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Economic Evaluation

Effectiveness and Cost-Effectiveness of 360 Disease-Modifying Treatment Escalation Sequences in Multiple Sclerosis

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ABSTRACT

Objectives: The rapid expansion in treatment options for relapsing-remitting multiple sclerosis (RRMS) of the past decade requires clinical decision making on the sequential prescription of these treatments. Here, we compare 360 treatment escalation sequences for patients with RRMS in terms of health outcomes and societal costs in The Netherlands.

Methods: We use a microsimulation model with a societal perspective, developed in collaboration with MS neurologists, to estimate the effectiveness and cost-effectiveness of 360 treatment sequences starting with first-line therapies in RRMS. This model integrated data on disease progression, disease-modifying treatment efficacy, clinical decision rules, age-dependent relapse rates, quality of life, healthcare, and societal costs.

Results: Costs and health outcomes were overlapping among different treatment escalation sequences. In our model for RRMS treatment, optimal lifetime health outcomes (20.24 ± 1.43 quality-adjusted life-years [QALYs], 6.11 ± 0.30 relapses) were achieved with the sequence peginterferon-dimethyl fumarate-ocrelizumab-natalizumab-alemtuzumab. The most cost-effective sequence (peginterferon-glatiramer acetate-ocrelizumab-cladribine-alemtuzumab) yielded numerically worse health outcomes per patient (19.59 ± 1.43 QALYs, 6.64 ± 0.43 relapses), but resulted in €98 127 ± €19 134 less costs than the most effective treatment sequence.

Conclusions: Effectiveness estimates of treatments have overlapping confidence intervals but the treatment sequence that yields most QALYs is not the most cost-effective option, also when taking uncertainty into account. It is important that neurologists are aware of cost constraints and its relationship with prescription behavior, but treatment decisions should be individually tailored.

Keywords: fully incremental analysis, net health benefit, relapsing-remitting multiple sclerosis, treatment ranking, treatment sequence

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Introduction

Neurologists have seen treatment options for multiple sclerosis (MS) expand rapidly in the past decade. The registration of new disease-modifying therapies (DMTs) provides increasing possibilities to offer patients tailored therapies. These novel therapies are usually classified as first-, second-, and third-line therapies, with an increasing efficacy but also an increasing risk of severe adverse events with increasing lines.[1,2] The main determinants of treatment allocation are the activity and severity of MS, safety issues and comorbidity, side effects, and patient characteristics such as having a pregnancy wish. Although these variables provide guidance in treatment allocation, only a subgroup of patients will continue the first prescribed drug. In a US study based on healthcare claims among patients with incident MS, 28.2% of patients received a second DMT of therapy during at least 1 year of follow-up (median 2.4 years), 5.8% a third DMT, and 0.9% a fourth DMT.[3] According to Dutch healthcare claims data, 40% of patients switched from their initial chosen therapy to a second DMT within 5 years, and 4.6% to a third DMT.[4] The sequential prescription of different drugs is frequently performed, but rarely studied, and hence, it is uncertain which sequence is optimal in terms of avoiding disease progression and reducing relapse rates in relapsing-remitting MS (RRMS).

Nevertheless, effectiveness of treatments is not the sole criterion on which to judge DMTs; the costs of the various treatments should also be taken into account. For example, the expansion of available treatments is associated with an increase in healthcare expenditures on DMTs for MS in The Netherlands from approximately €100 million per year in 2012 to approximately €170 million per year in 2019, an increase of approximately 8% per year. Cost-effectiveness analysis is the most commonly used assessment methodology applied by decision-making bodies such as the National Institute for Health and Care Excellence in England and the Dutch National Health Care Institute.

In this article, we rank 360 treatment sequences on both effectiveness and cost-effectiveness, based on a newly developed decision-analytic model of which the technical details have been published previously in this journal.[5] We estimate the societal costs and effects of all potential treatment sequence options according to the recently developed Dutch clinical guideline of the Dutch Association for Neurology.[2]

Methods

The decision-analytic model we used to identify optimal treatment sequences, of which the methods were published separately,[5] predicts several outcomes for each treatment sequence, such as lifetime relapses, the mean time spent per Expanded Disability Status Scale (EDSS) score, time to secondary progressive MS (SPMS) conversion, quality-adjusted life-years (QALYs), and societal costs. We note that this model simulates an escalation-approach for an average patient with RRMS as has been included in the randomized controlled trials (RCTs) on which this model is based, starting with a first-line DMT treatment.

QALYs

QALYs were calculated by combining length and quality of life (QOL). Length of life was based on mortality rates, and QOL was measured through health profiles of 382 Dutch patients with MS who filled out the general QOL instrument 3-level EQ-5D.[6] This health profile was subsequently transformed to a scale where 0 represents death and 1 represents perfect health (with negative values reflecting "worse than dead" health states), using a country-specific "tariff," which reflects the desirability of these health profiles through the eyes of the general public.[7] QALYs were obtained by multiplying the period spent in each state of health with its value. For example, living 3 years in EDSS 2 would yield $0.782 \times 3 = 2.346$ QALYs whereas living 3 years in EDSS 7 would yield 1.584 QALYs.

