Journal of Medical Economics

ISSN: (Print) (Online) Journal homepage: www.tandfonline.com/journals/ijme20

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To cite this article: T. Spelman, W. L. Herring, C. Acosta, R. Hyde, V. G. Jokubaitis, E. Pucci, A. Lugaresi, G. Laureys, E. K. Havrdova, D. Horakova, G. Izquierdo, S. Eichau, S. Ozakbas, R. Alroughani, T. Kalincik, P. Duquette, M. Girard, T. Petersen, F. Patti, T. Csepany, F. Granella, F. Grand'Maison, D. Ferraro, R. Karabudak, M. Jose Sa, M. Trojano, V. van Pesch, B. Van Wijmeersch, E. Cartechini, P. McCombe, O. Gerlach, D. Spitaleri, C. Rozsa, S. Hodgkinson, R. Bergamaschi, R. Gouider, A. Soysal, Castillo-Triviño, J. Prevost, J. Garber, K. de Gans, R. Ampapa, M. Simo, J. L. Sanchez-Menoyo, G. Iuliano, A. Sas, A. van der Walt, N. John, O. Gray, S. Hughes, G. De Luca, M. Onofrj, K. Buzzard, O. Skibina, M. Terzi, M. Slee, C. Solaro, Oreja-Guevara, C. Ramo-Tello, Y. Fragoso, V. Shaygannejad, F. Moore, C. Rajda, E. Aguera Morales & H. Butzkueven (2024) Comparative effectiveness and cost-effectiveness of natalizumab and fingolimod in rapidly evolving severe relapsing-remitting multiple sclerosis in the United Kingdom, Journal of Medical Economics, 27:1, 109-125, DOI: 10.1080/13696998.2023.2293379

To link to this article: https://doi.org/10.1080/13696998.2023.2293379

View supplementary material

Published online: 26 Dec 2023.

JOURNAL OF MEDICAL ECONOMICS
2024, VOL. 27, NO. 1, 109–125
https://doi.org/10.1080/13696998.2023.2293379
Article 0159-RT/2293379

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Comparative effectiveness and cost-effectiveness of natalizumab and fingolimod in rapidly evolving severe relapsing-remitting multiple sclerosis in the United Kingdom

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Supplemental data for this article can be accessed online at https://doi.org/10.1080/13696998.2023.2293379.

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ABSTRACT

Aim: To evaluate the real-world comparative effectiveness and the cost-effectiveness, from a UK National Health Service perspective, of natalizumab versus fingolimod in patients with rapidly evolving severe relapsing-remitting multiple sclerosis (RES-RRMS).

Methods: Real-world data from the MSBase Registry were obtained for patients with RES-RRMS who were previously either naive to disease-modifying therapies or had been treated with interferon-based therapies, glatiramer acetate, dimethyl fumarate, or teriflunomide (collectively known as BRACETD). Matched cohorts were selected by 3-way multinomial propensity score matching, and the annualized relapse rate (ARR) and 6-month–confirmed disability worsening (CDW6M) and improvement (CDI6M) were compared between treatment groups. Comparative effectiveness results were used in a cost-effectiveness model comparing natalizumab and fingolimod, using an established Markov structure over a lifetime horizon with health states based on the Expanded Disability Status Scale. Additional model data sources included the UK MS Survey 2015, published literature, and publicly available sources.

Results: In the comparative effectiveness analysis, we found a significantly lower ARR for patients starting natalizumab compared with fingolimod (rate ratio [RR] = 0.65; 95% confidence interval [CI], 0.57–0.73) or BRACETD (RR = 0.46; 95% CI, 0.42–0.53). Similarly, CDI6M was higher for patients starting natalizumab compared with fingolimod (hazard ratio [HR] = 1.25; 95% CI, 1.01–1.55) and BRACETD (HR = 1.46; 95% CI, 1.16–1.85). In patients starting fingolimod, we found a lower ARR (RR = 0.72; 95% CI, 0.65–0.80) compared with starting BRACETD, but no difference in CDI6M (HR = 1.17; 95% CI, 0.91–1.50). Differences in CDW6M were not found between the treatment groups. In the base-case cost-effectiveness analysis, natalizumab dominated fingolimod (0.302 higher quality-adjusted life-years [QALYs] and £17,141 lower predicted lifetime costs). Similar cost-effectiveness results were observed across sensitivity analyses.

Conclusions: This MSBase Registry analysis suggests that natalizumab improves clinical outcomes when compared with fingolimod, which translates to higher QALYs and lower costs in UK patients with RES-RRMS.

PLAIN LANGUAGE SUMMARY

There are several medications used to treat people with relapsing remitting multiple sclerosis, such as interferon-based therapies (Betaferon/Betaseron (US), Rebif, Avonex, Extavia), glatiramer acetate (Copaxone), teriflunomide (Aubagio), and dimethyl fumarate (Tecfidera), collectively named BRACETD. Other treatments for multiple sclerosis (MS) have a narrower use, such as natalizumab (Tysabri) or fingolimod (Gilenya), among others.

This study objective was to assess how well natalizumab and fingolimod helped treating MS (clinical effectiveness) and subsequently estimate what the cost of these treatments is in comparison to the benefit they bring to people with rapidly evolving severe MS that use them in the United Kingdom (UK) (cost-effectiveness).

We used an international disease registry (MSBase), which collects clinical data from people with MS in various centers around the world to compare the effectiveness of natalizumab, fingolimod and BRACETD treatments. We used a technique called propensity score matching to obtain results from comparable patient groups. People treated with natalizumab had better disease control, namely with fewer relapses and higher improvement on their disability level, than patients on fingolimod or BRACETD. Conversely, there were no differences between each group of people on a measure called disability worsening.

Based on these clinical results, we built an economic model that simulates the lifetime costs and consequences of treating people with MS with natalizumab in comparison with fingolimod. We found that using natalizumab was less costly and was more effective compared to using fingolimod in UK patients.

ARTICLE HISTORY
Received 28 July 2023
Revised 7 December 2023
Accepted 7 December 2023

KEYWORDS
Multiple sclerosis; natalizumab; fingolimod; real-world data; comparative effectiveness; cost-effectiveness

JEL CLASSIFICATION CODES
I10; I1; I; I11

Introduction

Multiple sclerosis (MS) is a chronic neurological disease that clinically manifests with episodic neurological dysfunction and increasing disability in a proportion of patients over time.[1,2] Persistent disability as a result of relapses or disease progression may be reduced by early access to high-efficacy therapies in patients with active disease.[3] However, there are high direct and indirect costs[4–6] associated with MS, which underscore the importance of comparative effectiveness and cost-effectiveness analyses for use in health technology assessments (HTAs) to inform pricing and reimbursement decisions. Although HTAs have traditionally relied on efficacy data from randomized controlled trials, real-world data (RWD) provide valuable evidence to support and build upon evidence from

clinical trials. Accordingly, HTA agencies are increasingly using RWD to evaluate existing treatment options, especially for conditions such as MS[7] with available disease registries.[8,9]

Large MS disease registries, such as the international MSBase Registry (MSBase),[7] provide RWD that can be used for both comparative clinical and economic evaluations. These registries provide researchers with rich data density on cohorts of patients with MS followed up longitudinally for long periods. This allows for the use of methods to adjust for differences in patient characteristics between groups, thus lowering the risk of bias in nonrandomized studies.[10] Traditional first-line DMTs for RRMS, based on their approved indication, are collectively referred to as BRACETD and include interferon-based therapies, glatiramer acetate, teriflunomide, and dimethyl fumarate.[11] Compared with interferon-based therapies and glatiramer acetate, therapies such as natalizumab or fingolimod are more effective in preventing relapses and delaying disability progression.[12] In the European Union, natalizumab and fingolimod are indicated in patients with highly active (HA) RRMS with inadequate response to first-line DMTs and in patients with rapidly evolving severe (RES) RRMS with or without prior DMT exposure.[13–15] However, the use of these therapies must be balanced with the increased risk of adverse events (AEs), such as the serious AE of progressive multifocal leukoencephalopathy (PML), as well as the risk of other infections, cardiac events, and active malignancies.[11,16,17]

We recently used real-world comparative effectiveness data to inform the economic evaluation of RRMS treatment escalation alternatives in patients with HA-RRMS in the United Kingdom (UK).[18] In this study, which was the first of its kind in the MS literature, we conducted an MSBase analysis in alignment with established health economic modeling requirements in MS. The results of this previous analysis suggested improved clinical and economic outcomes for therapy escalation to natalizumab versus fingolimod in patients with HA-RRMS with inadequate response to BRACETD. In recent years, high-efficacy treatments have been used earlier in the treatment paradigm[19]; therefore, assessing the effectiveness of natalizumab and fingolimod in the RES subpopulation, including in treatment-naive patients, is paramount. Additionally, extending our integrated analytical approach to the RES-RRMS population is key to a comprehensive assessment of the value of these DMTs across the HA- and RES-RRMS indications. Accordingly, the objective of the present study was to conduct a comparative effectiveness analysis using RWD from MSBase for use in a pharmacoeconomic model to estimate the cost-effectiveness of natalizumab compared with fingolimod in patients with RES-RRMS from a UK National Health Service perspective.

Methods

Study population

The study population comprised adult patients (age $\geq$ 18 years) with RES-RRMS (defined as $\geq$ 2 relapses in the previous year) starting treatment with natalizumab, fingolimod, or BRACETD who previously either were naive to DMTs or had been treated with a different BRACETD therapy, reflecting the regulatory indication of natalizumab and fingolimod currently approved by the European Medicines Agency. Patients starting treatment with BRACETD (for the first time or switching within BRACETD) were included as a common reference group to facilitate extrapolation and post discontinuation scenarios in the cost-effectiveness analysis.

The international MSBase Registry (MSBase)[7] is currently the largest single MS registry available worldwide. With over 80,000 patients with MS across more than 40 countries, data from MSBase provide a large source of RWD that can be used for comparison of DMT effectiveness in MS. Longitudinal data from 68,619 patients across 169 MS centers in 41 countries were extracted from MSBase on 8 August 2019 to identify patients meeting the RES-RRMS criteria. While participating centers are requested to perform a clinical assessment of their patients at least yearly, this was not used as an exclusion criterion. In the UK, RES-RRMS is defined as patients experiencing $\geq$ 2 disabling relapses in a year and $\geq$ 1 brain lesion identified by magnetic resonance imaging (MRI), according to the RES-RRMS definition in UK marketing authorizations[15] and HTA recommendations.[13,14] In this study, patients who met the criterion of $\geq$ 2 relapses in the previous year were eligible for inclusion in the analysis; the presence of brain lesions was not required for study inclusion, as MRI lesion data are not reliably collected in all MSBase centers.[7] The following patient data were also required as inclusion criteria: available data for a predefined set of matching variables, including Expanded Disability Status Scale (EDSS) at the time of treatment initiation (Table 1); a minimum treatment persistence of 3 months after treatment initiation; and at least 1 subsequent on-treatment EDSS record. Patients treated with non-BRACETD therapies prior to starting treatment with natalizumab, fingolimod, or BRACETD and patients enrolled in a randomized controlled trial in MS prior to the date of the qualifying relapse (the first, second, or subsequent relapse in the previous year) were excluded from the analysis.

To account for potential differences in baseline patient characteristics, matched cohorts for patients starting natalizumab, fingolimod, and BRACETD therapies were selected by performing 3-way multinomial propensity score matching.[20] In this analysis, baseline was defined as the date at which the index DMT (natalizumab, fingolimod, or BRACETD) was initiated. The predefined baseline variables used in the matching algorithm included age, sex, country, disease duration, baseline EDSS score, DMT history (including proportion of naive or treatment-experienced patients, proportion of disease duration on treatment, and pre-index DMT), and relapse history (number of relapses and steroid-treated relapses in the last 12 or 24 months before treatment switching). These variables were selected based on availability in the core MSBase dataset and on potential correlation with treatment outcomes, based on prior MSBase research and published literature.[18,21,22] Logistic regression was used to derive propensity scores for the natalizumab, fingolimod, and BRACETD cohorts, with the treatment group as the dependent variable and the predefined matching variables as independent model covariates. Cohort characteristics prior to matching

Table 1. Baseline patient characteristics for the MSBase cohorts after matching.

