Cost-Effectiveness Analysis of Dimethyl Fumarate in the Treatment of Relapsing Remitting Multiple Sclerosis: An Italian Societal Perspective

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ABSTRACT
BACKGROUND: Delayed-release dimethyl fumarate (also known as gastro-resistant dimethyl fumarate, hereafter dimethyl fumarate) is an oral disease-modifying therapy used for the treatment of Relapsing-Remitting Multiple Sclerosis (RRMS), an autoimmune chronic inflammatory condition of the central nervous system.
OBJECTIVE: The objective of this economic analysis was to compare cost-effectiveness of dimethyl fumarate with the alternatives used as first-line treatment of RRMS in Italy.
METHODS: The analysis was conducted from the Italian societal perspective. Health outcomes and costs were evaluated over a 50-year time horizon (equivalent to a lifetime horizon). Both health outcomes and costs were discounted at 3.5%. The cost-effectiveness analysis was conducted by adapting a Markov model, already used in previous similar economic analyses conducted in RRMS, to the Italian context. The Markov model estimated the clinical and economic consequences of treating RRMS patients with the following therapeutic options: dimethyl fumarate; interferon (IFN) beta-1a subcutaneous (SC) at two different doses, 22 mcg and 44 mcg; IFN beta-1b SC; glatiramer acetate (GA) SC 20 mg; oral teriflunomide. Clinical efficacy data were retrieved from an elaboration of an already published mixed treatment comparison (MTC). Both direct and indirect costs (disability, treatment acquisition, administration, monitoring, relapses, adverse events) were included in the analysis. One-way and probabilistic sensitivity analyses were carried out and cost-effectiveness acceptability curves generated.
RESULTS: In the base-case analysis, dimethyl fumarate was more efficacious than alternatives, in terms of both survival (19.634 vs. 19.440-19.600 life years for alternatives), and quality-of-life-adjusted survival (6.526 vs. 5.143- 6.189 QALYs for alternatives). The total lifetime cost per patient treated with dimethyl fumarate (€ 954,286) was lower than that of the other DMTs included in the analysis. Therefore, dimethyl fumarate was dominant compared with all analyzed alternatives. Dimethyl fumarate was also the therapeutic option with the highest benefit on disease burden. In fact, costs of disability management were lower than those of all the other first-line drugs included in the analysis. The results of one-way deterministic sensitivity analysis and probabilistic sensitivity analysis confirmed the reliability of base-case results.
CONCLUSIONS: The results of the cost-effectiveness analysis confirm that dimethyl fumarate is an optimal first-line treatment for RRMS in Italy, compared with the other first-line alternatives included in the economic analysis, when evaluated from the societal perspective.
Keywords
Dimethyl Fumarate, Disease-Modifying Therapy, Relapsing-Remitting Multiple Sclerosis, Cost-Effectiveness, Society
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heavily affect patients’ quality of life, and trigger considerable societal costs [3,4]. The annual cost of MS in Italy is estimated at € 5 billion [2]. The estimated average cost per patient/year from the perspective of the Italian society (i.e., including direct and indirect costs) amounts to € 45,000 [2]. It varies from € 22,900 in patients with mild disability (Expanded Disability Status Scale [5] (EDSS) score: 0-3), to € 40,100 in patients with moderate disability (EDSS: 4-6.5), to € 53,300 in patients with severe disability (EDSS: 7-9) [6]. Relapsing-remitting multiple sclerosis (RRMS) is the most common form of MS, accounting for 65% of the total number of MS patients worldwide [7]. Prevention of relapses and control of disability progression are by far the most important clinical objectives in RRMS. Over the last decades, the introduction of disease-modifying therapies (DMTs) contributed to change the natural history of RRMS and improve patients’ health status. First-line treatments such as interferon (IFN) beta and glatiramer acetate (GA) showed to be effective in limiting the neurological activity of the disease, reducing the risk of relapse, and delaying disability progression [8-11]. Nevertheless, an unmet clinical need in RRMS still remained. A certain proportion of patients do not adequately respond to these first-line DMTs. Furthermore, the use of first-line injectable therapies is associated with tolerability issues, most commonly with flu-like symptoms and injection site reactions, that may negatively impact on the quality of life and adherence [12]. More recently, novel treatments have been approved for the RRMS treatment, thus offering physicians and patients new options to contain the burden of the disease [13-15]. The development of these new oral therapies (delayed-release dimethyl fumarate also known as gastro-resistant dimethyl fumarate [15,16] and teriflunomide [14,17]) has been carried out to address the above-mentioned unmet needs in RRMS, simplify treatment paradigm, improve quality of life and provide therapeutic options with a different mechanism of action, compared to injectable therapies.

