitoxantrone

SMD – standardised mean difference

eTable 5: Logistic regression model used to estimate propensity scores

Fingolimod vs cladribine (reference)

Independent variable	Coefficient	p-value
Male sex	0.13	0.52
Age	0.02	0.11
EDSS at baseline	-0.08	0.22
Nr relapses in 12 months before baseline	0.14	0.60
MS duration	-0.03	0.03
Nr of previous MS therapies	0.08	0.37
T2 lesion nr: 1-2	0.92	0.57
T2 lesion nr: 3-8	-0.27	0.82
T2 lesion nr: 9+	0.03	0.98
New T2 or Gd lesion at baseline	-0.23	0.24
Recent activity: progression	0.85	0.01
Recent activity: relapse	-0.08	0.84
Recent activity: relapse and progression	0.43	0.16
Country: CA	1.57	<0.0001
Country: ES	0.66	0.03
Country: GB	2.98	<0.0001
Country: IT	1.48	<0.0001
Country: KW	2.98	<0.0001
Country: LB	4.27	<0.0001
Country: OM	2.03	0.02
Country: PT	2.57	<0.0001
Top previous DMT category: low	0.29	0.37
Top previous DMT category: moderate	0.81	0.01
Top previous DMT category: none	0.66	0.15

Natalizumab vs cladribine (reference)

Independent variable	Coefficient	p-value
Male sex	-0.40	0.05
Age	-0.04	<0.0001
EDSS at baseline	0.04	0.49
Nr relapses in 12 months before baseline	0.24	0.31
MS duration	-0.01	0.71

<i>Nr of previous MS therapies</i>	0.01	0.89
<i>T2 lesion nr: 1-2</i>	-1.08	0.45
<i>T2 lesion nr: 3-8</i>	-1.53	0.06
<i>T2 lesion nr: 9+</i>	-1.82	0.02
<i>New T2 or Gd lesion at baseline</i>	0.95	<0.0001
<i>Recent activity: progression</i>	0.53	0.08
<i>Recent activity: relapse</i>	0.00	0.99
<i>Recent activity: relapse and progression</i>	0.55	0.15
<i>Country: ES</i>	-0.63	0.03
<i>Country: IT</i>	0.80	0.01
<i>Country: KW</i>	1.35	<0.0001
<i>Country: LB</i>	2.35	0.03
<i>Country: TR</i>	1.57	<0.0001
<i>Top previous DMT category: low</i>	-2.26	<0.0001
<i>Top previous DMT category: moderate</i>	-1.52	<0.0001
<i>Top previous DMT category: none</i>	-1.61	<0.0001

Ocrelizumab vs cladribine (reference)

Independent variable	Coefficient	p-value
<i>Male sex</i>	0.29	0.05
<i>Age</i>	-0.01	0.26
<i>EDSS at baseline</i>	0.16	<0.0001
<i>Nr relapses in 12 months before baseline</i>	0.14	0.54
<i>MS duration</i>	0.001	0.86
<i>Nr of previous MS therapies</i>	-0.01	0.85
<i>T2 lesion nr: 1-2</i>	1.30	0.13
<i>T2 lesion nr: 3-8</i>	0.44	0.26
<i>T2 lesion nr: 9+</i>	0.44	0.17
<i>New T2 or Gd lesion at baseline</i>	-0.13	0.32
<i>Recent activity: progression</i>	0.75	<0.0001
<i>Recent activity: relapse</i>	0.18	0.57
<i>Recent activity: relapse and progression</i>	0.25	0.45
<i>Country: BE</i>	1.29	<0.0001
<i>Country: CA</i>	0.39	0.05
<i>Country: ES</i>	-0.54	0.02
<i>Country: IT</i>	0.58	0.05
<i>Country: KW</i>	1.45	<0.0001
<i>Country: PT</i>	-2.11	0.02
<i>Country: TR</i>	1.93	<0.0001
<i>Top previous DMT category: low</i>	-2.03	<0.0001
<i>Top previous DMT category: moderate</i>	-1.13	<0.0001
<i>Top previous DMT category: none</i>	-1.02	<0.0001