Patient characteristic[a]	Index DMT (starting or switching to)			Absolute standardized differences		
	Natalizumab ($n = 721$)	Fingolimod ($n = 721$)	BRACETD ($n = 721$)	Natalizumab vs fingolimod	Natalizumab vs BRACETD	Fingolimod vs BRACETD
Age, mean (SD), years	36.0 (9.3)	36.0 (9.7)	35.7 (9.4)	0.002	0.031	0.032
Sex, female, *n* (%)	535 (74.2)	514 (71.3)	519 (72.0)	0.065	0.050	0.015
Country, *n* (%)				0.047	0.066	0.014
Italy	104 (14.4)	97 (13.5)	184 (25.5)			
Czech Republic	92 (12.8)	145 (20.1)	167 (41.3)			
Turkey	37 (16.8)	131 (18.2)	52 (7.2)			
Spain	68 (9.4)	100 (13.9)	88 (12.2)			
Australia	134 (18.6)	118 (16.4)	70 (9.7)			
Other	286 (39.7)	130 (18.0)	160 (22.2)			
EDSS score, median (IQR)	2.5 (2.0, 3.5)	2.5 (2.0, 4.0)	2.5 (1.5, 4.0)	0.125	0.005	0.110
Disease duration, mean (SD), years	7.3 (7.2)	7.4 (7.1)	7.0 (7.1)	0.016	0.042	0.058
On-treatment proportion of disease duration, mean (SD)	0.4 (0.3)	0.4 (0.3)	0.4 (0.3)	0.014	0.012	0.025
Prior treatment with DMT, n (%)	550 (76.3)	553 (76.7)	549 (76.1)	0.010	0.003	0.013
Pre-index DMT, *n* (%)[b]				0.012	0.015	0.026
DMT naive	171 (23.7)	168 (23.3)	172 (23.9)			
Interferon beta-1b SC[c]	104 (14.4)	109 (15.1)	89 (12.3)			
Interferon beta-1a SC	162 (22.5)	148 (20.5)	191 (26.5)			
Interferon beta-1a IM	106 (14.7)	94 (13.0)	142 (19.7)			
Glatiramer acetate	140 (19.4)	156 (21.6)	92 (12.8)			
Teriflunomide	12 (1.7)	19 (2.6)	11 (1.5)			
Dimethyl fumarate	26 (3.6)	27 (3.7)	24 (3.3)			
Total relapse onsets in the prior 12 months, mean (SD)	2.2 (0.5)	2.3 (0.6)	2.2 (0.5)	0.121	0.019	0.144
Total relapse onsets in the prior 24 months, mean (SD)	2.8 (1.0)	2.9 (1.0)	2.7 (1.0)	0.120	0.043	0.160
Total steroid-treated relapse onsets in the prior 12 months, mean (SD)	1.5 (0.9)	1.5 (1.0)	1.4 (0.9)	0.030	0.028	0.056
Total steroid-treated relapse onsets in the prior 24 months, mean (SD)	1.8 (1.2)	1.9 (1.3)	1.8 (1.3)	0.033	0.032	0.063

Abbreviations. BRACETD, interferon-based therapies, glatiramer acetate, teriflunomide, and dimethyl fumarate; DMT, disease-modifying therapy; EDSS, Expanded Disability Status Scale; IM, intramuscular; IQR, interquartile range; SC, subcutaneous; SD, standard deviation.
[a]The baseline patient characteristics prior to matching for the MSBase cohorts are presented in Table S1 (Supplementary Material).
[b]The percentage distribution of therapies after the index date for the BRACETD treatment group is presented in Table S2 (Supplementary Material).
[c]The MSBase data did not distinguish between the use of interferon beta-1b SC (Betaferon® or Extavia®); as such, the matching algorithm did not distinguish between the 2 options.

are presented in Table S1 (Supplementary Material) and a Consolidated Standards of Reporting Trials (CONSORT)–like diagram detailing patient selection is presented in Figure 1.

Comparative effectiveness analysis

Outcome measures

The follow-up period for all patients included in the MSBase analysis began at the time of treatment initiation and ended with discontinuation of the primary treatment, conversion to secondary progressive MS (SPMS), the end of patient-specific EDSS data recorded in MSBase, or death. Outcomes considered in the comparative effectiveness analysis included annualized relapse rate (ARR), time to first relapse, time to 6-month–confirmed disability worsening (CDW6M), and time to 6-month–confirmed disability improvement (CDI6M). Time to 3-month–confirmed disability worsening (CDW3M) and time to 3-month–confirmed disability improvement (CDI3M) were also considered for scenario analysis.

Comparative effectiveness outcomes were implemented using the definitions previously described in Spelman et al.[18] A relapse was confirmed by the treating physician and was defined as the presentation of new symptoms or exacerbation of existing symptoms persisting for at least 24 h, without concurrent illness or fever, and separated in time by at least 30 days after a previous relapse.[23] Relapse confirmation with EDSS scores or MRI was not required. CDW6M and CDW3M were defined as an increase in EDSS score of at least 1 point from baseline sustained between 2 follow-up visits within no less than 6 months or 3 months, respectively (1.5 points if EDSS score at baseline was 0; 0.5 points if the baseline EDSS score was $\geq$ 5.5). CDI6M and CDI3M were defined as a decrease in EDSS score of at least 1 point from a baseline EDSS score $\geq$ 2 sustained between 2 follow-up visits within no less than 6 months or 3 months, respectively. CDW6M and CDI6M were modeled as separate outcomes and excluded EDSS scores within 30 days of a relapse. A 6-month confirmation of disability changes was required for the primary analysis based on regulatory preferences,[24] and a 3-month confirmation definition was used in scenario analysis.

To estimate EDSS transition probability matrices for use in the cost-effectiveness analysis, we identified all EDSS scores within calendar year intervals as long as they were at least 90 days apart from each other for all patients in each treatment cohort over the duration of the follow-up period. EDSS scores were considered invalid if they were reported within 90 days of each other, in order to have a minimum 3-month duration to exclude shorter fluctuations in EDSS levels, which are often due to relapses and do not represent long-term disability changes. EDSS changes persisting beyond 3 months were considered likely to represent true changes in disability

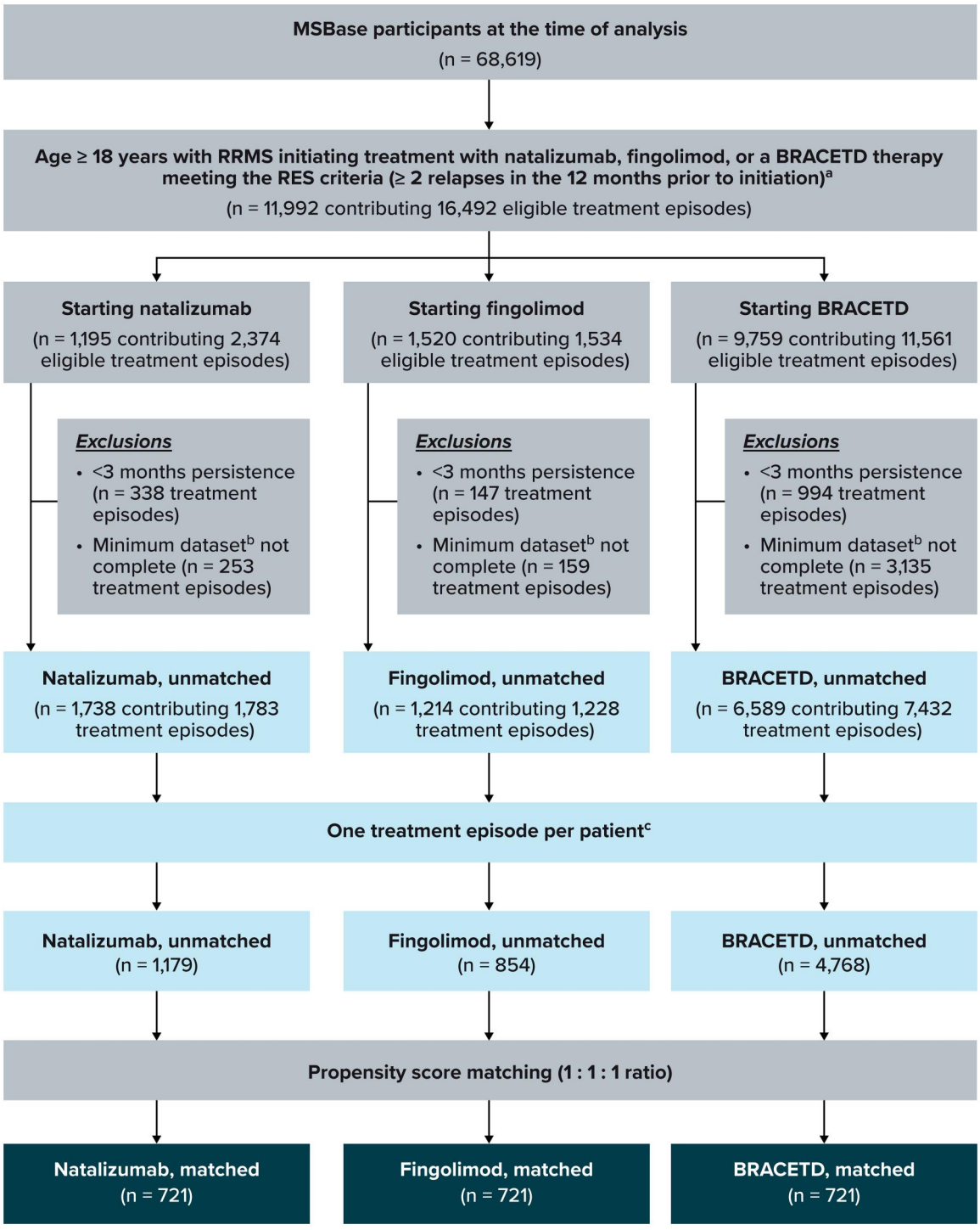

Figure 1. Patient selection flow chart for MSBase analysis. Abbreviations. BRACETD, interferon-based therapies, glatiramer acetate, teriflunomide, and dimethyl fumarate; EDSS, Expanded Disability Status Scale; RES, rapidly evolving severe; RRMS, relapsing-remitting multiple sclerosis. [a]Requires ≥2 relapses in the previous 12 months; a minimum treatment persistence of 3 months after treatment initiation; ≥3 months of data following therapy initiation, disability quantified with EDSS recorded at time of therapy initiation and at least 1 subsequent on-treatment EDSS record. [b]All variables included in the propensity score matching algorithm (Table 1 in the main text) were required for inclusion in the analysis. [c]For patients contributing multiple episodes within the same treatment group, the first episode was selected. For patients contributing multiple episodes to different groups, the smaller group was prioritized to maximize statistical power.

level, and hence included in the EDSS transition probability matrix analysis. Because these are changes within a calendar year, confirmation of the change in EDSS score during each yearly interval was not required. Patients were allowed to contribute multiple distinct yearly intervals to the transition matrix analysis. In alignment with the cost-effectiveness model structure, noninteger EDSS scores were rounded down.

Statistical analysis

All statistical analyses were performed as previously described[18] using Stata version 16 (RRID:SCR_012763) and R Project for Statistical Computing version 3.6.3 (RRID:SCR_001905). Comparative effectiveness analyses were conducted pairwise between each of the 3 treatment groups. Specifically, ARRs were analyzed overall and by baseline

EDSS score using a generalized estimating equation Poisson regression model. Time to first relapse, CDW6M, and CDI6M utilized a Kaplan-Meier approach and a marginal Cox regression model that adjusted for matching but did not adjust for other covariates. Patients with < 3 EDSS scores (e.g. baseline, change from baseline, and confirmation) were included in the CDW6M and CDI6M analyses; however, these patients were considered not to have a confirmed EDSS change. We used statistical tests appropriate for the clustered nature of the matched design and matched triplets were censored at discontinuation of the primary treatment or the last recorded on-treatment visit. The significance threshold was set at $p < .05$.

