ORIGINAL RESEARCH ARTICLE

Cost-Effectiveness Analysis of Ofatumumab for the Treatment of Relapsing-Remitting Multiple Sclerosis in Canada

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Abstract

Background Ofatumumab is a high-efficacy disease-modifying therapy (DMT) approved for first-line treatment of relapsing-remitting multiple sclerosis (RRMS) in Canada.

Objective The aim of this study was to evaluate the cost effectiveness of ofatumumab from a Canadian healthcare system perspective.

Methods A Markov cohort model was run over 65 years using annual cycles, 1.5% annual discount rate, and 100% treatment discontinuation at 10 years. The British Columbia database informed natural history transition probabilities. Treatment efficacy for DMTs were sourced from a network meta-analysis. Clinical trial data were used to estimate probabilities for treatment-related adverse events. Health utilities and costs were obtained from Canadian sources (if available) and the literature.

Results Among first-line indicated therapies for RRMS, ofatumumab was dominant (more effective, lower costs) over teriflunomide, interferons, dimethyl fumarate, and ocrelizumab. Compared with glatiramer acetate and best supportive care, ofatumumab resulted in incremental cost-effectiveness ratios (ICERs) of $24,189 Canadian dollars per quality-adjusted life-year (QALY) and $28,014/QALY, respectively. At a willingness-to-pay threshold of $50,000/QALY, ofatumumab had a 64.3% probability of being cost effective. Among second-line therapies (scenario analysis), ofatumumab dominated natalizumab and fingolimod and resulted in an ICER of $50,969 versus cladribine.

Conclusions Ofatumumab is cost effective against all comparators and dominant against all currently approved and reimbursed first-line DMTs for RRMS, except glatiramer acetate.

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Key Points for Decision Makers

From a Canadian public healthcare system perspective, ofatumumab is cost effective against all currently approved and reimbursed disease-modifying therapies for the treatment of relapsing-remitting multiple sclerosis (RRMS), and dominant compared with all disease-modifying therapies with a first-line indication, except glatiramer acetate.

Ofatumumab's cost effectiveness, alongside its high efficacy and favorable safety profile, demonstrate its value as an early treatment option in RRMS.

1 Introduction

Multiple sclerosis (MS) is a chronic, autoimmune disorder of the central nervous system characterized by inflammation, demyelination, and eventual axonal degeneration resulting in irreversible neurological impairments and disability [1]. About 85% of patients initially experience periodic relapses followed by complete or partial remission, known as relapsing-remitting MS (RRMS) [1]. There is a substantial economic burden of MS to the healthcare system, patients, caregivers, and society because of the chronic progressive disease course and a broad range of symptoms. In addition to high healthcare resource use, MS significantly impacts patient health-related quality of life leading to decreased independence, and productivity loss or unemployment [2].

Management of RRMS involves disease-modifying therapies (DMTs), which aim to reduce relapse frequency and severity, and prevent or decrease disability [1, 3]. In Canada, 16 DMTs are approved for patients with RRMS. Treatment selection is informed by level of disease activity, treatment efficacy, safety and tolerability, and likelihood of adherence [4]. Base therapies (DMTs approved for use as starting treatments) include injectables (glatiramer acetate and interferons) and orals (teriflunomide and dimethyl fumarate) [3]. They are generally considered to have mild to moderate efficacy (average relapse reduction of 30–50%) [4, 5].

In Canada, five DMTs have higher efficacy (average relapse reduction > 50%); the oral fingolimod and cladribine and the injectable monoclonal antibodies, natalizumab, ocrelizumab, and alemtuzumab. Evidence suggests that patients have better disease outcomes (i.e., slower disease progression and reduced long-term disability) when higher efficacy treatments are initiated earlier in the disease course [6]. However, most higher efficacy DMTs are associated with increased risk of adverse events (AEs), limiting treatment to patients with persistent or high initial disease activity due to a suboptimal response to other DMTs [7].

Therapies that selectively deplete B cells have demonstrated improved treatment outcomes in MS [8]. Ocrelizumab is approved in Canada for initial therapy but is often reserved for patients with more aggressive disease [3]. As with other monoclonal antibodies, ocrelizumab is given intravenously; however, its administration is associated with risk of infusion reactions, inconvenience of travelling to infusion clinics, time and resource use required for administration, and added financial burden to patients and the healthcare system. Therefore, there is a high unmet need for an easy-to-administer DMT with high efficacy and a favorable benefit–risk profile that can be used early in the treatment pathway.

Ofatumumab, the first fully human monoclonal anti-CD20 antibody, is approved in Canada for first-line therapy in the treatment of adult patients with RRMS with active disease. A network meta-analysis (NMA) ranked ofatumumab among the most efficacious DMTs with respect to disease progression and reduction in relapse rates [5]. Ofatumumab also has a favorable safety profile as observed in the ASCLEPIOS trials[1] [9]; adverse events (AEs) were balanced between ofatumumab and teriflunomide (a widely used first-line DMT), with no unexpected safety findings. In contrast to other monoclonal antibodies which are given intravenously, ofatumumab is a subcutaneous injection that can be self-administered at home, allowing greater patient independence, reduced healthcare resource utilization, and treatment access in areas outside of infusion facilities.