Alemtuzumab vs cladribine (reference)

Independent variable	Coefficient	p-value
<i>Male sex</i>	0.36	0.31
<i>Age</i>	-0.05	0.01
<i>EDSS at baseline</i>	0.31	0.002
<i>Nr relapses in 12 months before baseline</i>	0.95	0.02
<i>MS duration</i>	0.03	0.26
<i>Nr of previous MS therapies</i>	0.03	0.83
<i>T2 lesion nr: 1-2</i>	-14.80	0.99

T2 lesion nr: 3-8	-1.96	0.03
T2 lesion nr: 9+	-0.80	0.27
New T2 or Gd lesion at baseline	0.51	0.13
Recent activity: progression	0.39	0.48
Recent activity: relapse	-0.82	0.22
Recent activity: relapse and progression	-1.35	0.07
Country: BE	2.44	<0.0001
Country: CA	1.70	0.01
Country: ES	3.04	<0.0001
Country: GB	4.17	<0.0001
Country: IT	2.87	<0.0001
Country: KW	4.47	<0.0001
Country: TR	2.08	<0.0001
Top previous DMT category: low	-2.38	<0.0001
Top previous DMT category: moderate	-0.87	0.04
Top previous DMT category: none	-0.31	0.66

Coefficients indicate change in log odds of being treated with the comparator vs CLD. Only country variables with a significant contribution to the logistic model are shown.

eTable 6: Demographic, clinical and paraclinical characteristics of patients who fulfilled inclusion criteria but were not propensity score matched

	Clad- ribine	Fingo- limod	SMD	Clad- ribine	Natali- zumab	SMD	Clad- ribine	Ocreli- zumab	SMD	Clad- ribine	Alemtu- zumab	SMD
Nr of patients	132	450		171	133		59	464		320	55	
Registry (%)												
Cambridge	0 (0.0)	4 (0.9)		1 (0.6)	0 (0.0)		0 (0.0)	2 (0.4)		0 (0.0)	7 (12.7)	
Cardiff	0 (0.0)	2 (0.4)		0 (0.0)	4 (3.0)		0 (0.0)	52 (11.2)		0 (0.0)	10 (18.2)	
MSBase	132 (100.0)	444 (98.7)		170 (99.4)	129 (97.0)		59 (100.0)	410 (88.4)		320 (100.0)	38 (69.1)	
Female sex (%)	94 (71)	344 (74)		122 (72)	107 (80)		50 (85)	421 (89)		242 (79)	43 (78)	
Age, y	45.2 (13.0)	37.6 (10.6)	0.64	48.2 (11.6)	32.5 (8.5)	1.53	44.8 (10.9)	42.6 (10.9)	0.21	44.5 (12.3)	36.6 (8.9)	0.73
MS duration, y	10.1 (8.9)	8.8 (6.7)	0.17	12.9 (9.2)	7.9 (5.9)	0.64	12.0 (7.9)	12.4 (8.4)	0.05	11.5 (8.5)	8.9 (7.7)	0.32
Nr of relapses in prior 12 months	0.5 (0.6)	0.5 (0.7)	0.06	0.4 (0.6)	0.9 (0.9)	0.74	0.5 (0.8)	0.5 (0.7)	0.1	0.4 (0.6)	1.0 (0.9)	0.82
EDSS step	2.7 (1.9)	1.5 (1.4)	0.74	2.4 (1.7)	2.3 (1.8)	0.03	1.5 (1.2)	3.8 (1.9)	1.37	2.3 (1.7)	3.3 (2.0)	0.54
Disease activity over prior 12 months, n (%)												
none	81 (61.4)	241 (53.6)		108 (63.2)	33 (24.8)		38 (64.4)	183 (39.4)		213 (66.6)	15 (27.3)	
progression	0 (0.0)	26 (5.8)		9 (5.3)	16 (12.0)		1 (1.7)	87 (18.8)		15 (4.7)	5 (9.1)	
relapse	34 (25.8)	108 (24.0)		41 (24.0)	41 (30.8)		15 (25.4)	126 (27.2)		66 (20.6)	28 (50.9)	
relapse & progression	17 (12.9)	75 (16.7)		13 (7.6)	43 (32.3)		5 (8.5)	68 (14.7)		26 (8.1)	7 (12.7)	
Nr of previous therapies	1.4 (1.2)	1.5 (0.8)	0.03	1.8 (1.3)	2.1 (1.2)	0.23	1.6 (1.1)	2.2 (1.6)	0.41	1.9 (1.5)	1.8 (1.7)	0.08
Top previous therapy category, n (%)												
None	28 (21.2)	12 (2.7)		18 (10.5)	11 (8.3)		6 (10.2)	66 (14.2)		31 (9.7)	19 (34.5)	
Low-efficacy	42 (31.8)	364 (80.9)		74 (43.3)	29 (21.8)		45 (76.3)	41 (8.8)		122 (38.1)	2 (3.6)	
Moderate-efficacy	12 (9.1)	63 (14.0)		76 (44.4)	56 (42.1)		8 (13.6)	159 (34.3)		97 (30.3)	17 (30.9)	
High-efficacy	50 (37.9)	11 (2.4)		3 (1.8)	37 (27.8)		0 (0.0)	198 (42.7)		70 (21.9)	17 (30.9)	