For the transition matrix analysis, we estimated the probability of transitioning between each possible pair of EDSS scores (both progression and regression were allowed) within a single year using all valid yearly intervals for each treatment cohort.[25] A valid yearly interval includes any time range between January and December of a given year if the patient met the inclusion criteria defined in the study with at least two valid EDSS measurement scores at least 90 days apart from each other (in order to create a transition between EDSS levels). Following the memoryless property of the Markov-based cost-effectiveness modeling approach, all valid yearly intervals were given the same weight, including multiple intervals identified for the same patient and intervals occurring during different years of the follow-up period.

Cost-effectiveness analysis

We used the cost-effectiveness modeling approach used in our previous RWD model published in Spelman et al.,[18] which was developed in alignment with UK guidelines[26] and with modeling precedent in MS.[27,28] The model was programmed in Microsoft Excel (RRID: SCR_016137) for Windows with Visual Basic for Applications (Microsoft Corporation).

Modeling approach

The model used an established, Markov-based approach with annual cycle length and integer EDSS-based health states to track a cohort of patients with RES-RRMS as they experienced disability worsening or improvement and relapses associated with RRMS, conversion to SPMS, disability worsening and relapses associated with SPMS, and death. The model structure includes discrete EDSS health states for patients with RRMS (EDSS score 0 to 9.0) and SPMS (EDSS score 1.0 to 9.0) (Figure 2). Consistent with modeling precedent in MS,[27,28] disability worsening (i.e. transition to a higher EDSS score) was allowed in both RRMS and SPMS, while disability improvement (i.e. transition to a lower EDSS score) was allowed only in RRMS. Conversion from RRMS to SPMS was assumed to be associated with a 1-point increase in EDSS score; transition from SPMS back to RRMS was not permitted, consistent with clinical disease evolution in MS. Transitions of ≥1 EDSS score in a single cycle were considered in the model.

MS is a chronic, progressive disease without a cure; therefore, the analysis was conducted over a lifetime horizon from a UK National Health Service (i.e. a healthcare payer) perspective; shorter time horizons and a societal perspective were considered in scenario analyses. We used the 2021 Great British Pound (GBP; £) for the cost year in the analysis. In accordance with current UK methods of HTA,[26] a 3.5% annual discount was used for all costs and health outcomes, and in scenario analysis, we considered alternative discounting rates.

Data sources

Data for the cost-effectiveness analysis were drawn from RWD sources wherever possible. Synthesized clinical trial data, the published literature, and other publicly available data sources were used when necessary. An overview of data sources and specific contributions is shown in Figure S1 of the Supplementary Material.

Clinical data from MSBase. The primary clinical data for RRMS were obtained from the results of the MSBase comparative effectiveness analysis: baseline age, sex, and EDSS distribution (Table S3, Supplementary Material); hazard ratios (HRs) for CDW6M and CDI6M; rate ratios (RRs) for relapses for natalizumab and fingolimod (reference = BRACETD) (Table 2 and Tables S4-S7, Supplementary Material); and treatment-specific annual EDSS transition probability matrices and ARRs for each MSBase treatment cohort (Tables S8–S10, Supplementary Material). The base-case cost-effectiveness analysis used the MSBase results for the matched cohorts; results for the unmatched cohorts were considered in scenario analysis.

The MSBase cohorts had limited numbers of patients with an EDSS score ≥ 7.0; therefore, we used transition probabilities from the British Columbia Multiple Sclerosis (BCMS) database[29] and ARRs from a previous analysis[30] to extrapolate the MSBase results for these EDSS scores. The BCMS is a natural history database comprising all EDSS levels in both RRMS and SPMS that has been used previously to supplement data for higher EDSS levels[27,28]; the transition matrix and ARR extrapolation methodologies have been described previously.[18]

We implemented two options for using the MSBase results to model the effectiveness of natalizumab and fingolimod over time: (1) direct use of the treatment-specific EDSS transition matrices and ARRs by EDSS score for natalizumab and fingolimod and (2) application of HRs for CDW6M and CDI6M and RRs for relapse to the EDSS transition matrix and ARRs by EDSS score for BRACETD, producing comparative effectiveness–adjusted transition matrices and ARRs for natalizumab and fingolimod. In the base-case analysis, the model used the approach that most closely represented the clinical data, and therefore option 1 was used for the duration of follow-up observed in MSBase and option 2 was used for long-term extrapolation. The use of each approach was considered individually in scenario analysis.

Real-world data on annual discontinuation probabilities for natalizumab and fingolimod were also available from MSBase. However, a meaningful proportion of discontinuations

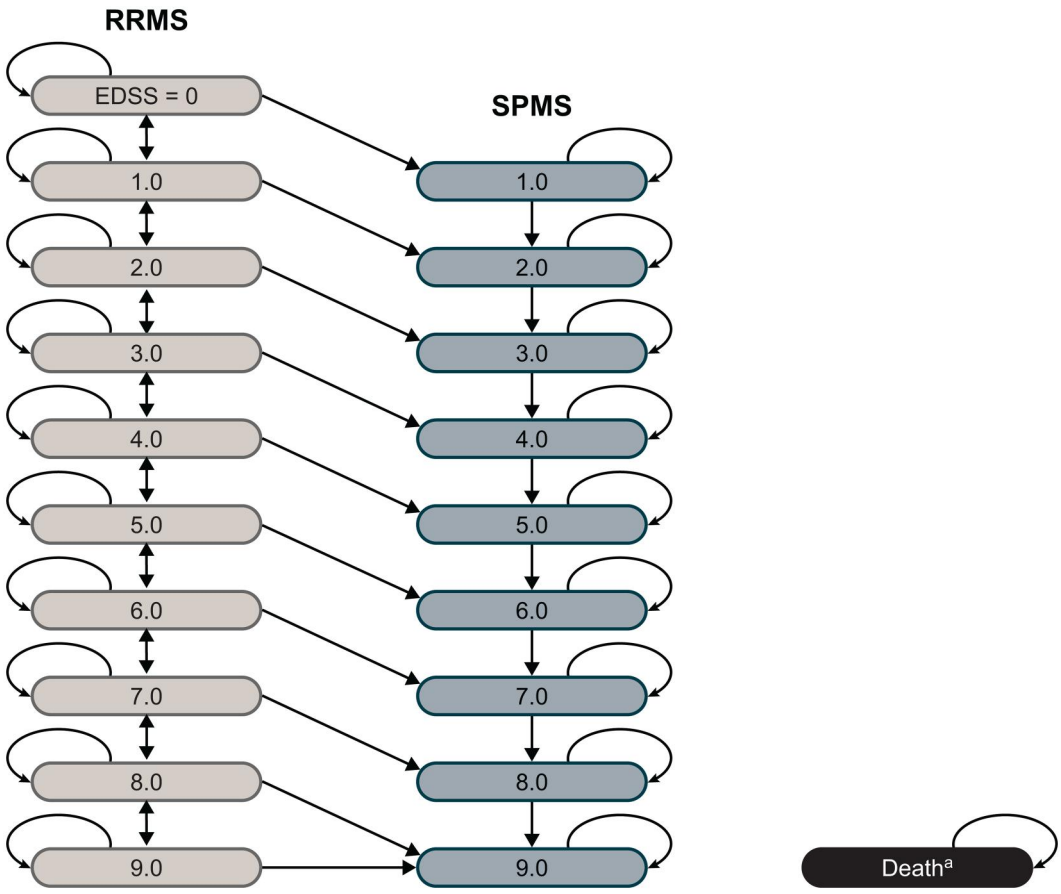

Figure 2. Model structure diagram for cost-effectiveness analysis. Abbreviations. EDSS, Expanded Disability Status Scale; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis. Note: EDSS changes of more than one level are permitted. [a]Death is reachable from all health states. Image modified under the Creative Commons 4.0 License and credited to Spelman, T., Herring, W.L., Zhang, Y. et al. Comparative Effectiveness and Cost-Effectiveness of Natalizumab and Fingolimod in Patients with Inadequate Response to Disease-Modifying Therapies in Relapsing-Remitting Multiple Sclerosis in the United Kingdom. PharmacoEconomics. 2022;40:323–339. https://doi.org/10.1007/s40273-021-01106-6.

observed in the MSBase data were scheduled treatment stops (e.g. maximum treatment durations), which are not consistent with the product labels for natalizumab and fingolimod in the UK. As such, discontinuation data from MSBase were not selected for the base case; however, the MSBase discontinuation probabilities with scheduled stops excluded were considered in scenario analysis (Table S11, Supplementary Material).

Other clinical data. The use of other clinical data for the base-case analysis was largely kept consistent with our previous analysis in patients with HA-RRMS.[18] Dosing regimens, including administration and monitoring requirements, for natalizumab (300 mg every 4 weeks) and fingolimod (0.5 mg daily) were based on publicly available information in alignment with previous analyses (Table S12, Supplementary Material). Annual discontinuation probabilities (Table 2) and AE incidence rates (Table S13, Supplementary Material), including for PML, were obtained from a synthesis of published clinical trial data[31–34] and other published literature[35,36] in alignment with our previous analysis.[18] Additionally, the model assumed treatment-stopping rules for progression to an EDSS score $\geq$ 7.0 and for conversion to SPMS, based on input from MSBase clinical experts. After stopping treatment, cohorts were assumed to progress according to natural history as described below. Alternative discontinuation probabilities, including real-world discontinuation from MSBase, were considered in scenario analysis.

Similar to our previous cost-effectiveness analysis in HA-RRMS,[18] the model used the EDSS transition probability matrix from the BCMS database[29] and ARRs by EDSS score from the placebo arm of the RES subpopulation from the AFFIRM study[30] after discontinuation of natalizumab or fingolimod until conversion to SPMS. Using a natural history dataset with patients meeting the RES criteria, such as the RES subpopulation from the placebo arm of the AFFIRM study, provided data that most closely matched the population of this analysis. Data from the London Ontario MS database[37] and from a previous cost-effectiveness analysis[30] were used for conversion to SPMS and for EDSS worsening and ARRs in SPMS, respectively. A constant standardized mortality ratio[38] of 2.88 (95% confidence interval [CI], 2.71–3.06) for patients with MS was applied multiplicatively to age- and sex-specific general population mortality probabilities from the UK.[39] Alternative mortality ratios by disease severity from an early study analyzing survival in patients with MS[40] were used in scenario analysis.

Cost and utility data. Annual acquisition, administration, and monitoring costs for natalizumab and fingolimod were

Table 2. Treatment-specific comparative effectiveness outcomes, costs, discontinuation rates, and adverse event outcomes used in the cost-effectiveness model.

	Natalizumab	Fingolimod
Comparative effectiveness outcomes (reference = BRACETD)[a]		
Mean years of follow-up (SD)	3.01 (2.26)	2.85 (1.93)
Rate ratio for ARR (95% CI)	0.46 (0.42-0.53)	0.72 (0.65-0.80)
Hazard ratio for CDW6M (95% CI)	1.01 (0.76-1.34)	0.84 (0.63-1.12)
Hazard ratio CDI6M (95% CI)	1.46 (1.16-1.85)	1.17 (0.91-1.50)
EDSS transition matrix for RRMS	See Table S8	See Table S9
ARRs by EDSS for RRMS	See Table S8	See Table S9
Treatment costs per year[b]		
Acquisition (all years)	£14,740.45	£19,175.63
Administration (year 1)	£3,348.52	£491.11
Administration (years 2+)	£3,348.52	£0.00
Monitoring (year 1)	£404.71	£762.34
Monitoring (years 2+)	£383.60	£411.93
Treatment discontinuation[c]		
Discontinuation per year	6.3%	10.3%
AE outcomes per year on treatment (weighted average including PML)[d]		
Costs	£149.05	£898.27
QALY decrement	0.0063	0.0073

Abbreviations. AE, adverse event; ARR, annualized relapse rate; BRACETD, interferon-based therapies, glatiramer acetate, teriflunomide, and dimethyl fumarate; CDI6M, 6-month–confirmed disability improvement; CDW6M, 6-month–confirmed disability worsening; CI, confidence interval; EDSS, Expanded Disability Status Scale; OWSA, one-way sensitivity analysis; PML, progressive multifocal leukoencephalopathy; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life-year; RRMS, relapsing-remitting multiple sclerosis; SD, standard deviation.