Costs

Costs consisted of DMT acquisition costs, other healthcare costs (eg, hospital visits and magnetic resonance imaging [MRI]), productivity losses, and informal care costs.[5] Prices were based on Dutch list prices for DMTs (see Appendix Fig. 1 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2021.11.1363) and the Dutch costing manual for other healthcare consumption.[8] Resource use was based on a Dutch survey among 382 patients with MS.[6] All costs were indexed to 2019 euros.

Decision-Analytic Model Properties

The model simulated the lifetime of an average patient with RRMS that was previously naïve to DMT. The mean age of the patient population and sex distribution was based on the mean age of disease onset (29 years) and proportion of females (74.2%) in the British Colombia Multiple Sclerosis (BCMS) database.[9] The BCMS natural history cohort contained patients meeting the Association of British Neurologists criteria to be eligible for interferon beta and glatiramer acetate, that is, older than 18 years, EDSS $\leq$6.5, and 2 relapses in the previous 2 calendar years. Further details are available in Palace et al.[9] Disease progression was modeled through 19 health states based on the EDSS score and type of MS (RRMS or SPMS; see Appendix Fig. 2 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2021.11.1363).[9] At baseline, patients were equally distributed in the RRMS EDSS 0, 1, 2, and 3 health states. Patients could experience a relapse or die of any state. Productivity losses were included through reduced labor participation in higher EDSS classes and short-term productivity losses when patients experienced a relapse. The model cycle length was 1 year and the time horizon was lifetime. In accordance with Dutch economic guidelines, the analyses were performed from a societal perspective and effects and costs were discounted with 1.5% and 4%, respectively.[8]

Clinical Decision Rules

Authors B.W. and J.S., consultant neurologists of the MS Center "ErasMS" of the Erasmus Medical University Center, provided the following clinical decision rules based on the trajectory for the majority of patients in Dutch clinical practice and the Dutch clinical guideline of the Dutch Society for Neurology.[2] Patients could receive up to 2 first-line treatments, 2 second-line treatments, and 1 third-line treatment, resulting in 360 escalation strategies assuming that patients would not receive the same DMT more than once (Table 1). In our model, fingolimod and ocrelizumab are regarded as second-line therapies in line with the Dutch clinical guideline.[2] Treatment switches were initiated by discontinuation because of side effects or recurring disease activity. After discontinuation on a first-line treatment, patients would switch to a "second first-line" treatment. Nevertheless, if they experienced disease activity (relapse or EDSS score progression), a second-line treatment was initiated (see Appendix Fig. 3 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2021.11.1363). We recognize that ideally the model would reflect the clinical practice of making MRI-informed treatment decisions. Nevertheless, these data were not available for inclusion in the decision-analytic model causing us to rely on estimates of the proportion of the patient population for which a treatment switch would be indicated based on MRI results (see Appendix Table 1 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2021.11.1363). The model has been shown to predict short-term treatment switch with acceptable accuracy reflecting Dutch clinical practice; the model predicted that 52.7% switched to any second DMT and 3.3% to any third DMT within 5 years compared with 50% and 4.6% observed in Dutch claims data.[4,5]

Natural History and Treatment Efficacy

The model estimated the benefit of DMT treatment by applying efficacy estimates from 2 network meta-analyses (NMAs) of RCTs on DMTs to the natural history of an untreated patient population (for details of the NMA, see Appendix 2 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2021.05.020 of Huygens and Versteegh[5]). The BCMS database was used as source for natural history of EDSS progression in patients with RRMS[9]; more details on the transition matrix can be found in our previous publication.[5] The ability of DMTs to delay EDSS progression was modeled by applying a DMT-specific relative risk derived from the NMA to the probability to move to a higher EDSS score in the natural history cohort.[5] The NMA indicated differences between DMTs in relative risks of EDSS progression compared with placebo but with overlapping confidence intervals.

The mean annualized relapse rate (ARR) was based on a random-effects meta-analysis of the ARR reported in placebo arms of the post-2005 RCTs included in the NMA (0.445). As relapses have been shown to decline with age,[10] we applied an age-dependent hazard rate to the mean ARR.[5] This effect is confirmed in analysis of reduction in relapse rates in MS trials by age both in the treated arm of trials (see Appendix Fig. 3 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2021.05.020 https://doi.org/10.1016/j.jval.2021.11.1363 of Huygens and Versteegh[5]) and in the placebo arm (see Dahlke et al[11] and Appendix Fig. 2 in Supplemental Materials found at https://doi.org/1

Table 1. Currently available DMTs in The Netherlands with line allocation according to Dutch practice guidelines.

Line 1	Line 2	Line 3
Dimethyl fumarate 240 mg PO (DIF)	Cladribine 3.5 mg PO (CLA3.5)	Alemtuzumab 12 mg IV (ALE)
Glatiramer 20 mg SC (GLA20)	Fingolimod 0.5 mg PO (FIN)	
Interferon β-1a 30 μg IM (IFNa30)	Natalizumab 300 mg IV (NAT)	
Interferon β-1a 44 μg SC (IFNa44)	Ocrelizumab 600 mg IV (OCR)	
Interferon β-1b 250 μg SC (IFNb250)		
Polyethylene glycol interferon β-1a 125 μg SC (PEG)		
Teriflunomide 14 mg PO (TER14)		

DMT indicates disease-modifying treatment; IM, intramuscularly; IV, intravenously; PO, orally; SC, subcutaneously.

