A Cost-Effectiveness Analysis of Biologic Compared with Chemical Disease Modifying Drugs in Treating Multiple Sclerosis in US

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INTRODUCTION

Treatment of MS is expensive! And the drug choice is really a hard but important decision to make. The current study aims to answer the following question: Do biologic DMT drugs for treating MS have a systematic advantage in cost-effectiveness compared with oral chemical drugs? This question is not explicitly answered by previous literature, as no study intentionally differentiate DMT drugs by chemical or biologic drug. Therefore, we conducted a comprehensive CEA model to examine the cost-effectiveness of biologic drugs for treating MS.

About Multiple Sclerosis

- Chronic immune mediated neurodegenerative disease of the central nervous system with US prevalence of ~900,000[2] and high economic burden[1]. Onset at young age, and 70% are female.
- Characterized by demyelinating lesions (physical damage on myelin sheath).
- Two Major Forms at Onset: Relapse-Remission MS (RRMS) (85%-90%), which will ultimately progress to Secondary Progressive MS (SPMS), and Primary Progressive MS (PPMS) (10%). The main difference for RRMS is recurrent relapses before clinical progression to SPMS. See **Figure 1**.
- Disease severity and progression mainly measured by Expanded Disability Scale Score (EDSS) and MRI to detect lesions on the myelin sheath.
- Very costly. Lifetime cost as high as $5 million[5] (2020 USD).

Treatment of MS

- There is no cure for MS, but disease-modifying therapy (DMT) drugs have been developed and used to prevent relapse and delay disease progression to SPMS[2].
- By now, there are 20 marketed DMT drugs available in US, see **Appendix Table 1**. The 20 drugs can be categorized as interferons, monoclonal antibody biologic drugs, and oral chemical drugs.
- The three categories differ by route, frequency of administration as well as costs and efficacy. Biologic drugs are administrated by outpatient intravenous (IV) infusions, and interferons are mainly self-injected at home.

Figure 1. Natural Disease Progression Pathway for RRMS

Choice of DMT drug

- Drug choice is usually decided jointly by the physician and patient based on patient's clinical profile, health status, and preference, with special preference for fingolimod and ocrelizumab.

The DMT drug market in US

- DMT drug market is highly concentrated. Best-selling biologics (Ocrelizumab, Natalizumab, Alemtuzumab) and best-selling chemical drugs (Dimethyl Fumarate, Fingolimod) accounts for >90% total market revenue.
- We found a clear trend of diminishing market size for interferons, dominating but decreasing market share for chemical drugs, and a lower but quickly rising market for infused biologic drugs, see **Appendix Exhibit 1**.

Research Motivation

- MS patients face a large choice set for DMT treatment, and the decision has a large impact on both patients' health, insurer's budget, and social welfare, given the nature of high economic burden. Therefore, cost-effectiveness, in addition to comparative effective, is paramount to evaluate for better clinical decisions. However, published CEA studies are mostly modeled from a health care sector's perspective[6-9], which overlooks the indirect burden of biologic drugs.
- We want to examine if biologic drugs are more cost-effective in general, given the small but increasing market share for biologic drugs

Research Question

Will most prescribed biologic drugs be more cost-effective than most prescribed chemical drugs in treating relapse-remission MS at a WTP threshold of $150,000 per QALY in US, from a US societal perspective?

METHODS

We designed a 20-state Markov disease transition model to capture the clinical pathway of RRMS patients to evaluate the cost-effectiveness of biologic DMT drugs compared with chemical DMT drugs. The model was adapted from the 21-state model used in the 2017 ICER Report for MS10. The main outcome is measured with gained quality-adjusted life year (QALY).

The model structure, key profiles and main assumptions are shown in **Figure 2**.

Comparator Arms

See **Table 1** for the comparator arms.

