



Cost-Consequence Analysis of Natalizumab Compared with Other High-Efficacy Treatments in Patients with Relapsing–Remitting Multiple Sclerosis

Luca Prosperini¹ · Vincenzo Brescia Brescia Morra^{2,3} · Carla Fornari⁴ · Laura Santoni⁵ · Daria Perini⁵ · Roberto Bergamaschi⁶ · Paolo Angelo Cortesi^{4,7}

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Abstract

Background Advances in the availability and regimen optimization of highly effective disease-modifying treatments (DMTs) for relapsing–remitting multiple sclerosis (RRMS) have led to questions about their comparative worth.

Objectives This study evaluates the costs and effects of natalizumab versus other highly effective DMTs and the impact, in terms of times and costs, of the new subcutaneous natalizumab formulation versus the intravenous formulation in patients with RRMS in Italy.

Methods This is a cost-consequence analysis from the Italian national health service and societal perspectives. A Markov model was developed to assess clinical and cost outcomes related to disease and DMTs. The model simulated two scenarios: one comparing natalizumab extended-dose regimen and ofatumumab and ocrelizumab, focusing on efficacy outcomes and costs, and one comparing intravenous and subcutaneous natalizumab with a focus on administration resource consumption, times, and costs. Model input data came from the literature.

Results DMTs had similar clinical and social outcomes: natalizumab slightly reduced disease progression, increased quality-adjusted life-years, and reduced the impact on days of productivity loss and informal care. Natalizumab also resulted in statistically significant 5-year cost reductions compared with ocrelizumab and ofatumumab. Subcutaneous natalizumab improved resource consumption compared with intravenous natalizumab, saving the time of healthcare professionals, patients, and caregivers and reducing administration costs. The subcutaneous formulation was associated with statistically significant total direct and indirect cost reductions at 5 years.

Conclusion 6-week dosing regimen of natalizumab showed a slight improvement of clinical and social outcomes and a statistically significant cost reduction compared with ocrelizumab and ofatumumab over a 5-year simulation. Moreover, subcutaneous administration reduced administration times and costs.

1 Introduction

Multiple sclerosis (MS) is a chronic, inflammatory, autoimmune disease of the central nervous system manifesting typically between 20 and 40 years of age and leading to accumulation of disability [1]. The disease represents an enormous health and societal burden [2, 3].

Current strategies in relapsing–remitting MS (RRMS) include mildly to moderately effective disease-modifying therapies (DMTs) and highly effective DMTs [1]. Within the

highly effective DMTs, natalizumab (Tysabri®) was the first to be approved by the European Medicines Agency [4]. The original approval was for intravenous natalizumab 300 mg every 4 weeks. However, in recent years, less frequent natalizumab administration using extended interval dosing (EID) has been used in real-world clinical practice to minimize the risk of progressive multifocal leukoencephalopathy [5]. This approach has been also implemented in Italy, as shown by data on clinical practice in Italian MS centers [6, 7]. In addition, a recent clinical trial confirmed that EID at 6 weeks provides similar benefits to patients as dosing at 4 weeks [8].

At the same time, new highly effective DMTs have entered the market. More specifically, two anti-CD20 monoclonal antibodies (ocrelizumab [Ocrevus®] and ofatumumab [Kesimpta®]) have provided new treatment options with less

Roberto Bergamaschi and Paolo Angelo Cortesi: Joint senior authors.

Extended author information available on the last page of the article

Key Points for Decision Makers

Recent advances in the availability and regimen optimization of highly effective disease-modifying treatments (DMTs) has led to questions about the relative benefits and costs of different DMTs in patients with relapsing-remitting multiple sclerosis (RRMS) from clinical, economic, and social viewpoints.

This is a complete assessment of the costs and effects of natalizumab compared with other highly effective DMTs in patients with RRMS in Italy from the national healthcare service and societal perspectives.

An extended-dose regimen of natalizumab slightly improved clinical and social outcomes and significantly reduced costs (> €1.4 million per 100 patients) compared with ocrelizumab and ofatumumab treatments over a 5-year simulation. Moreover, the subcutaneous formulation of natalizumab was associated with statistically significant reductions in time spent by healthcare professionals and patients on drug administration, which is related to a total direct cost reduction of €27,037 and a total indirect cost reduction of €110,503 compared with the intravenous formulation.

frequent administration (ocrelizumab) or different methods of administration (ofatumumab) [1]. The availability of new products and the change in natalizumab modality of administration have raised some questions about their relative value in terms of clinical, economic, and social viewpoints [8–10]. Further, a new subcutaneous formulation of natalizumab has been approved by the European Medicines Agency and recently reimbursed by the Italian Medicines Agency. The new subcutaneous formulation is indicated with a regimen of 300 mg every 4 weeks, and recent studies showed that it is comparable to the intravenous formulation in terms of efficacy, pharmacokinetics, pharmacodynamics, and safety [11, 12]. Moreover, evidence also suggests the use of EID at 6 weeks for the subcutaneous formulation [13] and that the subcutaneous formulation could reduce burdens associated with treatment administration [9].

Treatment value has frequently been assessed through economic evaluations such as cost-effectiveness and budget-impact analyses; however, cost-consequence analysis (CCA) is increasingly relevant and useful in healthcare systems as part of the decision-making process for treatment assessment [14, 15]. CCA, unlike cost-benefit or cost-effectiveness analysis, does not attempt to summarize outcomes in a single measure (such as the incremental cost-effectiveness ratio) or in financial terms. Instead, multiple disaggregated outcomes and costs are shown, and decision-makers must determine

the components most relevant to their own perspective [16–18]. CCAs are not restricted to any viewpoint, so readers and decision-makers can see the impact of their decisions on patient costs and on other sectors [18, 19]. Moreover, CCA may be particularly valuable to funders that are more concerned with patient-orientated outcomes such as patient wellbeing and satisfaction [16]. On the other hand, interpretation of CCA results is more subjective than other forms of economic evaluation, and results may be less generalizable because the choice of relevant costs and effects is often context specific [16]. The CCA is an alternative approach that provides valuable information to help healthcare decision-makers make their choices. The high economic and societal burden of MS and the availability of different highly effective DMTs represents a situation in which CCA could be a valuable tool to supplement the information provided by cost-benefit or cost-effectiveness analysis [15, 20, 21].

The aim of the present study was to simulate the mid-term clinical, health economic, and societal effects of natalizumab compared with the other highly effective monoclonal antibody DMTs, ocrelizumab and ofatumumab, in patients with RRMS in Italy from the national healthcare service and societal perspectives. A second objective of the study was to understand the impact of the new subcutaneous natalizumab formulation compared with the intravenous formulation, with a focus on administration times and costs, as we assumed that other costs and efficacy outcomes were comparable.