Given the increasing number of available DMTs, alongside the substantial economic burden associated with MS, it is critical to identify which treatment options are cost effective. The current study evaluated the cost effectiveness of ofatumumab against other DMTs and best supportive care (BSC; i.e., no active therapy) for the treatment of patients with RRMS with active disease from a Canadian public healthcare system perspective. A societal perspective was conducted as a scenario analysis.

2 Methods

2.1 Model Structure

A cohort multi-state Markov transition model was developed in Microsoft® Excel® for Microsoft 365 MSO (16.0.14326.20936) 64-bit Version 2018 (Build 14326.20962 Click-to-Run) to predict the costs and effectiveness of treatments with a first-line indication in adults with RRMS; a scenario analysis was conducted to compare against DMTs indicated for second-line use. A global deterministic model was adapted for Canada to include probabilistic sequential analyses [10, 11]. Table 1 presents the probabilistic distributions used for each parameter. The base case probabilistic analysis was conducted from the Canadian public healthcare system perspective and run over a lifetime time horizon (i.e., 65 years) using an annual cycle length and 1.5% annual discount rate for costs and effects [12]. A sensitivity analysis examined the impact of a 25-year time horizon. A half-cycle correction was applied to the calculation of costs (excluding drug costs), life-years, and quality-adjusted life-years

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[1] The ASCLEPIOS trials were two double-blind, double-dummy, phase III trials comparing subcutaneous ofatumumab (20 mg every 4 weeks after 20-mg loading doses at days 1, 7, and 14) with oral teriflunomide (14 mg daily) for up to 30 months. In both trials, patients receiving ofatumumab experienced significantly fewer relapses (primary endpoint; annualized relapse rate) relative to patients treated with teriflunomide (p < 0.001 for both). Additional details of the ASCLEPIOS trials have been published elsewhere [9].

Table 1 Distribution used for classes of parameters in probabilistic base-case analysis

Input	Probabilistic distribution
Patient proportions per EDSS state	Dirichlet
Percentage of males (%)	Beta
Age of cohort (years)	Gamma
Years since diagnosis	Gamma
Efficacy source for disease progression	Log-normal
Efficacy source for relapse rate	Log-normal
Relapse severity	Dirichlet
Discontinuation probabilities	Beta
RRMS relapse rate	Log-normal
Mortality multiplier for MS	Log-normal
Relapse rate (EDSS dependent)	Beta
AE probabilities	Beta
EDSS health state costs (direct)	Gamma
Relapse costs	Gamma
AE costs	Gamma
EDSS health state utilities	Beta
Disutilities for relapse	Beta
Disutilities for AEs	Beta

AE adverse event, *EDSS* expanded disability status scale, *MS* multiple sclerosis

(QALYs). Drug costs were excluded from half-cycle corrections as a conservative estimate, as drugs were given at different intervals throughout the year (e.g., 4-weekly or monthly vs annually at the start of a cycle), noting that costs for drugs provided on a 4-weekly or monthly basis may in fact be lower than estimated in the model. The primary outcome was the difference in costs and QALYs gained between ofatumumab and each individual comparator arm, presented as the incremental cost-effectiveness ratio (ICER). A willingness to pay (WTP) threshold of $50,000 Canadian dollars (CAD) per QALY gained was used to assess cost effectiveness [13, 14].

At model entry, patients were assigned to baseline Expanded Disability Status Scale (EDSS) state distributions informed by a pooled analysis of the ASCLEPIOS trials for patients with RRMS with active disease and in line with the Health Canada product monograph indication [9, 15]. A detailed description of baseline patient characteristics has previously been published elsewhere [9]. This study population is representative of Canadian patients treated for RRMS, with respect to the average starting age of treatment (37.8 years) and sex distribution (31.8% males). In the model, patients transitioned between EDSS states 0 through 9, and the death state (EDSS 10) (Fig. 1). Each year, patients could transition to a higher or lower EDSS state (i.e., worsen or improve, respectively), remain at their current state, or die. Patients could also discontinue therapy and switch to health states associated with BSC, with transition probabilities between EDSS states for BSC informed by natural history data from the British Columbia MS (BCMS) database (Table S1 in the electronic supplementary material [ESM]) [16]. This population-based dataset measured changes in EDSS from 1980 to 1995 and was used instead of the London Ontario cohort, which may not reflect present-day MS patients as data were collected from the 1970s to the 1980s [16, 17]. The London dataset also censored any improvement in EDSS states (i.e., backward transitions), resulting in faster progressions through states and underestimations of the cumulative QALYs gained [18]. As such, the BCMS dataset may be more reflective of the current treatment landscape [19], was suggested as the preferred source of natural history transitions [18], and was supported by clinical expert opinion. Furthermore, patients who reached an EDSS score of ≥ 7 while on DMTs would discontinue treatment and receive BSC, in line with Canadian clinical practice and current recommendations from the Association of British Neurologists [7].

In line with previous economic models, EDSS-dependent natural history annualized relapse rates (ARR) were informed by Patzold and Pocklington, and Orme and colleagues [20–22]. Relapse severity was sourced from a prospective cohort of patients with RRMS [23]; second event relapse severity data were used (mild, 47%; moderate, 35%; severe, 18%) as relapses could occur continually throughout the model.

