Title

Comparison of alemtuzumab with natalizumab, fingolimod, and interferon beta for multiple sclerosis: a longitudinal study

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ABSTRACT

Background: Alemtuzumab, an anti-CD52 antibody, is proven to be more efficacious than interferon beta-1a in treating relapsing-remitting multiple sclerosis, but its efficacy relative to more potent immunotherapies is unknown. We compared the effectiveness of alemtuzumab vs. natalizumab, fingolimod and interferon beta up to 5 years.

Methods: We used propensity-matched patients with relapsing-remitting multiple sclerosis from MSBase and six other cohorts. The primary endpoint was annualised relapse rate. The secondary endpoints were cumulative hazards of relapses, disability accumulation, and disability improvement events. Relapse rates were compared with negative binomial models. Cumulative hazards were estimated with conditional proportional hazards models.

Findings: The studied patients were treated between 1st August 1994 and 30th June 2016 . The cohorts consisted of 189 (alemtuzumab), 2155 (interferon), 828 (fingolimod) and 1160 (natalizumab) patients. Compared with interferon, alemtuzumab was associated with lower annualised relapse rate (0·19 [95% CI 0·14-0·23] vs. 0·53 [0·46-0·61], P<0·0001) and similar disability outcomes in the overall cohort, and lower risk of disability accumulation (hazard ratio=0·64, P=0·018) and a higher rate of disability improvement in patients with prior highly active disease (hazard ratio=3·9, P=0·035). Compared to fingolimod, relapse rate was lower on alemtuzumab (0·15 vs. 0·34, P<0·0001). Importantly, no differences in relapse rate (0·20 vs. 0·19, respectively, P=0·78) and disability accumulation rates were found between alemtuzumab and natalizumab. Disability improvement rates were lower on alemtuzumab than natalizumab (hazard ratio=0·35, P<0·0006), particularly during the first year after commencing therapy.

Interpretation: Alemtuzumab and natalizumab showed similar effects on relapse activity and disability accumulation rates in relapsing-remitting multiple sclerosis but natalizumab was associated with a greater chance of early disability improvement. Alemtuzumab was superior to fingolimod in mitigating relapse activity. Both natalizumab and alemtuzumab are highly effective immunotherapies for multiple sclerosis.

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TEXT

INTRODUCTION

Alemtuzumab, an anti-CD52 humanised monoclonal antibody, is a highly effective immunotherapy for relapsing-remitting multiple sclerosis (MS).[1-3] Through a profound pan-lymphocyte depletion and sustained modification of lymphocyte repertoire,[4] it achieves long-term disease stabilisation in most patients with previously active disease.[5,6] Pivotal trials have demonstrated its superior effect on relapse activity and disability accrual compared with interferon beta.[2,3]

Recent onset of highly active MS, escalation of therapy to natalizumab or alemtuzumab following failure of oral medications,[7] or switch from natalizumab to alemtuzumab or fingolimod because of a high risk of progressive multifocal leukoencephalopathy[8,9] are common scenarios in which alemtuzumab is used in clinical practice. However, there is no information about the effectiveness of alemtuzumab in comparison to other highly effective disease modifying therapies. Analyses of alemtuzumab versus other licensed agents were performed during submissions to reimbursement agencies (e.g. the National Institute for Health and Care Excellence, UK) but public versions of these documents are heavily redacted. The much needed evidence comparing alemtuzumab to other agents is unlikely to emerge from randomised trials because the cost of such long-term multi-arm trials is prohibitive.

High quality observational cohorts collect substantial amounts of longitudinal information representative of clinical practice. Several observational cohorts have recently generated valuable evidence regarding comparative treatment effectiveness of various therapies, which is highly concordant with clinical trials.[10] We have shown that in active MS, highly potent therapies, such as natalizumab or fingolimod, are more effective than are injectable immunotherapies (interferon beta and glatiramer acetate).[11,12]

We compared relapse activity, disability accumulation, and disability improvement between patients treated with alemtuzumab vs. other immunotherapies. First, we aimed to replicate the results of the pivotal trials of alemtuzumab vs. interferon beta. Then, we explored the effectiveness of alemtuzumab in comparison with natalizumab or fingolimod over up to five years of treatment.

METHODS

Study design and patients

MSBase is an international observational cohort study of MS. Eligible longitudinal clinical data were obtained from 71 MSBase centres in 21 countries (Argentina, Australia, Belgium, Canada, Czech Republic, Denmark, Spain, France, United Kingdom, Hungary, Israel, India, Iran, Italy, Kuwait, Macedonia, The Netherlands, Portugal, Romania, Turkey, United States) and from six non-MSBase centres (only patients treated with alemtuzumab) in the United Kingdom (Cambridge,[5] Cardiff, Bristol, Swansea,[6] and Dublin) and Germany (Dresden[13]) between 1st November 2015 and 30th June 2016 and evaluated for inclusion criteria.

The study was approved by the Melbourne Health Human Research Ethics Committee, and by the site institutional review boards (or exemptions were granted, according to local regulations).

The inclusion criteria were definite relapsing-remitting MS,[14,15] exposure to one of the study therapies, no prior exposure to haematopoietic stem cell transplantation, no participation in randomised clinical trials, minimum required recorded follow-up (12 months prior to treatment start and two on-treatment disability scores ≥6 months apart) and minimum dataset (consisting of sex, age, time of first MS symptom, dates of clinical relapses, clinical MS course, disability score at treatment commencement (-6 months

to +3 months), ≥6-months of continuous study therapy, ≥1 relapse experienced within the year before treatment, age ≤65 years, time from first MS symptom ≤10 years and Expanded Disability Status Scale (EDSS) score ≤6·5. Written informed consent was obtained from enrolled patients, as required.

Procedures

Treatment protocols, which involved alemtuzumab (12-24 mg i.v. daily for five days (cycle 1) or three days (cycle 2)), interferon beta-1a (44 µg s.c. thrice weekly), fingolimod (0·5 mg oral daily) and natalizumab (300 µg i.v. every four weeks) were described elsewhere.[5,6,11] Baseline was defined as the first commencement of the study therapy and patients were censored at discontinuing therapy, commencing the first post-baseline disease modifying therapy, or at the last recorded EDSS, whichever occurred first.

The analysed data were recorded as part of routine clinical practice, mostly at tertiary MS centres, with data entry at the time of clinical visits. The MSBase Observational Plan stipulates minimum annual evaluations of neurological status of the included patients, but patients with less frequent visits were not excluded. Data entry portals were iMed, MSBase online data entry system, PatientCare, MSDS or local data entry systems. Rigorous quality assurance procedure was applied (Table S2).[16]

Outcomes

The primary endpoint was the on-treatment annualised relapse rate. A relapse was defined as occurrence of new symptoms or exacerbation of existing symptoms persisting for ≥24 hours, in the absence of concurrent illness/fever, and occurring ≥30 days after a previous relapse. Confirmation of relapses by EDSS was not required. Individual annualised relapse rate between baseline and censoring was calculated.

Secondary endpoints were the cumulative hazard of relapses, disability accumulation events, disability improvement events, the proportion of patients free from disability accumulation, and the proportion of patients with disability improvement during the on-treatment follow-up. Disability was scored by accredited EDSS scorers (Neurostatus certification was required at the participating centres), excluding any score recorded within 30 days of a previous relapse. Disability accumulation was defined as an increase in EDSS by 1 step (1.5 step if baseline EDSS was 0 and 0.5 steps if baseline EDSS was >5.5) confirmed by subsequent EDSS scores over ≥6 months. Disability improvement was defined as a decrease in EDSS by 1 step (1.5 step if baseline EDSS was 1.5 and 0.5 steps if baseline EDSS was >6) confirmed by subsequent EDSS scores over ≥6 months.[17]

Statistical analysis

Matching and statistical analyses were conducted using R (version 3·0·3)[18], in three separate paired matched analyses of alemtuzumab vs. interferon beta, fingolimod, or natalizumab. Individual patients were matched on their propensity of receiving either of the compared therapies.[12,19] Individual propensity scores were calculated using a multivariable logistic improvement model of treatment allocation that utilised demographic and clinical variables available at the time of treatment assignation as independent variables: sex, age, time from first MS symptom, EDSS, number of relapses in the prior 12 months, number of prior MS therapies, and the perceived most effective prior MS therapy.

Patients were matched in a variable 2:1 ratio using nearest neighbour matching within a narrow caliper (0·1 standard deviations of the propensity score), without replacement. All subsequent analyses were designed as paired models with weighting to adjust for the variable matching ratio. A maximum cumulative weight for each

matched patient was 1. The common on-treatment follow-up was determined in each matched pair as the shorter of the two patient follow-up periods (pairwise censoring), to mitigate attrition bias, informative censoring and the effect of differential treatment persistence.[10]

Tests of statistical inference were carried out at α=0·05 with familywise Benjamini-Hochberg correction for false discovery rate. After assessing normality of data distribution, annualised relapse rates were compared with a weighted negative binomial model with cluster effect for matched patient pairs and adjusted for visit frequency. Relapse rates at years 1-5 were compared with weighted marginal negative binomial models with cluster term for patient pair. Cumulative hazards of relapses, and EDSS accumulation and improvement events were analysed with weighted conditional proportional hazards models with robust estimation of variance (Andersen-Gill) adjusted for visit frequency.[20] The proportions of patients free from relapse, EDSS accumulation and with EDSS improvement were evaluated with weighted conditional proportional hazards models (Cox) adjusted for visit frequency. Where the proportionality of hazards assumption was violated (assessed with Schoenfeld's global test[21]), interaction term for treatment and time was included in the multivariable models.