2 Methods

2.1 Pharmacoconomic Study Design: CCA

This pharmacoeconomic evaluation uses a cost-consequence approach to assess both the costs and the consequences (effects) of natalizumab therapy in patients with RRMS. The CCA separately estimates and evaluates the costs (expressed in €, year 2024 values) and the efficacy of compared treatments, allowing analysis of separately disaggregated cost components and efficacy outcomes. It also provides a comprehensive view, estimating costs and effects from different perspectives: national health service, patient, caregiver, and society.

Specifically, this analysis includes different types of outcomes and costs: direct healthcare and non-healthcare, indirect and intangible. The CCA was conducted by developing a cohort Markov model in Microsoft Excel for the Italian context. The model simulated disease progression in relation to DMTs, as DMTs can reduce disability worsening and relapse occurrence, which influences patient's health state, quality of life, and disease management costs. In the base-case scenario of the CCA, we compared intravenous and

subcutaneous natalizumab with ofatumumab or ocrelizumab, two high-efficacy therapeutic alternatives for patients with RRMS, with a focus on efficacy outcomes and costs. In this analysis, efficacy and the costs of subcutaneous natalizumab were assumed comparable to those with the intravenous formulation and so are not reported [11]. Further, we created an alternative scenario in which we compared intravenous and subcutaneous natalizumab with a focus on other issues related to the time and costs of drug administration, as other costs and efficacy outcomes were assumed comparable between the two formulations. The main aspects of the model are described in the following sections.

2.2 Intervention

The intervention considered in the economic evaluation, in both scenarios, was intravenous natalizumab 300 mg every 4 weeks in the first year of treatment and every 6 weeks from the second year (extended dose) [8, 13].

2.3 Comparators

In the base-case scenario, natalizumab was compared with the other two available high-efficacy RRMS treatments: (1) subcutaneous ofatumumab 20 mg at weeks 0, 1, and 2, followed by every 4 weeks (starting at week 4) and (2) intravenous ocrelizumab 300 mg, followed 2 weeks later by a second intravenous infusion of 300 mg and then a single intravenous infusion of 600 mg every 6 months.

In the alternative scenario, intravenous natalizumab was compared with subcutaneous natalizumab in terms of drug administration time and resource consumption from the perspective of the MS center, the patient, and society.

2.4 Model Description

The analysis was conducted using a cohort Markov model developed in Excel to compare natalizumab with other high-efficacy DMTs for the treatment of RRMS using disaggregated efficacy outcomes and costs in the Italian context. In the base-case scenario, the model simulated disease progression and estimated healthcare outcomes and costs associated with treatment and management of the disease, creating a simulated cohort for all the therapeutic options mentioned (natalizumab, ocrelizumab, and ofatumumab). In the model, the natural history of RRMS was regulated by three main events: disability progression, relapse occurrence, and mortality risk. RRMS is characterized by periods of relapse, which involve an exacerbation of MS symptoms. A relapse is defined as an exacerbation lasting at least 24 h and separated from the previous exacerbation by at least 30 days; most relapses last from a few days to several weeks [22]. In the model (Fig. 1), disease can progress through a series

of disability states, which are based on the Expanded Disability Status Scale (EDSS). The EDSS quantifies disability in patients with MS, and it is useful for monitoring changes in the level of disability over time. The EDSS scale represents the level of disability and ranges from 0 to 10, with 10 being death due to MS [23]. At the beginning of the simulation, patients are assigned to a disability level (EDSS score) ranging from 0 to 6.5 according to the AFFIRM trial [24] and assigned to one of the highly effective DMTs included in the analysis (natalizumab, ocrelizumab, or ofatumumab). Over time, patients can progress to higher or lower disability states (according to the EDSS), maintain the same disability level, move to a second highly effective DMT, or experience relapses (as reported in detail in Sects. 2.6.2 and 2.6.3) or death. This model assumed that patients can discontinue treatment due to adverse events or loss of efficacy or when they reach an EDSS level ≥ 7 . As such, the model has 18 health states, seven corresponding to EDSS levels (< 7) with a first highly effective DMT, seven with a second highly effective DMT, three EDSS levels (≥ 7) with no treatment, and one state related to death. Moreover, the model assumed that EDSS was the main determinant for evaluating costs and clinical outcomes.

The model adopted a 5-year time horizon and 1-year cycles, and applied a half-cycle correction. The 5-year time horizon was defined in line with previous CCAs conducted in Italy, which adopted a period required from regional and national payers for this type of analysis [25]. In accordance with guidelines from the Italian Medicines Agency [26, 27], a discount rate of 3% was applied.

2.5 Outcomes and Costs

In the base-case scenario, the model estimated different efficacy outcomes to capture in detail the impact of MS and DMTs. The estimated outcomes were relapse frequency, divided into severe (requiring hospitalization) and non-severe, disease progression in terms of EDSS level distribution, percentage of patients with $\text{EDSS} \leq 3$, $\text{EDSS} \geq 6$, $\text{EDSS} 7-9$, and overall survival (life-years). The model also estimated intangible outcomes such as quality-adjusted life-years (QALYs), which combine length and quality of life into a single metric, and social outcomes such as days required for informal care (lost leisure time for assistance from relatives/friends), days of work lost, and the percentage of unemployed patients. In the alternative scenario, comparing methods of administering natalizumab, the model assessed the following outcomes: active working time for healthcare professionals (clinician, nurse), infusion chair occupation time, the patient's time required for administration, the patient's informal care, and productivity loss for patients, society, and caregivers during the administration day.

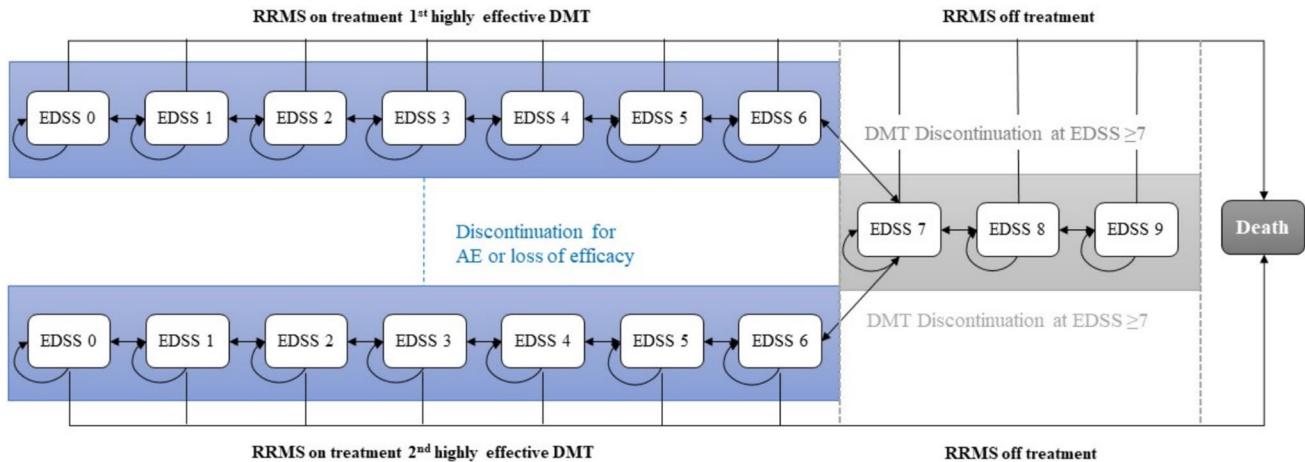


Fig. 1 The structure of the cohort Markov model shows the Expanded Disability Status Scale (EDSS) [21] health states (0–9) through which patients with relapsing–remitting multiple sclerosis (RRMS) could transition, or remain within, during each cycle. EDSS transitions can involve one or more levels of worsening or improvement, based on the annual transition probabilities estimated by Palace et al. [25]. For simplicity, EDSS transitions exceeding one level are not displayed. Transition to death is possible from all health states. At any time, patients treated with a first highly effective disease-modifying therapy (DMT) could discontinue treatment for adverse events (AEs) or loss of efficacy and could move to second highly effective DMT. Treatment is discontinued once an EDSS health state of 7 is reached. EDSS 0 = normal neurological examination, no disability in any