The objective of the analysis was to compare the cost-effectiveness profile of delayed-release dimethyl fumarate (hereafter defined as "dimethyl fumarate", for simplicity), vs. different alternatives used as first-line treatment of RRMS in Italy from the societal perspective. In this evaluation, the costs were measured in monetary units (euros) and the clinical effects in quality-adjusted life years (QALYs).

MATERIALS AND METHODS

Study design

The present cost-effectiveness analysis was conducted by adapting a Markov model (Figure 1), already used in previous, similar economic analyses conducted in RRMS [18-20], to the Italian context. The Markov model simulates the clinical history of the study population and estimates the clinical and economic consequences of treating with different first-line therapeutic options available in Italy. Pharmacological treatments of RRMS slow disability progression, occurrence of relapses, positively affecting quality of life, and favorably impacting life expectancy and costs. At the beginning of the simulation (baseline), patients are affected by RRMS and their disability level (measured through the EDSS [5]) can range from 0 to 6. Over time, EDSS score of each patient may increase (due to disability progression), decrease (disability remission), or stay unchanged (disability maintenance). Additionally, patients may have a certain risk of progressing to Secondary Progressive Multiple Sclerosis (SPMS). The probability of disability progression depends on MS form (RRMS or SPMS) and on EDSS score. The model consists of 21 health states: 10 states corresponding to the possible 10 disability levels (i.e. EDSS scores) in the RRMS form; 10 states corresponding to the possible 10 EDSS disability levels in the SPMS form; 1 death health state. The Markov model is based on one-year cycles. It was assumed that: i) treatments did not have any effect in preventing transition from RRMS to SPMS and in delaying disability progression in the SPMS form; ii) RRMS patients with EDSS score ≥7, and patients affected by SPMS (any EDSS level) did not receive disease-modifying treatment.

The model captures the most relevant clinical outcomes in RRMS, such as disability progression (through EDSS levels), occurrence of relapses, transition from RRMS to SPMS, and finally mortality of patients. As a result, it is possible to estimate patients’ overall survival (measured in life-years: LYs), quality-of-life-adjusted survival (measured in quality-adjusted life-years: QALYs), and overall costs.

In the analysis, dimethyl fumarate (TECFIDERA® – Biogen Netherlands B.V.) was evaluated vs. some of other pharmacological therapies used for the first-line treatment of RRMS in Italy: i) IFN beta-1a, subcutaneous (REBIF® 22 mcg; REBIF® 44 mcg – Merck Europe B.V);
ii) IFN beta-1b, subcutaneous (BETAFERON® – Bayer AG, EXTAVIA® – Novartis Europharm Ltd); iii) GA 20 mg, subcutaneous (COPAXONE® 20 mg – Teva Pharmaceuticals Ltd), iv) teriflunomide, oral (AUBAGIO® – Sanofi-Aventis Groupe). A societal perspective (including direct and indirect costs) was adopted to estimate the cost-effectiveness profile of the single alternatives over a 50-year time horizon (lifetime, considering that the analysis applies to a population of subjects in adulthood at the beginning of the simulation). Based on The National Institute for Health and Care Excellence (NICE) recommendations [21], a discount rate of 3.5% was applied to both the costs and the clinical results of the model after the first year of simulation.

Data source

Baseline characteristics

The study population was a hypothetical cohort of Italian RRMS patients who were eligible to first line DMTs. Patients’ clinical characteristics at baseline (age, gender, EDSS score) were derived from dimethyl fumarate clinical trials (CONFIRM [22], DEFINE [23]). The mean age of the cohort at the beginning of the simulation was 37.8 years and the percentage of male patients was 28.6%. The average EDSS score was 2.72; the initial distribution of the EDSS score is reported in Table I.