Robustness of the statistically significant differences to unidentified confounders was quantified with Hodges-Lehmann Γ.[22] Where no statistically significant differences were observed, analytical power was quantified as the minimum effect magnitude detectable within the available cohort at 1-β=0·8 using 200 simulations).

Two secondary analyses and four sensitivity analyses were completed. The secondary analyses compared the therapies (i) among patients with high pre-baseline relapse activity (defined as ≥2 relapses within 12 months or ≥3 relapses within 24 months pre-

baseline, irrespective of treatment status) with a 10:1 variable matching ratio to maximise analytical power and (ii) any prior on-treatment break-through relapses. The sensitivity analyses evaluated the robustness of the results to potential confounders, including matching (using 10:1 variable matching within a caliper of 0·4), pre-baseline follow-up (matching on the number of relapses in the prior 24 months), MS phenotype (allowing inclusion of patients with secondary progressive MS), follow-up duration (including patients with ≥2-year on-treatment follow-up), differential treatment persistence (using the 'intention-to-treat' paradigm, where patient follow-up was censored at the last recorded EDSS rather than at treatment discontinuation) and confirmation of EDSS accumulation/improvement events over ≥12 months.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

RESULTS

A total of 189, 2155, 828, and 1160 patients fulfilling the inclusion criteria and treated between 1st August 1994 and 30th June 2016, with alemtuzumab (treated after 1999), interferon beta (treated after 1994), fingolimod (treated after 2010), and natalizumab (treated after 2006) were identified, respectively (Figure 1, Table S3). One hundred and five (55%) patients treated with alemtuzumab received two treatment cycles and 84 patients (45%) required additional treatment cycles. As expected, the four

unmatched groups differed in their baseline characteristics (Table S4). Logistic regression models were used to calculate the propensity scores - the probability of exposure to either of the compared treatment pairs. From the results of the logistic models it follows that, patients commenced alemtuzumab at shorter disease duration, at a younger age, and tended to have higher EDSS scores and pre-baseline relapse activity compared to the three other therapies (Tables S4 and S5).

The numbers of patients retained in the matched cohorts for all three pairwise primary analyses are shown in Table 1. The matching procedure significantly decreased the between-group differences in propensity scores from 0·24-0·44 to 0·0001-0·0026, corresponding to a >99·4-99.97% improvement in the overall balance between the compared groups (Table S6). The close match on individual characteristics between the groups is demonstrated in Table 1 (standardised differences ≤15%). The median differences between baseline date and the date of the baseline EDSS were similar between the matched cohorts. As a result of pairwise censoring, on-treatment follow-up was identical in the matched groups, as shown in Table 1. The groups were not matched on the follow-up visit density (inter-visit interval), therefore all subsequent analyses were adjusted for visit frequency.

Patients treated with alemtuzumab had a lower annualised relapse rate than did those treated with interferon beta (mean [95% confidence intervals] 0·19 [0·14-0·23] vs. 0·53 [0·46-0·61], respectively, P<0·0001; Figure 2A). While a consistent decline in the relapse rate was observed in the interferon beta group over the five years on treatment (representing time-dependent decline in relapse activity[23]), the difference between the groups remained significant throughout the follow-up (Figure 2B). Cumulative hazard of relapse events was lower in the alemtuzumab group (hazard ratio 0·60, P=0·005, Figure 2C). The primary analysis did not show any statistically significant differences in the cumulative hazards of disability accumulation or improvement between

alemtuzumab and interferon beta (P=0·37) or the cumulative probability of remaining free from disability accumulation (P=0·69, Figure 2D). However, the secondary analyses (in addition to confirming that the hazard of relapse events was lower in the alemtuzumab group) showed that alemtuzumab was associated with a lower hazard of disability accumulation than interferon beta in patients with high pre-baseline relapse activity (hazard ratio 0·64, P=0.018) and higher probability of disability improvement in patients with previous on-treatment break-through relapses (hazard ratio 3·9, P=0.035, Table S7).

Similarly, patients treated with alemtuzumab showed lower annualised relapse rate than those treated with fingolimod (mean [95% confidence intervals] 0·15 [0·10-0·20] vs. 0·34 [0·26-0·41], P<0·0001; Figure 3A). This observation was consistent during years 1-3, for which sufficient cohorts were available (Figure 3B). The difference in cumulative hazard of relapses did not reach the level of statistical significance (P=0·18, Figure 3C). No between-group differences in the cumulative hazards of disability accumulation or improvement were observed (Figures 3D and 3E).

The comparison between alemtuzumab and natalizumab showed similar on-treatment annualised relapse rates over 4 years (mean [95% confidence intervals] 0·20 [0·14-0·26] vs. 0·19 [0·15-0·23], P=0·78; Figure 4A), confirmed by the lack of statistically significant difference in cumulative hazard of relapses (P=0·83, Figure 4C) and probability of remaining relapse free (P=0·65, Table S7). Cumulative hazard of disability accumulation events was also not significantly different between the compared groups (P=0·60, Figure 4D). However, alemtuzumab was associated with lower cumulative probability of disability improvement than natalizumab (hazard ratio 0·35, P<0·0006, Figure 4E). The significant difference in disability improvement was also confirmed among patients with high pre-baseline relapse activity (as shown in Table S7).

Generally, sensitivity analyses confirmed the outcomes of the primary and secondary analyses (with the exception of disability outcomes in the comparison of alemtuzumab vs. interferon beta). The comparisons of the rates of disability accumulation and improvement events confirmed over 6-months were also largely replicated in the sensitivity analysis requiring a 12-month confirmation interval. Modifying the matching ratio and caliper, pre-baseline observational period, inclusion of secondary progressive MS and minimum on-treatment follow-up did not significantly change the overall relapse and disability outcomes (see Table S7).

Where the primary analysis did not show any significant differences between the compared groups, analysis of the minimum detectable effect size was carried out (Table S8). The analyses were sufficiently powered to detect minimum differences of 0·13 relapse per year, 51-53% cumulative hazard of relapses, 35-66% cumulative hazard of disability accumulation and 39-42% cumulative probability of disability improvement. The differences in annualised relapse rates observed for alemtuzumab vs. interferon beta and fingolimod were resistant to unknown confounders with relative magnitudes of >100% and 60% of the reported effect of treatment (Hodges-Lehmann Γ), respectively.

DISCUSSION

In this observational propensity score-matched study of patients with relapsing-remitting multiple sclerosis, alemtuzumab and natalizumab were equally effective in reducing relapse frequency and preventing confirmed disability accumulation over four years. However, natalizumab was more likely to lead to disability improvement, particularly during the first year after commencing therapy. Compared to fingolimod, alemtuzumab was superior in reducing relapse activity. No differences were found

between alemtuzumab and fingolimod in their ability to modulate the risk of disability accumulation or improvement events over three years.

To enable interpretation of these results in the context of the original pivotal clinical trials, we have first conducted a comparison of alemtuzumab vs. high-dose interferon beta-1a. This study has partially replicated the results of these pivotal trials: alemtuzumab is superior to interferon beta in suppressing relapse activity and reducing disability accrual in patients with previously highly active MS. The observed on-treatment annualised relapse rates (0·19 vs. 0·53, alemtuzumab vs. interferon beta, respectively) are comparable to the relapse rates reported by the CAMMS223 (0·16 vs. 0·54)[1], CARE-MS1 (0·18 vs. 0·39)[3] and CARE-MS2 (0·26 vs. 0·52)[2] trials. The proportions of patients who did not experience 6-month confirmed disability accumulation events during the initial two years on treatment were similar between the present study (93% vs. 88%, alemtuzumab vs. interferon beta, respectively) and the CARE-MS1 trial (92% vs. 89%), with neither being significantly different. However there was a treatment effect on disability accumulation events in the CAMMS223 (6% vs. 16%) and CARE-MS2 (13% vs. 20%) trials at two years. It should be noted that the cohorts are not directly comparable; the alemtuzumab trials recruited patients with ≥2 relapses during the preceding two years, while inclusion into our primary analysis was based on ≥1 relapse during the preceding one year. Our secondary analyses, which only included patients with high pre-baseline activity (≥2 relapses during the one year or ≥3 relapses during the two years pre-baseline) and previous break-through on-treatment relapses showed improved disability outcomes in alemtuzumab compared with interferon beta (decreased cumulative hazard of disability accumulation and increased probability of disability improvement). Thus, our results from patients with highly active MS are concordant with those produced in the relevant comparative alemtuzumab versus interferon beta trials.

The on-treatment annualised relapse rates observed in the natalizumab and fingolimod groups (0·19 and 0·34, respectively) are in keeping with the previously reported on-treatment MS activity form MSBase[11,12] and the pivotal trials for natalizumab (0·20-0·24)[24] and are higher than the annualised relapse rates reported in the pivotal trials for fingolimod (0·16-0·20)[25,26]. In keeping with our previous observation of superior control of disease activity after escalating therapy to natalizumab compared with fingolimod, alemtuzumab was comparable to natalizumab but superior to fingolimod in preventing MS relapses. Both effects were sustained over at least 3-4 years following the commencement of therapy. While the hazard of disability accumulation was similar for alemtuzumab and both natalizumab and fingolimod, treatment with natalizumab increased the probability of confirmed disability improvement more than alemtuzumab. This extends prior observations that natalizumab, unlike fingolimod, is likely to increase the probability of partial recovery from the previously accumulated neurological disability, in particular during the initial years after first MS presentation.[12,27]

In the present study, we maximised analytical power by combining several high-quality longitudinal observational MS cohorts.[5,6] Cumulative follow-up and generalisability were maximised by inclusion of a broad spectrum of patients with the minimum follow-up requirements necessary to evaluate confirmed disability outcomes. Both, treatment-naïve patients and patients previously exposed to immunotherapies were included.