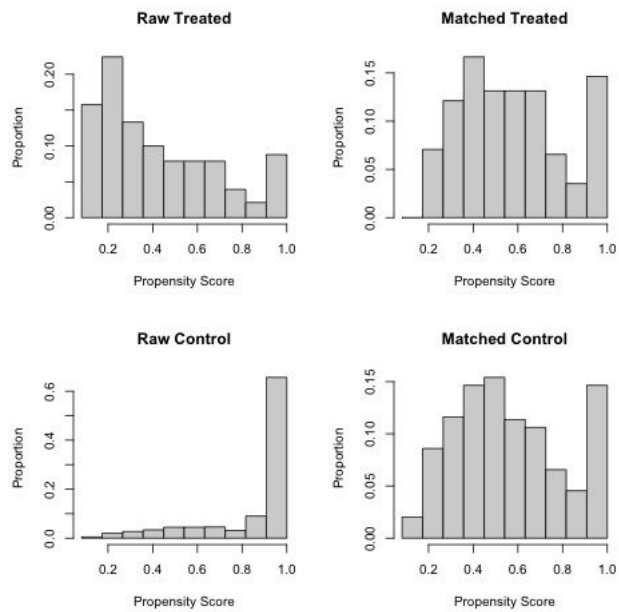
Top previous therapy category:

Low-efficacy: interferons, glatiramer acetate, teriflunomide; Moderate-efficacy: fingolimod, dimethyl fumarate, diroximel fumarate, daclizumab; High-efficacy: natalizumab, rituximab, ocrelizumab, mitoxantrone