The probabilities used to describe the natural history of the disease were derived from the dimethyl fumarate clinical trials (CONFIRM [22], DEFINE [23]) and from the London Ontario database, one of the most comprehensive and long-lasting observational registries on patients with multiple sclerosis, which collected patient information between 1972 and 2000 [24-26].

The annual relapse rates in absence of treatment were obtained from the dimethyl fumarate clinical trials [22,23], which documented relapse occurrence in the 12 months preceding study entry, for patients with EDSS <5. The trend of relapses for EDSS levels >5 was obtained from the study conducted by Patzold et al. [27]. Finally, relapse incidence data for patients affected by SPMS were obtained from the elaboration of a survey conducted in the UK [28].

Mortality rates, stratified by age and gender, were extracted from national registries of the Italian Statistics Institute (ISTAT) [29]. Such mortality rates have been adjusted by the additional death risk attributable to MS [30].

Furthermore, the impact of treatment-related adverse events (AEs) was assessed. For all the evaluated drugs, only serious and non-serious AEs occurring in dimethyl fumarate registrative studies were considered. All common AEs of dimethyl fumarate (annual incidence ≥5%) were included in the analysis. In addition, all AEs occurring with an annual incidence difference ≥3% between dimethyl fumarate and placebo were included in the analysis, regardless of the incidence of the event in the dimethyl fumarate group. The annual incidence of treatment-related AEs was calculated from a systematic review of the literature [31], using a weighted average between the studies.

<table>
<thead>
<tr>
<th>Baseline data</th>
<th>EDSS level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proportion of patients (%)</td>
<td>0 1 2 3 4 5 6 7 8 9</td>
</tr>
<tr>
<td>5.05</td>
<td>8.52 34.08 22.94 20.64 8.65 0.12 0.00 0.00 0.00</td>
</tr>
<tr>
<td>ARR – RRMS form, natural history (n. of events per year)</td>
<td>1.26 1.32 1.32 1.35 1.36 1.43 1.18 1.23 1.23 1.23</td>
</tr>
<tr>
<td>ARR – SPMS form, natural history (n. of events per year)</td>
<td>0.00 0.00 0.91 1.64 1.05 1.27 1.10 0.82 0.82 0.82</td>
</tr>
</tbody>
</table>

Table I. Baseline distribution by EDSS and related ARRs, in absence of treatment [22-28]

ARR = Annualized Relapse Rate; EDSS = Expanded Disability Status Scale; RRMS = Relapsing-Remitting Multiple Sclerosis; SPMS = Secondary Progressive Multiple Sclerosis
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**Clinical data**

Annual disability transition probabilities in the untreated population (measured through EDSS scores) were derived from dimethyl fumarate clinical trials (CONFIRM [22], DEFINE [23]) for RRMS EDSS states up to 7 and from the London Ontario dataset [24] for RRMS EDSS states 7-9 and for the SPMS form (see Appendix, Table I). Transition probabilities from RRMS to SPMS were derived from the London Ontario dataset [24] (see Appendix, Table IIA). Pharmacological treatment has the effect of modifying the natural evolution of the disease, by: i) limiting or delaying the progression towards higher levels of EDSS in the RRMS form; ii) decreasing the burden of relapses. Both clinical efficacy results were derived from an elaboration of the Mixed Treatment Comparison (MTC) conducted by Hutchinson et al. [32] which allowed to separate the specific values for each single interferon from pooled IFN treatments values. The MTC allows to calculate the hazard ratio values for disability worsening confirmed at 3 months (CDW3M) and risk ratio of incidence of relapses, for all active drugs, compared to a common comparator (placebo). Both efficacy results of the effect of treatments on ARR and CDW3M are summarized in Table II.

**Quality of life data**

Utilities of patients affected by RRMS, stratified by EDSS level, were obtained from dimethyl fumarate trial data, organizing the observations for each EDSS state and calculating the average EuroQoL 5 dimensions (EQ-5D-5L) score for each state [22,23]. Data are shown in Table III. Disutilities associated with SPMS disease states, as well as disutilities associated with relapse occurrence, were obtained by correcting RRMS-related utility values collected in dimethyl fumarate trials, for deterioration factors (i.e., disutilities), obtained from the survey conducted in the UK [28]. The disutility factors associated with SPMS and relapse occurrence (applied on an annual basis in both cases) amounted to -0.0437 and -0.0092, respectively.