Costs assessed in the base-case scenario were divided into direct healthcare costs, direct non-healthcare costs, and indirect costs. Direct healthcare costs included expenses related to pharmacologic treatment purchase and administration and therapy monitoring and costs associated with relapses and disability management. Direct non-healthcare costs included all expenses related to services employed for disease management: community services and investments in equipment and devices to facilitate a patient's mobility. Indirect costs are related to productivity losses and informal care.

In the alternative scenario, the model included the healthcare direct costs related to administration (cost for healthcare staff, chair occupation, and consumables), the non-healthcare direct costs (costs of transport and formal care or babysitting), and the indirect costs for administration (productivity loss for the patient, society, and the caregiver and loss of time for unpaid activities for patients).

2.6 Model Inputs

2.6.1 Population

The simulated cohort had an initial mean age of 36.8 years, and 70% of the subjects were female [24]; subjects in the cohort were distributed across different EDSS levels, using data from the AFFIRM trial: 5% EDSS 0, 29% EDSS 1, 33%

functional system; EDSS 1 = no dysfunction, minimal signs; EDSS 2 = minimal dysfunction; EDSS 3 = moderate dysfunction; EDSS 4 = relatively severe dysfunction not preventing ability to work or carry out normal activities of living, excluding sexual function; EDSS 5 = dysfunction severe enough to preclude working with maximal motor function, walking unaided up to several blocks; EDSS 6 = assistance required for walking; EDSS 7 = restricted to wheelchair; EDSS 8 = restricted to a bed but with effective use of arms; EDSS 9 = totally helpless bed patient; EDSS 10 = death. First highly effective DMT = natalizumab, ocrelizumab, or ofatumumab; second highly effective DMT = an hypothetical subsequent highly effective DMT with an efficacy computed as the mean of efficacy of the three alternatives compared

EDSS 2, 20% EDSS 3, 9% EDSS 4, 3% EDSS 5, 1% EDSS 6, and 0% each for EDSS 7, 8, and 9 [24]. The AFFIRM trial included 942 patients with RRMS aged 18–50 years selected from 99 centers in Europe, North America, Australia, and New Zealand. Patients must have had at least one nuclear magnetic resonance image showing lesions consistent with the disease and at least one relapse in the year preceding but not within the last 50 days before the study began.

2.6.2 Natural History of the Disease

The natural history of the disease and its related progression was simulated using annual disability state transition probabilities in patients with RRMS derived from the British Columbia Multiple Sclerosis database [28]. Transition probabilities remained constant over time. The transition matrix with annual transition probabilities among EDSS states is shown in Table S1 in the electronic supplementary material (ESM). The patients could move to higher and lower disability levels with no restrictions. The British Columbia study [28] estimated transition probabilities for RRMS and secondary progressive MS (SPMS) altogether. So, the model assumed that patients moving to SPMS continued to be treated and were subject to the same transition probabilities as patients with RRMS and did not include specific

natural history data related to SPMS. The assumption that patients with SPMS continued to be treated is consistent with study populations in the recent ASCLEPIOS I & II and OPERA [29] trials. Furthermore, the transition to SPMS is not always easy to diagnose because many different clinical definitions exist, and it is often diagnosed retrospectively, meaning that patients likely do not discontinue treatment at the time of progression to SPMS.

Natural history annual relapse rates in patients with RRMS and in relation to EDSS level were estimated using data from Patzold et al. [30] and the UK MS Survey [31] (Table 1). The model differentiated between relapse requiring and not requiring hospitalization. The proportion of relapses requiring hospitalization was estimated at 0.018 [31].

Annual death probabilities by age were estimated using mortality rates of the Italian general population for the year 2021, stratified by age and sex, reported by the National Institute of Statistics [32]. Death probabilities at each age were computed as a weighted average of male and female probabilities; the proportion of females to males was assumed to be constant in each age group. Annual death probabilities were then adjusted by the relative risk of death in the MS population compared with that in the general population (relative risk 1.7), derived from Jick et al. [33].

2.6.3 DMTs Efficacy Data

DMTs modify the natural evolution of the disease, delaying the progression towards the highest EDSS levels and reducing the occurrence of relapses. The impact of DMTs on the natural course of disability and on the occurrence of relapses was modelled independently, as recognized in RRMS simulation models [34]. Clinical efficacy on annualized relapse rate and confirmed disability progression at 24 weeks for the analyzed DMTs were computed using data from a network meta-analysis (NMA) of clinical trials [35]. Specifically, for each DMT, we extrapolated a relapse rate ratio using placebo as a reference to determine relapse reduction associated with each treatment option and a hazard ratio (HR) for disease progression (Table 1). HRs were then applied to the baseline cumulative hazard derived from natural history disability progression probabilities and then transformed to DMT progression probabilities, using the formula by Briggs et al. [36]. In the model, patients with EDSS < 7 could discontinue treatment because of adverse events or loss of efficacy. In this case, a second line of treatment was introduced for patients with EDSS < 7 in the model (who discontinued treatment because of adverse events or loss of efficacy) assuming hypothetical subsequent DMT with efficacy computed as the mean of efficacy of the three alternatives evaluated in the base-case scenario (natalizumab, ocrelizumab, and ofatumumab). This method balanced the