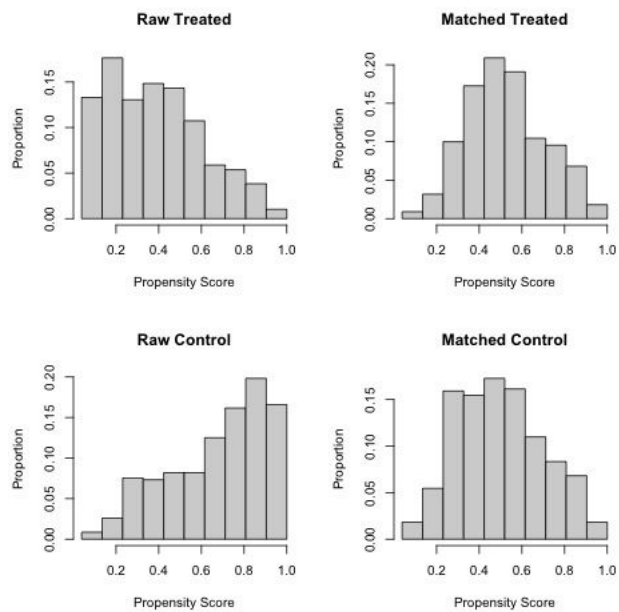
SMD – standardised mean difference

eFigure 1: Propensity Scores

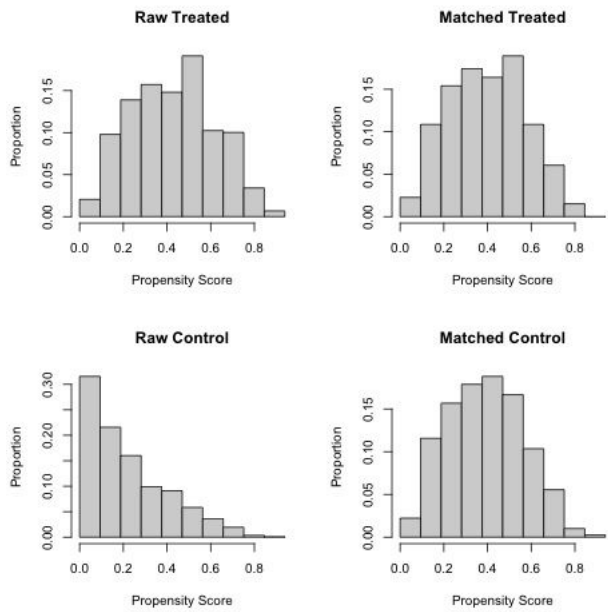
Propensity scores before and after matching among patients treated with fingolimod (treated) and cladribine (control)



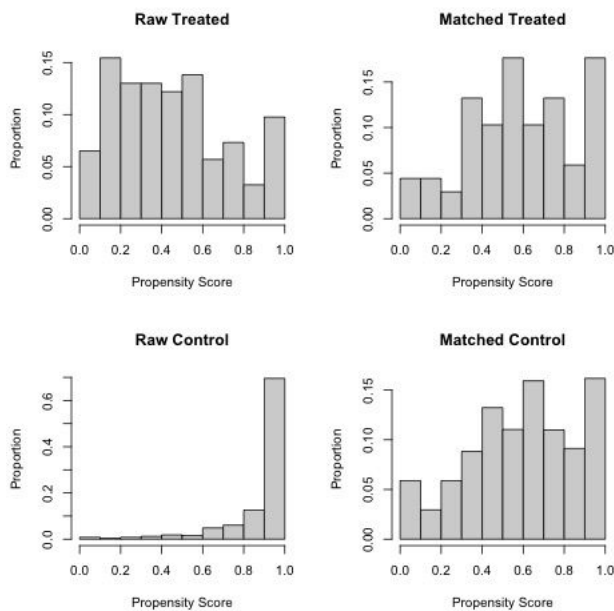
Propensity scores before and after matching among patients treated with natalizumab (treated) and cladribine (control)



Propensity scores before and after matching among patients treated with ocrelizumab (treated) and cladribine (control)