Fig. 1 Model structure. Rounded rectangles on the top row represent health states and rounded rectangles on the bottom row represent events that patients could experience at any time. Patients who reached an EDSS score of ≥ 7 while on treatment would discontinue treatment and receive BSC. *BSC* best supportive care, *EDSS* expanded disability status scale
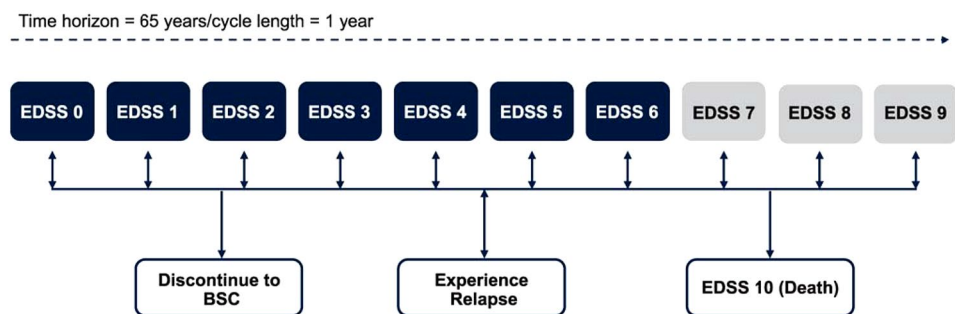
Table 2 Treatment efficacy and discontinuation probabilities for ofatumumab and comparators versus BSC from the network meta-analysis [5]

Treatment	6-Month confirmed disability progression, HR (SE)	Annualized relapse rate, RR (SE)	Discontinuation probabilities, % Risk (SE)
Base-case analysis (first-line therapies)			
Ofatumumab	0.43 (0.12)	0.30 (0.05)	10.64 (0.76)
Ocrelizumab	0.47 (0.16)	0.33 (0.05)	10.95 (2.93)
Teriflunomide	0.80 (0.15)	0.66 (0.06)	13.12 (1.33)
Dimethyl fumarate	0.68 (0.12)	0.50 (0.06)	12.24 (2.28)
Glatiramer acetate	0.78 (0.15)	0.65 (0.10)	11.54 (2.23)
Avonex	0.71 (0.12)	0.79 (0.06)	13.22 (2.07)
Rebif 22	0.71 (0.14)	0.69 (0.09)	15.44 (2.66)
Rebif 44	0.77 (0.21)	0.62 (0.05)	15.06 (1.69)
Betaseron	0.79 (0.14)	0.68 (0.07)	10.54 (2.75)
Extavia	0.79 (0.14)	0.68 (0.07)	10.54 (2.75)
BSC	1.00 (0.00)	1.00 (0.00)	0.00 (0.00)
Scenario-analysis (second-line therapies)			
Cladribine	0.54 (0.13)	0.42 (0.07)	9.02 (3.63)
Natalizumab	0.46 (0.10)	0.31 (0.05)	11.25 (3.20)
Fingolimod	0.67 (0.11)	0.46 (0.05)	11.44 (2.33)

BSC best supportive care, *HR* hazard ratio, *RR* relative risk, *SE* standard error

Age- and sex-specific all-cause mortality rates for the Canadian general population [24] were adjusted for the MS population by using an EDSS-dependent MS-specific hazard ratio (HR) (Table S2 in the ESM) [25].

2.2 Treatment-Specific Inputs

For patients receiving DMTs, natural history data were adjusted by a treatment effect derived from an NMA by Samjoo et al. [5], which estimated the comparative efficacy of DMTs versus placebo for 6-month confirmed disability progression (CDP-6) and ARR (Table 2). An analysis for CDP-6 was conducted with the individual patient data from ASCLEPIOS aligned with the definition from OPERA [5, 8]. The base-case analysis assumed no waning of treatment efficacy, as data are limited and the inclusion of waning may be considered as double counting of discontinuations [26]. However, treatment waning was considered in a sensitivity analysis and assumed to be associated with time on treatment; in alignment with previous models, efficacy was reduced to 75% after 3 years and 50% after 5 years [27].

Discontinuation rates for each treatment were calculated using the relative effect estimates from the NMA [5], using the annualized all-cause discontinuation probability of ofatumumab from ASCLEPIOS [9] as a reference arm (Table 2). To capture real-world management of patients with RRMS, the base-case analysis assumed constant discontinuation for 9 years, followed by 100% discontinuation for all treatments at 10 years according to clinician opinion (see Sect. 2.5). A sensitivity analysis examined constant discontinuation for all treatments over the full 65-year time horizon. Given the

limited data and high level of uncertainty regarding treatment discontinuation rates for induction therapies, the all-cause discontinuation probability for cladribine (scenario analysis) was adjusted to 16% after 2 years, as previously suggested for modeling other induction therapies [28].

AE probabilities (Table 3) were modeled as non-serious AEs and serious AEs (SAEs). The percent of patients with at least one AE or SAE was sourced from each of the treatments' pivotal trials, or from a pivotal trial where the treatment was a comparator.