[a]Detailed comparative effectiveness outcomes, including uncertainty parameters and distributions for the OWSA and PSA, are presented in Figure 3 and in Tables S4–S10 (Supplementary Material).

[b]Acquisition costs (from UK list prices[41]) were varied in the OWSA only, while administration and monitoring costs (from resource utilization frequencies and standard UK unit costs[42–44,67,68]) were varied in the PSA and OWSA. See Table S12 (Supplementary Material) for the specific resources used and their unit costs. For all costs, a gamma distribution was used with the standard errors assumed to be 10% of the means.

[c]Discontinuation probabilities (derived from pivotal clinical trials for natalizumab[33] and fingolimod[31,32]) were varied in the OWSA and the PSA using a beta distribution (sample sizes for beta distribution: $N = 627$ for natalizumab; $N = 856$ for fingolimod).

[d]Source information, uncertainty parameters, and sampling distributions for AE incidence rates, AE costs per event, and AE QALY decrements per event are provided in Table S13 (Supplementary Material).

estimated from UK list prices[41] using treatment-specific resource utilization frequencies[42–44] (Table 2 and Table S12, Supplementary Material). Percentage reductions for the fingolimod acquisition price were considered in scenario analysis, as fingolimod, unlike natalizumab, is covered by a confidential patient access scheme in the UK.[45] Direct and indirect costs associated with MS management and relapses and patient utility values by EDSS score in RRMS and SPMS were estimated from participants in a 2015 UK MS burden-of-illness study (Table 3)[4,5] Reflecting the base-case third-party payer perspective, only direct costs were used in the base-case analysis. Direct costs and quality-adjusted life-year (QALY) decrements associated with AEs are presented in Table S13 (Supplementary Material). Indirect costs were used in a scenario analysis considering the societal perspective, which also included caregiver disutilities by EDSS score from the published literature.[46]

Analysis of uncertainty

One-way and probabilistic sensitivity analyses were conducted to assess the impact of parameter uncertainty on the base-case cost-effectiveness results. The probability distributions for each parameter type were selected in alignment with best practices.[47,48] The specific distributions and uncertainty parameters used in the sensitivity analyses are described in the detailed notes accompanying each input parameter table. Specifically, the one-way sensitivity analysis (OWSA) evaluated the impact of uncertainty in one parameter (or group of parameters) at a time by estimating the model outcomes at the lower and upper bounds of the corresponding 95% CIs. In contrast, the probabilistic sensitivity analysis (PSA) evaluated the joint impact of parameter uncertainty by estimating the model outcomes for 10,000 random samples drawn from the probability distributions. Deterministic scenario analyses were also conducted on alternative model settings, approaches to using the MSBase results, treatment discontinuation probabilities, and other data sources. Because there are limitations to interpreting negative incremental cost-effectiveness ratios, sensitivity, and scenario analysis results were presented using the net monetary benefit (NMB) outcome with a willingness-to-pay threshold of £30,000 per QALY gained.

Table 3. Direct costs and utility values associated with MS management and relapses.

EDSS score[c]	Direct costs[a]		Utility values/decrement[b]	
	RRMS	SPMS	RRMS	SPMS
MS Management	Annual costs		Utility values	
0	£504.55	£621.96	0.908	0.888
1.0	£917.73	£1,131.27	0.797	0.777
2.0	£4,770.43	£5,880.46	0.705	0.685
3.0	£3,781.73	£4,661.71	0.583	0.563
4.0	£3,594.10	£4,430.42	0.615	0.595
5.0	£5,017.36	£6,184.85	0.579	0.559
6.0	£9,933.61	£12,245.07	0.490	0.470
7.0	£15,943.92	£19,653.94	0.407	0.387
8.0	£28,745.04	£35,433.77	0.167	0.147
9.0	£35,736.87	£44,052.54	−0.101	−0.121
Relapses	Cost per event		Utility decrement per event	
All EDSS scores	£438.49	£438.49	0.013	0.013

Source: 2015 UK MS Burden-of-Illness Survey[4,5] (inflated from 2016 to 2021 Great British Pounds using the consumer price index for health[67]).

Abbreviations. EDSS, Expanded Disability Status Scale; MS, multiple sclerosis; OWSA, one-way sensitivity analysis; PSA, probabilistic sensitivity analysis; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis.

[a]Direct management and relapse costs by EDSS for both RRMS and SPMS were varied for the PSA and the OWSA using a gamma distribution with standard errors assumed to be 20.0% of the means.

[b]Utility values by EDSS for RRMS and SPMS without relapse were varied for the PSA and the OWSA using a lognormal distribution (as differences from 1 to allow for negative utility values), with standard errors assumed to be 20% of the means. Relapse utility decrements were varied for the PSA and the OWSA using a beta distribution, with standard errors assumed to be 20% of the means.

Validation

The validity of the cost-effectiveness modeling approach (face validity) and implementation (internal validity) was assessed previously in alignment with best practices, as described in Spelman et al.[18] In the present study, external validity was evaluated by comparing our results with previously published cost-effectiveness analyses,[49–51] including analyses for the RES-RRMS indication.[35,52,53]

Results

Comparative effectiveness analysis

Patient characteristics

Patient selection for the MSBase analysis is shown in Figure 1. Among the patients meeting the RES-RRMS criteria, 1,179 patients starting treatment with natalizumab, 854 patients starting treatment with fingolimod, and 4,768 patients starting treatment with a BRACETD therapy were identified in MSBase. The matching algorithm identified a total of 721 patient triplets (natalizumab, fingolimod, BRACETD) for inclusion in the analysis, with baseline characteristics well-balanced across treatment groups (Table 1). The mean (standard deviation) follow-up time (or treatment duration) was 3.01 (2.26) years for patients starting treatment with natalizumab, 2.85 (1.93) years for patients starting fingolimod, and 3.30 (3.21) years for patients starting a BRACETD therapy. Prior to starting the study treatments, 23.3%–23.9% of patients were naive to DMTs and over 70% of patients in each matched cohort were being treated with interferon-based therapies (48.7%–58.5%) or glatiramer acetate (12.8%–21.6%). Interferon-based therapies and glatiramer acetate also represented the majority (85.3%) among patients starting a BRACETD therapy (Table S2, Supplementary Material). Dimethyl fumarate and teriflunomide therefore represented a minority of less than 15% of the total patients in the BRACETD group.

Relapses

The ARR was significantly lower for patients starting treatment with natalizumab compared with patients starting treatment with fingolimod (RR = 0.65 [95% CI, 0.57–0.73]) or BRACETD (RR = 0.46 [95% CI, 0.42–0.53]). The ARR was also lower for patients starting treatment with fingolimod compared with those starting to treatment with BRACETD (RR = 0.72 [95% CI, 0.65–0.80]) (Figure 3(a)). We observed significant improvements in time to first relapse in patients starting treatment with natalizumab compared with patients starting treatment with fingolimod (HR = 0.63 [95% CI, 0.53–0.74]) or BRACETD (HR = 0.41 [95% CI, 0.36–0.48]). Additionally, starting treatment with fingolimod was associated with an improved time to first relapse compared with starting treatment with BRACETD (HR = 0.66 [95% CI, 0.57–0.76]) (Figure 3(b)). Tables S4–S7 in the Supplementary Material further describe the relapse analyses, including data maturity and results for the unmatched MSBase cohorts.

Treatment-specific ARRs by EDSS score were estimated from the matched MSBase cohorts for patients starting treatment with natalizumab, fingolimod, or BRACETD for use in the cost-effectiveness model (Tables S8–S10, Supplementary Material). The ARRs by EDSS score were directionally aligned with the overall ARR and time to first relapse analyses. Treatment-specific ARRs by EDSS score were also estimated for the unmatched MSBase cohorts (estimates not shown) for use in cost-effectiveness scenario analysis.

Disability worsening and improvement

There were no significant differences in the rates of CDW6M between all 3 groups (Figure 3(c)). The rate of CDI6M for patients starting natalizumab was significantly higher compared with fingolimod (HR = 1.25 [95% CI, 1.01–1.55]) and BRACETD (HR = 1.46 [95% CI, 1.16–1.85]); the rate of CDI6M for patients starting or switching to fingolimod did not differ significantly from the CDI6M rate for BRACETD (HR = 1.17 [95% CI, 0.91–1.50]) (Figure 3(d)). Further details on the disability worsening and improvement analyses, including 3-month confirmation results, data maturity, and results for the unmatched MSBase cohorts are available in Tables S4–S7 of the Supplementary Material.

Treatment-specific EDSS transition probability matrices were estimated for each matched MSBase treatment cohort for use in the cost-effectiveness analysis (Tables S8–S10, Supplementary Material). These treatment-specific EDSS transition probability matrices reflect the impact of starting natalizumab, fingolimod, or BRACETD on the annual probabilities of transitioning between EDSS scores in RRMS. We also estimated EDSS transition probability matrices for the unmatched MSBase cohorts for use in scenario analysis (estimates not shown).

Cost-effectiveness analysis

Base-case analysis

The distribution of patients across health states over time for the natalizumab and fingolimod treatment cohorts in the base-case cost-effectiveness analysis is shown in Figure S2 (Supplementary Material). The clinical benefits observed in the comparative effectiveness analysis in patients with RES-RRMS treated with natalizumab translated to fewer lifetime relapses (26.26 vs. 28.42 [undiscounted]) and higher QALYs (7.86 vs. 7.56 [discounted]) compared with fingolimod (Table 4). The base-case cost-effectiveness analysis assumed that the only parameters impacting mortality differently between the natalizumab and fingolimod treatment cohorts were the incidence of PML and deaths due to PML. The relatively higher risk of PML associated with natalizumab led to a minor difference in life-years observed between the 2 treatment options (0.11 fewer life-years for natalizumab compared with fingolimod) (Table 4).