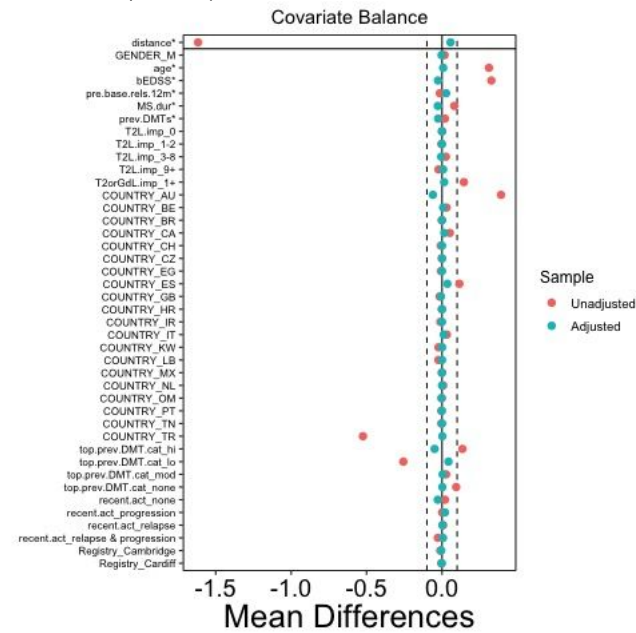
Propensity scores before and after matching among patients treated with alemtuzumab (treated) and cladribine (control)



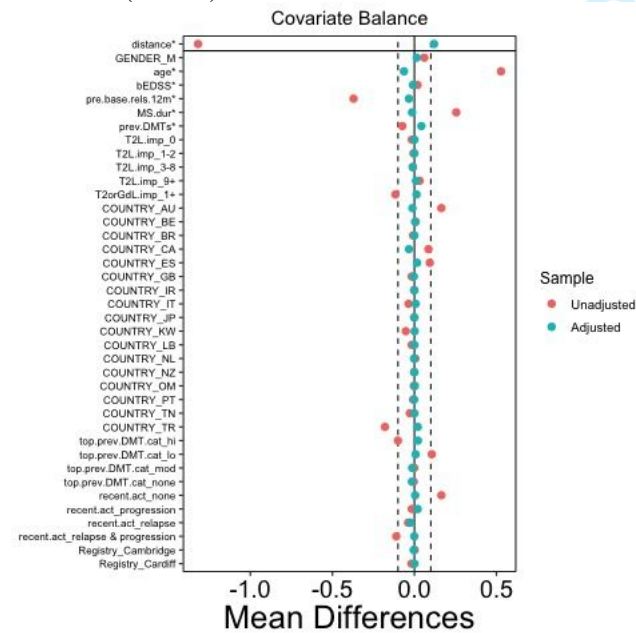
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eFigure 2: Love plots

Standardised mean differences before and after matching among patients treated with fingolimod (treated) and cladribine (control)

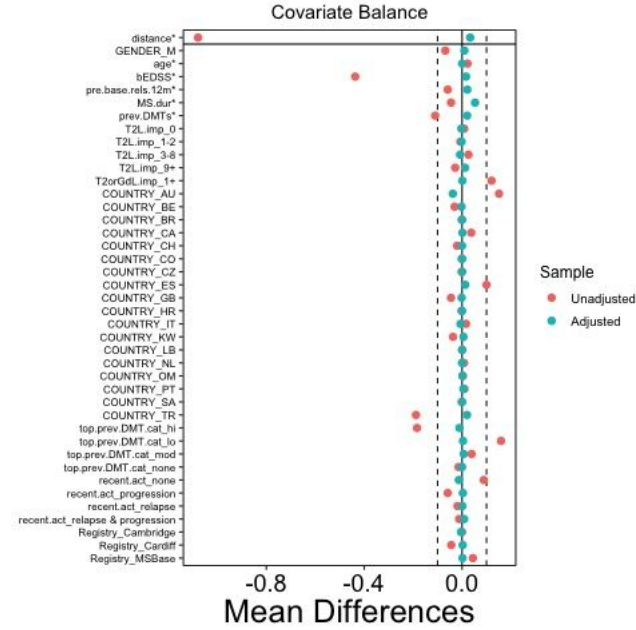


Standardised mean differences before and after matching among patients treated with natalizumab (treated) and cladribine (control)