Biologic Drug 's Arm	Oral Chemical Drug's Arm	Reference
Ocrelizumab (OCR) Natalizumab (NAT) Alemtuzumab (ALE)	Dimethyl Fumarate (DMF) Fingolimod (FIN)	Standard of Care (SOC) （No DMT. Symptom management only)

Model Parameters

- Key parameters including costs, utilities, transition probability matrix, and cost/disutility associated with adverse events.
- Parameter values, standard deviations, and distributions are mainly obtained from published network meta-analysis, national-representative surveys, real-world observational studies of RRMS patients, and assumptions

Sensitivity Analyses

- One-way deterministic sensitivity analysis tests the effect of modifying each parameter's upper and lower bound on the incremental net monetary benefit (INMB), one parameter at a time. Upper and lower bounds are determined by 95% confidence interval if obtainable, otherwise, we use ±10% or ±20% as the bound limits. Results presented as tornado graphs
- Multivariate probabilistic sensitivity analysis (PSA) to test the uncertainty effect of all parameters changing simultaneously. Relative risks follow log-normal distributions, costs and utilities follow gamma distributions. 1000 Monte Carlo simulations were performed. Results presented using acceptability curves.

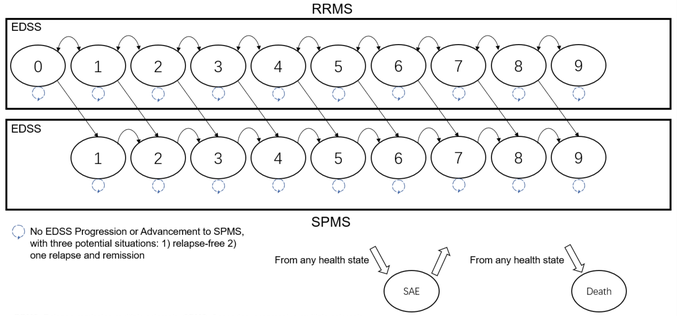
Figure 2. The Markov Model

Model Profile

- **Perspective: US Societal**
- **Model Type: Markov model with 20 states**
- **Time Horizon: 20 years**
- **Cycle Length: 1 year**
- **Utility Measure: Quality-adjusted life year**
- **Cost: 2021 USD Inflated by CPI (general & medical care)**
- **Discounts: 3% for both cost and utility**
- **WTP Threshold: $150,000 per QALY**
- **Outcome: ICER and INMB**
- **Sensitivity Analysis: One-way deterministic + probabilistic**

Model Assumptions

- **Cohort: age 29, 70% female, newly diagnosed, treatment-naïve, EDSS=0**
- **Disease stage progression: RRMS to SPMS & EDSS + 1**
- **Disability progression: EDSS + 1, +0, -1, no "jumps". No disease stage progression**
- **Relapse: indicates no disease-stage progression or disability progression**
- **Only one relapse episode per cycle**
- **No drug discontinuation or drug substitutions**



RRMS: Relapse-remission multiple sclerosis; **SPMS**: Secondary progressive multiple sclerosis; **EDSS**: Expanded Disability Status Scale; **SAE**: Severe adverse effect

RESULTS

Base Case Results

Table 2 presents the main results from base case. We found that ALE > OCR > NAT > DMF > FIN for all outcome variables. In ICER and INMB matrix, we found OCR > ALE > NAT > DMF > FIN (the ranking of cost-effectiveness). However, compared with SOC, no DMT drug is cost-effective.

Table 2. Expected outcomes, ICER matrix, and INMB matrix from base case

BASE CASE RESULTS AT THE END OF 20 YEAR

Treatment	Costs	QALYs	# Relapse	% to SPMS	Mortality	AVG EDSS
SOC	$ 860,685.55	10.32	13.13	66.51%	6.72%	5.505
DMF	$ 2,345,902.61	11.86	14.04	39.98%	5.41%	3.256
FIN	$ 2,547,715.24	11.65	13.92	44.94%	5.54%	3.647
OCR	$ 1,853,272.60	12.48	14.29	27.06%	4.87%	2.263
NAT	$ 2,285,564.40	12.15	14.15	34.89%	5.15%	2.859
ALE	$ 2,057,366.82	12.65	14.36	22.76%	4.72%	1.937

ICER MATRIX

Intervention \ Reference	SOC	DMF	FIN	OCR	NAT
DMF	962824.12				
FIN	1273034.57	Dominated			
OCR	460420.05	Dominant	Dominant		
NAT	779234.09	Dominant	Dominant	Dominated	
ALE	513827.95	Dominant	Dominant	1178890.90	Dominant

INMB MATRIX (WTP = $150,000 per QALY)

Intervention \ Reference	SOC	DMF	FIN	OCR	NAT
DMF	-1253832.58				
FIN	-1488249.19	-234416.61			
OCR	-669212.65	584,619.93	819,036.54		
NAT	-1150594.36	103,238.22	337,654.83	-481381.71	
ALE	-847338.29	406,494.29	640,910.91	-178125.63	303,256.07

Sensitivity Analysis

- **Figure 3** only present selective typical results from the 15 comparison pairs.