2.3 Cost Inputs

The annual, per-patient direct medical costs (Table 4) for management of EDSS 1–6 were sourced from Grima and colleagues [2]. The remaining EDSS state costs were calculated based on exponential extrapolation from Patwardhan and colleagues [29]. Professional care costs (i.e., costs associated with professional assistance by a nurse, personal assistance, and/or help at home) [30] were added to the total health state costs, as previously suggested [31]. A societal perspective that included MS-associated indirect costs (i.e., informal care, sick leave, and retirement due to MS; Table 4) was conducted as a scenario analysis [30].

Mild/moderate relapse costs ($7275) were informed by Karampampa and colleagues [30]. Severe relapse costs ($17,459) were extrapolated based on a systematic review [29] that suggested a severe relapse in RRMS costs 240% more than a mild or moderate relapse.

Treatment-related costs included drug acquisition (Table 5), administration and monitoring (Table 6), and AEs

Table 3 Adverse event probabilities for ofatumumab and comparators[a]

Treatment	Non-serious AE probabilities (%) (SE) Y1+	Serious AE probabilities (%) (SE) Y1+
Base-case analysis (first-line therapies)		
Ofatumumab	33.86 (6.77)	3.68 (0.74)
Ocrelizumab	45.33 (9.07)	3.79 (0.76)
Teriflunomide	32.39 (6.48)	3.04 (0.61)
Dimethyl fumarate	55.95 (11.19)	4.52 (0.90)
Glatiramer acetate	47.14 (9.43)	4.15 (0.83)
Avonex	45.35 (9.07)[b]	4.29 (0.86)
Rebif 22	45.35 (9.07)[b]	4.74 (0.95)[b]
Rebif 44	45.35 (9.07)	4.74 (0.95)
Betaseron	45.35 (9.07)[b]	4.10 (0.82)
Extavia	45.35 (9.07)[b]	4.10 (0.82)
BSC	0.00 (0.00)	0.00 (0.00)
Scenario analysis (second-line therapies)		
Cladribine	46.37 (9.27)	4.81 (0.96)
Natalizumab	41.42 (8.28)	5.66 (1.13)
Fingolimod	48.88 (9.78)	7.40 (1.48)

AE adverse event, *BSC* best supportive care, *SE* standard error, *Y1+* year 1 onward

[a]When more than one trial for a treatment was available, a weighted average of the AEs and SAEs probabilities were calculated. Annualized rates were calculated by adjusting the probability reported in the respective clinical trial by the total trial length or mean duration of treatment. When the reported probability included MS relapse as an event, the probability was adjusted to avoid double counting of relapses in the model

[b]Data not available; probabilities assumed to be equivalent to those reported for interferon β-1a 44 mg

Table 4 Costs by health state

Health state (EDSS)	Direct medical cost [2, 30] (SE), CAD	Indirect costs [30] (SE), CAD
0	1268 (254)	12,110 (2422)
1	1908 (382)	12,110 (2422)
2	2590 (518)	12,110 (2422)
3	4218 (844)	12,110 (2422)
4	5837 (1167)	31,660 (6332)
5	9746 (1949)	31,660 (6332)
6	15,143 (3029)	31,660 (6332)
7	36,461 (7292)	50,153 (10,031)
8	43,217 (8643)	50,153 (10,031)
9	52,936 (10,587)	50,153 (10,031)

CAD Canadian dollars, *EDSS* expanded disability status scale, *SE* standard error

(Table 6), with the accrual of costs assumed to apply for the entire time patients received treatment in the model. Drug acquisition costs were sourced from Ontario formularies [32, 33] and the manufacturer anticipated list price for ofatumumab using doses from Canadian product monographs. If there were multiple cost options for a comparator drug, the lowest option was used to represent the most conservative estimate. Administration and monitoring costs were calculated by multiplying the annual resource use (informed by Health Canada product monographs) by the respective unit cost (Table S3 and Table S4 in the ESM). Unit costs were sourced from the Ontario Schedule of Benefits, Ontario Case Costing Initiative, formularies, published literature, and clinician opinion [32–38]. Non-serious AE costs ($84) were assumed to be a physician visit [35], while serious AE costs ($363) were assumed to be an MS Day Case admission (ambulatory care, 18–69 years, Most Responsible Diagnosis Code G35) [34]. All costs were converted to 2021 CAD, using a Canadian Cost Inflation Tool which provided Canadian price index estimates for the health care component of the Consumer Price Index. The tool provided Canadian price index estimates for complete years, as reported by table 18-10-0004-01 of the Consumer Price Index (Health care; monthly, not seasonally adjusted) presented by Statistics Canada [39].