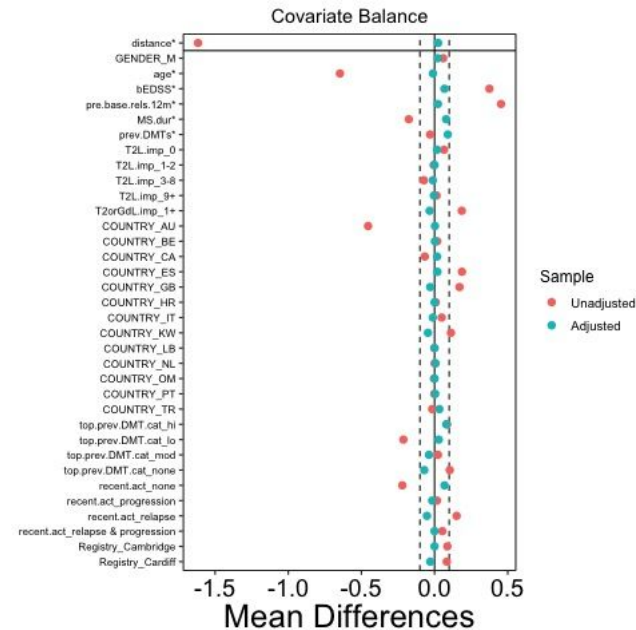


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Standardised mean differences before and after matching among patients treated with ocrelizumab (treated) and cladribine (control)



Standardised mean differences before and after matching among patients treated with alemtuzumab (treated) and cladribine (control)



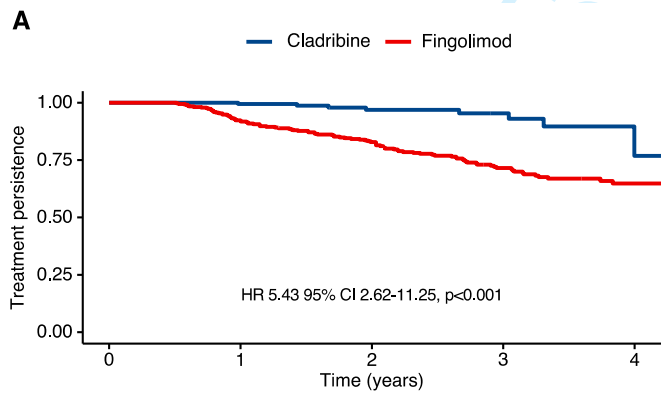
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eTable 7: Results of the sensitivity analyses