Because the assembled study cohort is, by definition, multicentric, we have undertaken multiple steps to mitigate the potential biases, including matching, pairwise censoring and adjusting the statistical models,[10] an approach whose efficacy was demonstrated in our previous studies.[11,12] The alemtuzumab cohorts were enriched for patients with early, highly active disease. Given the large number of patients treated with natalizumab, fingolimod or interferon beta available from the MSBase cohort, we were able to achieve close match on their demographic and clinical characteristics. Because

the probability of capturing treatment discontinuation was relatively lower in the alemtuzumab cohort, we have mitigated the risk of differential follow-up duration by pairwise censoring. It is arguable that our approach was underpowered to detect some clinically significant treatment effects.

The main limitation, in comparison to controlled studies, is the lack of systematic and comparable acquisition of safety data and of radiological outcomes. Magnetic resonance imaging is an important indicator of subclinical disease activity, with potential impact on disease management. If unreported and systematically different between the compared cohorts, it could represent an unidentified confounder. Another potential confounder is the effect of treating centre. Due to the limited overlap between the centres reporting patients treated with alemtuzumab and the three comparator therapies, we were not able to match on or adjust for centre, but we have mitigated the effect by adjusting the analyses for visit frequency, which served as an indicator of follow-up density. The above confounders could introduce additional variability in the reported results, e.g. diminishing the differences between alemtuzumab and interferon beta when compared to the pivotal randomised trials. Importantly, we have shown that our results were robust to hypothetical unmeasured confounders of the magnitude >60% of the difference in treatment effects. The definition of MS relapses used in our study did not require confirmation by change in EDSS, which reflects usual clinical practice; this was different from several clinical trials which required EDSS confirmation. This study compared treatment outcomes in observational data over 3-5 years. It is worth noting that disability accumulation events confirmed over 6-12 months are highly indicative of long-term disability outcomes.[17] Comparative evaluation of the long-term safety of alemtuzumab and natalizumab is warranted, as treatment safety represents an important component of disease management strategy and the risk-benefit ratios for individual patients should be carefully considered by clinicians.

In conclusion, we show that - over three to five years - alemtuzumab is a highly effective disease modifying therapy in relapsing-remitting MS, with a treatment effect largely comparable to natalizumab, and with greater effect on relapse rate than fingolimod or interferon beta-1a. Together with natalizumab, alemtuzumab represents a viable option for patients requiring highly effective immunotherapy for MS.

Contributors

Tomas Kalincik conceptualised and designed the study, recruited patients, contributed data, carried out statistical analysis, interpreted the results, have drafted and edited the manuscript. J. William L. Brown, Neil Robertson, Mark Willis, Neil Scolding, Claire M Rice, Alastair Wilkins, Owen Pearson, Tjalf Ziemssen, Michael Hutchinson, Christopher McGuigan, Vilija Jokubaitis, Tim Spelman, Dana Horakova, Eva Havrdova, Maria Trojano, Guillermo Izquierdo, Alessandra Lugaresi, Alexandre Prat, Marc Girard, Pierre Duquette, Pierre Grammond, Raed Alroughani, Eugenio Pucci, Patrizia Sola, Raymond Hupperts, Jeannette Lechner-Scott, Murat Terzi, Vincent Van Pesch, Csilla Rozsa, Francois Grand'Maison, Cavit Boz, Franco Granella, Mark Slee, Daniele Spitaleri, Javier Olascoaga, Roberto Bergamaschi, Freek Verheul, Steve Vucic, Pamela McCombe, Suzanne Hodgkinson, Jose Luis Sanchez-Menoyo, Radek Ampapa,·Magdolna Simo,·Tunde·Csepany, Cristina Ramo, Edgardo Cristiano, Michael Barnett recruited patients, contributed data, interpreted the results and have edited the manusript. Helmut Butzkueven, Alasdair Coles conceptualised the study, recruited patients, contributed data, interpreted the results and have edited the manuscript.

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The list of MSBase Study Group co-investigators and contributors is given in Table S1.

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DECLARATION OF INTERESTS

Tomas Kalincik reports grants from NHMRC, grants from Faculty of Medicine, Dentistry and Health Sciences, University of Melbourne, during the conduct of the study; grants, personal fees and non-financial support from Biogen, personal fees from Roche, personal fees and non-financial support from Genzyme-Sanofi, personal fees and non-financial support from Merck, personal fees and non-financial support from Novartis, personal fees from WebMD Global, personal fees from Teva, personal fees from BioCSL, outside the submitted work.

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Mark Willis did not disclose any conflict of interests.

Neil Scolding reports grants from Biogen, grants from Sanofi-Genzyme , grants from Merck-Serono , grants from Teva, grants from Novartis, outside the submitted work.

Clare Rice declares no conflicts of interests.

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Michael Barnett reports grants and institutional support from Genzyme-Sanofi, grants and institutional support and conference travel fees from Novartis, grants from Biogen, conference travel fees from Teva, outside the submitted work; and Dr Barnett is a co-founder of Medical Safety Systems, which provides automated pathology monitoring for patients prescribed immunotherapies (including alemtuzumab) in Australia.
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Alasdair Coles reports personal fees and honoraria, consulting fees and travel expenses for attending meetings from Genzyme, a Sanofi Company, outside the submitted work; In addition, Dr. Coles has a patent On the dose regime of alemtuzumab as a treatment of MS pending.

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3. Cohen JA, Coles AJ, Arnold DL, et al. Alemtuzumab versus interferon beta 1a as first-line treatment for patients with relapsing-remitting multiple sclerosis: a randomised controlled phase 3 trial. Lancet 2012; 380(9856): 1819-28.
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RESEARCH IN CONTEXT

Evidence before this study

A literature search was conducted using PubMed and EMBASE using the terms "multiple sclerosis" AND "alemtuzumab" AND ("natalizumab" OR "fingolimod" OR "interferon" OR glatiramer acetate"), without any language or date restriction and limited to reports of clinical trials OR observational studies (accessed 20th June 2016). Alemtuzumab, is a highly effective therapy for multiple sclerosis. Similar to natalizumab, another highly effective multiple sclerosis therapy, it has shown an effective control of relapse frequency and reduction in disability accrual. In a number of scenarios, clinicians and their patients are faced with the decision between alemtuzumab or natalizumab (such as early active treatment in aggressive multiple sclerosis, escalation of therapy following failure of other therapies or switch from natalizumab to alemtuzumab due to a high risk of natalizumab-associated serious adverse events). No evidence comparing the efficacy of alemtuzumab and natalizumab is available to guide these clinical decisions.

Added value of this study

This study provides a novel evidence concerning the effectiveness of alemtuzumab compared with natalizumab and fingolimod for multiple sclerosis. Alemtuzumab and natalizumab show similar effects on relapse activity and disability accumulation but natalizumab is associated with a greater chance of early disability reduction. Alemtuzumab is superior to fingolimod in mitigating relapse activity.

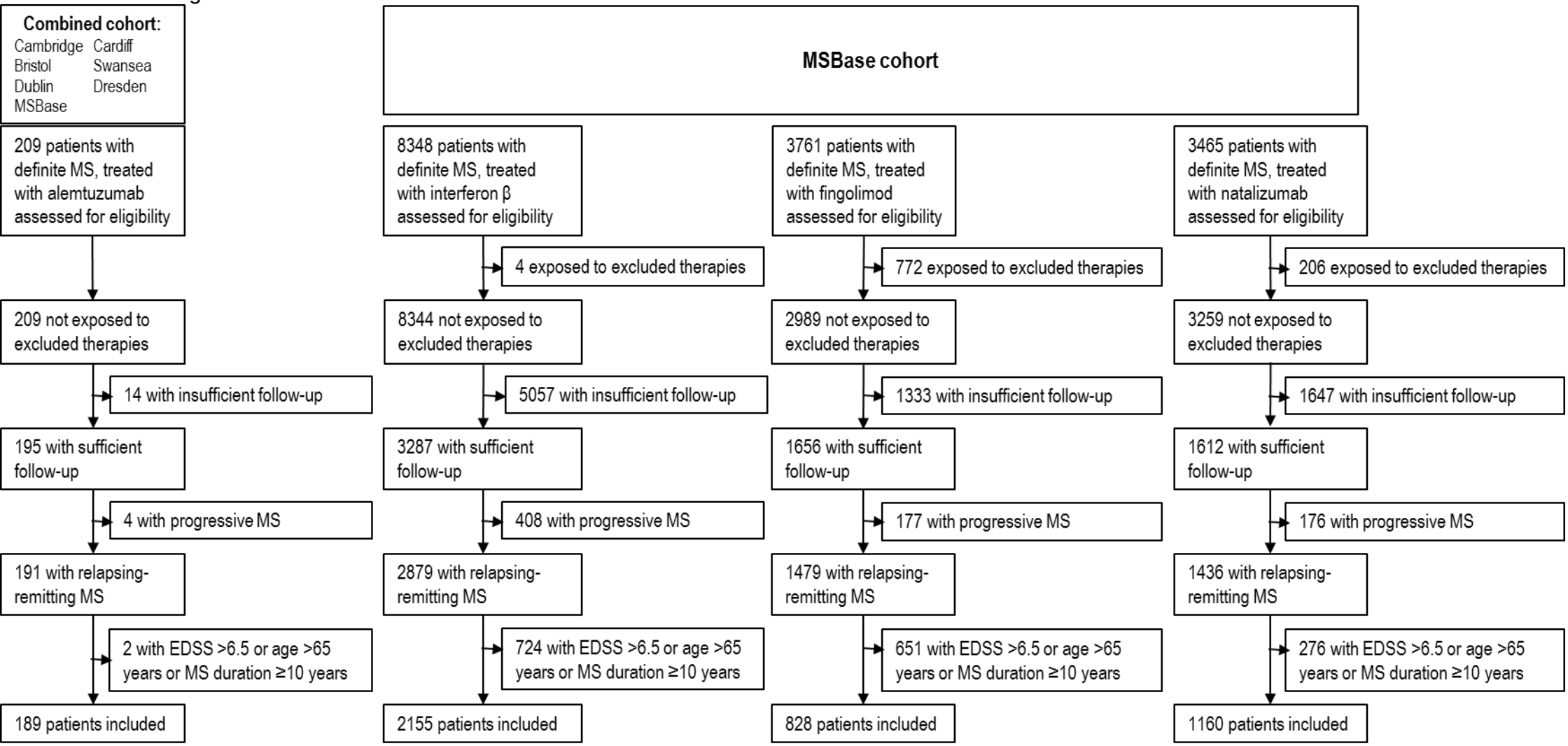
Implications of all the available evidence

Although alemtuzumab is better at controlling multiple sclerosis activity than is fingolimod, its effectiveness is similar to that of natalizumab. Therefore, treatment decisions between alemtuzumab and natalizumab should be primarily governed by the therapies' safety profiles.