2.4 Utilities and Disutilities

Utility data are provided in Table 7. Mean utility values for EDSS health states were derived from normative utility data for the Canadian population (EDSS 0) [40] and the functional form modeled Health Utilities Index Mark 3 (HUI3)

Table 5 Drug acquisition costs[a]

Treatment	Route	Unit cost (CAD)	Recommended dosage	Total cost Y1 (CAD)[b]	Total cost Y2+ (CAD)[b]	References
Base-case analysis (first-line therapies)						
Ofatumumab	Injection	2208.33	20 mg s.c. at Weeks 0, 1, and 2, then monthly beginning at week 4	30,917	26,500	Manufacturer's submitted price
Ocrelizumab	Infusion	8150.00	600 mg i.v. every 6 months[c]	32,600	32,600	OEAP Formulary [33]
Teriflunomide	Oral	60.25	14 mg QD	22,005	22,005	OEAP Formulary [33]
Dimethyl fumarate	Oral	18.39/120 mg 36.77/240 mg	120 mg BID; after 7 days increase to 240 mg BID	26,606	26,863	OEAP Formulary[33]
Glatiramer acetate	Injection	32.40	20 mg s.c. QD	11,834	11,834	ODB Formulary [32]
Avonex	Injection	476.94	300 µg i.m. once weekly	24,886	24,886	OEAP Formulary [33]
Rebif 22	Injection	150.83	22 µg 3 times weekly	23,610	23,610	OEAP Formulary [33]
Rebif 44	Injection	183.62	44 µg 3 times weekly	28,743	28,743	OEAP Formulary [33]
Betaseron	Injection	110.00	0.25 mg (8 MIU) s.c. every other day	20,089	20,089	OEAP Formulary[33]
Extavia	Injection	104.69	0.25 mg (8 MIU) s.c. every other day	19,119	19,119	OEAP Formulary [33]
BSC	Injection	0.00		0	0	
Scenario analysis (second-line therapies)						
Cladribine	Oral	3212.00	1.75 mg/kg body weight per year taken over 2 weeks, for 2 years[d]	44,968[e]	44,968[e,f]	OEAP Formulary [33]
Natalizumab	Infusion	3596.17	300 mg i.v. every 4 weeks	46,911	46,911	OEAP Formulary [33]
Fingolimod	Oral	73.91	0.5 mg QD	26,996	26,996	ODB Formulary [32]

BID twice daily, *BSC* best supportive care, *CAD* Canadian dollars, *i.m.* intramuscular, *i.v.* intravenous, *MIU* million international units, *ODB* Ontario Drug Benefit, *OEAP* Ontario Exceptional Access Program, *QD* daily, *s.c.* subcutaneous, *Y1* year 1, *Y2+* years 2 onward

[a]Drug dispensing fees or markups were excluded

[b]Annual period assumes 52.18 weeks or 365.25 days for all comparators

[c]The initial 600-mg dose is administered as two separate i.v. infusions: a 300-mg infusion, followed 2 weeks later by a second 300-mg infusion. Subsequent doses thereafter are administered as single 600-mg i.v. infusions every 6 months

[d]The total annual dose per patient is divided into two treatment courses, one at the beginning of the first month and the next at the beginning of the second month of the respective year. Each treatment week consists of 10–20 mg as a single daily dose. For example, a patient weighing 70 kg would take 7 tablets in treatment Weeks 1 and 2 for both year 1 and 2 of the treatment course (14 tablets annually)

[e]The cost for cladribine was calculated using the annual cost from the CADTH Canadian Drug Expert Committee Recommendation report for cladribine. The reported annual cost was adjusted to reflect a change in the unit price of cladribine: the submitted unit price was $3082.70; however, the unit price has since been updated to $3212.00 effective May 6, 2021.

[f]The cost for cladribine was only applied in year 2 unless the patient was treated with a third dose (25.6% of patients) [19], in which case the cost of cladribine would also be applied to year 3

utility data (using a parametric function with least squares minimization technique) from a Canadian study of MS patients from Nova Scotia (EDSS 1–9) [41]. Informal caregiver disutilities [42] were examined alongside indirect costs in a scenario analysis for the societal perspective. Relapse disutilities distinguished between mild or moderate and severe relapses, as used in previous economic models [19, 31, 43]. Given the limited literature, AE disutilities were derived based on assumptions and aligned with previous MS economic models [20].

2.5 Model Validation

In order to ensure the predictions obtained from this model were accurate to the MS population, the model underwent a validation assessment by an external vendor not involved in the original programming. This assessment included a review of the model scope, structure, assumptions, and calculations. The model also underwent internal validation through a review of all calculations and data inputs. As the model structure is aligned with previous submissions to Canadian Health Technology Assessment agencies, it was assumed that the model structure and approach is valid within the Canadian landscape. Additionally, the

Table 6 Drug administration, monitoring, and adverse event costs

Treatment	Total cost Y1 (CAD)	Total cost Y2+ (CAD)	AE annual costs[a] (CAD)	References
Base-case analysis (first-line therapies)				
Ofatumumab	1136	38	42	OCCI, Physician and Laboratory Services, nurse time [34–36, 44]
Ocrelizumab	3374	1581	52	Drug formulary, OCCI, Physician and Laboratory Services, Tam et al., nurse time [32, 34–38, 44]
Teriflunomide	1196	38	38	OCCI, Physician and Laboratory Services, nurse time [34–36, 44]
Dimethyl fumarate	1141	74	64	OCCI, Physician and Laboratory Services, nurse time [34–36, 44]
Glatiramer acetate	1125	38	55	OCCI, Physician and Laboratory Services, nurse time [34–36, 44]
Avonex	1261	84	54	OCCI, Physician and Laboratory Services, nurse time [34–36, 44]
Rebif 22	1261	84	56	OCCI, Physician and Laboratory Services, nurse time [34–36, 44]
Rebif 44	1261	84	56	OCCI, Physician and Laboratory Services, nurse time [34–36, 44]
Betaseron	1631	70	53	OCCI, Physician and Laboratory Services, nurse time [34–36, 44]
Extavia	1631	70	53	OCCI, Physician and Laboratory Services, nurse time [34–36, 44]
BSC	0	0	0	
Scenario analysis (second-line therapies)				
Cladribine	1158	82	57	OCCI, Physician and Laboratory Services, nurse time [34–36, 44]
Natalizumab	6397	3681	56	OCCI, Physician and Laboratory Services, Tam et al., nurse time [34–37, 44]
Fingolimod	1682	84	68	OCCI, Physician and Laboratory Services, nurse time [34–36, 44]