The model incorporated disutilities for AEs; such disutilities depend on the type of AE and the degree of severity (serious/non-serious) and have a temporary effect on patients’ quality of life (from a minimum of one day per year up to a maximum of six months per year, for some events such as fatigue and flu-like symptoms). Since all data were not available in literature, these values have been estimated and validated by clinical experts.

**Economic data**

According to the societal perspective, this economic analysis considered the following costs: disability, treatment acquisition, administration, monitoring, relapses, AEs.
Disability-related costs, including indirect costs, were obtained from the study conducted by Karampampa et al. [33]. To date, this is the only Italian study that evaluated costs by MS form. Table IV reports disability-related costs included in the model, expressed in euros inflated to June 2018 [34]. For EDSS levels 0-6 in RRMS form only costs for co-medications are included. The costs for DMTs and other disease management costs (e.g., monitoring, etc.) are considered in other calculation sections of the model.

The economic impact of pharmacological treatment was expressed as annual cost per patient calculated on the ex-factory price per pack (Table V), net of temporary law reductions and discounts applied to public structures of Italian NHS, multiplied by the number of units needed to cover 1 year of treatment.

Administration costs were assumed equal to € 0 as all treatments included in the analysis can be self-administered. Annual monitoring costs were calculated assuming that the patients would be compliant with main monitoring recommendations for RRMS [40] (Table VI), depending on the event.

Sensitivity analyses

Both univariate deterministic and multivariate probabilistic sensitivity analyses were conducted to identify model parameters with the largest effect on incremental...
cost-effectiveness ratio (ICER), and to evaluate the overall robustness of the base-case analysis. In the deterministic sensitivity analysis, the value of each parameter was separately varied to assess the impact on the results. For the deterministic analysis, parameter variation of ±10% around the base-case values were used (analyzed inputs: EDSS state costs, relapse costs, patient utilities, natural history relapse rates, dimethyl fumarate relapse rate, dimethyl fumarate disability progression rate and dimethyl fumarate drop-out rate).

Two additional deterministic sensitivity analyses were conducted as described below.

In the first analysis, disability costs by EDSS (extracted from Karampampa et al. and Ianuzzo et al. studies [33,45]) were replaced with costs from Battaglia et al. 2017 study [6]. This study was published more recently, but it did not report stratification of costs by MS form (i.e. RRMS vs. SPMS form). To fill this data gap, a RRMS vs. SPMS cost-ratio was calculated from Karampampa et al. study, and then applied to Battaglia’s cost estimates to determine the costs of the two forms of MS considered in the model.

In the second analysis, a comparison between dimethyl fumarate and generic GA 20 mg (COPEMYL® – Mylan S.p.A.) recently placed on the market in Italy [46] was conducted to measure the ICER difference vs. base-case.

The probabilistic sensitivity analysis was performed by simultaneously and randomly varying (through 1,000 replications) the values of all parameters. For the probabilistic analysis, the following probability distributions were used: lognormal for clinical variables (relapse risk reduction, disability progression hazard ratio, AEs incidence, etc.); beta for probabilities and utilities; gamma for costs.

RESULTS

Base-case

In the base-case analysis, dimethyl fumarate was more effective than comparators, both in terms of survival (19.634 LYs, compared with 19.440-19.600 LYs for alternatives), and quality-of-life-adjusted survival (6.526 QALYs, compared with 5.143-6.189 QALYs discounted for alternatives) (Table VII). The total lifetime cost per patient treated with dimethyl fumarate (€ 954,286) was lower than for the other alternatives included in the analysis (€ 962,893-1,007,743) (Table VII).

Therefore dimethyl fumarate was dominant (i.e., more effective and less costly) compared with IFNs, GA and teriflunomide, with an ICER ranging between € -20,627 and € -38,639, significantly below the willingness-to-pay (WTP) threshold of € 50,000 per QALY gained [47,48] (Table VII illustrates the results of the cost-effectiveness analysis).

Dimethyl fumarate was the therapeutic option with the highest benefit on disease burden. In fact, costs of disability management were lower than those of all the other first-line drugs included in the analysis.