0.1016/j.jval.2021.05.020 of Huygens and Versteegh[5]). Because treatment switching is a function of, among others, relapses, treatment switching is age dependent. For each DMT, an incidence rate ratio derived from the NMA was applied to the modeled natural history ARR to capture the ability of the DMT to prevent relapses.[5]

Analyses

We ranked 360 treatment sequences and a "no DMT treatment" option in terms of effectiveness expressed in lifetime QALYs and cost-effectiveness expressed as "net health benefit" (NHB) (NHB is calculated as where Q is total discounted QALYs, C is total discounted costs, and V is the value of a QALY. Here, the V was set at €50 000 per QALY, which reflects the Dutch willingness to pay threshold for health conditions that cause a loss of 41%-70% of quality-adjusted life expectancy relative to the Dutch average population[12]). Only clinically plausible treatment switches in treatment line were included.

For 3 treatments (the most effective, most cost-effective, and "no DMT treatment"), we report ARR over time, distribution of EDSS state membership over time, and distribution of RRMS/SPMS/death over time. We also estimated the incremental QALYs and costs between the most effective and most cost-effective treatment to indicate how much additional money has to be spent to obtain additional health benefits. Subsequently, we calculate how much population QALYs could be obtained when the additional expenditures associated with prescribing the most effective treatment sequences are used to invest in other healthcare interventions. We do so by using the recent estimates of opportunity costs in healthcare that estimated that €41 000 (95% credible interval €25 900-€110 400) in Dutch cardiovascular hospital care would yield 1 QALY.[13] We performed this calculation assuming a Dutch population of 17 000 patients with MS.[4]

All results presented here are taken from the probabilistic sensitivity analyses (PSAs) to adequately account for uncertainty. This PSA runs the decision-analytic model with different draws from the distribution around parameter values to take into account the impact of changes in parameter values on the results. In other words, the PSA results reflect how certain we can be of our results. The model ran 1000 simulations of 5000 patients in the PSA.

Results

All different treatment escalation sequences were overlapping in efficacy, with no treatment sequence in particular standing out. Based on the mean of the probabilistic analyses, the most effective treatment sequence in our model starts with peginterferon, followed by dimethyl fumarate for patients who discontinue this first-line treatment because of side effects. Patients who have disease activity (relapse or EDSS progression) on either peginterferon or dimethyl fumarate are then switched to second-line treatment ocrelizumab, then natalizumab, and finally third-line treatment alemtuzumab. This sequence yields 20.24 ± 1.43 QALYs, numerically the highest of all 360 sequences. Based on the mean of the probabilistic analyses, the most cost-effective sequence (peginterferon, glatiramer acetate, ocrelizumab, cladribine, alemtuzumab) yields 19.59 ± 1.43 QALYs. The full ranking of 360 treatments and "no treatment" based on effectiveness in our model is provided in Appendix Table 2 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2021.11.1363 and the ranking based on NHB in Appendix Table 3 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2021.11.1363, with a fully incremental analysis in Appendix Table 4 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2021.11.1363. In Table 2, we present the 10 treatment sequences that are optimal in terms of effectiveness and cost-effectiveness.

The most effective and the most cost-effective treatment sequence reduce disease progression in our model. Figure 1 shows that the most benefit is obtained in the earlier (0-3) and later (7-9) EDSS scores.

Similarly, the proportion of patients who transition to SPMS in our model is smaller in the most effective treatment sequence than in the most cost-effective sequence, but with limited impact on mortality (Fig. 2).

In our model, the lifetime average number of relapses per patient without treatment is 13.25 ± 0.13, which is reduced to 6.11 ± 0.30 with the most effective treatment sequence and to 6.64 ± 0.43 for the most cost-effective treatment sequence.

The incremental cost-effectiveness analysis shows that the most effective treatment sequence yields 0.65 ± 0.69 additional QALYs compared with the most cost-effective treatment sequence, at an incremental discounted cost of €98 127 ± €19 134. The uncertainty around these estimates is illustrated in Figure 3. Although the uncertainty in QALYs gained (along the x-axis) is fairly large, the majority of simulations fall above the reference line for cost-effectiveness, suggesting that additional costs are made for highly uncertain additional effects. Alternative uses of healthcare budgets can generate more health. If the 17 000 Dutch patients with MS were to receive the most effective treatment sequence rather than the most cost-effective treatment, this would yield 11 040 ± 11 764 additional lifetime population QALYs at additional lifetime population costs of €1 668 159 492 ± €325 281 757. Using Dutch estimates for opportunity costs, these expenditures could yield 41 504 ± 12 510 QALYs when spent on

Table 2. The 10 most effective and cost-effective treatment sequences (cost-effectiveness ordered on NHB).