AE adverse event, *BSC* best supportive care, *CAD* Canadian dollars, *OCCI* Ontario Case Costing Initiative, *Y1* year 1, *Y2+* years 2 onward

[a]AE costs were calculated as total weighted costs based on probability of non-serious and serious events for each comparator

appropriateness of Canadian-specific data sources and various clinical assumptions were validated by Canadian clinical experts. Clinician opinion was informed by three clinical experts from varying regions across Canada (Nova Scotia, Ontario, and British Columbia) during three rounds of advisory meetings where model inputs were reviewed and discussed until consensus was reached.

3 Results

3.1 Base-Case Results

Considering DMTs with a first-line indication, ofatumumab dominated (more effective, lower costs) teriflunomide, interferons, dimethyl fumarate, and ocrelizumab; and resulted in ICERs of $24,189 CAD per QALY gained versus glatiramer acetate and $28,014/QALY versus BSC (Table 8, Table S5 and Table S6 in the ESM). The base-case sequential analysis is presented in Table S7 and the efficiency frontier in Fig. S1 of the ESM. Ofatumumab and BSC make up the efficiency frontier; ofatumumab resulted in an ICER of $28,014 versus BSC, which falls below the $50,000/QALY WTP threshold. All other treatments, except glatiramer acetate, are dominated (less effective, higher costs), while glatiramer acetate is extendedly dominated (less effective, lower costs) by ofatumumab. The cost-effectiveness accessibility curve is presented in Fig. S2 in the ESM. At a WTP threshold of

$50,000/QALY gained, ofatumumab had the highest probability of being cost effective at 64.3%.

3.2 Scenario Analyses Results

Considering therapies indicated for second-line use, ofatumumab dominated natalizumab and fingolimod, and resulted in an ICER of $50,969 versus cladribine (Table 8). Ofatumumab had a probability of being cost effective of 40.8%. From a societal perspective, ofatumumab was dominant over all DMTs with a first-line indication (Table S8 in the ESM) and had the highest probability of being cost effective at 65.7%. The inclusion of indirect costs increased total costs relative to the base-case analysis, whereas the inclusion of caregiver disutilities reduced net QALYs relative to the base-case analysis.

3.3 Sensitivity Analyses Results

Using a 25-year time horizon, results aligned with the base case; ofatumumab resulted in ICERs versus glatiramer acetate ($30,826) and BSC ($34,957) and dominated all other DMTs with a first-line indication (Table S9 in the ESM). Similar to the base case, ofatumumab had the highest probability of being cost effective (59.3%). Constant treatment discontinuation also resulted in ICERs for ofatumumab versus glatiramer acetate ($26,971) and BSC ($29,681) and ofatumumab dominating all other DMTs with a first-line indication (Table S10 in the ESM); ofatumumab had the

Table 7 Summary of (dis)utilities

	(Dis)utilities (SE)	References
Patient health state utility		
EDSS		
0	0.86 (0.00)	Guertin et al.[a] [40]
1	0.73 (0.15)	Tappenden et al.[b] [41]
2	0.62 (0.12)	Tappenden et al.[b] [41]
3	0.54 (0.11)	Tappenden et al.[b] [41]
4	0.47 (0.09)	Tappenden et al.[b] [41]
5	0.40 (0.08)	Tappenden et al.[b] [41]
6	0.30 (0.06)	Tappenden et al.[b] [41]
7	0.17 (0.03)	Tappenden et al.[b] [41]
8	− 0.03 (− 0.01)	Tappenden et al.[b] [41]
9	− 0.31 (− 0.06)	Tappenden et al.[b] [41]
Caregiver disutility		
EDSS		
0	0.00 (0.11)	Acaster et al. [42]
1	0.00 (0.11)	Acaster et al. [42]
2	0.04 (0.11)	Acaster et al. [42]
3	0.04(0.11)	Acaster et al. [42]
4	0.14 (0.12)	Acaster et al. [42]
5	0.16 (0.11)	Acaster et al. [42]
6	0.17 (0.11)	Acaster et al. [42]
7	0.03 (0.08)	Acaster et al. [42]
8	0.09 (0.15)	Acaster et al. [42]
9	0.09 (0.15)	Acaster et al. [42]
Relapse disutility		
Mild	0.09 (0.01)	Prosser et al. [43]
Moderate	0.09 (0.01)	Prosser et al. [43]
Severe	0.30 (0.03)	Prosser et al. [43]
AE disutility		
Non-serious	0.00 (0.00)	Assumption[c]
Serious	0.04 (0.01)	Assumption[d]