Table VII. Results of cost-effectiveness analysis (base-case)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Pharmacological therapy costs + monitoring costs (€)</th>
<th>Disability costs related to EDSS (€)</th>
<th>Total costs (€)</th>
<th>Survival (LYs)</th>
<th>Quality of life adjusted survival (QALY)</th>
<th>ICER per LY (DMF vs. alternative)</th>
<th>ICER per QALY (DMF vs. alternative)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dimethyl fumarate – 240 mg</td>
<td>94,915</td>
<td>859,370</td>
<td>954,286</td>
<td>19.634</td>
<td>6.526</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>IFN beta-1a – 22 mcg</td>
<td>64,986</td>
<td>904,570</td>
<td>969,556</td>
<td>19.533</td>
<td>5.786</td>
<td>DMF dominates</td>
<td>DMF dominates</td>
</tr>
<tr>
<td>IFN beta-1a – 44 mcg</td>
<td>86,436</td>
<td>876,457</td>
<td>962,893</td>
<td>19.600</td>
<td>6.189</td>
<td>DMF dominates</td>
<td>DMF dominates</td>
</tr>
<tr>
<td>IFN beta-1b1 – 250 mcg</td>
<td>66,556</td>
<td>941,187</td>
<td>1,007,743</td>
<td>19.440</td>
<td>5.143</td>
<td>DMF dominates</td>
<td>DMF dominates</td>
</tr>
<tr>
<td>IFN beta-1b2 – 250 mcg</td>
<td>62,121</td>
<td>941,187</td>
<td>1,003,308</td>
<td>19.440</td>
<td>5.143</td>
<td>DMF dominates</td>
<td>DMF dominates</td>
</tr>
<tr>
<td>Glatiramer acetate – 20 mg</td>
<td>61,029</td>
<td>932,747</td>
<td>993,776</td>
<td>19.459</td>
<td>5.341</td>
<td>DMF dominates</td>
<td>DMF dominates</td>
</tr>
<tr>
<td>Teriflunomide – 14 mg</td>
<td>72,705</td>
<td>898,792</td>
<td>971,497</td>
<td>19.547</td>
<td>5.953</td>
<td>DMF dominates</td>
<td>DMF dominates</td>
</tr>
</tbody>
</table>

*a*Betaferon
*b*Extavia

DMF = Dimethyl Fumarate; EDSS = Expanded Disability Status Scale; ICER = Incremental Cost-Effectiveness Ratio; IFN = interferon; LY = Life-Year
Sensitivity analysis

One-way deterministic sensitivity analysis showed that in almost all tested alternative scenarios dimethyl fumarate remained dominant. Only in two cases dimethyl fumarate was not dominant: i) +10% dimethyl fumarate disability progression rate, vs. IFN beta-1a – 22 mcg (ICER = € 3,161 per QALY gained); ii) +10% dimethyl fumarate disability progression rate, vs. IFN beta-1a – 44 mcg (dimethyl fumarate and IFN beta-1a – 44 mcg had similar costs and similar efficacy).

In the two additional deterministic scenarios tested (disability costs from Battaglia et al. [6] and comparison between dimethyl fumarate and generic GA 20 mg) dimethyl fumarate remained dominant.

Figure 2 shows the results of probabilistic sensitivity analyses, expressed in terms of probability for dimethyl fumarate to be cost-effective or dominant (lower cost and higher health outcomes) with respect to the therapeutic alternatives included in the analysis. Overall, the cost-effectiveness profile of dimethyl fumarate was favorable, since the probability of being dominant compared to the alternatives included in the model was between around 61% and 92% and the probability of being cost-effective was between approximately 67% and 96% with a WTP threshold of € 50,000 per QALY gained [47,48].

DISCUSSION

The objective of this economic analysis was to compare cost-effectiveness of first-line alternatives used for the treatment of RRMS, from the Italian societal perspective. To our knowledge, this is one of the first Italian economic analyses adopting a societal perspective as primary analysis. Most economic analyses in Italy are designed to inform budget holders and reimbursement decision makers regarding direct costs supported by the Italian National Healthcare Service (NHS). Although this approach is reasonable and is usually recommended, we believe that any comprehensive health economic analysis should present results under a societal perspective as well, at least in the context of a sensitivity analysis, especially for those conditions, such as multiple sclerosis, where the societal component is extremely relevant. As shown in several economic reports [3,6,33], costs for reduced/lost productivity, out-of-pocket expenses, formal and informal caregiving, home adaptations, etc. have a significant economic impact on patients, families and, more broadly, on the entire social system.