10 most effective strategies				
Strategy	**Cost (in Euros)**	**Effect (in QALYs)**	**NHB**	**CE rank**
PEG-DIF-OCR-NAT-ALE	621 808 ± 179 489	20.24 ± 1.43	7.80 ± 3.86	123
PEG-TER14-OCR-NAT-ALE	623 201 ± 180 476	20.21 ± 1.44	7.75 ± 3.89	133
PEG-GLA20-OCR-NAT-ALE	621 830 ± 180 529	20.20 ± 1.44	7.76 ± 3.89	129
PEG-DIF-NAT-OCR-ALE	635 282 ± 181 989	20.00 ± 1.40	7.29 ± 3.88	197
DIF-PEG-OCR-NAT-ALE	630 347 ± 181 777	19.97 ± 1.26	7.36 ± 3.82	188
PEG-TER14-NAT-OCR-ALE	636 846 ± 182 645	19.97 ± 1.41	7.23 ± 3.90	202
PEG-GLA20-NAT-OCR-ALE	635 529 ± 182 638	19.95 ± 1.41	7.24 ± 3.90	200
DIF-IFNb250-OCR-NAT-ALE	629 698 ± 181 901	19.95 ± 1.26	7.35 ± 3.82	190
DIF-IFNa30-OCR-NAT-ALE	630 616 ± 181 964	19.94 ± 1.26	7.33 ± 3.82	194
DIF-IFNa44-OCR-NAT-ALE	630 314 ± 182 085	19.94 ± 1.26	7.33 ± 3.83	193
10 most cost-effective strategies				
Strategy	**Cost (in Euros)**	**Effect (in QALYs)**	**NHB**	**E rank**
PEG-GLA20-OCR-CLA3.5-ALE	523 681 ± 180 819	19.59 ± 1.43	9.12 ± 3.88	36
PEG-DIF-OCR-CLA3.5-ALE	526 968 ± 180 080	19.65 ± 1.41	9.11 ± 3.86	33
PEG-GLA20-CLA3.5-OCR-ALE	509 845 ± 186 076	19.29 ± 1.41	9.10 ± 3.98	77
PEG-TER14-OCR-CLA3.5-ALE	525 898 ± 180 998	19.61 ± 1.42	9.09 ± 3.88	35
PEG-DIF-CLA3.5-OCR-ALE	513 878 ± 184 811	19.36 ± 1.40	9.08 ± 3.95	73
PEG-TER14-CLA3.5-OCR-ALE	512 351 ± 186 010	19.32 ± 1.41	9.07 ± 3.98	75
IFNb250-GLA20-OCR-CLA3.5-ALE	503 720 ± 187 204	19.07 ± 1.26	9.00 ± 3.91	116
IFNb250-DIF-OCR-CLA3.5-ALE	506 869 ± 186 146	19.13 ± 1.23	8.99 ± 3.88	102
IFNb250-GLA20-CLA3.5-OCR-ALE	489 658 ± 192 813	18.78 ± 1.25	8.98 ± 4.02	185
IFNb250-TER14-OCR-CLA3.5-ALE	505 852 ± 187 064	19.09 ± 1.24	8.98 ± 3.90	114

ALE indicates alemtuzumab 12 mg; CE rank, cost-effectiveness rank; CLA3.5, cladribine 3.5 mg; DIF, dimethyl fumarate 240 mg; E rank, effectiveness rank; GLA20, glatiramer 20 mg; IFNa30, interferon β-1a 30 μg; IFNa44, interferon β-1a 44 μg; IFNb250, interferon β-1b 250 μg; NAT, natalizumab 300 mg; NHB, net health benefit; OCR, ocrelizumab 600 mg; PEG, polyethylene glycol interferon β-1a 125 μg; TER14, teriflunomide 14 mg.

cardiovascular care, that is, almost 4 times as much for the same budget.

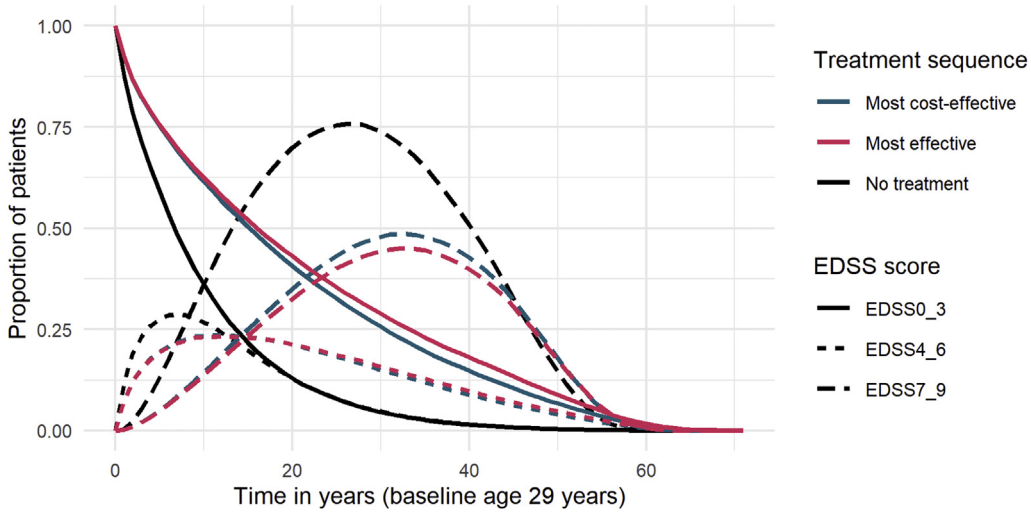
This considerable uncertainty within our model is also present in the other treatment sequences; in Figure 4, overlapping 2 dimensional boxplots for "ocrelizumab and cladribine" and "ocrelizumab and natalizumab" as second-line treatments can be observed, with most uncertainty extending along the y-axis (ie, in costs).