[a]Given that the modeled data for EDSS 0 resulted in a utility value that was not clinically plausible, the mean utility value for EDSS 0 was based on normative utility data for the Canadian population

[b]Mean utility values for EDSS health states 1–9 were obtained from the functional form modeled Health Utilities Index Mark 3 (HUI3) utility data in Fig. 1 of Tappenden et al. [41] using PlotDigitizer software

[c]Assumption that a non-serious AE disutility of 0.25 was experienced for 7 days

[d]Assumption that a serious AE disutility of 0.5 was applied for 1 month

AE adverse event, *EDSS* expanded disability status scale, *SE* standard error

highest probability of being cost effective at 64.2%. When including efficacy waning (Table S11 in the ESM), ofatumumab resulted in ICERs versus Rebif 22 ($2324), Extavia ($2610), glatiramer acetate ($49,754), and BSC ($55,148) and dominated all remaining DMTs with a first-line

indication. Ofatumumab had the third-highest probability of being cost effective (29.5%) behind BSC (37.1%) and glatiramer acetate (30.40%).

4 Discussion

This analysis is the first to show that ofatumumab is cost effective, and often dominant (more effective, lower costs), compared with currently approved and reimbursed DMTs for RRMS by the Canadian public healthcare system. When considering the broader societal perspective, ofatumumab dominated all DMTs with a first-line indication (i.e., ofatumumab provided more QALYs at a lower cost). Taken together, these findings may help guide treatment decision making for clinicians and their patients and highlight the cost effectiveness of using a high efficacy treatment such as ofatumumab early in the treatment pathway (i.e., as a first-line option).

Considering first-line indicated treatments, the cost effectiveness of ofatumumab is driven not only by the high treatment efficacy, reflected by the largest total QALYs, but also by the reduction in total costs against all comparators except glatiramer acetate and BSC. With the exception of BSC and glatiramer acetate, ofatumumab resulted in predicted cost savings over the lifetime model horizon ranging from $12,022 (vs Extavia) to $41,817 (vs ocrelizumab). The increase in costs associated with ocrelizumab, another high-efficacy B-cell therapy indicated for first-line use, is in part related to the greater healthcare resource utilization associated with intravenous administration in an infusion center. Ofatumumab also resulted in greater incremental QALYs, ranging from 1.327 (vs teriflunomide) to 0.132 (vs ocrelizumab), which could translate into reduced disease burden for the patient. Together, these results suggest that early initiation of treatment with ofatumumab benefits both the patient (i.e., greater QALYs gained) and the healthcare system (i.e., lower total costs). Considering DMTs indicated for second-line use, ofatumumab resulted in predicted cost savings of $29,775 versus fingolimod and $126,818 versus natalizumab, but did not result in cost savings versus cladribine. Like ocrelizumab, the increased costs associated with natalizumab are partly related to requirements for frequent intravenous infusion.

Two approved treatments for RRMS were not considered in this analysis: peginterferon β-1a and alemtuzumab. Comparators for our analysis were selected based on data available in the NMA by Samjoo et al. [5] and relevant treatment sequencing in clinical practice. Peginterferon β-1a was excluded from the NMA based on results indicating greater efficacy than other β-interferons and highly efficacious monoclonal antibodies [5], contrary to clinical experience, as suggested by the NICE technology appraisal committee

Table 8 Results of the base-case (first-line therapies) and scenario (second-line therapies) probabilistic analyses

Treatment	Total cost (CAD)	LY	QALY	Incremental cost of ofatumumab vs comparator (CAD)	Incremental QALY of ofatumumab vs comparator	ICER ($ per QALY) vs ofatumumab
Base case analysis (first-line therapies)						
Ofatumumab	743,015 (739,331–746,700)	28.406 (28.392–28.420)	9.277 (9.215–9.339)			
Ocrelizumab	784,832 (780,987–788,678)	28.383 (28.369–28.398)	9.145 (9.077–9.212)	− 41,817 (− 43,364 to − 40,270)	0.132 (0.091–0.173)	Ofatumumab dominant
Teriflunomide	761,998 (757,775–766,221)	28.170 (28.155–28.184)	7.950 (7.894–8.006)	− 18,983 (− 20,410 to − 17,555)	1.327 (1.293–1.361)	Ofatumumab dominant
Dimethyl fumarate	771,029 (766,988–775,070)	28.238 (28.224–28.253)	8.341 (8.284–8.397)	− 28,014 (− 29,340 to − 26,688)	0.936 (0.903–0.969)	Ofatumumab dominant
Glatiramer acetate	713,474 (709,330–717,619)	28.190 (28.175–28.205)	8.056 (7.997–8.115)	29,541 (28,116 to 30,966)	1.221 (1.187–1.256)	$24,189
Avonex	770,188 ($766,116–774,259)	28.216 (28.202–28.231)	8.118 (8.062–8.175)	− 27,173 (− 28,451 to − 25,894)	1.158 (1.127–1.189)	Ofatumumab dominant
Rebif 22	756,048 (751,998–760,098)	28.202 (28.187–28.217)	8.085 (8.028–8.142)	− 13,033 (− 14,393 to − 11,672)	1.192 (1.158–1.226)	Ofatumumab dominant
Rebif 44	781,810 (777,612–786,008)	28.178 (28.163–28.193)	7.994 (7.936–8.052)	− 38,795 (− 40,362 to − 37,227)	1.283 (1.244–1.321)	Ofatumumab dominant
Betaseron	759,927 (755,753–764,100)	28.189 (28.175–28.204)	8.041 (7.982–8.099)	− 16,911 (− 18,335 to − 15,487)	1.236 (1.202–1.270)	Ofatumumab dominant
Extavia	755,037 (750,843–759,232)	28.189 (28.174–28.204)	8.032 (7.977–8.088)	− 12,022 (− 13,518 to − 10,527)	1.245 (1.209–1.280)	Ofatumumab dominant
BSC	689,506 (685,203–693,810)	28.073 (28.059–28.088)	7.367 (7.317–7.416)	53,509 (52,339 to 54,679)	1.910 (1.883–1.937)	$28,014
Scenario analysis (second-line therapies)						
Cladribine	715,734 (711,796–719,671)	28.311 (28.297–28.325)	8.742 (8.683–8.800)	27,282 (25,948 to 28,615)	0.535 (0.502–0.568)	$50,969
Natalizumab	869,833 (865,872–873,793)	28.382 (28.368–28.396)	9.138 (9.078–9.198)	− 126,818 (− 128,603 to − 125,032)	0.139 (0.103–0.174)	Ofatumumab dominant
Fingolimod	772,790 (768,805–776,776)	28.251 (28.236–28.265)	8.422 (8.364–8.479)	− 29,775 (− 31,093 to − 28,457)	0.855 (0.822–0.888)	Ofatumumab dominant