Patients starting treatment with natalizumab were predicted to have higher treatment-related direct costs than patients starting fingolimod (£92,502 vs. £89,525) owing to a longer time spent on treatment (5.61 years vs. 4.43 years) (Table 4). However, the higher treatment-related costs for natalizumab were offset by the reduction in disease management and relapse costs associated with the improved health outcomes for natalizumab. Overall, patients starting natalizumab were predicted to have lower overall direct costs than patients starting fingolimod (£492,341 vs £509,482). Taken together, the higher predicted lifetime QALYs (0.302 higher per patient) and lower predicted lifetime costs (£17,141 lower per patient) for natalizumab indicated that natalizumab dominated fingolimod in the base-case cost-effectiveness analysis. At a willingness- to-pay threshold of £30,000

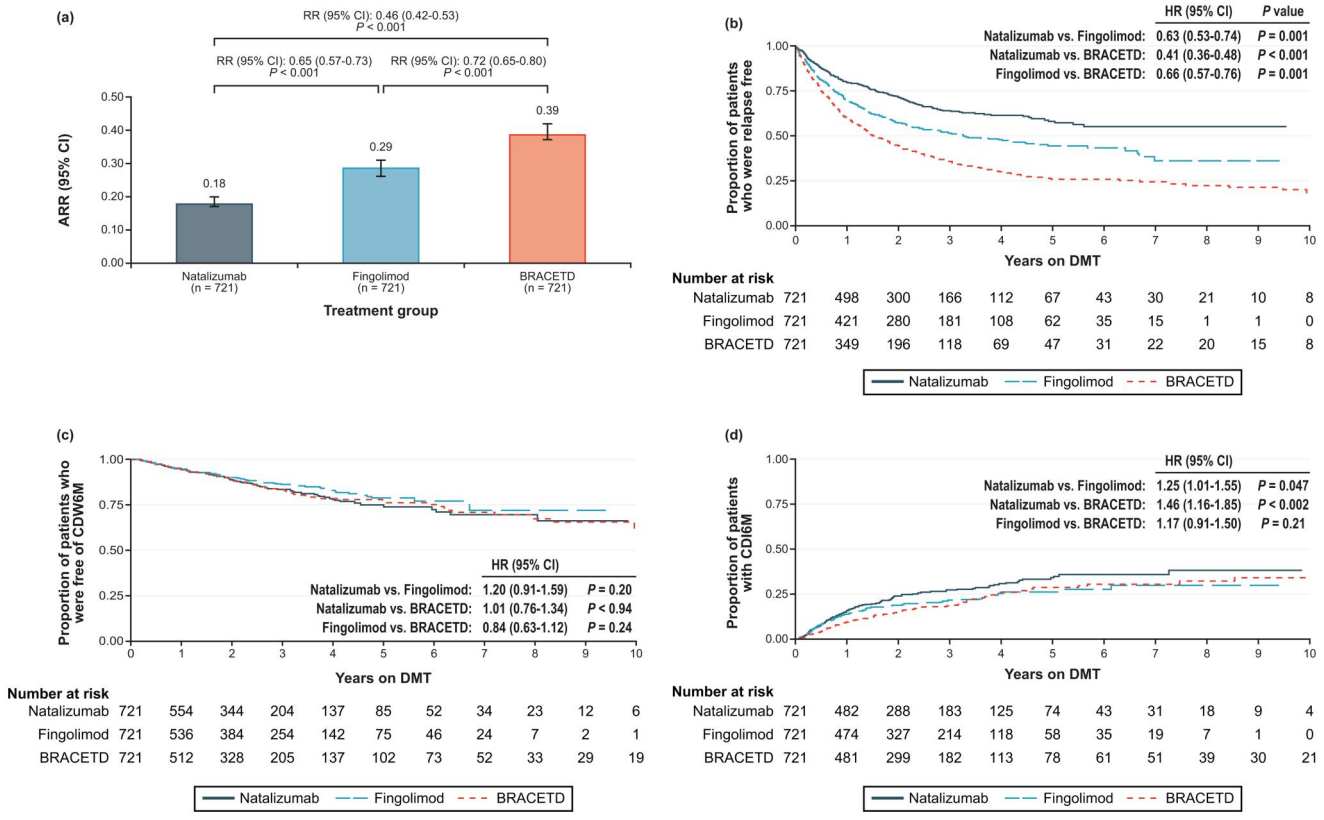

Figure 3. Comparative effectiveness analysis results for natalizumab and fingolimod compared with BRACETD. Abbreviations. ARR, annualized relapse rate; BRACETD, interferon-based therapies, glatiramer acetate, teriflunomide, and dimethyl fumarate; CDI6M, 6-month–confirmed disability improvement; CDW6M, 6-month–confirmed disability worsening; CI, confidence interval; DMT, disease-modifying therapy; HR, hazard ratio; RR, rate ratio. Note: The comparison of natalizumab with fingolimod is presented for context only and is not used in the cost-effectiveness model.

Table 4. Base-case natalizumab versus fingolimod cost-effectiveness analysis results.

Outcomes per patient	Natalizumab	Fingolimod	Incremental (%)
Expected health outcomes			
Time on treatment (years)	5.61	4.43	1.179 (26.6)
Number of relapses (undiscounted)	26.26	28.42	−2.165 (−7.6)
LYs	20.50	20.60	−0.107 (−0.5)
QALYs	7.86	7.56	0.302 (4.0)
Expected cost outcomes			
Direct, treatment-related	£92,502	£89,525	£2,977 (3.3)
Direct, MS management	£392,857	£409,133	−£16,276 (−4.0)
Direct, relapses	£6,145	£6,844	−£699 (−10.2)
Direct, adverse events	£836	£3,979	−£3,143 (−79.0)
Total direct costs	£492,341	£509,482	−£17,141 (−3.4)
Cost-effectiveness outcomes			
Incremental cost per QALY gained	−£56,725	Natalizumab dominates fingolimod	
NMB at £30,000 per QALY gained	£26,206		

Abbreviations. CE, cost-effectiveness; LY, life-year; MS, multiple sclerosis; NMB, net monetary benefit; QALY, quality-adjusted life-year.

per QALY gained, the base-case NMB was estimated at £26,206 (Table 4).

Sensitivity and scenario analyses

Sensitivity and scenario analysis results are presented in Figures 4 and S3 (Supplementary Material), respectively. Natalizumab remained dominant over fingolimod for all the parameters varied in the OWSA (Figure 4(a) and Table S14, Supplementary Material) and for 94.3% of the 10,000 iterations included in the PSA (Figure 4(b)).

In the scenario analysis considering potential fingolimod patient access scheme discounts, natalizumab remained dominant with up to a 20.2% discount in the fingolimod list price. Additionally, natalizumab remained cost-effective with fingolimod discounts up to 27.3% and 30.9% at willingness-to-pay thresholds of £20,000 per QALY gained and £30,000 per QALY gained, respectively (Figure S3, Supplementary Material).

We performed additional scenario analyses to explore the impact of alternative model settings, approaches to using the MSBase results, discontinuation probabilities, and other data sources. Natalizumab remained dominant over fingolimod in all of the scenario analyses considered (Table S15, Supplementary Material). In scenarios considering alternative model settings, shortening the modeling time horizon and

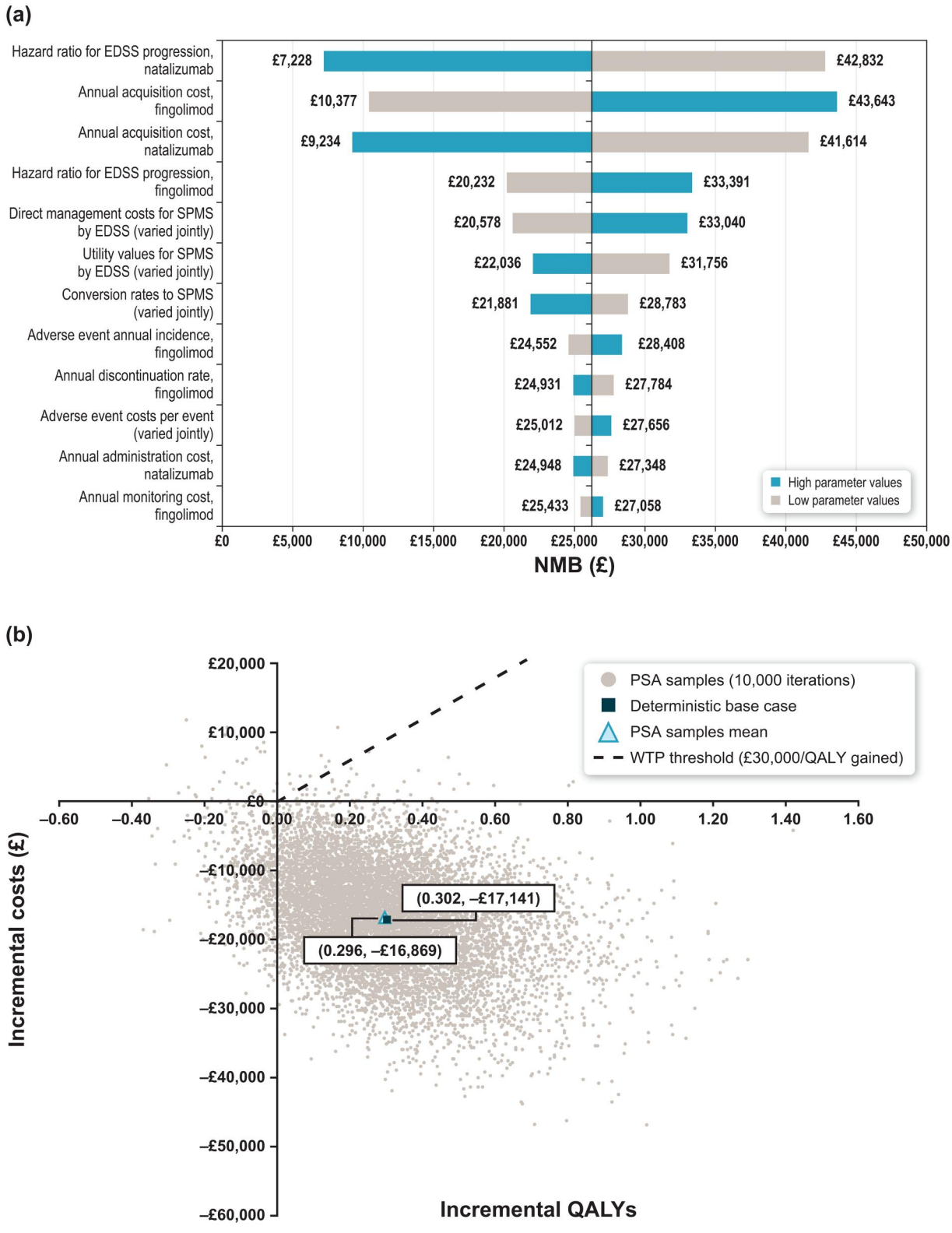

Figure 4. One-way and probabilistic sensitivity analysis results for cost-effectiveness analysis. Abbreviations. EDSS, Expanded Disability Status Scale; NMB, net monetary benefit; OWSA, one-way sensitivity analysis; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life-year; SPMS, secondary progressive multiple sclerosis; WTP, willingness to pay. Note: OWSA results are presented in panel a using the NMB outcome with a WTP threshold of £30,000 per QALY gained. Results of the PSA are presented in panel b.

increasing the annual discount rate yielded lower incremental QALYs and cost savings, whereas decreasing the annual discount rate yielded higher incremental QALYs and cost savings. The inclusion of caregiver disutilities in the analysis increased incremental QALYs, while consideration of a full societal perspective also increased the cost savings associated with natalizumab. Using data from the unmatched MSBase cohorts for baseline RRMS estimates and treatment

effectiveness resulted in higher incremental QALYs and increased cost savings. Incremental QALYs and cost savings were lower when comparative effectiveness–adjusted EDSS transition matrices and ARRs were used exclusively and higher when only treatment-specific EDSS transition matrices and ARRs were used. Modeling treatment effectiveness using 3-month confirmation of EDSS score changes did not meaningfully impact model outcomes. Applying uniform treatment discontinuation probabilities for both natalizumab and fingolimod decreased the clinical benefit of natalizumab, as evidenced by reduced incremental QALYs, while increasing cost savings. In exploratory scenario analyses using real-world discontinuation data from MSBase with scheduled treatment stops excluded, natalizumab remained dominant compared with fingolimod. Finally, considering alternative mortality data by EDSS score and using cost and utility data from the 2005 burden-of-illness survey both resulted in increased incremental QALYs but decreased cost savings (Table S15, Supplementary Material).

Discussion

The present economic evaluation of natalizumab as a treatment option for patients with RES-RRMS builds on the innovative approach of our previous analysis in patients with HA-RRMS[18] by tailoring a real-world comparative effectiveness analysis to the requirements of cost-effectiveness modeling in MS. Consistent with our previous findings, the results of this study suggest that natalizumab improves both clinical and economic outcomes when compared with fingolimod in patients with RES-RRMS. Taken together, these two partner analyses provide a comprehensive picture of the real-world value of natalizumab in the UK across the HA-RRMS and RES-RRMS indications.