Discussion

Decision-analytic modeling provides an opportunity to integrate different data sources and to estimate the total lifetime benefit of treatment sequences in MS. The results presented here integrate disease progression from MS registries, DMT efficacy from RCTs in an NMA, age-dependent relapse hazard rate from health insurance data, QOL and medical consumption data from a cross-sectional survey data in patients with MS, and clinical decision rules from neurologists. We demonstrated that the most effective treatment escalation sequences are not the most cost-effective treatment sequences and show that implementing the most effective treatment sequences in the treatment of patients with MS according to our model could reduce resources available for overall population health. A methodological insight is that the common health technology assessment method of using a fully incremental analysis has downsides when comparing a large number of treatment alternatives. For example, the treatment sequence that ranks fifth in terms of cost-effectiveness (peginterferon-dimethyl fumarate-cladribine-ocrelizumab-alemtuzumab, NHB = 9.08 ± 3.95) is extendedly dominated in the fully incremental analysis. This shows that the fully incremental analysis is useful to identify the most cost-effective sequence, but may not be informative for clinicians who wish to be able to choose from a set of the most cost-effective sequences that perform fairly similar in terms of NHB.

Indeed, despite numerical differences, our model results on the effectiveness of treatment sequences do not reveal major outliers. Therefore, besides showing trends, it does not clearly favor a priori any sequence for the individual patient. This information could be of use when neurologists and patients discuss potential treatment switches. This discussion is and should remain centered around individual patient characteristics and preferences. Regarding cost-effectiveness, our model may help to raise awareness among policy makers and neurologists that choices regarding therapy have a consequence on how much health can be gained in a population given healthcare budget constraints. In the development of the MS market, novel therapeutic approaches with more favorable ratios of costs and QALYs could have a profound impact on clinical decision making in the consultation room.

Figure 1. EDSS state membership over time. Most cost-effective treatment sequence: peginterferon, glatiramer acetate, cladribine, ocrelizumab, alemtuzumab. Most effective treatment sequence: peginterferon, dimethyl fumarate, ocrelizumab, natalizumab, alemtuzumab.



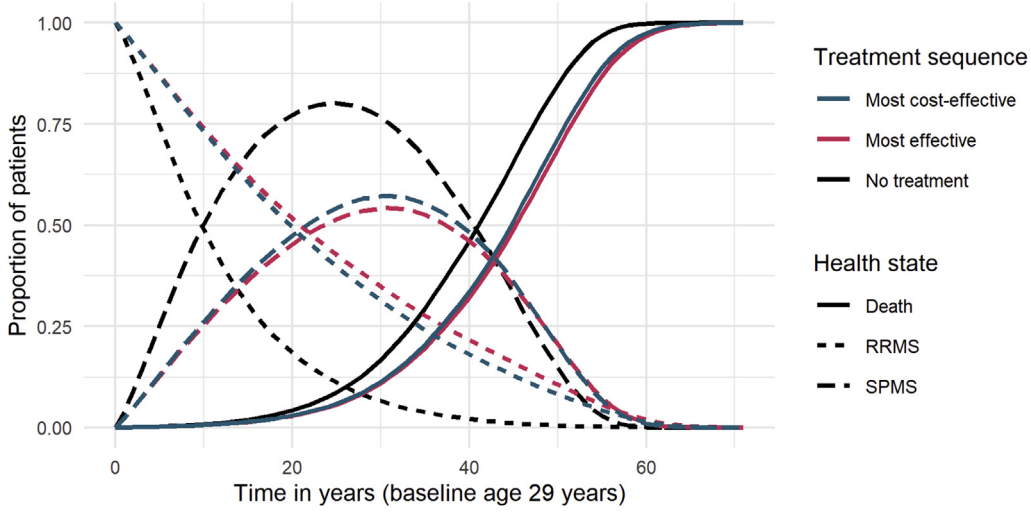
EDSS indicates Expanded Disability Status Scale.

Limitations

The 3 most important limitations that are inherent to the design of our decision-analytic model are the use of NMA for the estimation of DMT efficacy, the limited applicability of the model to individual patients with MS, and the clinical decision rules.

