VALUE IN HEALTH 22 (2019) 168–176

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/jval

Economic Evaluation

Cost-Effectiveness of Alemtuzumab in the Treatment of Relapsing Forms of Multiple Sclerosis in the United States

Viktor Chirikov, PhD [1], Ingrid Ma, PharmD [2], Namita Joshi, PhD [1], Dipen Patel, PhD [1], Alden Smith, PharmD [3], Cindy Giambrone, PharmD [2], Noelle Cornelio, BS [1], Lobat Hashemi, ScD [3,]*

[1]*Pharmerit International, Bethesda, MD, USA;* [2]*Previously employed by Sanofi, Cambridge, MA, USA;* [3]*Sanofi, Cambridge, MA, USA*

ABSTRACT

Objective: To evaluate the cost-effectiveness of alemtuzumab compared with fingolimod, natalizumab, ocrelizumab, and generic glatiramer acetate 20 mg among patients with relapsing multiple sclerosis (RMS) in the United States. **Study Design:** Markov model with annual periods from payer perspective. **Methods:** The modeled population represented pooled patients from the CARE-MS I and II trials. Therapies' comparative efficacy at reducing relapses and slowing disability worsening was obtained from network meta-analyses. Safety information was extracted from package inserts. Withdrawal rates, treatment waning, resource use, cost, and utility inputs were derived from published studies and clinical expert opinion. To project the natural history of disease worsening, data from the British Columbia cohort was used. **Results:** Alemtuzumab dominated comparators by accumulating higher total quality-adjusted life-years (QALYs) (8.977) and lower total costs ($421 996) compared with fingolimod (7.955; $1 085 814), natalizumab (8.456; $1 048 599), ocrelizumab (8.478; $908 365), and generic glatiramer acetate (7.845; $895 661) over a 20-year time horizon. Alemtuzumab's dominance was primarily driven by savings in treatment costs because alemtuzumab has long-term duration of response and is initially administered as 2 annual courses, with 36.1% of patients requiring retreatment over 5 years, whereas comparators are used chronically. In model scenarios where alemtuzumab's long-term duration of response was assumed not to hold and therapy had to be administered annually, probabilistic sensitivity analyses showed that alemtuzumab remained cost-effective versus ocrelizumab at a willingness-to-pay threshold of $100 000/QALY in 74% to 100% of model runs. **Conclusions:** Alemtuzumab was a cost-effective therapy. Model results should be used to optimize clinical and managed care decisions for effective RMS treatment.

Keywords: fingolimod, immune competence, natalizumab, ocrelizumab, relapsing multiple sclerosis, response

Introduction

Multiple sclerosis (MS) is a chronic degenerative disorder of the central nervous system associated with disrupted transmission of nerve impulses.[1] It affects approximately 572 000 individuals in the United States and mostly affects individuals between 20 and 50 years of age,[2,3] with mean and median peak age of onset at 30 and 23.5 years, respectively,[4] and is at least twice as prevalent among women than among men.[2] Common symptoms such as fatigue, depression, urinary incontinence, gait abnormalities, paresthesia, vision problems, and cognitive changes have significant impact and reduce patients' health-related quality of life and work productivity.[5–7] Furthermore, MS is the second most costly chronic condition in direct all-cause medical expenditure in the United States (after congestive heart failure)[8] and costs more than $4 million in total lifetime costs per patient.[9]

Relapsing forms of multiple sclerosis (RMS) are the most prevalent type of MS, affecting approximately 85% to 90% of MS patients, and are characterized by patients experiencing relapses that may be interspersed with periods of disease remission.[10] Therapy for RMS entails modifying the disease course by reducing relapse frequency and slowing disability worsening.[1] In November 2014, alemtuzumab (Lemtrada) was approved by the US Food and Drug Administration for the treatment of patients with RMS. Alemtuzumab was evaluated in 3 randomized, rater-blinded, active-comparator clinical trials compared with subcutaneous interferon beta-1a (IFNβ-1a) in treatment-naïve patients (CAMMS223, NCT00050778; CARE-MS I, NCT00530348)[11,12] and patients with an inadequate response to prior treatment (CARE-MS II, NCT00548405).[13] The trial data showed benefits over 2 years in relapse and disability outcomes and freedom from clinical disease and magnetic resonance imaging activity; most frequent

* *Address correspondence to:* Lobat Hashemi, ScD, 50 Binney Street, Cambridge, MA 02142, USA.
E-mail: lobat.hashemi@sanofi.com

https://doi.org/10.1016/j.jval.2018.08.011

adverse events (AEs) with alemtuzumab were infusion-associated reactions and autoimmune AEs. Alemtuzumab-treated patients who followed up in extension studies for an additional 3 years (5 years total) have continued to demonstrate durable efficacy in the absence of continuous treatment,[14] where only 25.6% received 1 additional course, 9.0% received 2 additional courses, and 1.5% received 3 additional courses.[15,16]

Review of recent RMS cost-effectiveness literature found studies that compare disease-modifying therapies (DMTs) that were approved before 2014[17–20] but do not cover high-efficacy treatments such as alemtuzumab that were approved after 2014. Previous meta-analyses comparing all available oral, injectable, and infusion therapies have found alemtuzumab to be among the highest-ranked DMTs with respect to reducing relapses and disability worsening.[21,22] Yet, there is no available consensus on the relative place of each DMT in the treatment regimen for RMS. Similarly, lack of clarity exists with respect to the relative cost-effectiveness of each DMT.[5]

The objective of this study was to evaluate the cost-effectiveness of alemtuzumab versus fingolimod, natalizumab, ocrelizumab, and generic glatiramer acetate 20 mg among a pooled population of patients with RMS in the United States.

Methods

Previous literature has identified multiple methodological challenges in assessing cost-effectiveness analyses in RMS.[23] In this study, we reviewed and applied the latest recommendations for conducting cost-effectiveness analysis in MS.[24]

Model Structure

A Markov model with annual periods was constructed, similar to a previous widely used model structure,[25] and run over a time horizon of 20 years from a US payer perspective. A hypothetical cohort of patients with RMS was tracked as they progressed through disability states or naturally regressed to lower disability states (Fig. 1).