The comparative effectiveness analysis conducted in this study indicated significant improvements in disability and reduced relapse rates in patients with RES-RRMS starting treatment with natalizumab compared with those starting fingolimod or BRACETD. Patients on natalizumab experienced a 25% increase in the rate of CDI6M and a 35% decrease in ARR compared with patients on fingolimod. In agreement with these findings, the results of other RWD studies[54–57] and trial-based indirect treatment comparisons[58] suggest that natalizumab offers higher effectiveness, as evidenced by improved relapse rates and disability control, compared with fingolimod in patients with clinically active RRMS. It is notable that many of the RWD studies published to date report a mean of less than 2 relapses in the previous year. Two publications, however, reported a mean number of relapses above 2 in the prior year,[59,60] which is closer to the current study population with regards to baseline relapse activity. The results of both of these studies indicated that, overall, natalizumab compared favorably to fingolimod regarding relapse and disability-based outcomes,[59,60] consistent with the results currently presented. Lastly, our comparative effectiveness results indicated a decreased ARR and improved time to first relapse in patients starting fingolimod compared with patients starting BRACETD, corroborating the results of previously published RWD analyses comparing fingolimod to injectable-based first-line treatments (interferon-based therapies and glatiramer acetate).[61,62] In the present analysis, dimethyl fumarate and teriflunomide represented a small proportion of the BRACETD group (<15%). Previous studies have shown comparable effectiveness for dimethyl fumarate and fingolimod;[63,64] however, the proportion of dimethyl fumarate within the BRACETD group in our analysis may have been insufficient to influence the results of the overall BRACETD group compared with fingolimod.

The clinical benefits estimated from MSBase in the present study translated to improved long-term outcomes and disease-related costs in the cost-effectiveness analysis. Despite the higher treatment-related costs of natalizumab associated with a longer time on treatment, there were substantial savings in nontreatment-related costs, which were attributable to improved health outcomes. Consequently, natalizumab dominated fingolimod in the base-case cost-effectiveness analysis, with 0.302 higher predicted lifetime QALYs and £17,141 lower predicted lifetime costs per patient. This equated to an NMB of £26,206 at a willingness-to-pay threshold of £30,000 per QALY gained. These results are consistent with the findings of other studies comparing the cost-effectiveness of natalizumab and fingolimod in the RRMS population.[35,49,-52] While cost-effectiveness analyses specifically in patients with RES-RRMS are limited, an analysis in Sweden similarly found that natalizumab dominates fingolimod[52] and a UK-based study found that natalizumab was cost-effective in comparison with fingolimod at UK list prices.[35] However, both of these prior RES-RRMS cost-effectiveness analyses relied on clinical trial efficacy data instead of real-world effectiveness data.

The analyses conducted in this study have several limitations typical of RWD analyses and economic evaluations. First, these analyses are subject to the limitations of a real-world registry such as MSBase, including the representativeness of the RES-RRMS cohorts identified in MSBase to the UK RES-RRMS population and any potential bias associated with unmeasured confounding variables (e.g. lack of MRI data) between the MSBase cohorts after 3-way propensity score matching. Another limitation associated with the use of the MSBase analysis is the duration of follow-up and consequent reliance on extrapolation beyond the observed follow-up period, which was required to estimate clinical and economic outcomes over a lifetime horizon. Additionally, while the analyses presented in this study predominantly used contemporary RWD sources, the clinical data for higher EDSS scores and SPMS were derived from older databases[29,30,37] and the base-case treatment discontinuation and AE incidence data were taken from pivotal clinical trials.[31–33] As highlighted by the scenario analyses conducted for the cost-effectiveness analysis, relying on RWD for treatment discontinuation probabilities for natalizumab and fingolimod introduces uncertainty due to scheduled treatment stops (i.e. maximum treatment durations), which are not consistent with the product labels for natalizumab and fingolimod in the UK. The UK-specific cost data for our analysis were drawn from multiple sources, which may introduce some limited uncertainty in the predicted cost-

effectiveness results. Finally, the analysis does not include other recently approved DMTs (e.g. alemtuzumab, cladribine, and ocrelizumab) as potential comparators for natalizumab because of sample size limitations within MSBase at the time of the analysis. As additional data on the real-world effectiveness of these alternative comparators become available, broader assessments of the economic value of DMTs in the RES-RRMS population may be conducted.

Clinical data used in the comparative effectiveness analysis were sourced from MSBase, an international registry that included approximately 68,000 patients on the date of data extraction in August 2019. While MSBase included patient data from the UK, the sample size was insufficient to conduct a UK-specific MSBase analysis. Thus, factors such as patient characteristics and variability in real-world clinical practice between countries may limit the generalizability of our analyses to the UK RES-RRMS population. In contrast, the inputs included in the cost-effectiveness analysis in this study were specific to the UK. Cost-effectiveness analyses are often country-specific, limiting the generalizability of the predicted economic outcomes to other settings, as inputs such as resource utilization and healthcare costs may vary significantly between countries.

Finally, we have seen continuously increasing use of natalizumab extended interval dosing, where natalizumab is administered less frequently (approximately every 6 weeks) to reduce the risk of PML instead of the approved dosing every 4 weeks.[65,66] Moreover, in the beginning of 2021, a new subcutaneous formulation of natalizumab was approved in Europe. Both of these events could reduce the cost of natalizumab beyond what is reflected in this analysis, potentially leading to further improvements in the cost-effectiveness of natalizumab in comparison with fingolimod.

Conclusion

In summary, the results of this study suggest that starting treatment with natalizumab improves both clinical and economic outcomes in patients with RES-RRMS compared with starting treatment with fingolimod, from a UK National Health Service perspective. This evaluation provides additional evidence of the value of natalizumab as a treatment option for patients with RES-RRMS and complements the existing body of literature to consider in healthcare decision-making. Taken together with our previous analysis in patients with HA-RRMS, these 2 partner analyses complete the picture of the real-world value of natalizumab in the UK across the HA-RRMS and RES-RRMS indications. Furthermore, these studies represent the first analyses modeling treatment effectiveness using the results of a real-world comparative effectiveness analysis conducted in alignment with established health economic modeling requirements in MS.

The results of this study, together with other real-world clinical and economic evidence emerging in the literature, can be used to inform discussions on how to optimize the use of limited healthcare resources to maximize the health of the population. Healthcare policy decisions should be continuously revisited to ensure they are reflecting the most recent evidence. This also requires a careful consideration of the quality of the data generated, its applicability to a given healthcare system, and the implications that may arise from changing healthcare policy decisions with the aim of improving the quality of life of the people with MS and their caregivers.

Transparency

Declaration of funding

This research was supported by Biogen International GmbH (Baar, Switzerland). RTI Health Solutions, an independent nonprofit research organization, received funding under a research contract with Biogen International GmbH to conduct the cost-effectiveness analysis and provide publication support in the form of manuscript writing, styling, and submission. MSBase receives general financial support from Biogen, Genzyme, Merck (MSD), Merck Serono, Novartis, Roche, and Teva.

Declaration of financial/other relationships

TS is a statistical contractor for the MSBase Foundation and has received compensation for serving on steering committees and advisory boards for Biogen.

WLH is an employee of RTI Health Solutions, an independent nonprofit research organization, which received funding pursuant to a contract with Biogen.

CA is an employee of Biogen and holds shares or stocks from Biogen as part of his remuneration.

RH was an employee and shareholder of Biogen at the time of the conduction of the research and data analysis for this project.

VJ is an employee of Monash University; she receives research grant support from the National Health and Medical Research Council of Australia, MS Research Australia and F.Hoffmann-La Roche.

EP has received equipment from "Associazione Marchigiana Sclerosi Multipla e altre malattie neurologiche."

AL has received personal compensation for consulting, serving on a scientific advisory board, speaking or other activities from Alexion, Biogen, Bristol Myers Squibb, Janssen, Merck Serono, Novartis, and Sanofi/Genzyme. Her institutions have received research grants from Novartis and Sanofi/Genzyme.

GL has received travel and/or consultancy compensation from Sanofi-Genzyme, Roche, Teva, Merck, Novartis, Celgene, Biogen.

RG did not declare any conflict of interest.

EKH has received honoraria and research support from Biogen, Merck Serono, Novartis, Roche, and Teva; has served in advisory boards for Actelion, Biogen, Celgene, Merck Serono, Novartis, and Sanofi Genzyme; and has been supported by the Czech Ministry of Education research project Cooperatio LF1 and National Institute for Neurological Research (Programme EXCELES, ID project No LX22NPO5107) funded by the European Union-Next Generation EU.

DH was supported by the Charles University: Cooperatio Program in Neuroscience by the project National Institute for Neurological Research (Programme EXCELES, ID Project No. LX22NPO5107) funded by the European Union – Next Generation EU, and by General University Hospital in Prague project MH CZ-DRO-VFN64165. She also received compensation for travel, speaker honoraria and consultant fees from Biogen Idec, Novartis, Merck, Bayer, Sanofi Genzyme, Roche, and Teva, as well as support for research activities from Biogen Idec.

SE received speaker honoraria and consultant fees from Bristol Meyers, Novartis, Biogen, Roche, Teva, Janssen, Merck, and Sanofi.

SO did not declare any conflict of interest.

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

TK has served on scientific advisory boards for the MS International Federation and the World Health Organization, Bristol Myers Squibb, Roche, Janssen, Sanofi Genzyme, Novartis, Merck and Biogen and the steering committee for the Brain Atrophy Initiative by Sanofi Genzyme; received conference travel support and/or speaker honoraria from WebMD Global, Eisai, Novartis, Biogen, Roche, Sanofi-Genzyme, Teva, BioCSL and Merck; and received research or educational event support from Biogen, Novartis, Genzyme, Roche, Celgene and Merck.

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

MG has received consulting fees from Teva Canada Innovation, Biogen, Novartis and Genzyme Sanofi, and lecture payments from Teva Canada Innovation, Novartis and EMD. He has also received a research grant from Canadian Institutes of Health Research.

TP has received funding from Biogen, Merck, Novartis, Sanofi-Aventis, Roche, and Genzyme.

FP has received personal compensation for serving on advisory boards for Almirall, Alexion, Biogen, Bristol, Merck, Novartis, and Roche, and research grants from Biogen, Merck, Roche, FISM, Reload Association (Onlus), the Italian Health Ministry, and the University of Catania.

TC has received speaker honoraria and conference travel support from Bayer Schering, Biogen, Merck, Novartis, Roche, Sanofi-Aventis, and Teva.

FG has received an institutional research grant from Roche; served on scientific advisory boards for Biogen, Novartis, Merck, Sanofi, and Roche; and received funding for travel and speaker honoraria from Biogen, Merck, Sanofi, and BMS.

FGH has received honoraria or research funding from Biogen, Genzyme, Novartis, Teva Neuroscience, and ATARA Pharmaceuticals.

DF has received travel grants and/or speaker honoraria from Merck, TEVA, Novartis, Biogen and Sanofi-Genzyme.

RK has received consulting fees, payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events, support for attending meetings and/or travel, and participation on a data safety monitoring board or advisory board from Gen Turkey.

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

MT has received consulting fees and speaker honoraria from Biogen, Novartis, Roche, Merck, Bristol Myers Squibb, and Genzyme, and has received research grants for her Institution from Biogen, Merck, Novartis, and Roche.

VVP received travel grants from Merck Healthcare KGaA (Darmstadt, Germany), Biogen, Sanofi, Bristol Meyer Squibb, Almirall and Roche. His institution has received research grants and consultancy fees from Roche, Biogen, Sanofi, Merck Healthcare KGaA (Darmstadt, Germany), Bristol Meyer Squibb, Janssen, Almirall, Novartis Pharma, and Alexion.

BVW has received research and travel grants, honoraria for MS-Expert advisor, and speaker fees from Almirall, Biogen, BMS, Imcyse, Janssen, Sanofi, Merck, Novartis, Roche and Teva.

EC did not declare any conflict of interest.

PM has received speaker fees and travel grants from Novartis, Biogen, T'évalua, and Sanofi.

Oliver Gerlach did not declare any conflict of interest.

DS has received honoraria as a consultant on scientific advisory boards by Bayer-Schering, Novartis and Sanofi-Aventis, and compensation for travel from Novartis, Biogen, Sanofi Aventis, Teva, and Merck.