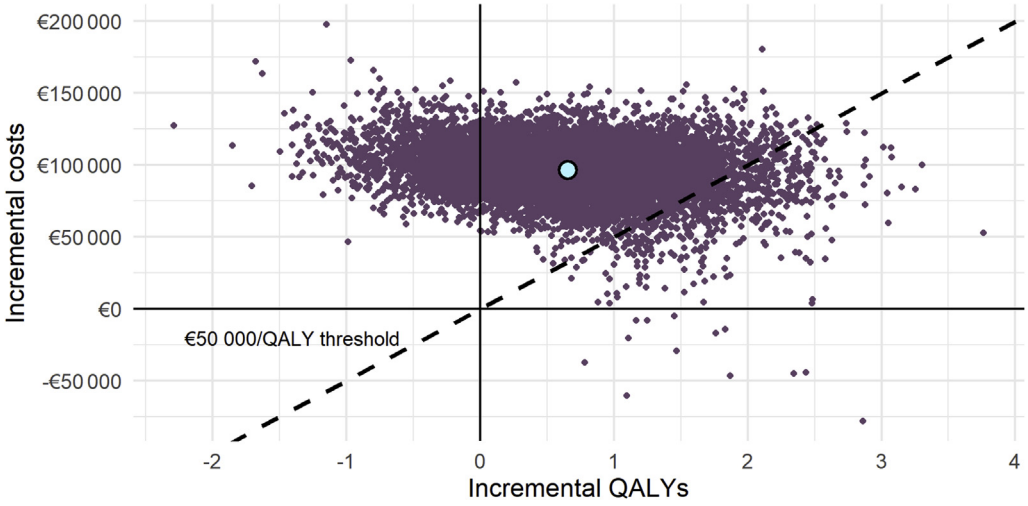
The use of an NMA for treatment efficacy of DMTs has several challenges.[14] First, patients included in the RCTs included in the NMA may not be representative of patients treated in clinical practice. In addition, patients in historical clinical trials may differ substantially from patients in contemporary real-world cohorts. Uitdehaag et al[15] showed there was substantial variation in RCT baseline characteristics over time, including a reduction of ARR in interferon beta-1a–treated patients over time. To account for this time trend, the baseline ARR was based on a meta-analysis of the placebo arms of post-2005 trials. In general, disease activity has been observed to become increasingly milder in more contemporary MS cohorts, which could be an interplay among several factors.[16] It is unknown to what extent the relative effects of DMTs versus comparators are affected by these trends over time. Second, we assumed that the efficacy of the DMTs was not dependent on its timing or place in the treatment sequence, whereas RCTs mostly include treatment-naïve patients. For example, Rojas et al[17] compared baseline characteristics of 27 896 participants in 18 RCTs and 61 710 participants in 73 real-world data sets and observed a higher proportion of treatment-naïve patients in the RCTs. Although this study did not stratify for the targeted inclusion of patients with RRMS versus SPMS in the RCT designs, it shows that RCTs focus on people with MS early in their treatment history.

Figure 2. MS type over time. Most cost-effective treatment sequence: peginterferon, glatiramer acetate, cladribine, ocrelizumab, alemtuzumab. Most effective treatment sequence: peginterferon, dimethyl fumarate, ocrelizumab, natalizumab, alemtuzumab.



MS indicates multiple sclerosis; RRMS, relapse remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis.

Figure 3. Incremental cost-effectiveness plane illustrating the uncertainty around the difference in QALYs (x-axis) and costs (y-axis) between the most effective and most cost-effective treatment sequence. The single dots represent the result in incremental costs and effects of one run of the model with a specific set of parameter values. The blue dot represents the mean incremental costs and QALYs. The dashed line represents the €50 000 per QALY threshold: All dots below the line represent the PSA iterations with an ICER below this threshold (cost-effective), and all dots above the line represent the PSA iterations with an ICER above this threshold (not cost-effective).

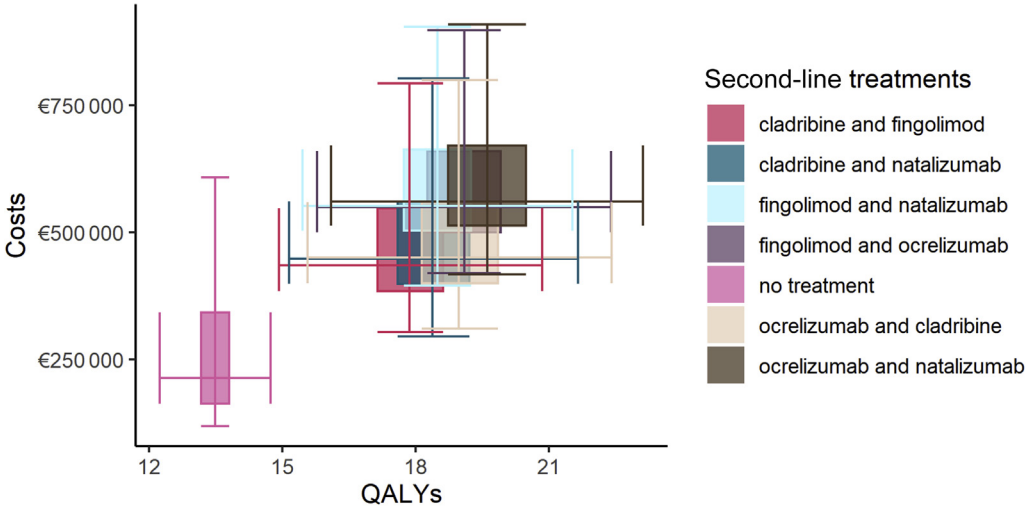


ICER indicates incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life-year.