The results of these one-to-one comparisons between dimethyl fumarate and some of the other available options in first-line RRMS show that dimethyl fumarate is a cost-effective option in the treatment of RRMS. In all comparisons dimethyl fumarate resulted dominant (lower costs and better health outcomes) vs. all the alternatives included in the analysis.

Figure 2. Probabilistic sensitivity analysis: acceptability curves of dimethyl fumarate vs. therapeutic alternatives included in the analysis.

1 Betaferon®
2 Extavia®
IFN = interferon
Furthermore, the results of one-way deterministic and probabilistic sensitivity analyses confirm the reliability and robustness of base-case results quite convincingly. Two additional scenarios were evaluated. In the first scenario, disability costs by EDSS used in the base-case were replaced with costs reported by Battaglia et al. [6]. This study was published more recently but did not report stratification of costs by MS form (i.e. RRMS vs. SPMS form). To fill this data gap, a RRMS vs. SPMS cost-ratio was calculated from Karampampa et al. study [33] used in the base-case, and then applied to Battaglia’s cost estimates to determine the costs of the two forms of MS. Dimethyl fumarate remained dominant in this additional scenario. In the second scenario, a comparison between dimethyl fumarate and generic GA 20 mg recently placed on the market in Italy [46] was conducted to measure the ICER difference vs. base-case. Dimethyl fumarate remained dominant also in this scenario.

This analysis, adopting the Italian societal perspective, reinforces the findings of a previous analysis conducted on dimethyl fumarate and adopting the Italian NHS perspective [49]. Furthermore, the results from the Italian analysis are in line with those reported for USA [50] and other countries of Europe [51-55].

In the context of any economic assessment, it is worth critically appraising the methodology of the analysis, and the main limitations. In our view, the most relevant issue of this economic assessment is the absence of head-to-head studies evaluating dimethyl fumarate vs. other active drugs, designed to test superiority of most important endpoints (relapse occurrence, disability progression). The evidence used to conduct the analysis was derived from a MTC published by Hutchinson et al. [32]. Although the precision of the estimates might be lower than a randomized clinical trial as it combines different sources, the MTC is a common and acceptable approach to assess the relative treatment effects of multiple treatments when these data are not available from head-to-head clinical trials. In addition, the number of MTCs published in recent years has increased exponentially [56] and the use of the MTC tool for conducting drug-economic assessments is well established [57]. Moreover, the assessments conducted by NICE and Scottish Medicine Consortium (SMC) on this MTC have not revealed significant methodological weaknesses as well as the review conducted by the authors of the present economic analysis.

A further limitation of the study was that we could not conduct a cost-effectiveness comparison of dimethyl fumarate vs. two alternatives used in first line treatment of RRMS: IFN beta-1a 30 mcg, once a week, intramuscular and GA 40 mg, three times a week, subcutaneous. The primary source used to retrieve clinical efficacy data, the MTC conducted by Hutchison et al. [32], did not report results of such comparators.

Another limitation of this analysis is that we were not able to calculate adjusted, country-specific (i.e. Italian) utility data, as we did not have access to the primary data source (patient level data from registration studies).

Other considerations concern model setting. As shown in the literature, most of the health-economic models in multiple sclerosis are based on the principle that pharmacological treatment reduces both disability progression and relapse burden [20,58-60]. The final consequence of this effect is the delay of EDSS progression and of disease transformation from RRMS to SPMS.

With regards to the optimal outcome choice for modelling, there is an interesting debate about the use of new “holistic” parameters, such as the so called “No Evidence of Disease Activity” (NEDA) [61]. NEDA is a composite parameter that includes the following factors: absence of measurable clinical activity (defined as absence of relapse and absence of progression) and absence of activity measured on magnetic resonance. This parameter could be added to the other two outcomes (relapse, progression of disability) to estimate more accurately the clinical benefits of pharmacological treatment.