CR has received speaker honoraria from Bayer Schering, Novartis, and Biogen, and congress and travel expense compensations from Biogen, Teva, Merck and Bayer Schering.

SH has received consulting fees from Biogen, Novartis, Roche, Merck. Her institution has received grants from Biogen, Merck, Novartis and Roche.

RB has received speaker honoraria from Biogen, Sanofi, Merck, Novartis, Roche, Janssen, and Bristol Myers Squibb; research grants from Biogen, Merck, Novartis, Roche, and Sanofi; and congress and travel compensations from Biogen, Merck, Novartis, Sanofi, Roche, Janssen, and Bristol Myers Squibb.

AS did not declare any conflict of interest.

TCT has received speaker, consulting fees and/or travel funding from Almirall, Biogen, Bristol Myers Squibb, Janssen, Merck, Novartis, Roche, Sanofi-Genzyme and Teva.

JP has received travel compensation from Novartis, Biogen, Genzyme, Teva, and speaking honoraria from Biogen, Novartis, Genzyme and Teva.

JG has received conference travel support from Roche and Merck, speaker honoraria from Biogen, and research support from Roche.

KG served on scientific advisory boards for Roche, Janssen, Sanofi-Genzyme, Novartis and Merck. Additionally, he has received conference fee and travel support from Novartis, Biogen, Sanofi-Genzyme, Teva, Abbvie and Merck and received educational event support from Novartis.

RA has received conference travel support from Novartis, Teva, Biogen, Bayer, and Merck, and has participated in clinical trials by Biogen, Novartis, Teva and Actelion.

MS has received speaker honoraria from Novartis, Biogen, Bayer Schering, Sanofi, Merck, and Roche, and congress/travel compensation from Teva, Biogen, Merck, Bayer Schering, Novartis, and Roche.

JLSM has accepted travel compensation from Merck, and Biogen; speaker honoraria from Novartis, Sanofi and Merck; and has participated in Data Safety Monitoring Board or Advisory Board by Merck, Sanofi and Novartis.

GI has received congress and travel compensation from Bayer Schering, Biogen, Merck, Novartis, Sanofi Aventis, and Teva.

AS no conflicts of interest.

AVDW has served on advisory boards and receives unrestricted research grants from Novartis, Biogen, Merck and Roche. She has received speaker's honoraria and travel support from Novartis, Roche, and Merck. She receives grant support from the National Health and Medical Research Council of Australia and MS Research Australia.

NJ has received funding for commercial MS studies sponsored by Novartis, Roche, Biogen, and Sanofi. He has received speaker's honoraria from Merck. He has had conference travel and registration reimbursement from Novartis.

OG has received honoraria as consultant on scientific advisory boards for Genzyme, Biogen, Merck, Roche, and Novartis; has received travel grants from Biogen, Merck, Roche, and Novartis; has participated in clinical trials by Biogen and Merck. Her institution has received research grant support from Biogen.

SH has received unrestricted educational grants or speaker honoraria from Biogen, Merck Serono, Novartis, Roche, and Sanofi Genzyme.

GDL has served on scientific advisory boards for Merck, Biogen, Novartis, Roche, and Sanofi Genzyme and has received funding for travel and speaker honoraria from Biogen, Merck, Novartis, Sanofi Genzyme, and Roche.

GI has received speaking honoraria from Almirall, Biogen, Merck, Novartis, Roche, Sanofi, and Teva.

KB has received speaker honoraria and/or education support from Biogen, Teva, Novartis, Genzyme-Sanofi, Roche, Merck and Alexion; has been a member of advisory boards for Merck and Biogen.

OS has received honoraria and consulting fees from Bayer Schering, Novartis, Merck, Biogen, and Genzyme.

MT has received travel grants from Merck, Novartis, Bayer-Schering, and Teva and has participated in clinical trials by Sanofi-Aventis, Roche, and Novartis.

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

CS has served on scientific advisory boards for Merck, Genzyme, Almirall, and Biogen and has received honoraria and travel grants from Sanofi Aventis, Novartis, Biogen, Merck, Genzyme, and Teva.

COG has received honoraria as a consultant on scientific advisory boards or as speaker from Biogen, Celgene-BMS, Janssen, Merck, Novartis, Roche, Sanofi-Genzyme, Sandoz, TEVA and Viatris.

CRT has received consulting fees, speaker honoraria, suport for attending meetings and/or travel, participation on advisory board and research grants for her institution from Biogen, Novartis, Sanofi, Bristol, Roche, Almirall, Janssen, Sandoz and Merck.

YF received honoraria as a consultant on scientific advisory boards by Novartis, Teva, Roche, and Sanofi-Aventis and compensation for travel from Novartis, Biogen, Sanofi Aventis, Teva, Roche, and Merck.

VS did not declare any conflict of interest.

FM has participated in clinical trials sponsored by EMD Serono and Novartis.

CR participated as clinical investigator and/or received consultation and/or speaker fees and/or conference travel grants from: Biogen, Merck, Novartis, Sanofi Genzyme, Roche, Teva.

EAM has received honoraria as a speaker from Biogen, Merck, Novartis and Sanofi-Genzyme and for serving on scientific advisory boards from Novartis.

HB is an employee of Monash University and has received institutional funding (Monash University) from Biogen, F. Hoffmann-La Roche Ltd, Merck, Alexion, CSL, and Novartis; has carried out contracted research for Novartis, Merck, F. Hoffmann-La Roche Ltd, and Biogen; and has taken part in speakers' bureaus for Biogen, Genzyme, UCB, Novartis, F. Hoffmann-La Roche Ltd, and Merck. Has received personal compensation from Oxford Health Policy Forum for the Brain Health Steering Committee.

Author contributions

The comparative effectiveness study was conducted by MSBase. TS and HB conducted and supervised the analysis of the MSBase Registry data, respectively. The remaining MSBase-affiliated authors contributed to the collection and interpretation of the data.

The cost-effectiveness study was conducted by RTI Health Solutions. WLH developed the cost-effectiveness model, identified country-specific non-clinical inputs, and contributed to the interpretation of analytical results.

CA and RH supervised the study for both the clinical and cost-effectiveness analysis.

Both MSBase and RTI Health Solutions operated under separate research contracts with Biogen and were funded by Biogen International GmbH.

All authors reviewed the data and contributed to the final interpretation of results.

Acknowledgements

This manuscript is dedicated to our valued colleague Yara Fragoso who sadly passed away during the development of this manuscript. The authors would like to acknowledge Mattia Gianinazzi, Biogen International GmbH, for his contributions to this study. The authors would also like to acknowledge the following MSBase Registry contributors: Alexandre Prat, Pierre Grammond, Cavit Boz, Jeannette Lechner-Scott, Patrizia Sola, Recai Turkoglu, Michael Barnett, Saloua Mrabet, Ricardo Fernandez Bolaños, Krisztina Kovacs, Imre Piroska, Maria Edite Rio, Cees Zwanikken, Magd Zakaria, Eniko Dobos, Jabir Alkhaboori, Liesbeth Van Hijfte, Erik van Munster, Tunde Erdelyi, Gabor Rum, Edgardo Cristiano, Nevin Shalaby, Angel Perez Sempere, Jose Andres Dominguez, Ilya Kister, Norma Deri, Mike Boggild, Jens Kuhle, Anita Trauninger, Istvan Deme, Ayse Altintas, Jihad Inshasi, Maria Laura Saladino, Marcos Burgos, Neil Shuey, Jamie Campbell, and Dheeraj Khurana. The authors thank Cassondra Saande, Emily Gill, and Bethan Pickering of RTI Health Solutions for medical writing and graphical design assistance. Biogen International GmbH provided funding for publication support in the form of manuscript writing, styling, and submission.

Data availability statement

The clinical data analyzed for this study were obtained under a license agreement with MSBase (www.msbase.org). However, no patient-level data were disclosed as part of the study. Therefore, all data relevant to the study have been presented in the article and supplementary materials.

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

Previous presentation

Portions of this research were presented virtually in poster format at the 8th Joint Americas Committee for Treatment and Research in Multiple Sclerosis - European Committee for Treatment and Research in Multiple Sclerosis (ACTRIMS-ECTRIMS) Meeting from September 11-13, 2020.

Ethics approval and consent

Informed consent from all patients according to local laws is required for participation in MSBase, and the project has received human research ethics committee approval or exemption at each contributing center.

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References

[1] Bainbridge JR, Corboy JR. Multiple sclerosis. In: Dipiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey ML, editors. Pharmacotherapy: a pathophysiologic approach. 7th ed. New York: McGraw-Hill Companies, Inc.; 2008.

[2] Barbin L, Rousseau C, Jousset N, et al. Comparative efficacy of fingolimod vs natalizumab: a french multicenter observational study. Neurology. 2016;86(8):771–778. doi: 10.1212/WNL.0000000000002395.

[3] Baroncini D, Ghezzi A, Annovazzi PO, et al. Natalizumab versus fingolimod in patients with relapsing-remitting multiple sclerosis non-responding to first-line injectable therapies. Mult Scler. 2016; 22(10):1315–1326. doi: 10.1177/1352458516650736.

[4] Bebo B, Cintina I, LaRocca N, et al. The economic burden of multiple sclerosis in the United States: estimate of direct and indirect costs. Neurology. 2022;98(18):e1810–e1817. doi: 10.1212/WNL.0000000000200150.

[5] Biogen Idec UK. Natalizumab (tysabri) for the treatment of adults with highly active relapsing remitting multiple sclerosis. Single Technology Appraisal (STA) Submission to the National Institute for Health and Clinical Excellence. NICE Manufacturer's Submission. 2007.

[6] Bozkaya D, Livingston T, Migliaccio-Walle K, et al. The cost-effectiveness of disease-modifying therapies for the treatment of relapsing-remitting multiple sclerosis. J Med Econ. 2017;20(3): 297–302. doi: 10.1080/13696998.2016.1258366.

[7] Braune S, Lang M, Bergmann A. Efficacy of fingolimod is superior to injectable disease modifying therapies in second-line therapy of relapsing remitting multiple sclerosis. J Neurol. 2016;263(2): 327–333. doi: 10.1007/s00415-015-7970-6.

[8] Briggs A, Claxton K, Sculpher M. Decision modelling for health economic evaluation. Oxford: Oxford University Press; 2006.