The disability states in the model were defined using steps 0 (normal) through 9 (helpless patient confined to bed and unable to communicate effectively or eat/swallow) of the Kurtzke Expanded Disability Status Scale (EDSS).[26] In each model period, patients were allowed to stay in the same disability state, progress to a higher (worse) disability state, regress to a lower (better) disability state, or die. Step 10 (death) in the EDSS scale was not included; instead, mortality was modeled as described later.

The probability of dying in any state was assumed to depend on the current EDSS state and was modeled indirectly using mortality ratios for each EDSS state multiplied by age- and sex-specific background mortality.[20] The probability of transitioning to a higher or lower disability state was assumed to depend on the patient's current EDSS health state. Furthermore, within each state, patients could experience a relapse (the rate of which was also EDSS-specific) that may or may not have resulted in hospitalization.

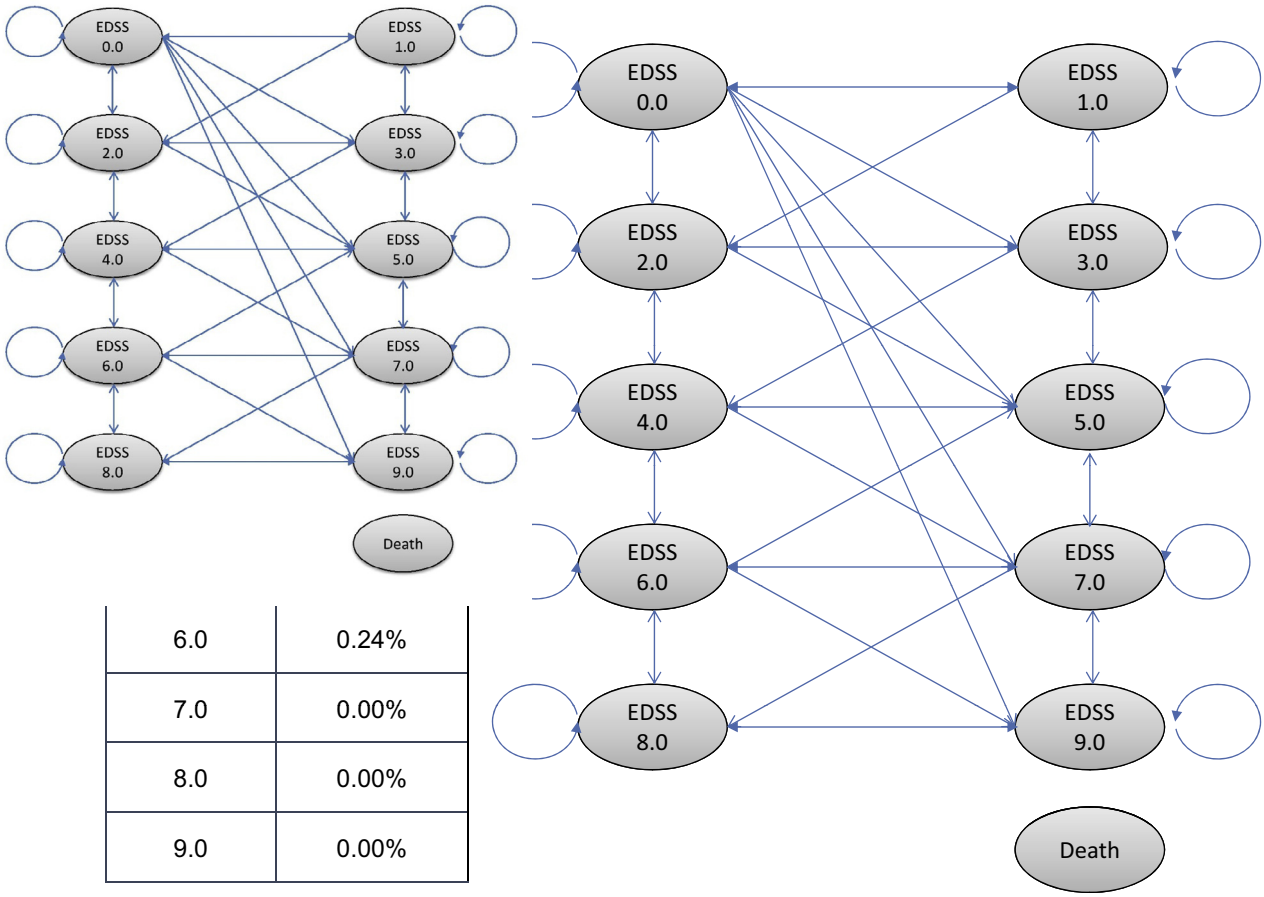

Fig. 1 – Schematic representation of the cost-effectiveness model structure and initial distribution of patients in each EDSS state. EDSS, Kurtzke Expanded Disability Status Scale.

Treatment efficacy was modeled using therapy-specific relative risk ratios (RRs) for annualized relapse rate and hazard ratios (HRs) for disability worsening, as compared with best supportive care (BSC). For natalizumab, fingolimod, and generic glatiramer acetate 20 mg, treatment efficacy estimates were derived from a network meta-analysis (NMA) published by Fogarty et al.[21] Because ocrelizumab was not included in the NMA, the treatment efficacy estimates for that comparator were derived using data from the primary ocrelizumab publications for the OPERA I and II trials.[27] The RRs and HRs used to measure efficacy were multiplied by the natural RMS rates for relapse and disability worsening, respectively, to adjust the projected natural course and manifestations of the disease.

The model also assumed that treatment efficacy may diminish over time and therefore incorporated treatment waning multipliers to bring the HRs closer to null in the later years of the time horizon. A proportion of patients could withdraw from treatment each year and were assumed to switch to BSC. Patients could also experience AEs from treatment. Each disability state was associated with EDSS-specific annual disease management cost and disutility (loss of quality of life compared with perfect health). Each relapse or AE was also associated with cost and disutility. The drug acquisition, administration, and monitoring costs for each DMT were calculated for each year of treatment. As patients progressed through the model, the costs and utilities were summed up over the time horizon and discounted at 3% every year to calculate total cumulative cost and total number of quality-adjusted life-years (QALYs) for patients on each treatment over the 20-year time horizon. The difference in cumulative costs and QALYs was used to calculate the incremental cost-effectiveness ratio (ICER), measuring the additional cost required to gain 1 additional QALY by treating patients with alemtuzumab versus comparators.