FIGURES

Figure 1

Flow diagram

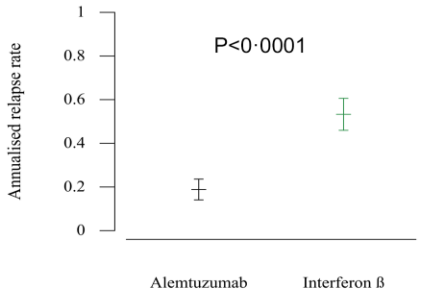


EDSS, Expanded Disability Status Scale; MS, multiple sclerosis

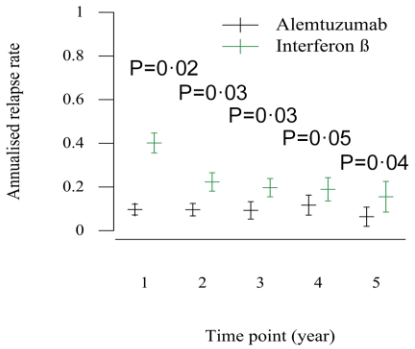
Figure 2

Comparison of the treatment outcomes for alemtuzumab vs. interferon beta

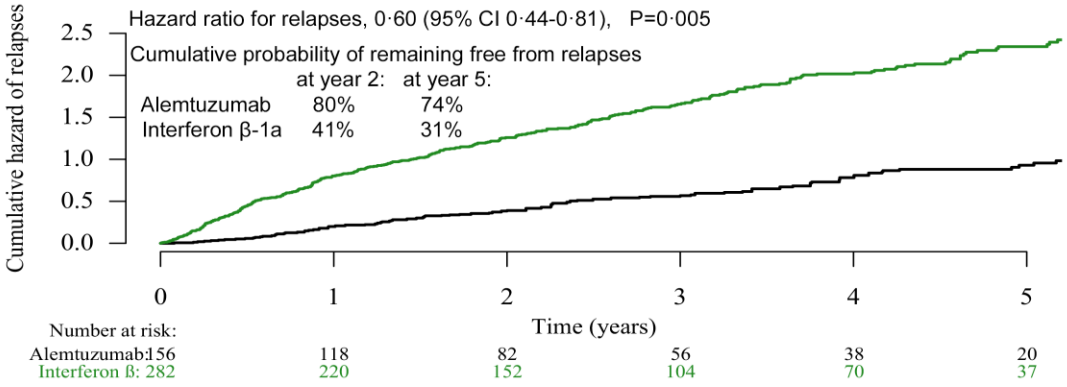
A Overall Annualised Relapse Rate



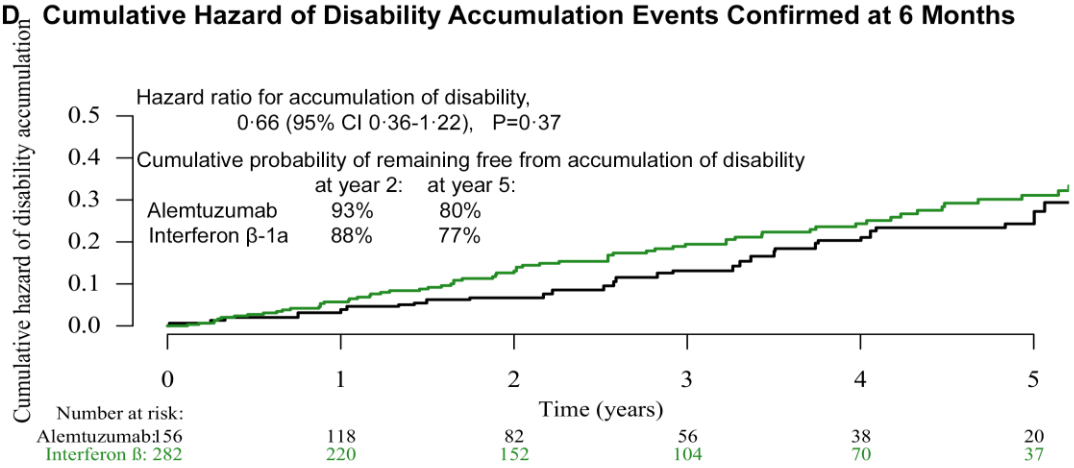
B Annual Relapse Rate at Years 1-5



C Cumulative Hazard of Relapses



D Cumulative Hazard of Disability Accumulation Events Confirmed at 6 Months



E Cumulative Probability of Disability Improvement Events Confirmed at 6 Months

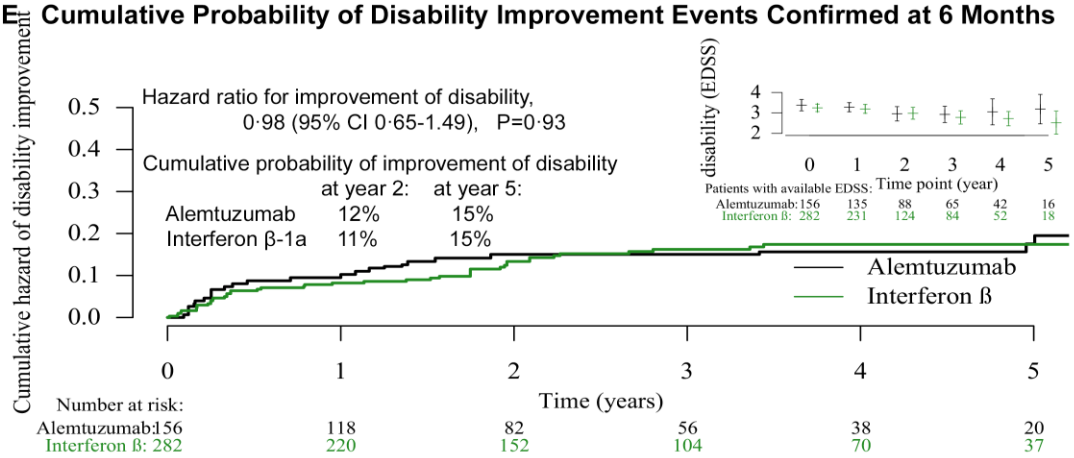
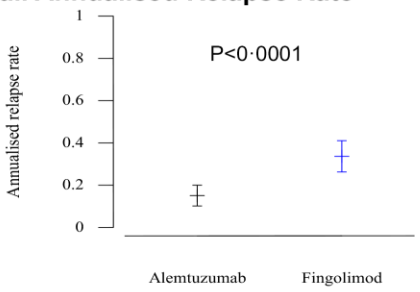