These findings indicate that estimates of DMT efficacy based on these RCTs should be interpreted very cautiously in relation to contemporary MS cohorts with sequential treatments. Third, combining data of different RCTs in MS is challenging because differences in patient characteristics between trials can influence relative treatment efficacy when the efficacy of certain DMTs is only based on a single RCT. For example, it has been shown that the placebo arm of 1 trial in MS was superior over that of another trial in MS, even after propensity score adjustment.[18] The resulting uncertainty of DMT effectiveness was to some extent mitigated through PSA that takes into account the distribution of efficacy outcomes instead of taking a mean point estimate. Despite these limitations, the combination of the NMA and the clinical decision rules showed to have good short-term prediction of the number of treatment switches within the first 5 years for patients with Dutch MS, validating short-term predictive value of the model.[4,5]

Aside from efficacy data, other parameters of the decision-analytic model are based on data from average patients with MS, and therefore, the applicability of our results to individual patients with their own unique patient characteristics and

Figure 4. Boxplot of probabilistic sensitivity results, data grouped by second-line treatment combinations. Treatment sequences are grouped by second-line treatment combination regardless of the order in which they are prescribed and regardless of the preceding first-line treatment (eg, fingolimod followed by natalizumab and natalizumab followed by fingolimod are grouped together). The squares represent the interquartile range (ie, from the 25 to 75 percentile). The whiskers represent the 95% confidence interval.



QALY indicates quality-adjusted life-year.

preferences (eg, comorbidities, treatment adherence, pregnancy wishes, and preferences for administration mode) is limited. The current model does not allow the estimation of differential effects between subgroups, such as patients at high and low risk of relapses. Recent work by Chalkou et al[19] explores the estimation of effect modifiers from patient-level data and integrating it in NMA, which may allow individualized treatment effect estimates in future work. As with subgroups, this study did not include patient preferences for properties of treatments such as mode and frequency of administration. Another recent publication has shown that oral treatments are preferred by patients with MS over injections and that treatment efficacy is a dominant driver of patient preference.[20] Nevertheless, preferences were not included as the utility (on the QALY scale) derived of receiving preferred treatment is unknown, which is an important avenue for future research.

In addition, the decision rules are country and to some extent even physician specific. Here, it was assumed that patients use a maximum of 2 first-line DMTs after which they switch to second-line DMTs, whereas in clinical practice a third first-line DMT may be prescribed to only a small proportion of patients. In addition, fingolimod and ocrelizumab are second-line DMTs according to the Dutch clinical guidelines; nevertheless, in other countries (eg, United States), these DMTs can also be prescribed as first-line treatment. Indeed, apart from escalation treatments modeled here, induction treatments (initial treatments with those DMTs listed as "second-line" in this study) have been shown to improve health outcomes.[21] Because this study followed the Dutch guideline, induction strategies were not included although these treatments are provided when the clinical phenotype warrants this. This may affect the results of cost-effectiveness studies, as, for example, ocrelizumab was found to be the most cost-effective first-line treatment in the United States.[22] Additionally, MRI activity plays an increasing role in the determination of DMT response in clinical practice.[23] The impact of including radiological MS activity reflecting the performance of individual sequences in treatment decision making is not accounted for in our model.

Conclusions

We show that a decision-analytic model, which integrates different types of evidence and extrapolates over the lifetime of patients, is a useful model to estimate the optimal treatment escalation sequence for patients with MS. The most effective treatment sequence identified by this model for the average patient with RRMS yields 20.24 ± 1.43 lifetime QALYs and reduces disease progression and relapses, but confidence intervals of treatment sequences overlap. Contrarily, costs differ substantially and the most cost-effective treatment sequence yields less QALYs in individual patients (19.59 ± 1.43 QALYs). In a setting where the healthcare budget is limited, this sequence allows treating more patients and consequently optimizes population health outcomes rather than individual health outcomes. After patient characteristics and preferences have been considered, our findings can inform treatment choices. To include the results in clinical decision making, incorporation of cost-effectiveness in clinical guidelines is of importance, requiring both a fully incremental analysis and an NHB ranking.

Supplemental Material

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.jval.2021.11.1363.