For a summary of all model assumptions, please refer to Appendix Table 1 (see Supplemental Materials found at https://doi.org/10.1016/j.jval.2018.08.011).

Model Inputs

Population characteristics

The modeled patient population had an initial EDSS distribution representative of patients from alemtuzumab clinical trials who were treatment naïve (CARE-MS I) or had an inadequate response to prior treatment (CARE-MS II; Fig. 1). The mean age of the population was 34.3 years, and the female-to-male ratio was 1.9, similar to the patient characteristics of other RMS trials.

Data sources

The model uses data from the British Columbia Multiple Sclerosis (BCMS) longitudinal observational cohort[28,29] to project the natural history of disability worsening for patients receiving BSC, which was assumed to represent progression in patients not treated with DMT. The untreated BCMS cohort is a population-based dataset of MS patients established in 1980, in which the disability scores of RMS patients were obtained during face-to-face neurologist-administered patient interviews. Although no single perfect natural history dataset exists, the BCMS cohort has been identified as the most appropriate natural history comparator cohort validated for the purposes of cost-effectiveness models in RMS.[29] The BCMS cohort allows for EDSS score improvement using "real-time" EDSS assessments. In addition, the BCMS cohort is a larger cohort (N = 2837) than the next most commonly used natural history source, the London Ontario (LO) cohort (N = 1099), and as such its use results in reduced sampling variability. It also covers a more recent time period (1980-1995) than the LO dataset. The treatment-specific annual transition probability matrix for BCMS is provided in Appendix Table 2 (see Supplemental Materials found at https://doi.org/10.1016/j.jval.2018.08.011).

Although the LO cohort has been the source of natural history data for most cost-effectiveness models in RMS to date, it has been severely criticized.[24] It censors any improvement in EDSS state, which does not allow patients to spontaneously regress to a lower RMS disease state; this leads to more rapid EDSS progression and underestimates the time patients stay in a particular EDSS state and the cumulative QALYs lived. Further, the LO data collected are relatively old and do not truly reflect the progression rate of MS patients as per the current clinical paradigm.

For transparency regarding the choice of natural history data source, we also compared cost-effectiveness results using pooled data from the placebo arms of the DEFINE (NCT00420212) and CONFIRM (NCT00451451) clinical trials and the LO dataset, as conducted previously in comparisons for dimethyl fumarate.[20] Owing to the lack of data for disease worsening beyond EDSS state 7 in the placebo arms of DEFINE/CONFIRM, the transition probability matrix for EDSS states 8 and 9 used transition probabilities derived from the LO.[20]

As the data sources for the comparative efficacy of available DMTs at reducing relapses and slowing disability worsening in RMS, we used a published NMA conducted by academicians with the National Centre for Pharmacoeconomics in Ireland and the Luxembourg Institute of Health[21] (Table 1). Given that ocrelizumab was not included in the NMA because of its recent approval, an indirect comparison (Bucher method) using estimates from OPERA I and II trials on ocrelizumab versus subcutaneous IFNβ-1a[27] and anchored on the NMA results for IFNβ-1a versus BSC, was conducted. The approach can be assumed valid because prior NMAs found only negligible treatment-effect modification owing to baseline patient characteristics,[21,30] whereas NICE guidance suggests that anchored indirect comparisons implicitly control for

Table 1 – Comparative treatment efficacy of disease-modifying therapies for relapsing multiple sclerosis.

Treatment	Confirmed disability worsening, HR (95% CI)		Annualized relapse rate, RR (95% CI)
	3 months	6 months (base case)	
Alemtuzumab	0.32 (0.17-0.59)	0.41 (0.27-0.63)	0.31 (0.26-0.36)
Ocrelizumab	0.41 (0.27-0.61)	0.45 (0.28-0.73)	0.35 (0.26-0.48)
Natalizumab	0.55 (0.42-0.73)	0.46 (0.33-0.63)	0.31 (0.27-0.36)
Fingolimod	0.75 (0.62-0.90)	0.69 (0.53-0.88)	0.47 (0.41-0.53)
Generic glatiramer acetate 20 mg	0.81 (0.63-1.03)	0.75 (0.56-0.98)	0.65 (0.59-0.71)
Placebo (BSC)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)

BSC indicates best supportive care; CI, confidence interval; HR, hazard ratio; RR, relative risk ratio.

cross-study differences in prognostic characteristics.[31] Overall, the effect size and associated confidence intervals were similar to inputs used in the analysis conducted by the Institute for Clinical and Economic Review.[30]

The base case for our analysis used the HR estimates for 6-month confirmed disability worsening (CDW).

Relapse rates

The effect of treatment on relapse rates was modeled by applying the treatment-specific RR ratios (Table 1) to natural history relapse rates derived from Held et al[32] (see Appendix Table 3 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2018.08.011). Patients' relapse severity was assumed to differ depending on whether the relapse led to a hospitalization or not. The proportion of patients with relapses who needed hospitalization was assumed to be 30.7% across all EDSS states and was applied similarly across comparators.[33]

Treatment withdrawal rates

Compared with other DMTs, which need to be administered on a chronic or a defined periodic basis, the administration of alemtuzumab is different. Alemtuzumab has long durability of treatment effect and is dosed initially as 2 annual treatment courses, administered as intravenous (IV) infusions. The first treatment course is on 5 consecutive days and the second course is administered on 3 consecutive days, 12 months later. Retreatment of up to 2 treatment courses may be administered more than 1 year after a previous course and consists of 3 consecutive days of alemtuzumab. In the extension study of alemtuzumab over 5 years, patients who had clinical or magnetic resonance imaging disease activity received alemtuzumab retreatment after the initial 2 annual treatment courses.[34] All patients on alemtuzumab received treatment in the first 2 years; 63.9% received no retreatment over 5 years, whereas 36.1% received any retreatment in years 3, 4, or 5 (25.6% received 1 additional course, 9.0% received 2 additional courses, and 1.5% received 3 additional courses (see Appendix Table 4 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2018.08.011).[34,35]

Therefore, withdrawal from other DMTs was assumed to result in similar treatment efficacy as switching to BSC, whereas the treatment effect of alemtuzumab was assumed to persist even after the initial 2 years of administration. The withdrawal rate for all therapies except alemtuzumab was assumed to be constant at 10% for each of the first 2 years followed by 3% for each subsequent year until the end of the time horizon, as used previously.[20,36]

Although clinically unlikely, under conservative model assumptions of no durable treatment effect for alemtuzumab after year 10 of the time horizon, we also examined scenarios in which alemtuzumab was administered each year. In those scenarios, treatment discontinuation of either alemtuzumab or comparators resulted in BSC treatment efficacy in the next model period and thereafter.