Table 1 Clinical parameters

Description	Value	SE	Source
Annual relapse rate			
EDSS 0	0.71	0.16	Patzold et al. [30];
EDSS 1	0.73	0.07	Orme et al. [31]
EDSS 2	0.68	0.07	
EDSS 3	0.72	0.11	
EDSS 4	0.71	0.08	
EDSS 5	0.59	0.07	
EDSS 6	0.49	0.09	
EDSS 7	0.47	0.13	
EDSS 8	0.51	0.27	
EDSS 9	0.52	0.52	
DMTs efficacy			
Relapse rate ratio (vs placebo)			
Natalizumab IV	0.31	0.14	Samjoo et al. [35]
Ofatumumab	0.30	0.15	
Ocrelizumab	0.33	0.14	
Second hypothetical DMT	0.31	0.14	Model assumption
Confirmed disease progression (at 24 weeks)			
HR (vs placebo)			
Natalizumab IV	0.46	0.22	Samjoo et al. [35]
Ofatumumab	0.54	0.24	
Ocrelizumab	0.47	0.32	
Second hypothetical DMT	0.49	0.26	Model assumption
DMT discontinuation probabilities			
Natalizumab IV	0.11	0.02	Samjoo et al. [35]
Ofatumumab	0.11	0.02	
Ocrelizumab	0.11	0.02	
Utilities			
EDSS 0	0.923	0.045	Battaglia et al. [2]
EDSS 1	0.882	0.048	
EDSS 2	0.836	0.048	
EDSS 3	0.777	0.052	
EDSS 4	0.783	0.048	
EDSS 5	0.755	0.047	
EDSS 6	0.718	0.047	
EDSS 7	0.579	0.049	
EDSS 8	0.310	0.050	
EDSS 9	0.040	0.074	

DMT disease-modifying treatment, EDSS Expanded Disability Status Scale, HR hazard ratio, IV intravenous, SE standard error

effect of all possible secondary therapy options. A sensitivity analysis employing the mean of DMT pairs not included as first-line treatment was conducted to assess the effect of model assumptions on results. Discontinuation probabilities for the three DMTs were populated using data from an NMA [35], whereas we assumed no discontinuation for the hypothetical subsequent DMT (Table 1). Moreover, patients

discontinued treatment when they reached an EDSS level ≥ 7 , and no subsequent treatments were introduced in this case.

Finally, the model indirectly included adverse events in the treatment discontinuation rate, as previous studies have shown that the impact of these events, including progressive multifocal leukoencephalopathy, constitutes a minimal part of the overall MS burden [37, 38].

2.6.4 Utilities Data

Utilities by EDSS in patients with RRMS were obtained from a study on MS burden [2] using specific data for Italy and applied in the base-case scenario (Table 1). Utilities applying UK tariffs [39] were multiplied by life-years in each disease state (EDSS level) to compute QALYs. Moreover, the model included a disutility equal to 0.18 for patients experiencing one or more relapses, regardless of EDSS level [31]. This value was calculated as the mean difference in utilities between patients without a relapse and those who had experienced a relapse in the past 3 months, after controlling for EDSS level.

2.6.5 Social and Services Use Outcomes

The base-case scenario analysis considered social outcomes, such as the number of days used for informal care, workdays lost, and the percentage of patients unemployed. The parameters (Table 2) for estimating these results were obtained from the Italian study by Battaglia et al. [2].

In the alternative scenario analysis, when comparing costs and outcomes related to therapy administration between natalizumab variants, the model used data from the EASIER study [9] to evaluate the day time lost by a patient for treatment administration; the productivity loss for the patient, society, and the caregiver; the loss of time for unpaid activities for the patient; and the healthcare direct services: the time needed for healthcare staff (clinician and nurse) and use of healthcare services (chair occupation)

during administration. Furthermore, direct healthcare costs relating to transport between home and the MS center (and return) and formal assistance (e.g. babysitters/caregivers) were also considered. The model parameters are reported in Table S2 in the ESM.

2.6.6 Costs

The following direct healthcare costs were considered in the base-case scenario analysis: disease management related to disability, acquisition of pharmacological treatment, drug treatment administration, patient monitoring, and relapses.

Costs for disease management by EDSS were obtained from an analysis conducted in Italian healthcare administrative databases combined with clinical data from MS disease registries [3]. Table 3 illustrates the healthcare cost data attributable to the disease that were entered into the model (base-case scenario).

The model evaluated the costs related to acquiring, monitoring, and administering DMTs. Costs were calculated as an annual cost, based on the ex-factory prices of the individual packs [40] and on discounts for the Italian national health service. Values for each included DMT are reported in Table S3 in the ESM. Costs for natalizumab and ofatumumab are different for the first year of administration compared with subsequent years, depending on the different doses used for treatment.

DMT administration costs were assessed at €9.71 based on the tariff reported by the G.U. 2013 [41], whereas other costs related to treatment management were included as monitoring costs. For subcutaneous ofatumumab, administration costs were considered only for the first three, assuming they were administered under medical supervision to evaluate any systemic and local adverse events.

Annual monitoring costs of the three treatments were estimated with an ad hoc survey in three MS reference centers in Italy (Biogen, data on file). Specifically, the survey concerned clinical and instrumental tests that are usually performed at the centers to monitor the health status of

Table 2 Social parameters per the Expanded Disability Status Scale (EDSS)

Social outcomes	Parameter	EDSS									
		0	1	2	3	4	5	6	7	8	9
Informal care (days per year)	Value	29	29	29	29	124	124	124	220	220	220
	SE	5.7	5.7	5.7	5.7	24.9	24.9	24.9	44.0	44.0	44.0
Patient productivity loss (days per year)	Value	31	31	31	31	172	172	172	325	325	325
	SE	6.2	6.2	6.2	6.2	34.4	34.4	34.4	65.0	65.0	65.0
Unemployed (%)	Value	31	31	31	31	55	55	55	84	84	84
	SE	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.2	0.2	0.2

Values derived from Battaglia et al. [2]. The SE is computed as model assumptions

SE standard error

patients in the first, second, third, and subsequent years of treatment and tests performed before starting therapy. The number of annual exams, estimated with the survey, was then multiplied by the unit cost according to the tariff of services reported in the G.U. 2013 [41]. The monitoring costs for treated patients used in the model are shown in Table S3 in the ESM. The costs of the first year also included tests and exams provided before starting the therapy.

Costs of treatment acquisition, administration, and monitoring of the subsequent hypothetical DMT were assumed to be the same as the mean cost of the three DMTs compared in this analysis: natalizumab, ofatumumab, and ocrelizumab. A sensitivity analysis to evaluate the impact of this assumption was conducted.

The cost of relapse (€432.73) was obtained from an analysis conducted in Italian healthcare administrative databases combined with clinical data in MS disease registries [3]. The cost of diagnosis-related group n.13 "Multiple sclerosis and cerebellar ataxia" (€1419.00) [41] was attributed to severe relapses requiring hospitalization.

The direct non-healthcare costs were also considered in the base-case scenario analysis. These are direct non-healthcare costs relating to services used for disease management: (1) community services and (2) investments in equipment and devices to facilitate patient mobility. The annual costs per patient used in the model varied according to the level of EDSS (Table 3) and were taken from the 2017 study by Battaglia et al. [2].

Indirect costs included in the analysis were also obtained from Battaglia et al. [2] and are shown in Table 3.

In the alternative scenario analysis, we compared intravenous and subcutaneous regimens. Healthcare direct costs per administration of intravenous or subcutaneous natalizumab

were estimated using time and unit costs reported in the EASIER study [9]: €67/h for clinicians, €27/h for nurses, and €0.30/h for chair occupation. From the same study, we extrapolated and introduced into the model the cost per transport from home to MS center (and return) (€30.68 per administration) and formal care (babysitting/caregiver: €2.38 per intravenous infusion or €1.28 per subcutaneous administration) as direct non-healthcare costs.