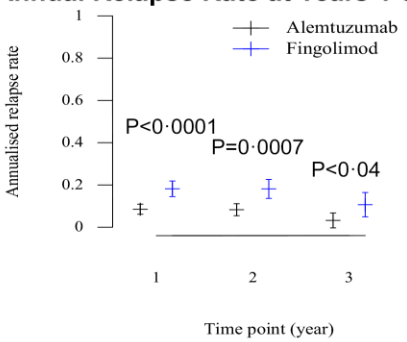
Figure 3

Comparison of the treatment outcomes for alemtuzumab vs. fingolimod

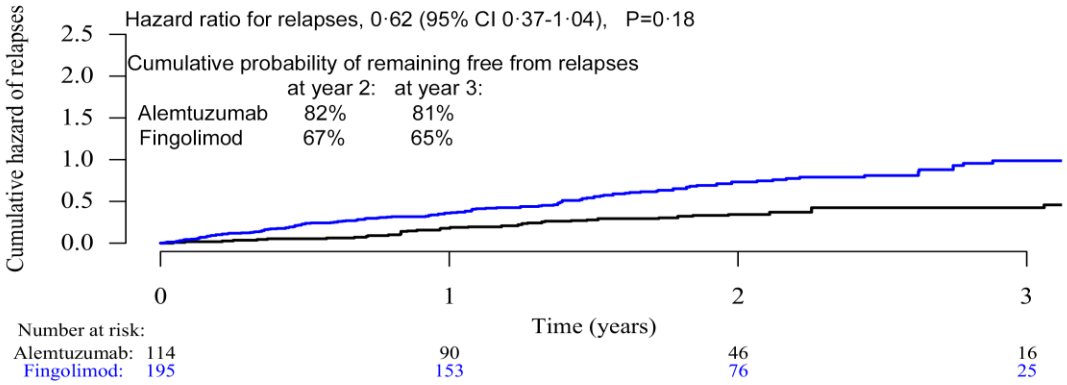
A Overall Annualised Relapse Rate



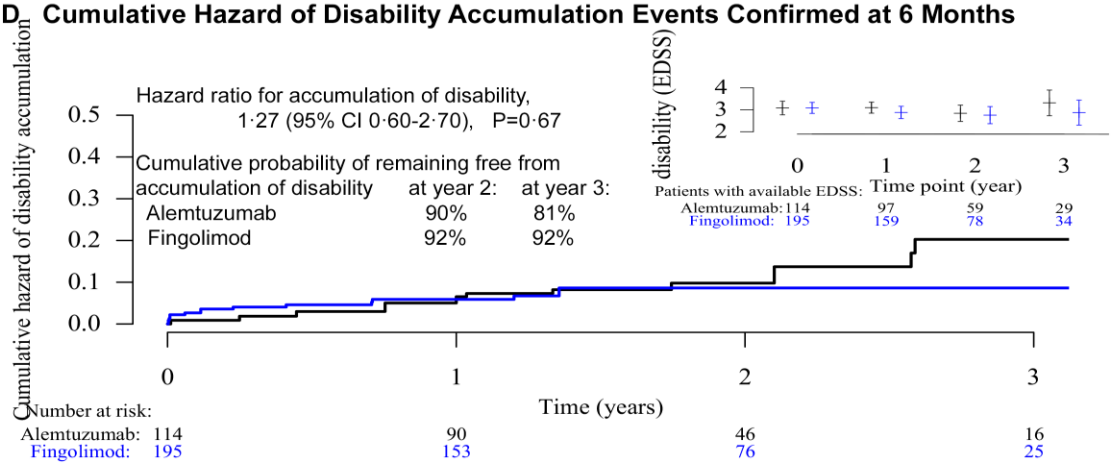
B Annual Relapse Rate at Years 1-3



C Cumulative Hazard of Relapses



D Cumulative Hazard of Disability Accumulation Events Confirmed at 6 Months



E Cumulative Probability of Disability Improvement Events Confirmed at 6 Months

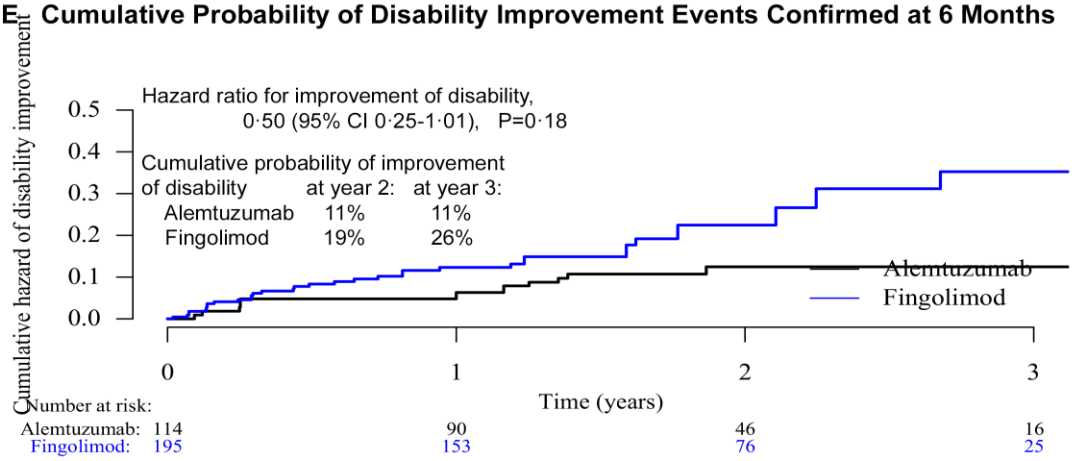


Figure 4

Comparison of the treatment outcomes for alemtuzumab vs. natalizumab

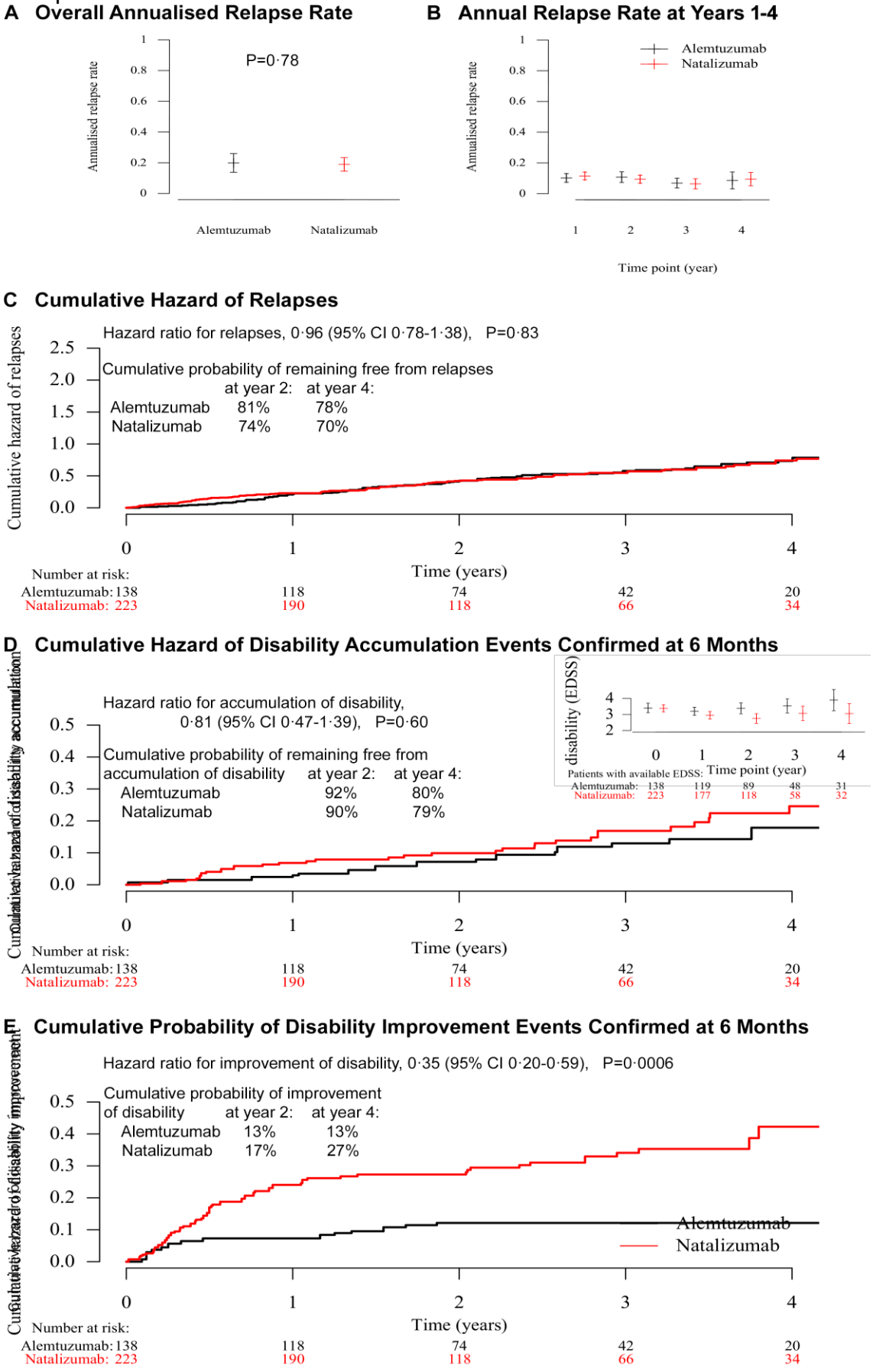


Table 1
Characteristics of the matched patient groups at baseline

	Alemtuzumab (n=124)	Interferon beta (n=218)	d	Alemtuzumab (n=114)	Fingolimod (n=195)	d	Alemtuzumab (n=138)	Natalizumab (n=223)	d
sex, female (%)	91 (73%)	161 (74%)		82 (72%)	142 (73%)		97 (70%)	147 (66%)	
age, yr, mean ± SD	33 ± 8	33 ± 9	0·01	33 ± 8	34 ± 10	0·09	33 ± 9	33 ± 10	0·02
disease duration, yr, median (IQR)	3·2 (2-6·2)	2·6 (1·2-6·4)	0·01	3·9 (2·4-6·6)	4·2 (1·6-8·1)	0·13	3·3 (2·1-6·3)	2·7 (1-7·6)	0·13
relapses 12 months pre-baseline, mean ± SD	2 ± 1·2	1·9 ± 0·9	0·06	1·8 ± 1·1	1·7 ± 0·8	0·03	2 ± 1·3	2 ± 1	0·03
disability, EDSS step, median (IQR)	3 (2-4)	3 (2-4)	0·12	3 (1·6-4)	3 (1·5-4·5)	0·00	3 (2-4·5)	3 (2-4·5)	0·01
difference between baseline date and the date	0 (-38 to +13)	-15 (-51 to 0)	0.18	0 (-54 to +10)	-18 (-71 to 0)	0.20	0 (-39 to +7)	1 (-47 to 0)	0.01

of baseline EDSS, median (IQR)									
inter-visit interval, months, median (IQR)	9 (7-13)	4 (2-7)	0·72	9 (6-12)	3 (2-5)	1·17	9 (6-12)	3 (1-5)	1·12
previous therapies, nr, median (IQR)	0 (0-1)	0 (0-1)	0·01	1 (0-1)	1 (0-2)	0·11	0 (0-1)	0 (0-1)	0·15
most active previous therapy, patients									
Interferon beta/Glatiramer acetate	31 (25%)	62 (28%)		46 (40%)	85 (44%)		47 (34%)	97 (43%)	
Teriflunomide	0	0		0	0		0	0	
Dimethyl fumarate	0	0		0	0		0	0	
Fingolimod	0	0		0	0		2 (1%)	4 (2%)	
Natalizumab	3 (2%)	4 (2%)		14 (12%)	22 (11%)		0	0	
Mitoxantrone	3 (2%)	4 (2%)		2 (2%)	5 (3%)		0	0	
Other	0	0		0	0		0	0	

None	87 (70%)	148 (68%)		52 (46%)	83 (43%)		89 (64%)	122 (55%)	
post-baseline pairwise-censored follow-up on study therapy, yr, median (IQR)	2·1 (1·0-3·9)	2·1 (1·0-3·9)	0·00	1·7 (1·1-2·3)	1·7 (1·1-2·3)	0·00	2·1 (1·4-3·4)	2·1 (1·4-3·4)	0·00

d, standardised difference (Cohen’s d); SD, standard deviation; EDSS, Expanded Disability Status Scale; IQR, interquartile range

Supplementary Appendix

Table of contents

Table S1
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From the MSBase Administrations Dr Jill Byron, Ms Lisa Morgan and Ms Eloise Hinson.
From Rodanotech, Geneva, Switzerland; Mr Samir Mechati, Mr Matthieu Corageoud, Mr Alexandre Bulla.