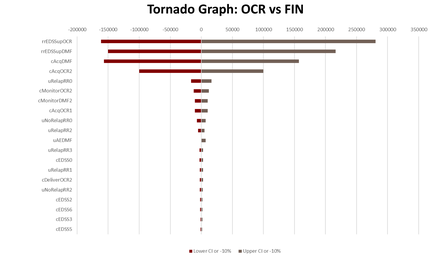
Deterministic sensitivity analysis

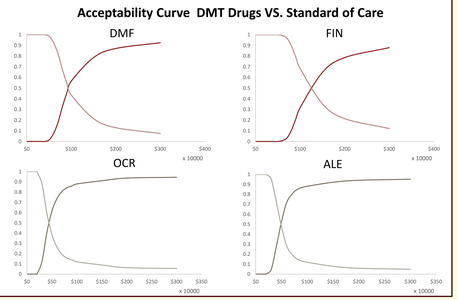
- From the Tornado graph for OCR vs. FIN, we identified relative risk of disability progression, drug acquisition cost, RRMS utility with relapse at EDSS<3; drug monitor cost; utility loss due to AE that substantially affect model results.

Probabilistic sensitivity analyses

- Compared with Standard-of-Care, no drug is cost-effective under WTP $150K on average.
- Chemical drugs become cost-effective when WTP > $ 1 million / QALY.
- Biologic drugs become cost-effective when WTP > $ 0.5 million / QALY on average.
- Results comparing between different DMT drugs are robust to willingness-to-pay threshold.
- Only exception: ALE becomes cost-effective compared to OCR when WTP > $2 million /QALY.

Figure 3. Selective Results from Sensitivity Analyses





DISCUSSIONS

Main findings

- Total cost for treating MS in the 20 years: ~ $2 million.
- Biologic drugs represent comprehensively higher clinical and economic value compared to all oral chemical drugs. OCR is most cost-effective, followed by ALE, NAT, DMF, and FIN, which contradicts to the reported clinician's preference for fingolimod.
- Although all DMT drug presents a better clinical outcome compared to standard of care, the improvement is too limited to be cost-effective at an acceptable willingness-to-pay threshold, from another side, the prices are too high!
- Results are sensitive to relative risk of disability progression, drug acquisition cost, utility level with mild disability; drug monitor cost; utility loss due to AE. Results are robust to probabilistic parameter variations.
- Biologics are easier to attain cost-effectiveness as WTP increases compared to oral chemical drugs.

Contributions by the current study

- First CEA study on MS that compares all best-selling biologics vs. chemical oral drugs from a societal perspective.
- Improved the existing Markov model to be more straightforward and clearer.
- Create a new angle (biologics vs. chemical) in MS treatment evaluation.

Limitations

- Strong assumptions (no EDSS jumps, no drug discontinuity, and switches…).
- Transition probabilities are relatively outdated: need to follow new clinical trials.
- Require refinements to better approach clinical treatment settings.

Conflict of Interest
Authors declare no conflict of interests
Funding
This study received no funding

CONCLUSIONS

- Ocrelizumab, Alemtuzumab, Natalizumab are most cost-effective, followed by Dimethyl Fumarate and Fingolimod.
- Biologic drugs have near-dominant cost-effectiveness compared to chemical drugs, even after including drug-related indirect costs for biologics, contradicting to some clinical consensus of favoring fingolimod.
- No DMT drug is cost-effective compared with SOC due to limited effectiveness and high drug costs.

But we still need treatment! Therefore, we call for:

- Innovation with more effective drugs to increase the denominator.
- Actions from government and companies to control for drug price.

Supplemental Materials (Scan the QR Code)

Reference and Appendix

Please scan the QR code to find references, and appendix tables/figures

Questions and thoughts

Interested in our study? Have questions, thoughts, and suggestions? We love them!