Furthermore, data on indirect costs related to natalizumab administration and included only in the alternative scenario analysis were taken from the EASIER study [9]: €13.50/h of patient's productivity loss, €15.92/h of patient and society productivity loss, €2.89/h of patient's loss of time for unpaid activities, and €13.16/h of caregiver's productivity loss.

Inflation adjustments were applied using the Italian inflation rates from the Italian National Institute of Statistics [42].

2.7 Uncertainty Estimation for Model Outcomes and Sensitivity Analysis

A probabilistic sensitivity analysis was implemented to compute confidence intervals (CIs) for outcome and cost estimates. After assigning a distribution and uncertainty range to main input parameters, a Monte Carlo simulation was conducted with repeated sampling sets of all inputs over 1000 simulation runs (Table S4 in the ESM). Mean values and the 2.5 and 97.5 percentiles are reported for each outcome and cost estimated by the model for each DMT.

A sensitivity analysis was conducted to evaluate possible bias related to model assumptions on efficacy and cost parameters of second-line high-efficacy DMTs. Specifically, the sensitivity analysis assumed a hypothetical subsequent

Table 3 Direct and indirect costs for disease management per the Expanded Disability Status Scale (EDSS)

Cost parameter	Value by EDSS										Source
	0	1	2	3	4	5	6	7	8	9	
Direct											
Disease management	Value	2081	2081	2081	2081	4349	4349	4349	10,339	10,339	10,339
	SE	416	416	416	416	870	870	870	2068	2068	2068
Community services	Value	73	73	73	73	903	903	903	5648	5648	5648
	SE	14.6	14.6	14.6	14.6	180.6	180.6	180.6	1129.6	1129.6	1129.6
Investments	Value	79	79	79	79	985	985	985	1600	1600	1600
	SE	15.8	15.8	15.8	15.8	197.0	197.0	197.0	320.0	320.0	320.0
Indirect											
Informal care	Value	892	892	892	892	5105	5105	5105	12,328	12,328	12,328
	SE	178.4	178.4	178.4	178.4	1021.0	1021.0	1021.0	2465.6	2465.6	2465.6
Patient productivity loss	Value	1717	1717	1717	1717	9542	9542	9542	18,045	18,045	18,045
	SE	343.3	343.3	343.3	343.3	1908.4	1908.4	1908.4	3609	3609	3609

Annual cost per patient in €, year 2024 values

SE standard error

DMT with efficacy and costs computed as the mean of efficacy or costs of the two DMT alternatives not used as first-line treatment.

2.8 Model Validation

The validity of the conceptual model was enhanced through consultation with clinical experts in MS. The model structure was reviewed to ensure it accurately represented the natural history of the disease and the clinical pathways. The model structure was also compared against other conceptual models reported in the literature for the evaluation of DMTs in MS.

Input data validation was conducted with a comprehensive literature review, and clinical experts validated the model inputs.

The computerized model was developed using Microsoft Excel and underwent testing by two modeling experts. The model was tested for extreme sets of input parameters, patient flow simulations, results, and uncertainty analysis calculations and for interface assessment.

Finally, model outcomes were defined and revised by clinical experts. The outcomes were also compared with published studies on DMTs for patients with MS. The results were consistent with the available literature, which included findings from both model simulations and empirical data. Sensitivity and scenario analyses were conducted to assess the impact of changing model inputs on the results.

3 Results

The simulation was conducted in a cohort of 100 patients with RRMS, so reported results should be considered for 100 patients treated. The results are divided in two main parts: the base-case scenario, comparing natalizumab, ocrelizumab, and ofatumumab, and the alternative scenario, comparing intravenous and subcutaneous natalizumab in terms of times and costs of drug administration.

3.1 Base-Case Scenario

The outcomes estimated by the model for each DMT are reported in Table 4. Five years of therapy with natalizumab reduced the relapse frequency by 5.52 compared with ocrelizumab therapy in 100 patients, whereas relapse frequency increased compared with ofatumumab therapy (+ 2.46). Natalizumab slightly reduced disease progression compared with other DMTs (highest percentage of patients with EDSS < 3 at 5 years) and increased the QALYs gained by patients. Natalizumab also reduced

the disease impact on social outcomes. Over 5 years, it reduced productivity loss by 316 days per 100 patients compared with ocrelizumab and by 1091 days compared with ofatumumab. Similarly, days spent on informal care were reduced by 206 days compared with ocrelizumab and by 713 days compared with ofatumumab. However, none of the numerically detected differences in favor of natalizumab reached statistical significance.

The costs estimated by the model for each DMT are reported in Table 5. Natalizumab resulted in a significant 5-year reduction in treatment acquisition, monitoring, and administration costs of €1,556,511 (95% CI 1,372,247–1,726,694) and €1,385,341 (1,235,654–1,528,994) for 100 patients treated, compared with ocrelizumab and ofatumumab, respectively. Natalizumab significantly reduced monitoring costs compared with ocrelizumab (−58,953 [95% CI −52,118 to −64,769]) at 5 years, whereas it significantly increased monitoring costs in comparison with ofatumumab (+ 22,898 [95% CI 16,749–29,690]). Administration costs for natalizumab at 5 years were significantly higher than for other therapies included in the analysis.

Generally, relapse and disease management costs were numerically lower than for other DMTs, with the exception of relapse management costs, which were higher than those related to ofatumumab. None of these differences were statistically significant. Natalizumab treatment showed a numerical but non-significant reduction in direct non-healthcare costs (community services, investment) and indirect costs in comparison with other DMTs.

Natalizumab therapy significantly reduced total direct costs of €1,604,423 (95% CI 1,440,586–1,772,457) compared with ocrelizumab and €1,368,817 (95% CI 1,227,014–1,522,746) compared with ofatumumab over 5 years for every 100 patients treated. Adding savings associated with reductions in indirect costs, natalizumab reduced costs by €1,631,994 (95% CI 1,465,944–2,149,953) versus ocrelizumab and €1,465,143 (95% CI 1,034,764–1,930,023) versus ofatumumab.

3.2 Alternative scenario analysis

The alternative scenario compared intravenous and subcutaneous natalizumab with EID at 6 months in terms of healthcare staff active working time required per administration, infusion chair occupancy time, and the time of patients and society (Table 6) and related costs (Table S5 in the ESM) for natalizumab administration.