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REFERENCES

1. Ziektemodulerende Behande-ling van multiple sclerose bij volwassenen: addendum bij de richtlijn multiple sclerose 2012. Nederlandse Vereniging voor Neurologie. Disease modifying treatments for multiple sclerosis in adults: addendum to the multiple sclerosis guideline 2021. Dutch association for neurology. https://www.msnetwerk.nl/wp-content/uploads/2020/03/Bijlage-2-clean-Richtlijn-Ziektemodulerende-Behandeling-van-Multiple-Sclerose-bij-volwassenen-%E2%80%93-28-2-2020-1.pdf. Accessed October 28, 2021.
2. Smolders JF, Beer JJ, Frequin ST, et al. Ziektemodulerende behandeling van mutiple sclerose bij volwassenen: addendum bij de richtlijn multiple sclerose [Disease modifying treatment for multiple sclerosis in adults: addendum to the multiple sclerosis guideline.]. *Tijdschr Neurol Neurochir*. 2021;122(1):17–21.
3. Kern DM, Cepeda MS. Treatment patterns and comorbid burden of patients newly diagnosed with multiple sclerosis in the United States. *BMC Neurol*. 2020;20(1):296.
4. Monitor MS-Geneesmiddelen 2019. Zorginstituut Nederland. Monitor MS-drugs. https://www.zorginstituutnederland.nl/publicaties/rapport/2019/06/13/monitor-ms-geneesmiddelen-2019. Accessed October 28, 2021.
5. Huygens S, Versteegh M. Modeling the cost-utility of treatment sequences for multiple sclerosis. *Value Health*. 2021;24(11):1612–1619.
6. Uitdehaag B, Kobelt G, Berg J, Capsa D, Dalén J. European Multiple Sclerosis Platform. New insights into the burden and costs of multiple sclerosis in Europe: results for the Netherlands. *Mult Scler*. 2017;23(suppl 2):117–129.
7. Lamers LM, McDonnell J, Stalmeier PF, Krabbe PF, Busschbach JJ. The Dutch tariff: results and arguments for an effective design for national EQ-5D valuation studies. *Health Econ*. 2006;15(10):1121–1132.

8. Kanters TA, Bouwmans CAM, van der Linden N, Tan SS, Hakkaart-van Rooijen L. Update of the Dutch manual for costing studies in health care. *PLoS One*. 2017;12(11):e0187477.
9. Palace J, Bregenzer T, Tremlett H, et al. UK multiple sclerosis risk-sharing scheme: a new natural history dataset and an improved Markov model [published correction appears in BMJ Open. 2014;4(1):e004073]. *BMJ Open*. 2014;4(1):e004073.
10. von Wyl V, Décard BF, Benkert P, et al. Influence of age at disease onset on future relapses and disability progression in patients with multiple sclerosis on immunomodulatory treatment. *Eur J Neurol*. 2020;27(6):1066–1075.
11. Dahlke F, Arnold DL, Aarden P, et al. Characterisation of MS phenotypes across the age span using a novel data set integrating 34 clinical trials (NO. MS cohort): age is a key contributor to presentation. *Mult Scler*. 2021;27(13):2062–2076.
12. Kosteneffectiviteit in de praktijk. Zorginstituut Nederland. Cost-effectiveness in practice. https://www.zorginstituutnederland.nl/publicaties/rapport/2015/06/26/kosteneffectiviteit-in-de-praktijk. Accessed October 28, 2021.
13. van Baal P, Perry-Duxbury M, Bakx P, Versteegh M, van Doorslaer E, Brouwer W. A cost-effectiveness threshold based on the marginal returns of cardiovascular hospital spending. *Health Econ*. 2019;28(1):87–100.
14. Sormani MP. Indirect comparisons of treatment effects: network meta-analyses. *Mult Scler*. 2017;23(4):510–512.
15. Uitdehaag BMJ, Barkhof F, Coyle PK, Gardner JD, Jeffery DR, Mikol DD. The changing face of multiple sclerosis clinical trial populations. *Curr Med Res Opin*. 2011;27(8):1529–1537.
16. Sorensen PS, Sellebjerg F, Hartung HP, Montalban X, Comi G, Tintoré M. The apparently milder course of multiple sclerosis: changes in the diagnostic criteria, therapy and natural history. *Brain*. 2020;143(9):2637–2652.
17. Rojas JI, Pappolla A, Patrucco L, Cristiano E, Sánchez F. Do clinical trials for new disease modifying treatments include real world patients with multiple sclerosis? *Mult Scler Relat Disord*. 2020;39:101931.
18. Signori A, Pellegrini F, Bovis F, Carmisciano L, de Moor C, Sormani MP. Comparison of placebos and propensity score adjustment in multiple sclerosis nonrandomized studies. *JAMA Neurol*. 2020;77(7):902–903.
19. Chalkou K, Steyerberg E, Egger M, Manca A, Pellegrini F, Salanti G. A two-stage prediction model for heterogeneous effects of treatments. *Stat Med*. 2021;40(20):4362–4375.
20. Jonker MF, Donkers B, Goossens LMA, et al. Summarizing patient preferences for the competitive landscape of multiple sclerosis treatment options. *Med Decis Making*. 2020;40(2):198–211.
21. Harding K, Williams O, Willis M, et al. Clinical outcomes of escalation vs early intensive disease-modifying therapy in patients with multiple sclerosis. *JAMA Neurol*. 2019;76(5):536–541.
22. Zimmermann M, Brouwer E, Tice JA, et al. Disease-modifying therapies for relapsing-remitting and primary progressive multiple sclerosis: a cost-utility analysis. *CNS Drugs*. 2018;32(12):1145–1157.
23. Gasperini C, Prosperini L, Tintoré M, et al. Unraveling treatment response in multiple sclerosis: a clinical and MRI challenge. *Neurology*. 2019;92(4):180–192.