Treatment waning

For both alemtuzumab and comparators, the comparative treatment efficacy for disability worsening and annualized relapse rates were assumed to be unchanged for years 0 to 5 of the time horizon (full 100% treatment effect). For years 6 to 9, 75% treatment effectiveness was assumed, whereas for years 10+ until the end of the time horizon, 50% treatment effectiveness was assumed.[37]

Mortality rates

The model calculated a weighted average mortality rate based indirectly on the age and sex of the modeled population, using the background all-cause mortality rates for US men and women aged 20 to 100 years for 2010, as obtained from the Centers for Disease Control and Prevention, multiplied by a mortality factor[38] corresponding to each EDSS health state (see Appendix Table 5 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2018.08.011).[20]

Adverse events

Adverse events (AEs) including warnings and precautions were extracted from package inserts (PIs) for each DMT, and selected for inclusion based on the following algorithm. The selection of AE's followed a systematic approach, as used previously in RMS.[20] First, AEs listed on the PI with at least 5% overall incidence or with at least 3% higher incidence in the drug arm than in the placebo arm of the clinical trials were taken into consideration. The list of AEs was then sorted first by the magnitude of the difference between the drug and placebo arms in each comparator trial and then sorted by the absolute AE incidence in the drug arm.

From this sorted list, the top 5 AEs were selected for each comparator. Additional AEs were also considered based on significant cost burden as reported by clinical experts. The time rate of AEs obtained from clinical trials of various durations was converted to annualized risk using a standard formula (see Appendix Table 6 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2018.08.011).[39] The incidence of AEs for comparators was assumed to remain constant for all years of the model time horizon while the patient cohort continued on therapy. Because of alemtuzumab's unique dosing frequency, the incidence of AEs for alemtuzumab, except infusion reactions, was constant every year for 9 years of the model time horizon (ie, treatment and retreatment with alemtuzumab for up to 5 years plus another 4 years of possible AEs after discontinuation). The incidence of infusion reactions was restricted to each year on alemtuzumab treatment.

The disutility and duration for each AE were obtained from a variety of sources or based on clinical expert opinion when no data were available (see Appendix Table 7 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2018.08.011). The average annual cost for AE treatment was calculated using the annualized incidence, duration, and resource use and monitoring rates for each AE, multiplied by the unit cost for each resource use category, sourced from the National Fee Analyzer using 50th percentile (median) charge data (see Appendix Table 8 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2018.08.011).[40]

Cost inputs

The model included costs associated with disability worsening through EDSS states, where each individual EDSS state was associated with annual direct care costs consisting of medical care and formal care costs. The cost of relapse leading to hospitalization was assumed as the cost of managing a high-intensity episode of relapse, inflated to 2016 US dollar value ($20 607), whereas that of managing a relapse not leading to hospitalization was assumed as the average cost of managing a low- or moderate-intensity episode of relapse, inflated to 2016 US dollar value ($1673).[41] The natural history costs by EDSS state were obtained from a published study and inflated to 2016 US dollar value (see Appendix Table 9 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2018.08.011).[20,42]

The wholesale acquisition costs for each treatment included in the model were sourced from Redbook.[43] Table 2 lists the annual acquisition costs for each treatment included in the model. Administration costs were assumed to be zero for fingolimod and glatiramer acetate 20 mg, whereas costs related to infusion or

Table 2 – Annual treatment-related costs based on wholesale acquisition costs sourced from Redbook (July 2016).

Treatment	Administration method	Treatment acquisition cost	Administration cost	Monitoring costs	
				Year 1	Year 2+
Alemtuzumab					
Course 1 (year 1)	IV infusion	$101 219	$2 038	$6 376	NA
Courses 2-5 (years 2-5)	IV infusion	$60 731	$1 223	NA	$5 306
Fingolimod	Oral capsule	$82 043	$0	$4 473	$4 112
Generic glatiramer acetate 20 mg	Self-injected subcutaneously	$63 236	$0	$3 642	$3 165
Natalizumab	IV infusion by health professional every 4 weeks	$75 361	$2 222	$6 768	$6 125
Ocrelizumab	IV infusion at weeks 0 and 2, then every 6 months	$65 000	$1 010 (year 1) $831 (year 2)	$4 211	$3 650

IV indicates intravenous.

administration for ocrelizumab, natalizumab, and alemtuzumab were included in accordance with each PI and clinical experts.

Utility inputs

Baseline utility by EDSS state was sourced from Palace et al[29] (see Appendix Table 10 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2018.08.011). The annual utility loss per relapse was −0.0252 for relapses leading to hospitalization and −0.0076 for relapses not leading to hospitalization, assuming 1 month duration of relapse[24] multiplied by utility loss values for relapse from Prosser et al.[44]

Sensitivity and Scenario Analysis

A list of data parameter sensitivity analyses were conducted by setting alemtuzumab's 6-month disability worsening and relapse rate efficacy ratios at the upper and lower 95% confidence interval values, varying alemtuzumab treatment acquisition costs (±10%), assessing the sensitivity around the cost of managing relapse (±20%), and varying the model time horizon and treatment withdrawal rate for the comparators. In addition, we examined select model scenarios of interest and conducted probabilistic sensitivity analysis (PSA) to assess the uncertainty around all model parameters simultaneously.

Table 3 – Base-case results by treatment (6-month HRs for disability worsening and BCMS natural history data).