The outcomes estimated for the alternative scenario analysis are reported in Table 6. Subcutaneous natalizumab reduced all times related to administration. Switching to the subcutaneous formulation significantly reduced

Table 4 Clinical and social outcomes: base-case scenario

Outcomes	5-year value			Difference (vs natalizumab)	
	Natalizumab	Ocrelizumab	Ofatumumab	Ocrelizumab	Ofatumumab
Clinical					
Relapse, N	110.41 (88.09–137.40)	115.93 (92.55–146.01)	107.94 (83.91–136.94)	5.52 (−28.23 to 38.63)	−2.46 (−36.35 to 31.05)
Severe relapse ^a , N	1.11 (0.69–1.68)	1.17 (0.71–1.77)	1.09 (0.67–1.67)	0.06 (−0.27 to 0.42)	−0.02 (−0.37 to 0.32)
Non-severe relapse, N	109.30 (87.11–136.01)	114.77 (91.42–144.48)	106.86 (83.31–135.52)	5.47 (−27.99 to 38.15)	−2.44 (−35.98 to 30.82)
EDSS distribution, % pts					
0–3	72.62 (67.83–77.13)	72.13 (64.67–78.02)	70.77 (64.50–75.77)	−0.49 (−8.47 to 6.43)	−1.85 (−8.62 to 4.53)
4–6	23.40 (20.30–26.41)	23.65 (19.80–28.05)	24.53 (21.31–28.00)	0.25 (−4.13 to 5.12)	1.13 (−2.91 to 5.20)
7	1.81 (1.10–2.81)	1.94 (0.96–3.66)	2.20 (1.23–3.69)	0.13 (−1.26 to 1.96)	0.39 (−0.91 to 1.88)
8–9	1.47 (0.87–2.31)	1.58 (0.76–3.06)	1.80 (0.98–3.05)	0.11 (−1.07 to 1.62)	0.33 (−0.79 to 1.63)
10	0.69 (0.19–2.22)	0.69 (0.19–2.22)	0.69 (0.19–2.22)	0.00 (0.00–0.00)	0.00 (0.00–0.00)
EDSS ≤3, % pts	72.62 (67.83–77.13)	72.13 (64.67–78.02)	70.77 (64.50–75.77)	−0.49 (−8.47 to 6.43)	−1.85 (−8.62 to 4.53)
EDSS ≥6, % pts	14.63 (10.55–19.16)	15.11 (9.74–22.40)	16.41 (11.63–22.47)	0.48 (−6.01 to 8.04)	1.79 (−4.29 to 8.37)
EDSS 7–9, % pts	3.28 (1.97–5.10)	3.52 (1.74–6.72)	4.00 (2.19–6.70)	0.24 (−2.34 to 3.60)	0.72 (−1.67 to 3.52)
LYs, years	464.71 (461.20–465.86)	464.71 (461.20–465.86)	464.71 (461.20–465.86)	0.00 (0.00–0.00)	0.00 (0.00–0.00)
Social					
QALYs, years	379.74 (358.58–398.72)	379.39 (357.30–399.02)	378.77 (357.52–397.73)	−0.35 (−5.04 to 3.68)	−0.97 (−5.21 to 2.83)
Informal care, days	25,011.73 (20,832.43–29,453.80)	25,217.35 (20,942.84–29,752.18)	25,724.55 (21,492.50–30,625.12)	205.62 (−2443.69 to 3330.91)	712.81 (−1882.59 to 3587.78)
Productivity loss, days	30,955.56 (26,165.07–36,502.47)	31,271.55 (25,868.56–37,733.39)	32,046.15 (26,589.20–38,173.85)	315.99 (−3641.23 to 5411.11)	1090.60 (−2584.63 to 5133.44)
Unemployed pts, %	38.74 (33.24–44.87)	38.91 (33.14–45.19)	39.37 (33.52–45.42)	0.18 (−2.35 to 3.30)	0.63 (−1.73 to 3.40)

Probabilistic sensitivity analysis results. Data are presented as means (95% confidence interval) on a 5-year timeframe per 100 patients

DMT disease-modifying treatment, EDSS Expanded Disability Status Scale, LYs life-years, pts patients, QALYs quality-adjusted LYs

^aSevere relapse indicates relapse requiring hospitalization

chair occupation time by 2933 h per 100 patients over 5 years. This change also reduced clinician working time by 220 h and nurse working time by 448 h over the same period. Furthermore, the time patients needed for infusions reduced by 5589 h per 100 patients over 5 years, and caregivers experienced a decrease in lost productivity of 2737 h. The reductions were all statistically significant. The costs for treatment administration were also significantly reduced using subcutaneous versus intravenous therapy, except for costs related to transport to reach the place of administration (MS center), which was the same for the two formulations (Table S5 in the ESM). The subcutaneous formulation resulted in a total direct cost reduction at 5 years per 100 patients treated of €27,027 (95% CI 16,3104–38,973) and a social cost reduction of €110,502 (95% CI 66,540–164,301).

3.3 Sensitivity Analysis

The sensitivity analysis on efficacy and cost parameters related to the second-line treatment confirmed the results of the main analysis, apart from the differences due to the probabilistic nature of the results. Results are reported in Tables S6–S9 in the ESM.

4 Discussion

The CCA provides a picture of different effects (clinical, economic, and social) associated with the three highly effective DMTs included in the analysis: natalizumab, ocrelizumab, and ofatumumab. In our analysis, outcomes related to different perspectives (national healthcare service, patient,

Table 5 Direct and indirect costs: base-case scenario

Costs	5-year value			Difference (vs natalizumab)	
	Natalizumab	Ocrelizumab	Ofatumumab	Ocrelizumab	Ofatumumab
Direct healthcare					
DMT (drug, monitoring, and administration)	5,934,556 (5,815,033–6,060,271)	7,522,204 (7,379,008–7,647,727)	7,263,650 (7,160,463–7,340,768)	1,587,648 (1,402,707–1,758,598)	1,329,094 (1,179,543–1,470,807)
Relapse	49,213 (29,720–73,904)	51,620 (31,239–75,904)	48,062 (29,314–71,479)	2407 (–12,153 to 17,587)	–1150 (–16,195 to 13,686)
Severe relapse ^a	1566 (840–2632)	1643 (850–2764)	1531 (787–2628)	78 (–435 to 597)	–34 (–541 to 459)
Non-severe relapse	47,647 (28,575–72,588)	49,977 (29,759–74,274)	46,531 (27,561–69,406)	2330 (–11,714 to 16,875)	–1116 (–15,766 to 13,243)
EDSS	1,338,391 (1,136,234–1,546,957)	1,345,199 (1,135,636–1,581,231)	1,360,790 (1,158,496–1,575,650)	6808 (–79,109 to 107,991)	22,399 (–56,061 to 114,318)
Direct non-healthcare					
Community services	159,699 (123,989–204,614)	163,696 (121,802–227,582)	172,779 (131,323–229,656)	3998 (–44,033 to 60,319)	13,080 (–31,089 to 64,570)
Investments	136,889 (110,792–166,250)	138,678 (109,752–173,799)	143,104 (116,275–175,088)	1789 (–20,300 to 29,478)	6215 (–15,772 to 31,190)
Indirect					
Informal care	933,097 (774,249–1,101,522)	943,657 (776,138–1,145,305)	969,591 (800,301–1,168,543)	10,559 (–124,308 to 173,614)	36,494 (–91,412 to 171,699)
Productivity loss	1,728,961 (1,462,075–2,047,548)	1,745,922 (1,437,000–2,087,767)	1,788,794 (1,487,185–2,167,473)	16,962 (–211,169 to 281,791)	59,833 (–143,797 to 289,277)
Total					
Direct	7,658,120 (7,408,004–7,913,210)	9,262,543 (9,008,365–9,504,311)	9,026,937 (8,793,389–9,252,891)	1,604,423 (1,440,586–1,772,457)	1,368,817 (1,227,014–1,522,746)
Indirect	2,662,058 (2,294,246–3,049,802)	2,689,579 (2,280,522–3,181,446)	2,758,385 (2,376,373–3,237,480)	27,521 (–338,054 to 439,273)	96,327 (–238,902 to 455,404)
Total	10,320,178 (9,859,706–10,794,798)	11,952,122 (11,436,478–12,537,800)	11,785,322 (11,299,405–12,322,607)	1,631,944 (1,201,997–2,149,953)	1,465,143 (1,034,764–1,930,023)