Cladribine vs fingolimod	unmatched, n		matched, n		Annualised relapse rate	Cumulative hazard of relapses	Cumulative hazard of disability accumulation	Cumulative hazard of disability improvement
	Cladribine	Fingolimod	Cladribine	Fingolimod				
Analysis					HR (95%CI)			
Primary analysis	330	853	198	403	1.84 (1.36-2.50)	1.71 (1.12-2.63)	1.08 (0.47-2.47)	0.38 (0.13-1.10)
<i>'as treated' design</i>	329	788	189	372	1.65 (1.18-2.34)	1.74 (1.04-2.93)	0.96 (0.36-2.53)	0.52 (0.21-1.29)
<i>'Per protocol' design with 18 month follow-up</i>	260	696	136	263	1.92 (1.25-3.00)	1.98 (1.17-3.36)	0.73 (0.43-1.55)	0.80 (0.33-1.93)
Cladribine vs natalizumab	unmatched, n		matched, n		Annualised relapse rate	Cumulative hazard of relapses	Cumulative hazard of disability accumulation	Cumulative hazard of disability improvement
	Cladribine	Natalizumab	Cladribine	Natalizumab				
Analysis					HR (95%CI)			
Primary analysis	391	464	220	331	0.52 (0.32-0.83)	0.55 (0.33-0.93)	0.35 (0.13-0.94)	0.67 (0.36-1.17)
<i>'as treated' design</i>	390	417	198	308	0.48 (0.28-0.80)	0.46 (0.26-0.83)	0.92 (0.31-2.70)	0.75 (0.39-1.44)
<i>'Per protocol' design with 18 month follow-up</i>	309	367	151	212	0.59 (0.35-0.98)	0.64 (0.38-1.07)	0.51 (0.21-1.30)	0.89 (0.48-1.67)
Cladribine vs ocrelizumab	unmatched, n		matched, n		Annualised relapse rate	Cumulative hazard of relapses	Cumulative hazard of disability accumulation	Cumulative hazard of disability improvement
	Cladribine	Ocrelizumab	Cladribine	Ocrelizumab				
Analysis					HR (95%CI)			
Primary analysis	439	1131	380	667	0.67 (0.48-0.92)	0.61 (0.42-0.88)	0.45 (0.26-0.78)	0.80 (0.50-1.29)
<i>'as treated' design</i>	438	1116	390	755	0.60 (0.43-0.84)	0.55 (0.38-0.82)	0.57 (0.35-0.93)	0.87 (0.53-1.44)
<i>'Per protocol' design with 18 month follow-up</i>	357	969	293	604	0.53 (0.39-0.75)	0.54 (0.36-0.81)	0.67 (0.41-1.12)	0.82 (0.50-1.33)

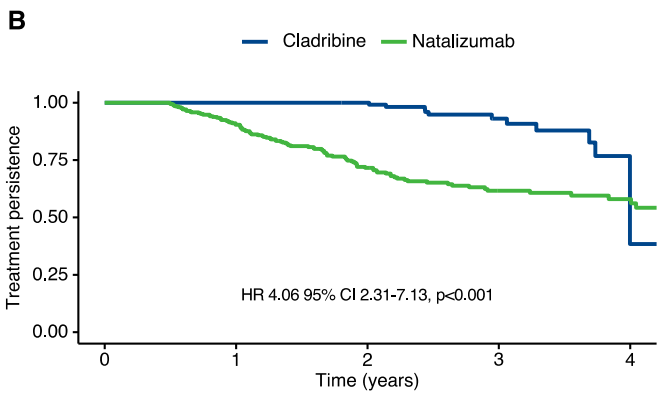
Cladribine vs alemtuzumab	unmatched, n		matched, n		Annualised relapse rate	Cumulative hazard of relapses	Cumulative hazard of disability accumulation	Cumulative hazard of disability improvement
	Cladribine	Alemtuzumab	Cladribine	Alemtuzumab				
Analysis								HR (95%CI)
Primary analysis	481	123	173	68	0.22 (0.11-0.42)	0.51 (0.10-0.65)	0.73 (0.26-2.07)	1.3 (0.50-3.38)
'as treated' design	480	123	179	67	0.19 (0.08-0.41)	0.16 (0.06-0.41)	0.63 (0.21-1.91)	0.90 (0.81-2.06)
'Per protocol' design with 18 month follow-up	392	113	143	51	0.77 (0.42-1.43)	0.82 (0.41-1.65)	0.72 (0.31-1.69)	1.46 (0.78-2.71)