These considerations appear important for future assessment, when data on composite outcomes of disease activity will be certainly collected more systematically and will induce health economists to modify the clinical framework of economic models. For the time being, we can only assume that, if there is a correlation among reduction of relapse burden, delayed disability progression, and prolongation of active-disease free survival, then a new health-economic approach based on NEDA should even favor the most effective therapies, thus confirming dimethyl fumarate dominance, in our specific case.

Furthermore, the model configuration is limited to the first line of treatment and cannot simulate the successive sequences of treatment. Although including this factor would better reflect clinical practice in real world, it could however mask the true value of a specific DMT, as any benefits may result from other subsequent treatments and the benefits/costs of subsequent treatments would also be “diluted” from discounting, placing more weight on sooner...
outcomes. Moreover, none therapeutic algorithm is reported in the Italian guidelines for the MS treatment.

Another consideration could be done. The probabilities used to describe the natural history of the disease were derived in part from the London Ontario database, which collected patient information some decades ago between 1972 and 2000. Despite this, even today The London Ontario study is one of the most comprehensive and long-lasting observational registries on patients with multiple sclerosis.

Furthermore, the AEs included in the model are only those of dimethyl fumarate. This is a conservative assumption and likely can impact the results of the analysis against dimethyl fumarate.

Finally, the analysis does not capture the quality-of-life benefits and any intangible costs associated with a potential switch from injectable therapies (such as IFN and GA) and oral therapies, such as dimethyl fumarate (and teriflunomide). Again, a thorough assessment of such benefits is hard to make because of the lack of ad-hoc data, but it is plausible to assume that the quantification of these factors in the analyses could be favorable to oral therapies vs. injectable therapies.

In conclusion, all the limitations acknowledged in this analysis have been managed with the aim of adopting a conservative approach, thus not favoring dimethyl fumarate.

CONCLUSIONS

The results of this cost-effectiveness analysis confirm that dimethyl fumarate is an optimal first-line treatment for RRMS in Italy, compared with the other first-line alternatives included in the economic evaluation, when evaluated from the societal perspective.

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Conflicts of interest
LGM: research grant from Biogen, Almirall, Roche, Bayer. Speaker’s fee from Almirall, Roche, Biogen, Bayer.
GF and RB: EBMA Consulting employees. EBMA Consulting received consulting fees from Biogen Italy for analysis conduction.
PC: research grant from Angelini. Speaker’s fee from Pfizer, Roche.
EP and LS: employees of Biogen Italia
LP: 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; research grants from the Italian MS Society (Associazione Italiana Sclerosi Multipla) and Genzyme.
APPENDIX

<table>
<thead>
<tr>
<th>From EDSS level</th>
<th>To EDSS level</th>
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<td></td>
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<td>Transition probabilities for RRMS form</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>0.311</td>
</tr>
<tr>
<td>1</td>
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</tr>
<tr>
<td>2</td>
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<tr>
<td>3</td>
<td>0.019</td>
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Transition probabilities for SPMS form

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<td></td>
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<tr>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
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<tr>
<td>7</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>-</td>
</tr>
<tr>
<td>9</td>
<td>-</td>
</tr>
</tbody>
</table>

Table IA. Transition probabilities among disability progression levels, by multiple sclerosis form [22–24]

EDSS = Expanded Disability Status Scale; RRMS = Relapsing Remitting Multiple Sclerosis; SPMS = Secondary Progressive Multiple Sclerosis

<table>
<thead>
<tr>
<th>EDSS level</th>
<th>Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
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<tr>
<td>2</td>
<td>0.032</td>
</tr>
<tr>
<td>3</td>
<td>0.117</td>
</tr>
<tr>
<td>4</td>
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<td>7</td>
<td>0.254</td>
</tr>
<tr>
<td>8</td>
<td>0.153</td>
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<tr>
<td>9</td>
<td>1.000</td>
</tr>
</tbody>
</table>

Table IIA. Transition probabilities from RRMS to SPMS form [24]

EDSS = Expanded Disability Status Scale; RRMS = Relapsing Remitting Multiple Sclerosis; SPMS = Secondary Progressive Multiple Sclerosis
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