Probabilistic sensitivity analysis results, cost are presented in €, year 2024 values, as mean € (95% confidence intervals) on a 5-year timeframe per 100 patients

DMT disease-modifying treatment, EDSS Expanded Disability Status Scale, IV intravenous

^aSevere relapse indicates relapse requiring hospitalization

and society) are shown in their natural units, offering a specific estimation of each and leaving to decision-makers to determine which treatment provides the highest value.

The three DMTs assessed reported similar clinical and social outcomes, where natalizumab slightly reduced disease progression, increased the number of QALYs, and reduced the disease impact on social outcomes: days of productivity loss and informal care. More notably, natalizumab significantly reduced the 5-year treatment costs

compared with ocrelizumab and ofatumumab. Natalizumab also reduced direct non-healthcare costs and indirect costs, albeit this was not statistically significant. Overall, natalizumab resulted in a cost reduction of €1,631,944 (95% CI 1,201,997–2,149,953) versus ocrelizumab and €1,465,143 (95% CI 1,034,764–1,930,023) versus ofatumumab. As reported in the analysis, the cost saving associated with natalizumab was also related to the extended dose regimen that reduced the frequency of administration from every 4

Table 6 Disease-modifying treatment administration times: alternative scenario

Outcomes	5-year value		Difference (Natalizumab SC vs natalizumab IV)
	Natalizumab IV	Natalizumab SC	
Healthcare			
Administration time			
Clinician	497.06 (384.55–622.94)	277.14 (207.50–359.66)	–220.09 (–333.25 to –121.74)
Nurse	1287.47 (1014.44–1642.67)	839.07 (642.73–1057.16)	–448.17 (–743.08 to –194.08)
Chair occupation time	7691.84 (5779.64–9900.88)	4757.86 (3638.36–6127.52)	–2932.60 (–4837.44 to –1444.36)
Indirect			
Day time for administration			
Patient	17,542.03 (13,560.42–22,405.59)	11,950.95 (9179.95–15,135.11)	–5588.73 (–10,083.04 to –1755.41)
Productivity loss			
Patient and society	4022.37 (3054.93–5147.52)	2776.54 (2102.38–3552.48)	–1245.63 (–2263.63 to –383.71)
Society	9866.48 (7560.15–12,504.36)	6748.29 (5134.25–8684.56)	–3112.74 (–5687.23 to –981.43)
Patient loss of time for unpaid activities	7266.21 (5633.04–9260.57)	4698.36 (3521.45–6065.31)	–2564.98 (–4262.30 to –1105.54)
Productivity loss for caregiver	8744.81 (6854.39–10,872.85)	6008.39 (4632.74–7576.55)	–2737.04 (–4771.31 to –977.04)

Probabilistic sensitivity analysis results. Data are presented as mean hours (95% confidence intervals) on a 5-year timeframe per 100 patients

IV intravenous, SC subcutaneous

to every 6 weeks after the first year of treatment in clinical practice [8]. The reduced frequency of natalizumab administration led to a drug saving with similar benefits of the previous 4-weekly regimen, and a drug cost (acquisition, monitoring, and administration) saving of €1,587,648 (95% CI 1,402,707–1,758,598) and €1,329,094 (95% CI 1,179,543–1,470,807) for 100 patients treated, in comparison with ocrelizumab and ofatumumab, respectively. This use of natalizumab and the associated savings pose new considerations in the highly effective treatment approach, also considering the impact on other outcomes and costs.

Other economic evaluations have been published in recent years; however, they were mainly cost-effectiveness analyses and were conducted in Canada, Portugal, and the USA, rather than Italy [43–45]. Further, Baharnoori et al. [43] was the only study that compared the three DMTs included in our analysis. In that study, ofatumumab was compared with ocrelizumab in a base-case analysis and with natalizumab in an alternative scenario analysis. The study was conducted from a Canadian healthcare service perspective, reporting ofatumumab as a dominant option compared with ocrelizumab (Δ cost: \$CAN – 41,817 [95% CI –43,364 to –40,270]; Δ QALY: 0.132 [95% CI 0.091–0.173]) and compared with natalizumab (Δ cost: \$CAN – 126,818 [95% CI –128,603 to –125,032]; Δ QALY: 0.139 [95% CI 0.103–0.174]). It is always challenging to compare analyses that use the viewpoints of two different healthcare services, first because we have different costs and tariffs, but also because, in this case, the studies reported differences in the methods and data input. The Canadian analysis used the same NMA as a reference for the relative efficacy data of

ofatumumab compared with ocrelizumab and natalizumab; however, the analysis used the CDP-6 HR estimated using the OPERA-aligned criteria instead of the HR obtained using the predefined criteria of the ofatumumab trial [35]. We used the HR based on the predefined criteria of the ofatumumab trial, given that these were the criteria applied in the trial and considering that the use of OPERA criteria are more appropriate for a comparison with only ocrelizumab. Furthermore, the Canadian analysis was conducted using natalizumab 300 mg every 4 weeks instead of the extended dose regimen used in our analysis.

One other CCA has been published in the literature [46], but it estimated the medium-/long-term clinical and health economic effects of an immediate initiation of the anti-CD20 monoclonal antibodies ocrelizumab and ofatumumab (at time of first treatment) compared with an early (after 1 year), a late (after 5 years), and no switch to anti-CD20 after standard DMT (dimethyl fumarate or glatiramer acetate) in patients with relapsing MS from the societal perspective in Germany. This analysis, which did not include natalizumab, showed that immediate use of anti-CD20 or an early switch to anti-CD20 was associated with an overall better health state, higher productivity, and cost neutrality compared with no switch from standard DMTs over the 5- and 10-year time horizons. We know of one other CCA that has been conducted in the treatment of MS, but this analysis compared peg-interferon beta-1a with subcutaneous interferon beta-1a and did not include treatment with natalizumab [47].