[9] Briggs AH, Weinstein MC, Fenwick EA, et al. Model parameter estimation and uncertainty analysis: a report of the ISPOR-SMDM modeling good research practices task force working group-6. Med Decis Making. 2012;32(5):722–732. doi: 10.1177/0272989X12458348.
[10] British National Formulary. Medicines complete. 2021 [cited 2021 Nov 2]. Available from: https://www.medicinescomplete.com/mc/bnf/current/.
[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(6):769–774. doi: 10.1177/1352458506070775.
[12] Calabresi PA, Radue EW, Goodin D, et al. Safety and efficacy of fingolimod in patients with relapsing-remitting multiple sclerosis (FREEDOMS II): a double-blind, randomised, placebo-controlled, phase 3 trial. Lancet Neurol. 2014;13(6):545–556. doi: 10.1016/S1474-4422(14)70049-3.
[13] Cohen JA, Barkhof F, Comi G, et al. Oral fingolimod or intramuscular interferon for relapsing multiple sclerosis. N Engl J Med. 2010;362(5):402–415. doi: 10.1056/NEJMoa0907839.
[14] Confavreux C, Vukusic S. Natural history of multiple sclerosis: a unifying concept. Brain. 2006;129(Pt 3):606–616. doi: 10.1093/brain/awl007.
[15] Craig BA, Sendi PP. Estimation of the transition matrix of a discrete-time markov chain. Health Econ. 2002;11(1):33–42. doi: 10.1002/hec.654.
[16] Curtis L, Burns A. Unit costs of health and social care 2020. Personal Social Services Research Unit; 2020.
[17] Electronic Medicines Compendium. Last medicine updates. 2022 [cited 2022 August 11]. Available from: https://www.medicines.org.uk/emc/.
[18] European Medicines Agency. Guideline on clinical investigation of medicinal products for the treatment of multiple sclerosis. March 31, 2015; [cited 2019, March 30] Available from: https://www.ema.europa.eu/en/clinical-investigation-medicinal-products-treatment-multiple-sclerosis.
[19] European Medicines Agency. Tysabri product information. June 8, 2022; [cited 2023, January 12]. Available from: https://www.ema.europa.eu/en/documents/product-information/tysabri-epar-product-information_en.pdf.
[20] Gani R, Giovannoni G, Bates D, et al. Cost-effectiveness analyses of natalizumab (tysabri) compared with other disease-modifying therapies for people with highly active relapsing-remitting multiple sclerosis in the UK. Pharmacoeconomics. 2008;26(7):617–627. doi: 10.2165/00019053-200826070-00008.
[21] Giovannoni G, Lang S, Wolff R, et al. A systematic review and mixed treatment comparison of pharmaceutical interventions for multiple sclerosis. Neurol Ther. 2020;9(2):359–374. doi: 10.1007/s40120-020-00212-5.
[22] Guo S, Pelligra C, Saint-Laurent Thibault C, et al. Cost-effectiveness analyses in multiple sclerosis: a review of modelling approaches. Pharmacoeconomics. 2014;32(6):559–572. doi: 10.1007/s40273-014-0150-1.
[23] He A, Merkel B, Brown JWL, et al. Timing of high-efficacy therapy for multiple sclerosis: a retrospective observational cohort study. Lancet Neurol. 2020;19(4):307–316. doi: 10.1016/S1474-4422(20)30067-3.
[24] He A, Spelman T, Jokubaitis V, et al. Comparison of switch to fingolimod or interferon beta/glatiramer acetate in active multiple sclerosis. JAMA Neurol. 2015;72(4):405–413. doi: 10.1001/jamaneurol.2014.4147.
[25] Hoepner R, Kolb EM, Dahlhaus S, et al. Predictors of severity and functional outcome in natalizumab-associated progressive multifocal leukoencephalopathy. Mult Scler. 2017;23(6):830–835. doi: 10.1177/1352458516667241.
[26] Hogervorst MA, Pontén J, Vreman RA, et al. Real world data in health technology assessment of complex health technologies. Front Pharmacol. 2022;13:837302. doi: 10.3389/fphar.2022.837302.
[27] Jalkh G, Abi Nahed R, Macaron G, et al. Safety of newer disease modifying therapies in multiple sclerosis. Vaccines (Basel). 2020;9(1):12. doi: 10.3390/vaccines9010012.
[28] Kalincik T, Horakova D, Spelman T, et al. Switch to natalizumab versus fingolimod in active relapsing-remitting multiple sclerosis. Ann Neurol. 2015;77(3):425–435. doi: 10.1002/ana.24339.
[29] 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(5):387–401. doi: 10.1056/NEJMoa0909494.
[30] Kingwell E, van der Kop M, Zhao Y, et al. Relative mortality and survival in multiple sclerosis: findings from British Columbia, Canada. J Neurol Neurosurg Psychiatry. 2012;83(1):61–66. doi: 10.1136/jnnp-2011-300616.
[31] Kobelt G, Berg J, Lindgren P, et al. Costs and quality of life of patients with multiple sclerosis in Europe. J Neurol Neurosurg Psychiatry. 2006;77(8):918–926. doi: 10.1136/jnnp.2006.090365.
[32] Kobelt G, Thompson A, Berg J, et al. New insights into the burden and costs of multiple sclerosis in Europe. Mult Scler. 2017;23(8):1123–1136. doi: 10.1177/1352458517694432.
[33] Lasalvia P, Hernández F, Castañeda-Cardona C, et al. Cost-effectiveness of natalizumab compared with fingolimod for relapsing-remitting multiple sclerosis treatment in Colombia. Value Health Reg Issues. 2020;23:13–18. doi: 10.1016/j.vhri.2019.08.481.
[34] Lorscheider J, Benkert P, Lienert C, et al. Comparative analysis of natalizumab versus fingolimod as second-line treatment in relapsing-remitting multiple sclerosis. Mult Scler. 2018;24(6):777–785. doi: 10.1177/1352458518768433.
[35] Lorscheider J, Benkert P, Lienert C, et al. Comparative analysis of dimethyl fumarate and fingolimod in relapsing-remitting multiple sclerosis. J Neurol. 2021;268(3):941–949. doi: 10.1007/s00415-020-10226-6.
[36] Makady A, van Veelen A, Jonsson P, et al. Using real-world data in health technology assessment (HTA) practice: a comparative study of five HTA agencies. Pharmacoeconomics. 2018;36(3):359–368. doi: 10.1007/s40273-017-0596-z.
[37] Michels RE, de Fransesco M, Mahajan K, et al. Cost effectiveness of cladribine tablets for the treatment of relapsing-remitting multiple sclerosis in The Netherlands. Appl Health Econ Health Policy. 2019;17(6):857–873. doi: 10.1007/s40258-019-00500-8.
[38] MidMeds. Siemens Multistix 10 SG Professional Urine Reagent Test Strips. December 2, 2021. Available from: http://www.midmeds.co.uk/siemens-bayer-multistix-p-234.html.
[39] Montgomery SM, Maruszczak MJ, Slater D, et al. A discrete event simulation to model the cost-utility of fingolimod and natalizumab in rapidly evolving severe relapsing-remitting multiple sclerosis in the UK. J Med Econ. 2017;20(5):474–482. doi: 10.1080/13696998.2016.1276070.
[40] National Health Service. 2019/20 National cost collection data publication. 2019-20; [cited 2021, November 2]. Available from: https://www.england.nhs.uk/publication/2019-20-national-cost-collection-data-publication/.
[41] National Institute for Health and Care Excellence. Fingolimod for the treatment of highly active relapsing–remitting multiple sclerosis. April 2012. Technology Appraisal No. 254.
[42] National Institute for Health and Care Excellence. Guide to the methods of technology appraisal. 2022; [cited 2023, September 18]. Available from: https://www.nice.org.uk/process/pmg36/chapter/introduction-to-health-technology-evaluation.
[43] National Institute for Health and Care Excellence. List of technologies with approved patient access schemes. 2022; [cited 2022, February 16]. Available from: https://www.nice.org.uk/about/what-we-do/patient-access-schemes-liaison-unit#list-of-arrangements.
[44] National Institute for Health and Care Excellence. Natalizumab for the treatment of adults with highly active relapsing-remitting multiple sclerosis. August 2007. Technology Appraisal No. 127.
[45] Nottingham University Hospitals. High cost tests referred to other labs. [cited 2017, February 9]. Available from: https://www.nuh.nhs.uk/staff-area/microbiology/turnaround-times/high-cost-referred-tests/.

[46] O'Day K, Meyer K, Miller RM, et al. Cost-effectiveness of natalizumab versus fingolimod for the treatment of relapsing multiple sclerosis. J Med Econ. 2011;14(5):617–627. doi: 10.3111/13696998.2011.602444.

[47] O'Day K, Meyer K, Stafkey-Mailey D, et al. Cost-effectiveness of natalizumab vs fingolimod for the treatment of relapsing-remitting multiple sclerosis: analyses in Sweden. J Med Econ. 2015;18(4):295–302. doi: 10.3111/13696998.2014.991786.

[48] Office for National Statistics. Consumer Price Index. 2021. [cited 2021, December 1]. Available from: https://www.ons.gov.uk/economy/inflationandpriceindices/timeseries/d7bz/mm23.

[49] Office for National Statistics. National life tables, United Kingdom, 2014-2016. 2018; [cited 2018, January 30]. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/datasets/nationallifetablesunitedkingdomreferencetables.

[50] Palace J, Bregenzer T, Tremlett H, et al. UK multiple sclerosis risk-sharing scheme: a new natural history dataset and an improved markov model. BMJ Open. 2014;4(1):e004073. doi: 10.1136/bmjopen-2013-004073.

[51] Pokorski RJ. Long-term survival experience of patients with multiple sclerosis. J Insur Med. 1997;29(2):101–106.

[52] Polman CH, O'Connor PW, Havrdova E, et al. A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. N Engl J Med. 2006;354(9):899–910. doi: 10.1056/NEJMoa044397.

[53] Prosperini L, Saccà F, Cordioli C, et al. Real-world effectiveness of natalizumab and fingolimod compared with self-injectable drugs in non-responders and in treatment-naive patients with multiple sclerosis. J Neurol. 2017;264(2):284–294. doi: 10.1007/s00415-016-8343-5.

[54] Rassen JA, Shelat AA, Franklin JM, et al. Matching by propensity score in cohort studies with three treatment groups. Epidemiology. 2013;24(3):401–409. doi: 10.1097/EDE.0b013e318289dedf.

[55] Roos I, Diouf I, Sharmin S, et al. Comparative effectiveness in multiple sclerosis: a methodological comparison. Mult Scler. 2023;29(3):326–332. doi: 10.1177/13524585231151394.

[56] Ryerson LZ, Foley J, Chang I, et al. Risk of natalizumab-associated PML in patients with MS is reduced with extended interval dosing. Neurology. 2019;93(15):e1452–e1462. doi: 10.1212/WNL.0000000000008243.

[57] Scalfari A, Neuhaus A, Degenhardt A, et al. The natural history of multiple sclerosis: a geographically based study 10: relapses and long-term disability. Brain. 2010;133(Pt 7):1914–1929. doi: 10.1093/brain/awq118.

[58] 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(1):552–568. doi: 10.1111/j.1749-6632.1965.tb20235.x.

[59] Simpson A, Mowry EM, Newsome SD. Early aggressive treatment approaches for multiple sclerosis. Curr Treat Options Neurol. 2021;23(7):19. doi: 10.1007/s11940-021-00677-1.

[60] Spelman T, Herring WL, Zhang Y, et al. Comparative effectiveness and cost-effectiveness of natalizumab and fingolimod in patients with inadequate response to disease-modifying therapies in relapsing-remitting multiple sclerosis in the United Kingdom. Pharmacoeconomics. 2022;40(3):323–339. doi: 10.1007/s40273-021-01106-6.

[61] Spelman T, Horakova D, Ozakbas S, et al. Switching to natalizumab or fingolimod in multiple sclerosis: comparative effectiveness and effect of pre-switch disease activity. Mult Scler Relat Disord. 2023;70:104477. doi: 10.1016/j.msard.2022.104477.

[62] Spelman T, Kalincik T, Zhang A, et al. Comparative efficacy of switching to natalizumab in active multiple sclerosis. Ann Clin Transl Neurol. 2015;2(4):373–387. doi: 10.1002/acn3.180.

[63] Thompson A, Kobelt G, Berg J, et al. New insights into the burden and costs of multiple sclerosis in Europe: results for the United Kingdom. Mult Scler. 2017;23(2_suppl):204–216. doi: 10.1177/1352458517708687.

[64] Tramacere I, Del Giovane C, Filippini G. Association of immunotherapies with outcomes in relapsing-remitting multiple sclerosis. JAMA. 2016;315(4):409–410. doi: 10.1001/jama.2015.18984.

[65] Trojano M, Tintore M, Montalban X, et al. Treatment decisions in multiple sclerosis—insights from real-world observational studies. Nat Rev Neurol. 2017;13(2):105–118. doi: 10.1038/nrneurol.2016.188.

[66] Vargas WS, Perumal JS. Fingolimod and cardiac risk: latest findings and clinical implications. Ther Adv Drug Saf. 2013;4(3):119–124. doi: 10.1177/2042098613481023.

[67] Vollmer B, Ontaneda D, Harris H, et al. Comparative discontinuation, effectiveness, and switching practices of dimethyl fumarate and fingolimod at 36-month follow-up. J Neurol Sci. 2019;407:116498. doi: 10.1016/j.jns.2019.116498.

[68] Wingerchuk DM, Weinshenker BG. Disease modifying therapies for relapsing multiple sclerosis. BMJ. 2016;354:i3518. doi: 10.1136/bmj.i3518.