Table S2
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 MSBase 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.
- Records of the initiation of the progressive MS prior to its clinical onset were excluded.
- Visits with missing visit date or the recorded date before the clinical MS onset or after the date of MSBase 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 fcalculated 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.
- Consecutive entries for certain disease modifying therapies were merged into a continuous treatment entry, given that the gap between the entries did not exceed 190 days for mitoxantrone, 365 days for cladribine, 90 days for other disease modifying therapies.
- The default duration of treatment effect was recorded as 190 days (mitoxantrone), 5 years (alemtuzumab) or 365 days (cladribine) from treatment commencement.

Table S3
Patient disposition per centre

Centre	Patients
Hospital Fernandez, Capital Federal, Argentina	3
INEBA - Institute of Neuroscience Buenos Aires, Buenos Aires, Argentina	5
Instituto de Neurociencias Cordoba, Cordoba, Argentina	1
Hospital Italiano, Buenos Aires, Argentina	14
Sanatorio Allende, Cordoba, Argentina	3
Brain and Mind Centre, Sydney, Australia	10
University of Melbourne, Melbourne, Australia	117
University Newcastle, Newcastle, Australia	74
Geelong Hospital, Geelong, Australia	8
St Vincents Hospital, Fitzroy, Melbourne, Australia	3
Monash Medical Centre, Melbourne, Australia	1
Liverpool Hospital, Sydney, Australia	18
Box Hill Hospital, Melbourne, Australia	100
Westmead Hospital, Sydney, Australia	23
Flinders University, Adelaide, Australia	47
Royal Brisbane and Women's Hospital, Brisbane, Australia	22
The Alfred, Melbourne, Australia	5
Austin Health, Melbourne, Australia	5
Royal Brisbane and Women's Hospital, Brisbane, Australia	2
Cliniques Universitaires Saint-Luc, Brussels, Belgium	60
CSSS Saint-Jérôme, Saint-Jerome, Canada	7
Jewish General Hospital, Montreal, Canada	5
Hopital Notre Dame, Montreal, Canada	166
CISSS Chaudière-Appalache, Levis, Canada	147
Neuro Rive-Sud, Quebec, Canada	53
General University Hospital and Charles University in Prague, Prague, Czech Republic	721
Nemocnice Jihlava, Jihlava, Czech Republic	16
Kommunehospitalet, Arhus C, Denmark	38
Hospital Universitario Virgen de Valme, Seville, Spain	64
Hospital Universitario Donostia, San Sebastián, Spain	34
Hospital Clinico San Carlos, Madrid, Spain	29
Hospital Universitario Virgen Macarena, Sevilla, Spain	300
Hospital de Galdakao-Usansolo, Galdakao, Spain	17
Hospital Germans Trias i Pujol, Badalona, Spain	15
MS Clinic, Hopital Tenon , Paris, France	2
Craigavon Area Hospital, Craigavon, United Kingdom	5
Royal Victoria Hospital, Belfast, United Kingdom	5
South East Trust, Belfast, United Kingdom	3
University of Cambridge, Cambridge, United Kingdom	84
University Hospital of Wales, Cardiff; Southmead Hospital, Bristol; Abertawe Bro Morgannwg University Local Health Board, Swansea, United Kingdom	82
University Hospital Carl Gustav Carus, Dresden, Germany	9
Veszprém Megyei Csolnoky Ferenc Kórház zrt., Veszprem, Hungary	14
Jahn Ferenc Teaching Hospital, Budapest, Hungary	59
Semmelweis University Budapest, Budapest, Hungary	16
University of Debrecen, Debrecen, Hungary	16
Péterfy Sandor Hospital, Budapest, Hungary	18
Josa András Hospital, Nyiregyhaza, Hungary	7
Petz A. County Hospital , Gyor, Hungary	6
BAZ County Hospital, Miskolc, Hungary	8
Szent Imre Hospital, Budapest, Hungary	9
Assaf Harofeh Medical Center, Beer-Yaakov, Israel	14
Bombay Hospital Institute of Medical Sciences, Mumbai, India	3
St Vincent's University Hospital, Dublin, Ireland	8
Isfahan University of Medical Sciences, Isfahan, Iran	4
Ospedale Clinicizzato, Chieti, Italy	173
Azienda Sanitaria Unica Regionale Marche - AV3, Macerata, Italy	83

University of Bari, Bari, Italy	560
University of Florence, Florence, Italy	14
C. Mondino National Neurological Institute, Pavia, Italy	32
Ospedali Riuniti di Salerno, Salerno, Italy	29
University of Parma, Parma, Italy	49
Azienda Ospedaliera di Rilievo Nazionale San Giuseppe Moscati Avellino, Avellino, Italy	47
Nuovo Ospedale Civile Sant'Agostino/Estense, Modena, Italy	79
Amiri Hospital, Kuwait City, Kuwait	94
Clinic of Neurology Clinical Center, Skopje, Macedonia	4
University Hospital Nijmegen, Nijmegen, Netherlands	29
Francicus Ziekenhuis, Roosendaal, Netherlands	4
Zuyderland Ziekenhuis, Sittard, Netherlands	79
Jeroen Bosch Ziekenhuis, Den Bosch, Netherlands	1
Groene Hart Ziekenhuis, Gouda, Netherlands	25
Hospital São João, Porto, Portugal	11
Central Military Emergency University Hospital, Bucharest, Romania	1
KTU Medical Faculty Farabi Hospital, Trabzon, Turkey	50
19 Mayis University, Samsun, Turkey	64
New York University Langone Medical Center, New York, United States	3

Table S4
Characteristics of the included unmatched patients at baseline

	alemtuzumab	interferon β	fingolimod	natalizumab
patients, nr (% female)	189 (69%)	2155 (72%)	828 (73%)	1160 (71%)
age, yr, mean ± SD	33 ± 8	34 ± 9	38 ± 10	36 ± 9
disease duration, yr, median (quartiles)	3.2 (1.8-5.9)	3.6 (1.3-7.9)	7.8 (3.8-14.1)	7.4 (3.3-12.4)
relapses 12 months pre-baseline, mean ± SD	2.3 ± 1.4	1.5 ± 0.7	1.4 ± 0.7	1.7 ± 0.9
disability, EDSS step, median (quartiles)	3.5 (2-5.5)	2 (1.5-3)	2.5 (1.5-4)	3 (2-4)
visit interval, months, median (quartiles)	9 (6-12)	3 (1-5)	4 (3-5)	3 (1-5)
treatment cycles, patients				
1	12 (6%)	-	-	-
2	93 (49%)	-	-	-
3	60 (31%)	-	-	-
4	15 (8%)	-	-	-
5	9 (5%)	-	-	-
previous therapies, nr, median (quartiles)	0 (0-1)	0 (0-1)	1 (1-2)	1 (1-2)
most active previous therapy, patients				
Interferon β / Glatiramer Acetate	49 (26%)	523 (24%)	566 (68%)	956 (82%)
Teriflunomide	0	0	2 (0.002%)	5 (0.004%)
Dimethyl fumarate	0	0	4 (0.005%)	2 (0.002%)
Fingolimod	2 (1%)	3 (0.001%)	0	51 (4%)
Natalizumab	15 (8%)	4 (0.002%)	112 (14%)	0
Mitoxantrone	3 (2%)	18 (1%)	20 (2%)	0
other	2 (1%)	4 (0.002%)	1 (0.001%)	0
none	118 (62%)	1606 (75%)	123 (15%)	146 (13%)
post-baseline follow-up on study therapy, yr, median (quartiles)	5.4 (3.5-7.5)	2.8 (1.5-5.1)	1.9 (1.3-2.7)	2.2 (1.6-3.6)

SD, standard deviation; EDSS, Expanded Disability Status Scale

Table S5
Logistic regression models used to estimate the propensity scores

Alemtuzumab (reference) **vs. Interferon β**

	Coefficient	Std.Error	z	Pr(>|z|)	
(Intercept)	4.83479	0.41071	11.772	< 2e-16	*
sex [male]	-0.10662	0.19113	-0.558	0.576955	
age	0.01367	0.01016	1.346	0.178415	
disease duration	0.07927	0.02336	3.393	0.000692	*
baseline disability, EDSS	-0.61612	0.05615	-10.974	< 2e-16	*
relapses, previous 1 year	-0.66905	0.08348	-8.014	1.11e-15	*
previous treatment starts	-0.68819	0.21652	-3.178	0.001481	*
the most active previous therapy					
[azathioprine]	-17.17696	571.95611	-0.030	0.976042	
[cladribine]	11.20600	882.74346	0.013	0.989872	
[fingolimod]	-2.05513	1.11778	-1.839	0.065978	.
[interferon/glat.acetate]	0.59337	0.34280	1.731	0.083463	.
[mitoxantrone]	0.91399	0.80023	1.142	0.253388	
[natalizumab]	-2.90462	0.83616	-3.474	0.000513	*