Our study also performed an alternative scenario analysis comparing intravenous and subcutaneous natalizumab formulations approved by the European Medicines Agency and

recently reimbursed in Italy. This scenario analysis was performed to assess and compare more specific effects (times and costs) associated with administration from the perspectives of the MS center, patients, and society. In this scenario, subcutaneous natalizumab improved all outcomes compared with intravenous natalizumab, saving the time of healthcare professionals, patients, and caregivers and reducing the costs associated with administration. These findings suggest that the subcutaneous formulation of natalizumab would further enhance the benefits of the intravenous formulation, in terms of both direct costs (administration) and indirect costs (informal care and productivity loss).

This economic evaluation also had some limitations. The health states included in the model were based on EDSS level, which focuses on functional mobility without including other important aspects of MS progression such as cognitive impairment [48]. However, the use of EDSS level to define RRMS health states remains the standard approach to building decision analytical models and is accepted by the UK National Institute for Health and Care Excellence health technology assessment agency [49]. The model might underestimate minor changes using integer EDSS values to define health states, but this approach was selected to follow modeling tractability and consistency with published literature and previous HTA assessment [41, 43–46, 49]. Furthermore, EDSS is widely used by neurologists in clinical practice to monitor changes in the level of disability over time. Economic evaluation based on decision-analytical models rely on data from different sources, so differences between studies used to retrieved data input bring additional limitations. Some studies, such as that used for the MS natural history and EDSS progression, were based on data collected from 1980 to 1995 and so may be outdated. However, they are probably the most robust data that can be used to model the natural history of MS with an adequate observation period. The model assumed that patients moving to SPMS continued to be treated and were subject to the same transition probabilities as patients with RRMS and did not include specific natural history data related to SPMS. The assumption that patients with SPMS continued to be treated is consistent with study populations in the recent ASCLEPIOS I & II and OPERA [19] trials. Furthermore, the transition to SPMS is not easy to diagnose because many different clinical definitions exist, and it is often diagnosed retrospectively, meaning that patients likely do not discontinue treatment at the time of progression to SPMS. Efficacy data come from an indirect treatment comparison of clinical trials with adjusted outcomes and short study periods. However, the populations included in the different studies are similar enough to allow the NMA. Furthermore, we chose the efficacy data obtained from the more robust analysis, considering the inclusion of natalizumab, ofatumumab, and ocrelizumab: time to 6-month confirmed disability progression and predefined

criteria of ofatumumab trial as outcome, instead of selecting sub-analysis based on other specific trials such as OPERA. In the model, we assumed a switch to a second highly effective treatment after the failure or discontinuation of the first for any reason. We chose to simulate a transition to a hypothetical DMT treatment with efficacy and cost calculated as the average of efficacy and cost of the three alternatives evaluated in the base-case scenario. This choice was made to avoid the issue associated with the treatment sequence, the possible effect associated with different DMTs after the first, and the creation of treatment sequences in which reliable data on different efficacy are lacking. Moreover, a sensitivity analysis regarding the model assumption on efficacy and costs of second-line treatment confirmed that outcomes or costs are not biased by model assumption. Furthermore, this method balances the effect and cost of the second therapy, allowing a focus on the impact of the first treatment and providing a more accurate comparison between the three DMTs used at the beginning of the simulation. Moreover, the alternative scenario analysis was limited to natalizumab formulations because no administration-specific data for ocrelizumab and ofatumumab were available. Finally, in the model, we were unable to capture the difference between the three DMTs assessed in terms of pregnancy and vaccination. Natalizumab exposure in pregnancy has not been associated with specific fetal malformations or increased miscarriage risk, but there are still no adequate data on ocrelizumab and ofatumumab [50]. Although there is no evidence that natalizumab can influence the efficacy of vaccines, B-cell-depleting agents such as ocrelizumab and ofatumumab have been associated with blunted humoral responses to several vaccines [51]. These aspects can improve the actual benefit–cost profile of natalizumab compared with the other two DMTs.

5 Conclusion

To our knowledge, this is the first CCA to assess in detail all effects associated with natalizumab, ocrelizumab, and ofatumumab from the Italian perspective. The results showed a significant cost reduction associated with natalizumab compared with ofatumumab and ocrelizumab and a positive trend in clinical improvements, including fewer relapses and less disability progression, alongside societal effects improvements such as increased patient productivity and reduced caregiver burden. Further, the subcutaneous natalizumab formulation resulted in a positive impact on time, resource consumption, and costs associated with administration compared with the intravenous formulation.

This study provides useful information to help health-care decision makers understand the effects associated with these treatments, giving the opportunity to focus on

those considered more relevant for their viewpoint and the context in which the decisions are taken.

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Declarations

Conflict of interest R Bergamaschi has received honoraria for speaking from Biogen, Merck Serono, Roche, Novartis, Celgene, Janssen, and Sanofi Genzyme; research grants from Biogen, Merck Serono, Roche, Novartis, and Sanofi Genzyme; and congress and travel/accommodation expenses from Biogen, Merck Serono, Roche, Novartis, and Sanofi Genzyme. V Brescia Morra has received research grants from the Italian MS Society and Roche and honoraria from Bayer, Biogen, Merck, Mylan, Novartis, Roche, Sanofi-Genzyme, and Teva. L Prosperini has received consulting fees from Biogen, Merck, Novartis, and Roche; speaker honoraria from Biogen, Genzyme, Merck, Serono, Novartis, Roche, and Teva; travel grants from Biogen, Genzyme, Novartis, Roche, and Teva; and research grants from the Italian MS Society (Associazione Italiana Sclerosi Multipla) and Genzyme. PA Cortesi has received speaker honoraria from Novartis and Roche. C Fornari has no conflicts of interest. D Perini and L Santoni are employees of and may hold stock in Biogen.

Ethical approval Ethical approval is not required for simulation-based studies in the present study's jurisdiction.

Consent to participate Not applicable.

Consent for publication Not applicable.

Data and code availability Model input data are available within the paper, and simulation models are available upon request.

Author contributions All authors contributed to the development of the economic model and approved its final version. All the authors revised and approved the conducted analyses and results. All authors are responsible for the revision of the manuscript. All authors read and approved the final version of the manuscript.

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Authors and Affiliations

Luca Prosperini¹ · Vincenzo Brescia Brescia Morra^{2,3} · Carla Fornari⁴  · Laura Santoni⁵ · Daria Perini⁵ · Roberto Bergamaschi⁶ · Paolo Angelo Cortesi^{4,7}

✉ Carla Fornari
carla.fornari@unimib.it

¹ Department of Neurosciences, MS Centre, S. Camillo-Forlanini Hospital, Rome, Italy

² Multiple Sclerosis Unit, Policlinico Federico II University Hospital, Naples, Italy

³ Department of Neuroscience, Reproductive Science and Odontostomatology, University of Naples Federico II, Naples, Italy

⁴ Research Centre on Public Health (CESP), University of Milano-Bicocca, Via Cadore 48, Monza, Italy

⁵ Biogen Italia, Milan, Italy

⁶ IRCCS Mondino Foundation, Pavia, Italy

⁷ Laboratory of Public Health, IRCCS Istituto Auxologico Italiano, Milan, Italy