Treatment	Total costs	Total life-years	Total QALYs	Incr. costs	Incr. QALYs	ICER
Alemtuzumab	$421 996	14.7589	8.9772	NA	NA	NA
Disease-related*	$193 258	NA	9.0179			
Treatment-related†	$226 406	NA	NA			
Adverse events	$2 332	NA	−0.0407			
Ocrelizumab	$908 365	14.7215	8.4781	−$486 368	0.4991	Dominated
Disease-related*	$212 795	NA	8.4874	−$19 537	0.5305	
Treatment-related†	$693 632	NA	NA	−$467 226	NA	
Adverse events	$1 937	NA	−0.0093	$395	−0.0314	
Natalizumab	$1 048 599	14.7198	8.4557	−$626 602	0.5215	Dominated
Disease-related*	$211 912	NA	8.4678	−$18 654	0.5501	
Treatment-related†	$835 330	NA	NA	−$608 924	NA	
Adverse events	$1 357	NA	−0.0121	$976	−0.0286	
Fingolimod	$1 085 814	14.6826	7.9549	−$663 817	1.0223	Dominated
Disease-related*	$227 448	NA	7.9740	−$34 190	1.0439	
Treatment-related†	$857 109	NA	NA	−$630 703	NA	
Adverse events	$1 256	NA	−0.0191	$1 076	−0.0216	
Generic glatiramer acetate 20 mg	$895 661	14.6731	7.8447	−$473 664	1.1325	Dominated
Disease-related*	$235 155	NA	7.8449	−$41 897	1.1729	
Treatment-related†	$660 318	NA	NA	−$433 913	NA	
Adverse events	$187	NA	−0.0003	$2 146	−0.0404	
Best supportive care	$253 755	14.6354	7.3578	$168 241	1.6193	$103 895
Disease-related*	$253 755	NA	7.3578	−$60 497	1.6600	
Treatment-related†	$0	NA	NA	−$226 406	NA	
Adverse events	$0	NA	0	$2 332	−0.0407	

HR indicates hazard ratio; ICER, incremental cost-effectiveness ratio; Incr., incremental; NA, not applicable; QALY, quality-adjusted life-year.
* Costs and QALYs owing to disability and relapse.
† Treatment acquisition cost, administration cost, and monitoring cost.

Table 4 – Model scenarios for alemtuzumab compared with ocrelizumab.

Parameter	Incremental costs	Incremental QALYs	ICER
Baseline results (main assumptions) a. 6-month disability worsening HR estimates for alemtuzumab and ocrelizumab b. Natural history data as per BCMS dataset c. Treatment on alemtuzumab for up to 5 years	−$486 368	0.4991	Alemtuzumab dominant
Scenario 1: a. 3-month disability worsening HR estimates for alemtuzumab and ocrelizumab b. Natural history data as per BCMS dataset c. Treatment on alemtuzumab for up to 5 years	−$490 499	0.6870	Alemtuzumab dominant
Scenario 2: a. 6-month disability worsening HR estimates for alemtuzumab and ocrelizumab b. Natural history data as per placebo arms in DEFINE/CONFIRM trials and LO dataset[20] c. Treatment on alemtuzumab for up to 5 years	−$249 571	0.3897	Alemtuzumab dominant
Scenario 3: a. 3-month disability worsening HR estimates for alemtuzumab and ocrelizumab b. Natural history data as per placebo arms in DEFINE/CONFIRM trials and LO dataset[20] c. Treatment on alemtuzumab for up to 5 years	−$258 614	0.5776	Alemtuzumab dominant
Conservative scenarios related to no long-term durability of effect for alemtuzumab			
Scenario 4: a. 6-month disability worsening HR estimates for alemtuzumab and ocrelizumab b. Natural history data as per BCMS dataset c. Alemtuzumab administered annually after year 10 with 3% withdrawal rate for both drugs	−$127 775	0.4616	Alemtuzumab dominant
Scenario 5: a. 6-month disability worsening HR estimates for alemtuzumab and ocrelizumab b. Natural history data as per BCMS dataset c. Alemtuzumab administered annually after year 10 with 10% withdrawal rate for both drugs	−$12 295	0.6382	Alemtuzumab dominant
Scenario 6: a. 6-month disability worsening HR estimates for alemtuzumab and ocrelizumab b. Natural history data as per BCMS dataset c. Alemtuzumab administered annually after year 10 with 20% withdrawal rate for both drugs	$42 925	0.7850	$54 681 per QALY

BCMS indicates British Columbia Multiple Sclerosis; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; LO, London, Ontario; QALY, quality-adjusted life-year.

Results

Base-case results indicated that alemtuzumab dominated fingolimod, natalizumab, ocrelizumab, and generic glatiramer acetate 20 mg because it was less costly and more effective over the 20-year time horizon (Table 3). The total 20-year costs of managing patients were lower for alemtuzumab ($421 996) compared with fingolimod ($1 085 814), natalizumab ($1 048 599), ocrelizumab ($908 365), and generic glatiramer acetate 20 mg ($895 661). Patients on alemtuzumab also had the highest number of 20-year cumulative QALYs (8.977) compared with fingolimod (7.955), natalizumab (8.456), ocrelizumab (8.478), and generic glatiramer acetate (7.845). The time-to-dominance for alemtuzumab was, respectively, 3, 3, 4, and 4 years. Furthermore, patients on alemtuzumab had the lowest total number of relapses, whether leading to hospitalization or not (see Appendix Table 11 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2018.08.011).

The PSA confirmed the base-case results that alemtuzumab dominated comparators as patients accrued lower incremental total costs and higher incremental QALYs (see Appendix Table 12 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2018.08.011). When applying the choice for faster-progression natural disease history data from DEFINE/CONFIRM/LO (see Appendix Table 13 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2018.08.011), PSA results corroborated that alemtuzumab is dominant, regardless of the natural history data source.

Detailed parameter sensitivity and model scenario analyses were conducted comparing alemtuzumab versus ocrelizumab, which was the most effective of the 4 comparators. Varying the time horizon of the model, discount rate, setting the HRs for disability worsening at the upper and lower range of the 95% confidence intervals, and changing the assumption for withdrawal rate on ocrelizumab were most influential in affecting incremental costs and QALYs, but none of the parameters altered

the conclusion that alemtuzumab was more effective and less costly than ocrelizumab (see Appendix Fig. 1 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2018.08.011).