Data are presented as mean (95% confidence interval).

BSC best supportive care, *CAD* Canadian dollars, *ICER* incremental cost-effectiveness ratio, *LY* life-years, *QALY* quality-adjusted life-year

[26]. Alemtuzumab was excluded due to increased risk of serious and life-threatening safety concerns and is indicated as a third-line DMT limited to patients with highly active disease and inadequate response to at least two other DMTs [7]. Given ofatumumab's favorable safety profile and first-line indication, comparing ofatumumab and alemtuzumab was deemed irrelevant in the context of treatment sequencing in clinical practice.

The current analysis has limitations common to economic models. Treatment efficacy was modeled based on clinical trial outcomes extrapolated over a lifetime horizon, which introduces uncertainties surrounding the long-term effectiveness of DMTs in RRMS [18]. As such, the base-case analysis set treatment discontinuation to 100% by 10 years to reflect the clinical opinion that the majority of patients are no longer on the same treatment after this time. Although treatment switching often occurs in clinical practice [3], this

feature was not included in the present analysis due to a lack of clinical data to inform treatment efficacy for subsequent lines of therapy, an approach that is consistent with previous economic analyses [18, 19]. Alternative scenarios were provided to investigate constant discontinuation over a lifetime horizon, and the impact of a shorter time horizon (25 years). Our analyses also investigated the inclusion of a waning effect that gradually reduced treatment efficacy beyond 2 years, consistent with assumptions used in previous models and HTA recommendations [18, 27]; however, inclusion of waning may be considered as double counting of discontinuations, as previously suggested [26]. Lastly, while some references used to interpret and inform inputs into the model were dated (due to a lack of alternative Canadian-specific date sources), all data used to inform inputs in the model are from commonly used references, represent Canadian data and were appropriately inflated. Results of the sensitivity analyses demonstrated that the cost effectiveness of ofatumumab was generally robust to the various assumptions made, with the inclusion of efficacy waning having the largest impact on the results.

Cross-trial comparisons of discontinuation rates and AE-related outcomes are also subject to limitations [5]. Induction therapies like cladribine tend to have low discontinuation rates due to the predetermined treatment administration schedule. In most cases, patients can no longer discontinue treatment once the induction phase of treatment occurs. As a result, given the small amount of data available and the high level of uncertainty regarding discontinuation rates of cladribine, the NMA-derived all-cause discontinuation probability was applied for years 1 and 2, with a withdrawal rate of 16% thereafter, as suggested in the Canadian Agency for Drugs and Technologies in Health (CADTH) submission for alemtuzumab [28], another 2-year induction therapy. Modeling of treatment-specific AE-related outcomes also poses challenges, including (i) inadequate power to assess safety outcomes, (ii) patients were not blinded to treatment in some pivotal open-label trials, (iii) lack of meaningful understanding of long-term safety profiles, (iv) dissimilar safety profiles between drugs, and (v) infrequent reporting of definitions for AE-related outcomes in clinical trial publications [5]. Accordingly, the present model distinguishes between non-serious and serious AEs in an attempt to capture the majority of AEs observed in clinical practice.

5 Conclusion

Ofatumumab is cost effective compared with currently approved and reimbursed DMTs for the treatment of patients with RRMS in Canada at a threshold of $50,000 per QALY gained. Given ofatumumab's high efficacy, favorable risk–benefit profile, easy and accessible route of administration, and demonstrated cost effectiveness, it should be considered a valuable early treatment option for patients with RRMS.

Declarations

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870   M. Baharnoori et al.

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