Alemtuzumab (reference) **vs. Fingolimod**

	Coefficient	Std.Error	z	Pr(>|z|)	
(Intercept)	0.78359	0.47883	1.636	0.101741	
sex [male]	0.14652	0.23931	0.612	0.540369	
age	0.05385	0.01332	4.043	5.28e-05	*
disease duration	0.09866	0.02669	3.697	0.000218	*
baseline disability, EDSS	-0.62584	0.07279	-8.598	< 2e-16	*
relapses, previous 1 year	-0.75061	0.11190	-6.708	1.97e-11	*
previous treatment starts	0.50871	0.18517	2.747	0.006011	*
the most active previous therapy					
[azathioprine]	-17.84382	1569.65081	-0.011	0.990930	
[cladribine]	13.22411	2399.54476	0.006	0.995603	
[fingolimod]	-19.28791	1661.61895	-0.012	0.990738	
[interferon/glat.acetate]	1.53649	0.34143	4.500	6.79e-06	*
[mitoxantrone]	0.07270	0.90885	0.080	0.936245	
[natalizumab]	0.54180	0.58717	0.923	0.356151	
[dimethyl fumarate]	15.78815	1130.34093	0.014	0.988856	
[teriflunomide]	15.24303	1577.02981	0.010	0.992288	

Alemtuzumab (reference) **vs. Natalizumab**

	Coefficient	Std.Error	z	Pr(>|z|)	
(Intercept)	0.75124	0.45410	1.654	0.098059	.
sex [male]	0.34616	0.21922	1.579	0.114319	
age	0.02076	0.01122	1.851	0.064215	.
disease duration	0.06619	0.02457	2.693	0.007071	*
baseline disability, EDSS	-0.28078	0.06028	-4.658	3.19e-06	*
relapses, previous 1 year	-0.33535	0.08911	-3.763	0.000168	*
previous treatment starts	0.36423	0.21001	1.734	0.082855	.
the most active previous therapy					
[azathioprine]	-17.84255	1668.79190	-0.011	0.991469	
[fingolimod]	1.97703	0.84384	2.343	0.019135	*
[interferon/glat.acetate]	2.00707	0.36181	5.547	2.90e-08	*
[mitoxantrone]	-17.40004	1343.03379	-0.013	0.989663	
[natalizumab]	-17.88766	591.72883	-0.030	0.975884	
[dimethyl fumarate]	15.61481	1686.86823	0.009	0.992614	
[teriflunomide]	15.16167	1053.31694	0.014	0.988515	

* statistically significant associations, · trends

Table S6
Propensity scores

	Alemtuzumab	Interferon β	dif.	Alemtuzumab	Fingolimod	dif.	Alemtuzumab	Natalizumab	dif.
before matching, mean	0.700	0.939	0.238	0.456	0.896	0.440	0.548	0.912	0.364
after matching, mean	0.796	0.796	0.0001	0.674	0.671	0.003	0.684	0.682	0.002
mean % difference matched vs. unmatched			-99.97%			-99.4%			-99.6%

Table S7
Results of the secondary and sensitivity analyses

alemtuzumab vs. interferon β-1a	n, unmatched		n, matched		annualised relapse rate	cumulative hazard of relapses	cumulative hazard of the first relapse
analysis	alemtuzumab	interferon β	alemtuzumab	interferon β			
primary analysis	**189**	**2155**	**156**	**282**	**0.19 vs 0.53, p=3.5e-16**	**HR=0.6, p=0.0052**	**HR=0.59, p=0.072**
secondary analyses							
high pre-baseline activity (>=3 relapses over 24 months or >=2 relapses over 12 months pre-baseline), 10:1 match	150	1053	118	696	0.19 vs 0.58, p=9.8e-80	HR=0.38, p=1.5e-09	HR=0.27, p<0.001
any prior on-treatment break-through relapses	28	491	17	148	0.36 vs 0.58, p=0.011	HR=0.61, p=0.3	HR=0.34, p=2.6e-06
sensitivity analyses							
10:1 match with broad caliper (0.4)	189	2155	159	1049	0.18 vs 0.51, p=2.4e-16	HR=0.4, p=5.2e-14	HR=0.25, p<0.001
matching on 24-month pre-baseline relapse activity	189	2155	150	270	0.14 vs 0.52, p=1.6e-41	HR=0.31, p=3.9e-12	HR=0.23, p<0.001
relapsing and secondary progressive MS	191	2201	159	290	0.16 vs 0.52, p=1.5e-38	HR=0.35, p=1.1e-08	HR=0.26, p<0.001
minimum of 2-year on-treatment follow-up	168	1391	124	218	0.16 vs 0.38, p=3e-17	HR=0.46, p=7.3e-06	HR=0.35, p=2.7e-11
intention to treat	189	2155	156	282	0.18 vs 0.51, p=2.6e-52	HR=0.4, p=8.8e-11	HR=0.75, p=0.33

alemtuzumab vs. interferon β-1a	cumulative hazard of disability accumulation events		cumulative hazard of the first disability accumulation event		cumulative hazard of disability improvement events		cumulative hazard of the first disability improvement event	
analysis	confirmed at 6 months	confirmed at 12 months	confirmed at 6 months	confirmed at 12 months	confirmed at 6 months	confirmed at 12 months	confirmed at 6 months	confirmed at 12 months
primary analysis	**HR=0.66, p=0.37**	**HR=0.59, p=0.31**	**HR=0.69, p=0.42**	**HR=0.63, p=0.33**	**HR=0.98, p=0.93**	**HR=0.84, p=0.65**	**HR=1.4, p=0.4**	**HR=1.1, p=0.76**
secondary analyses								
high pre-baseline activity (>=3 relapses over 24 months or >=2 relapses over 12 months pre-baseline), 10:1 match	HR=0.64, p=0.018	HR=0.65, p=0.029	HR=0.92, p=0.71	HR=0.74, p=0.096	HR=0.98, p=0.94	HR=0.68, p=0.41	HR=2.1, p=0.00047	HR=1.9, p=0.0033
any prior on-treatment break-through relapses	HR=1.1, p=0.93	HR=1.1, p=0.93	HR=0.83, p=0.86	HR=0.83, p=0.86	HR=3.9, p=0.035	HR=3.9, p=0.03	HR=4.2, p=0.0037	HR=4.2, p=0.0037
sensitivity analyses								
10:1 match with broad caliper (0.4)	HR=0.82, p=0.21	HR=0.79, p=0.15	HR=1, p=0.93	HR=0.77, p=0.065	HR=0.99, p=0.96	HR=0.51, p=0.013	HR=1.3, p=0.14	HR=1.2, p=0.46
matching on 24-month pre-baseline relapse activity	HR=0.97, p=0.89	HR=0.91, p=0.74	HR=1.4, p=0.28	HR=1.1, p=0.73	HR=1, p=0.92	HR=1.1, p=0.9	HR=1.2, p=0.72	HR=1.2, p=0.74
relapsing and secondary progressive MS	HR=0.9, p=0.69	HR=0.82, p=0.56	HR=1.3, p=0.46	HR=0.99, p=1	HR=1.1, p=0.71	HR=1.1, p=0.87	HR=1.4, p=0.33	HR=1.4, p=0.35
minimum of 2-year on-treatment follow-up	HR=0.9, p=0.77	HR=0.87, p=0.79	HR=0.89, p=0.78	HR=0.88, p=0.79	HR=0.89, p=0.75	HR=0.76, p=0.52	HR=1.1, p=0.84	HR=0.96, p=0.9
intention to treat	HR=0.72, p=0.2	HR=0.67, p=0.12	HR=1.1, p=0.79	HR=0.87, p=0.7	HR=1.3, p=0.55	HR=1.1, p=0.79	HR=1.8, p=0.05	HR=1.9, p=0.045

The table shows observed annualised relapse rate or hazard ratios (HR) for the evaluated outcomes, together with the corresponding p values. Of the two compared disease modifying therapies (DMT), interferon β served as a reference. The p values (adjusted for false discovery rate) ≤0.05 are highlighted in red. Disability outcomes confirmed at 6 months are the secondary endpoints. Disability outcomes confirmed at 12 months represent sensitivity analyses.