Under conservative model scenarios in which the disease was modeled using the BCMS natural history data[20] and alemtuzumab was assumed to have no long-term durability of effect after year 10 of the time horizon and was administered annually after that year (Table 4), the magnitude of the incremental costs decreased, but alemtuzumab continued to dominate or be cost-effective compared with ocrelizumab (scenarios 4 through 6) at a willingness-to-pay threshold (WTP) of $100 000.

Under a similar conservative scenario (not shown) that also assumed no withdrawal rate for ocrelizumab up to year 10, followed by 10% annual withdrawal rates for both alemtuzumab and ocrelizumab, incremental total costs were −$388 561 and incremental QALYs were −0.0543. In this scenario, alemtuzumab could be considered cost-saving despite the lower effectiveness.

In the PSA for each of the 6 scenarios in Table 4, the likelihood that alemtuzumab was cost-effective compared with ocrelizumab varied. In the most conservative scenario (scenario 6), where alemtuzumab was assumed to have no durability of effect after year 10 and administered every year after year 10, and the withdrawal rate for both alemtuzumab and ocrelizumab was 20% annually, the likelihood of alemtuzumab being cost-effective varied between 37% (at WTP = $50 000), 74% (at WTP = $100 000), and 91% (at WTP = $200 000) (Fig. 2).

Supplementary model scenarios assuming zero costs or QALY losses associated with AEs, no treatment waning effect for alemtuzumab or comparators, discontinuing treatment at EDSS = 7.0, incorporating societal perspective (indirect costs in Appendix Table 9; see Supplemental Materials found at https://doi.org/10.1016/j.jval.2018.08.011), and using an alternative published source for natural history relapse rate[45] had only marginal effects on model results.

Discussion

Alemtuzumab dominated the other 4 DMTs by being either cost-effective or cost-saving across a range of tested assumptions and scenarios. Similar to other published analyses, we modeled a long-time horizon of 20 years to reflect that RMS disability accumulates over an extended period.[20,30,46,47] An independent analysis by the Institute for Clinical and Economic Review (ICER) has recently shown that alemtuzumab is the most cost-effective treatment option for RMS when compared with the regimens examined in this study and other regimens, such as dimethyl fumarate, glatiramer acetate 40 mg, IFNβ-1a, and peginterferon beta-1a.[30] The ICER analysis noted that NMA efficacy estimates by Fogarty et al (data source used in our study) are close to ICER's own meta-analysis on relapses and only negligibly differ for the disability progression outcome.[30] Results from our extended indirect treatment comparison for ocrelizumab versus BSC were consistent with ICER's estimates.

The cost-effectiveness of alemtuzumab in our study was driven not only by higher treatment effectiveness but also by much lower treatment-related cost. Because other DMTs have to be administered on a chronic or defined periodic basis, the cumulative costs of treatment for fingolimod ($857 109), natalizumab ($835 330), ocrelizumab ($693 632), and generic glatiramer acetate 20 mg ($895 661) were higher than that of alemtuzumab ($226 406), which is initially administered as 2 courses because of its long-term durability of effect with 36.1% of patients requiring retreatment over 5 years. Generally, differences in total costs between alemtuzumab and comparators decreased with assumptions for higher withdrawal rates for chronic therapies as

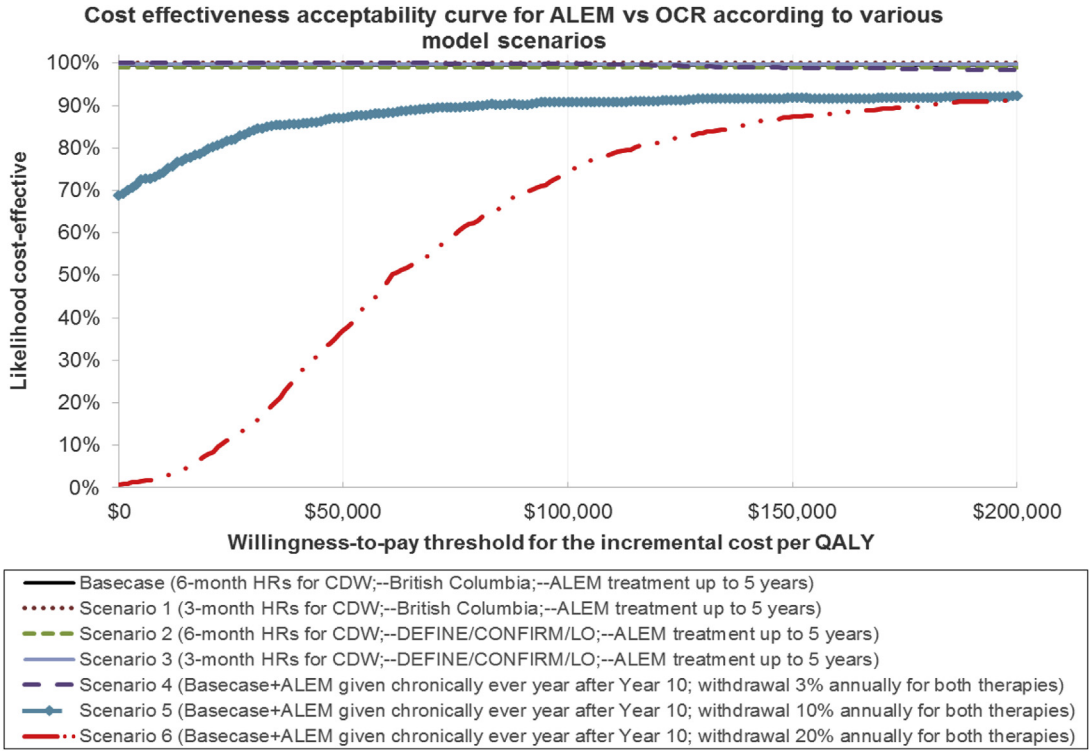

Fig. 2 – Likelihood of alemtuzumab (ALEM) being cost-effective compared with ocrelizumab (OCR) under select model scenarios.

proportionally more patients switched to BSC and accumulated lower treatment costs.

AEs of alemtuzumab may be examined more closely than those of other comparators owing to concern among payers regarding high-cost AEs, such as immune thrombocytopenia; but our study confirmed that AEs have only a small impact on overall cost-effectiveness results, in line with results from prior analyses.[20]

Because of AEs, patients are likely to discontinue their treatment or move to an alternative treatment regimen, but our model may not fully represent MS management in clinical practice. To the extent possible, we examined in sensitivity analyses various assumptions for treatment withdrawal.