eFigure 3: Treatment persistence



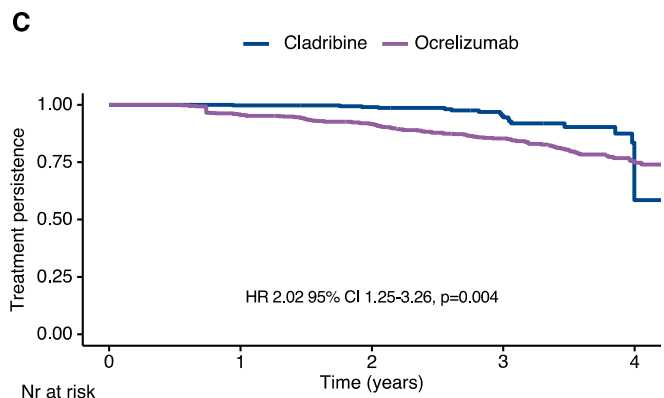
Nr at risk

— Cladribine	189	175	112	54	19
— Fingolimod	372	341	251	165	72



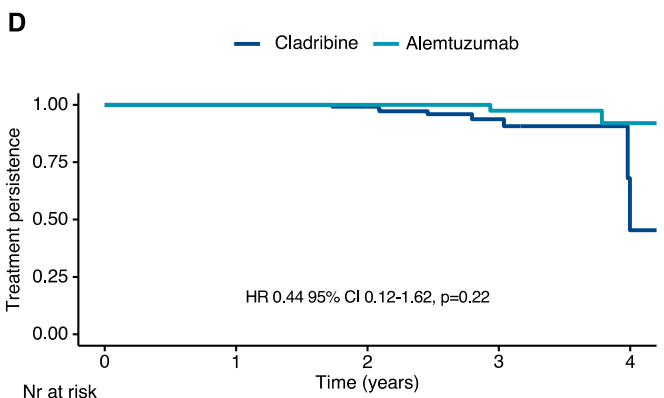
Nr at risk

— Cladribine	198	184	124	59	18
— Natalizumab	308	272	173	93	45



Nr at risk

— Cladribine	390	374	283	152	48
— Ocrelizumab	755	713	573	364	166



Nr at risk

— Cladribine	172	164	115	45	13
— Alemtuzumab	60	59	52	44	20

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3 Hazard ratio indicates risk of treatment discontinuation of study therapy vs cladribine
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For Peer Review

STROBE Statement—Checklist of items that should be included in reports of *cohort studies*

	Item No	Recommendation	Page No
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	1
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	2
Objectives	3	State specific objectives, including any prespecified hypotheses	3
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4-5
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6
		(b) For matched studies, give matching criteria and number of exposed and unexposed	6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4-5
Bias	9	Describe any efforts to address potential sources of bias	5-6
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	6-7
		(b) Describe any methods used to examine subgroups and interactions	6
		(c) Explain how missing data were addressed	5-6
		(d) If applicable, explain how loss to follow-up was addressed	6
		(e) Describe any sensitivity analyses	7
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Fig 1
		(b) Give reasons for non-participation at each stage	Fig 1
		(c) Consider use of a flow diagram	Fig 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 1
		(b) Indicate number of participants with missing data for each variable of interest	Table 1
		(c) Summarise follow-up time (eg, average and total amount)	Table 1
Outcome data	15*	Report numbers of outcome events or summary measures over time	7-8

1	Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted	8-10
2			estimates and their precision (eg, 95% confidence interval). Make clear	
3			which confounders were adjusted for and why they were included	
4				
5			(b) Report category boundaries when continuous variables were	N/A
6			categorized	
7				
8			(c) If relevant, consider translating estimates of relative risk into absolute	N/A
9			risk for a meaningful time period	
10	Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions,	11-12
11			and sensitivity analyses	
12				
13	Discussion			
14	Key results	18	Summarise key results with reference to study objectives	12
15	Limitations	19	Discuss limitations of the study, taking into account sources of potential	14-15
16			bias or imprecision. Discuss both direction and magnitude of any	
17			potential bias	
18				
19	Interpretation	20	Give a cautious overall interpretation of results considering objectives,	16
20			limitations, multiplicity of analyses, results from similar studies, and	
21			other relevant evidence	
22				
23	Generalisability	21	Discuss the generalisability (external validity) of the study results	15
24				
25	Other information			
26	Funding	22	Give the source of funding and the role of the funders for the present	18
27			study and, if applicable, for the original study on which the present	
28			article is based	
29				

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at <http://www.strobe-statement.org>.