alemtuzumab vs. fingolimod	n, unmatched		n, matched		annualised relapse rate	cumulative hazard of relapses	cumulative hazard of the first relapse
analysis	alemtuzumab	fingolimod	alemtuzumab	fingolimod			
primary analysis	**189**	**828**	**114**	**195**	**0.15 vs 0.34, p=1.4e-11**	**HR=0.62, p=0.18**	**HR=0.59, p=0.065**
secondary analyses							
high pre-baseline activity (>=3 relapses over 24 months or >=2 relapses over 12 months pre-baseline), 10:1 match	150	372	82	261	0.16 vs 0.32, p=7e-07	HR=0.63, p=0.24	HR=0.62, p=0.039
any prior on-treatment break-through relapses	28	646	22	173	0.23 vs 0.28, p=0.92	HR=0.83, p=0.94	HR=0.78, p=0.66
sensitivity analyses							
10:1 match with broad caliper (0.4)	189	828	116	532	0.15 vs 0.3, p=1.3e-14	HR=0.7, p=0.27	HR=0.51, p=4.6e-06
matching on 24-month pre-baseline relapse activity	189	828	95	167	0.15 vs 0.34, p=0.00039	HR=0.49, p=0.0054	HR=0.39, p=0.00023
relapsing and secondary progressive MS	191	862	115	192	0.15 vs 0.31, p=0.0016	HR=0.68, p=0.3	HR=0.67, p=0.21
minimum of 2-year on-treatment follow-up	168	388	77	107	0.13 vs 0.27, p=0.00025	HR=0.67, p=0.36	HR=0.74, p=0.49
intention to treat	189	828	114	195	0.19 vs 0.36, p=1e-04	HR=0.62, p=0.12	HR=0.52, p=0.0077

alemtuzumab vs. fingolimod	cumulative hazard of disability accumulation events		cumulative hazard of the first disability accumulation event		cumulative hazard of disability improvement events		cumulative hazard of the first disability improvement event	
analysis	confirmed at 6 months	confirmed at 12 months	confirmed at 6 months	confirmed at 12 months	confirmed at 6 months	confirmed at 12 months	confirmed at 6 months	confirmed at 12 months
primary analysis	**HR=1.3, p=0.67**	**HR=0.38, p=0.29**	**HR=1.7, p=0.39**	**HR=1.2, p=0.85**	**HR=0.5, p=0.18**	**HR=0.48, p=0.19**	**HR=0.5, p=0.17**	**HR=0.61, p=0.36**
secondary analyses								
high pre-baseline activity (>=3 relapses over 24 months or >=2 relapses over 12 months pre-baseline), 10:1 match	HR=0.93, p=0.94	HR=0.78, p=0.7	HR=1.1, p=0.81	HR=0.82, p=0.76	HR=0.6, p=0.4	HR=0.66, p=0.57	HR=0.73, p=0.54	HR=0.63, p=0.38
any prior on-treatment break-through relapses	HR=0.94, p=1	HR=1.7, p=0.7	HR=1, p=0.97	HR=1.5, p=0.9	HR=1.1, p=1	HR=0.75, p=0.94	HR=0.96, p=0.98	HR=1, p=1
sensitivity analyses								
10:1 match with broad caliper (0.4)	HR=0.89, p=0.94	HR=1.1, p=0.95	HR=0.95, p=0.93	HR=0.82, p=0.61	HR=0.54, p=0.12	HR=0.59, p=0.26	HR=0.6, p=0.095	HR=0.62, p=0.12
matching on 24-month pre-baseline relapse activity	HR=1.4, p=0.73	HR=1.3, p=0.73	HR=1.7, p=0.44	HR=1.3, p=0.74	HR=0.64, p=0.53	HR=0.61, p=0.51	HR=0.72, p=0.7	HR=0.77, p=0.71
relapsing and secondary progressive MS	HR=0.71, p=0.63	HR=0.62, p=0.58	HR=1, p=1	HR=0.71, p=0.66	HR=0.69, p=0.5	HR=0.71, p=0.63	HR=0.77, p=0.65	HR=1, p=1
minimum of 2-year on-treatment follow-up	HR=1.7, p=0.53	HR=1.7, p=0.55	HR=1.3, p=0.81	HR=1.5, p=0.82	HR=0.41, p=0.088	HR=0.41, p=0.097	HR=0.4, p=0.096	HR=0.45, p=0.17
intention to treat	HR=1, p=0.99	HR=1.2, p=0.8	HR=1.4, p=0.73	HR=1.4, p=0.69	HR=0.55, p=0.24	HR=0.62, p=0.49	HR=0.67, p=0.53	HR=0.79, p=0.69

The table shows observed annualised relapse rate or hazard ratios (HR) for the evaluated outcomes, together with the corresponding p values. Of the two compared disease modifying therapies (DMT), fingolimod served as a reference. The p values (adjusted for false discovery rate) ≤0.05 are highlighted in red. Disability outcomes confirmed at 6 months are the secondary endpoints. Disability outcomes confirmed at 12 months represent sensitivity analyses.

alemtuzumab vs. natalizumab	n, unmatched		n, matched		annualised relapse rate	cumulative hazard of relapses	cumulative hazard of the first relapse
analysis	alemtuzumab	natalizumab	alemtuzumab	natalizumab			
primary analysis	**187**	**1160**	**138**	**223**	**0.2 vs 0.19, p=0.78**	**HR=1, p=0.83**	**HR=0.87, p=0.65**
secondary analyses							
high pre-baseline activity (>=3 relapses over 24 months or >=2 relapses over 12 months pre-baseline), 10:1 match	148	711	103	382	0.17 vs 0.2, p=0.25	HR=0.97, p=0.92	HR=0.97, p=0.93
any prior on-treatment break-through relapses	28	953	19	188	0.28 vs 0.3, p=0.16	HR=0.83, p=0.97	HR=0.5, p=0.012
sensitivity analyses							
10:1 match with broad caliper (0.4)	187	1160	139	662	0.18 vs 0.19, p=0.49	HR=1, p=0.93	HR=0.78, p=0.093
matching on 24-month pre-baseline relapse activity	187	1160	111	181	0.21 vs 0.23, p=0.73	HR=1.1, p=0.93	HR=0.9, p=0.73
relapsing and secondary progressive MS	189	1198	141	226	0.19 vs 0.2, p=0.65	HR=1, p=1	HR=0.74, p=0.3
minimum of 2-year on-treatment follow-up	166	684	106	160	0.18 vs 0.17, p=0.86	HR=1.2, p=0.76	HR=0.83, p=0.68
intention to treat	187	1160	138	223	0.19 vs 0.23, p=0.041	HR=0.86, p=0.73	HR=0.66, p=0.056

alemtuzumab vs. natalizumab	cumulative hazard of disability accumulation events		cumulative hazard of the first disability accumulation event		cumulative hazard of disability improvement events		cumulative hazard of the first disability improvement event	
analysis	confirmed at 6 months	confirmed at 12 months	confirmed at 6 months	confirmed at 12 months	confirmed at 6 months	confirmed at 12 months	confirmed at 6 months	confirmed at 12 months
primary analysis	**HR=0.81, p=0.6**	**HR=0.92, p=0.84**	**HR=1.1, p=0.84**	**HR=0.71, p=0.53**	**HR=0.35, p=0.00058**	**HR=0.46, p=0.061**	**HR=0.73, p=0.57**	**HR=0.59, p=0.34**
secondary analyses								
high pre-baseline activity (>=3 relapses over 24 months or >=2 relapses over 12 months pre-baseline), 10:1 match	HR=0.83, p=0.68	HR=0.88, p=0.79	HR=0.98, p=0.95	HR=0.5, p=0.047	HR=0.44, p=0.0023	HR=0.54, p=0.069	HR=0.74, p=0.38	HR=0.79, p=0.52
any prior on-treatment break-through relapses	HR=1.2, p=0.82	HR=1.3, p=0.82	HR=1, p=1	HR=1, p=0.98	HR=1.2, p=0.88	HR=1.7, p=0.31	HR=1.2, p=0.92	HR=1.3, p=0.92
sensitivity analyses								
10:1 match with broad caliper (0.4)	HR=0.81, p=0.58	HR=0.92, p=0.92	HR=1, p=0.95	HR=0.64, p=0.092	HR=0.35, p=0.00032	HR=0.46, p=0.038	HR=0.54, p=0.0012	HR=0.56, p=0.0049
matching on 24-month pre-baseline relapse activity	HR=0.77, p=0.75	HR=0.92, p=0.91	HR=0.62, p=0.41	HR=0.6, p=0.45	HR=0.43, p=0.01	HR=0.4, p=0.01	HR=0.62, p=0.3	HR=0.54, p=0.17
relapsing and secondary progressive MS	HR=0.81, p=0.65	HR=0.86, p=0.7	HR=0.79, p=0.64	HR=0.52, p=0.22	HR=0.34, p=2e-04	HR=0.47, p=0.069	HR=0.59, p=0.2	HR=0.59, p=0.23
minimum of 2-year on-treatment follow-up	HR=0.79, p=0.79	HR=0.84, p=0.73	HR=0.35, p=0.017	HR=0.33, p=0.015	HR=0.69, p=0.35	HR=0.56, p=0.21	HR=0.91, p=0.83	HR=0.86, p=0.72
intention to treat	HR=0.79, p=0.73	HR=0.92, p=0.87	HR=0.95, p=0.91	HR=0.81, p=0.72	HR=0.4, p=0.00056	HR=0.47, p=0.036	HR=0.79, p=0.68	HR=0.68, p=0.56

The table shows observed annualised relapse rate or hazard ratios (HR) for the evaluated outcomes, together with the corresponding p values. Of the two compared disease modifying therapies (DMT), natalizumab served as a reference. The p values (adjusted for false discovery rate) ≤0.05 are highlighted in red. Disability outcomes confirmed at 6 months are the secondary endpoints. Disability outcomes confirmed at 12 months represent sensitivity analyses.

Table S8
Results of the power analyses

	annualised relapse rate	cumulative hazard of relapses	cumulative hazard of disability progression	cumulative probability of disability regression
interferon β	-	-	40%	42%
fingolimod	-	53%	66%	39%
natalizumab	0.13	51%	35%	-

The table shows minimum detectable differences for alemtuzumab vs. interferon β, fingolimod or natalizumab, for the disease outcomes whose analyses did not reach the predefined level of statistical significance. The differences are shown as relapses per year (for annualised relapse rate) or proportion of the cumulative hazard (for the cumulative hazard of relapses, disability progression or disability regression).