Other study limitations included the Markovian assumption that the probability of transitioning to another EDSS state was contingent only on the current EDSS state, irrespective of any previous transitions or the length of time in the current state, which may not fully reflect the nature of disease in real-world settings. In addition, differential severity levels of relapse besides those that lead to hospitalization and those that do not were not considered; nevertheless, the sensitivity analysis showed that relapse model parameters had only a negligible impact on model results. Finally, any benefits in terms of patient convenience resulting from two initial courses for alemtuzumab instead of chronic treatment were not captured in the model.

Worth noting in our study is the use of the more recent BCMS cohort as the natural history data source. Modeling RMS using the BCMS cohort has been validated previously against data from the United Kingdom and has been used by an Independent Scientific Committee, including members from Health Departments of England, Wales, Scotland, Northern Ireland, and the UK National Institute of Health Research's Health Technology Assessment Programme, to evaluate the cost-effectiveness of the UK Multiple Sclerosis Risk Sharing Scheme.[29] Previous cost-effectiveness models in RMS have predominantly used the LO cohort as the data source for natural disease history progression. The use of the LO cohort, however, has intrinsic flaws because it only allows patients to remain in the same EDSS state or progress, which clinically is uncharacteristic of RMS as some patients naturally regress to a better EDSS disability state even in the absence of DMT treatment. As expected, using the DEFINE/CONFIRM/LO dataset in sensitivity analysis to model the natural disease history of RMS resulted in more conservative cost-effectiveness estimates for alemtuzumab as patients progressed much faster through the EDSS states.

Conclusions

Alemtuzumab is a cost-effective DMT for the treatment of patients with RMS when compared with fingolimod, natalizumab, ocrelizumab, and generic glatiramer acetate 20 mg. Model results from our study should be used to optimize disease management decisions for the effective treatment of RMS. Future research should consider other sources of natural history data, especially as DMTs become standard of therapy and patient responses to treatment may alter the underlying disease progression. Definitive real-world evidence on the adherence, withdrawal, combination therapy, gaps in care, and switching patterns among DMT agents in RMS is not yet available, and future research should incorporate that evidence when it becomes so.

Acknowledgments

The authors would like to thank Catherine O'Connor of Pharmerit International for medical writing assistance, which was funded by Sanofi, and Enrique Alvarez, Kavita Nair, Colin Mitchell, Darren Baker, Nadia Daizadeh, Julia Morawski, Laura Saltonstall, and Isabel Firmino for article review.

Supplemental Materials

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.jval.2018.08.011.

REFERENCES

1. Grima DT, Torrance GW, Francis G, et al. Cost and health related quality of life consequences of multiple sclerosis. Mult Scler 2000;6(2):91–8.
2. National Multiple Sclerosis. Who gets MS? (Epidemiology). https://www.nationalmssociety.org/What-is-MS/Who-Gets-MS. Accessed October 24, 2018.
3. Campbell JD, Ghushchyan V, Brett McQueen R, et al. Burden of multiple sclerosis on direct, indirect costs and quality of life: National US estimates. Mult Scler Relat Disord 2014;3(2):227–36.
4. Marangoni C, Nanni MG, Grassi L, et al. Bipolar disorder preceding the onset of multiple sclerosis. Neuroimmunol Neuroinflamm 2015;2:195–9.
5. Owens GM. Economic burden of multiple sclerosis and the role of managed sare organizations in multiple sclerosis management. Am J Manag Care 2016;22(6 Suppl):s151–8.
6. Oleen-Burkey M, Castelli-Haley J, Lage MJ, et al. Burden of a multiple sclerosis relapse: the patient's perspective. Patient 2012;5(1):57–69.
7. Zwibel HL, Smrtka J. Improving quality of life in multiple sclerosis: an unmet need. Am J Manag Care 2011;17(Suppl 5 Improving):S139–45.
8. Adelman G, Rane SG, Villa KF. The cost burden of multiple sclerosis in the United States: a systematic review of the literature. J Med Econ 2013;16(5):639–47.
9. Owens GM, Olvey EL, Skrepnek GH, et al. Perspectives for managed care organizations on the burden of multiple sclerosis and the cost-benefits of disease-modifying therapies. J Manag Care Pharm 2013;19(1 Suppl A):S41–53.
10. Gold R, Wolinsky JS, Amato MP, et al. Evolving expectations around early management of multiple sclerosis. Ther Adv Neurol Disord 2010;3(6):351–67.
11. Cohen JA, Coles AJ, Arnold DL, et al. Alemtuzumab versus interferon beta 1a as first-line treatment for patients with relapsing-remitting multiple sclerosis: a randomised controlled phase 3 trial. Lancet 2012;380(9856):1819–28.
12. CAMMS223 Trial Investigators, Coles AJ, Compston DA, et al. Alemtuzumab vs. interferon beta-1a in early multiple sclerosis. N Engl J Med 2008;359(17):1786–801.
13. Coles AJ, Twyman CL, Arnold DL, et al. Alemtuzumab for patients with relapsing multiple sclerosis after disease-modifying therapy: a randomised controlled phase 3 trial. Lancet 2012;380(9856):1829–39.
14. Barkhof F, Cohen JA, Coles AJ, et al Alemtuzumab slows brain volume loss over 5 years in patients with active relapsing-remitting multiple sclerosis with most patients not receiving treatment for 4 years: CARE MS I and II extension study. Paper presented at ECTRIMS2015, Barcelona, Spain.
15. Coles AJ, Cohen JA, Fox EJ, et al. Alemtuzumab CARE-MS II 5-year follow-up: efficacy and safety findings. Neurology 2017;89(11):1117–26.
16. Havrdova E, Arnold DL, Cohen JA, et al. Alemtuzumab CARE-MS I 5-year follow-up: Durable efficacy in the absence of continuous MS therapy. Neurology 2017;89(11):1107–16.
17. Goldberg LD, Edwards NC, Fincher C, et al. Comparing the cost-effectiveness of disease-modifying drugs for the first-line treatment of relapsing-remitting multiple sclerosis. J Manag Care Pharm 2009;15(7):543–55.
18. Lee S, Baxter DC, Limone B, et al. Cost-effectiveness of fingolimod versus interferon beta-1a for relapsing remitting multiple sclerosis in the United States. J Med Econ 2012;15(6):1088–96.
19. Noyes K, Bajorska A, Chappel A, et al. Cost-effectiveness of disease-modifying therapy for multiple sclerosis: a population-based study. Neurology 2011;77(4):355–63.
20. Mauskopf J, Fay M, Iyer R, et al. Cost-effectiveness of delayed-release dimethyl fumarate for the treatment of relapsing forms of multiple sclerosis in the United States. J Med Econ 2016;19(4):432–42.
21. Fogarty E, Schmitz S, Tubridy N, et al. Comparative efficacy of disease-modifying therapies for patients with relapsing remitting multiple sclerosis: Systematic review and network meta-analysis. Mult Scler Relat Disord 2016;9:23–30.

22. Tramacere I, Del Giovane C, Salanti G, et al. Immunomodulators and immunosuppressants for relapsing-remitting multiple sclerosis: a network meta-analysis. Cochrane Database Syst Rev 2015:CD011381.
23. Hawton A, Shearer J, Goodwin E, et al. Squinting through layers of fog: assessing the cost effectiveness of treatments for multiple sclerosis. Appl Health Econ Health Policy 2013;11(4):331–41.
24. Guo S, Pelligra C, Thibault CS-L, et al. Cost-effectiveness analyses in multiple sclerosis: a review of modelling approaches. Pharmacoeconomics 2014;32(6):559–72.
25. Chilcott J, Miller DH, McCabe C, et al. Modelling the cost effectiveness of interferon beta and glatiramer acetate in the management of multiple sclerosisCommentary: Evaluating disease modifying treatments in multiple sclerosis. BMJ 2003;326(7388):522.
26. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology 1983;33(11):1444–52.
27. Hauser SL, Bar-Or A, Comi G, et al. Ocrelizumab versus interferon beta-1a in relapsing multiple sclerosis. N Engl J Med 2017;376(3):221–34.
28. Palace J, Bregenzer T, Tremlett H, et al. UK multiple sclerosis risk-sharing scheme: a new natural history dataset and an improved Markov model. BMJ Open 2014;4(1):e004073.
29. Palace J, Duddy M, Bregenzer T, et al. Effectiveness and cost-effectiveness of interferon beta and glatiramer acetate in the UK Multiple Sclerosis Risk Sharing Scheme at 6 years: a clinical cohort study with natural history comparator. Lancet Neurol 2015;14(5):497–505.
30. Institute for Clinical and Economic Review. Disease-Modifying Therapies for Relapsing-Remitting and Primary-Progressive Multiple Sclerosis: Effectiveness and Value: Evidence Report. Boston, MA: ICER; 2017.
31. Phillippo DM, Ades A, Dias S, et al. Methods for population-adjusted indirect comparisons in health technology appraisal. Med Decis Making 2018;38(2):200–11.
32. Held U, Heigenhauser L, Shang C, et al. Predictors of relapse rate in MS clinical trials. Neurology 2005;65(11):1769–73.
33. Leist TP, Stangel M, Macdonell R, et al. Teriflunomide shows consistent clinical efficacy on severe relapses ac ross temso and tower: 2 phase 3 trials. Value Health 2015;18:A279.
34. Fox EJ, Arnold DL, Cohen JA, et al Durable efficacy of alemtuzumab on clinical outcomes over 5 years in CARE-MS II with most patients free from treatment for 4 years. Poster presented at ECTRIMS2015, October 7–10, 2015, Barcelona, Spain.
35. Havrdova E, Arnold D, Cohen J, et al Durable efficacy of alemtuzumab on clinical outcomes over 5 years in treatment-naive patients with active relapsing-remitting multiple sclerosis with most patients not receiving treatment for 4 years: CARE-MS I extension study. Mult Scler J.
36. Tappenden P, McCabe C, Chilcott J, et al. Cost-effectiveness of disease-modifying therapies in the management of multiple sclerosis for the Medicare population. Value Health 2009;12(5):657–65.
37. National Institute for Clinical Excellence. Alemtuzumab for treating relapsing-remitting multiple sclerosis. Technology Appraisal Guidance TA312. NICE; 2014.
38. Pokorski RJ. Long-term survival experience of patients with multiple sclerosis. J Insur Med 1997;29(2):101–6.
39. Fleurence RL, Hollenbeak CS. Rates and probabilities in economic modelling: transformation, translation and appropriate application. Pharmacoeconomics 2007;25(1):3–6.
40. Chim CS, Kumar SK, Orlowski RZ, et al. Management of relapsed and refractory multiple myeloma: novel agents, antibodies, immunotherapies and beyond. Leukemia 2018;32(2):252–62.
41. O'Brien JA, Ward AJ, Patrick AR, et al. Cost of managing an episode of relapse in multiple sclerosis in the United States. BMC Health Serv Res 2003;3(1):1.
42. Kobelt G, Berg J, Atherley D, et al. Costs and quality of life in multiple sclerosis: a cross-sectional study in the USA. SSE/EFI Working Paper Series in Economics and Finance; 2004.
43. Kariyawasan CC, Hughes DA, Jayatillake MM, et al. Multiple myeloma: causes and consequences of delay in diagnosis. QJM 2007;100(10):635–40.
44. Prosser LA, Kuntz KM, Bar-Or A, et al. Cost-effectiveness of interferon beta-1a, interferon beta-1b, and glatiramer acetate in newly diagnosed non-primary progressive multiple sclerosis. Value Health 2004;7(5):554–68.
45. Patzold U, Pocklington PR. Course of multiple sclerosis. First results of a prospective study carried out of 102 MS patients from 1976-1980. Acta Neurol Scand 1982;65(4):248–66.
46. Frasco MA, Shih T, Incerti D, et al. Incremental net monetary benefit of ocrelizumab relative to subcutaneous interferon β-1a. J Med Econ 2017;20(10):1074–82.
47. Yang H, Duchesneau E, Foster R, et al. Cost-effectiveness analysis of ocrelizumab versus subcutaneous interferon beta-1a for the treatment of relapsing multiple sclerosis. J Med Econ 2017;20(10):1056–65.