



Cost–consequence analysis of ofatumumab for the treatment of relapsing–remitting multiple sclerosis in Canada

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Aim: The costs and consequences of initial and delayed ofatumumab treatment were evaluated in relapsing–remitting multiple sclerosis with active disease in Canada. **Materials & methods:** A Markov cohort model was used (10-year horizon, annual cycle length, 1.5% discounting). Scenario analyses examined ofatumumab as first-line treatment versus 3 and 5 years following switch from commonly used first-line therapies. **Results:** Ofatumumab resulted in improvements in clinical outcomes (relapses and disease progression) and productivity (employment and full-time work), and reduction of economic burden (administration, monitoring and non-drug costs) that were comparable to other high-efficacy therapies (ocrelizumab, cladribine and natalizumab). Switching to ofatumumab earlier in the disease course may improve these outcomes. **Conclusion:** Results highlight the value of a high-efficacy therapy such as ofatumumab as initial treatment (i.e., first-line) in newly diagnosed relapsing–remitting multiple sclerosis patients with active disease.

Plain language summary

What is this article about? Relapsing–remitting multiple sclerosis (RRMS) is the most common type of MS, an autoimmune disease that impacts the central nervous system, and is characterized by attacks (i.e., relapses) followed by complete or partial remissions. RRMS is associated with increased disability, costs, and reduced productivity due to disease progression. Early treatment with a high-efficacy therapy might improve outcomes and reduce costs. The study objective was to evaluate the costs and consequences of initial administration of the high-efficacy therapy ofatumumab, as well as after treatment with other commonly used first-line therapies, in patients with RRMS with active disease in Canada.

What were the results? Ofatumumab resulted in improvements in clinical outcomes (relapses and disease progression) and productivity (employment and full-time work), and reduction of economic burden (administration, monitoring and non-drug costs) that were comparable to other high-efficacy therapies (ocrelizumab, cladribine and natalizumab). Switching to ofatumumab earlier in the disease course may improve these outcomes versus commonly administered first-line therapies.

What do the results of the study mean? Results suggest that a high-efficacy therapy, like ofatumumab, would be a valuable early treatment option for patients with RRMS.

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Multiple sclerosis (MS) is a chronic and unpredictable neuroinflammatory disease which accumulates in irreversible physical and neurological impairment [1]. In relapsing–remitting MS (RRMS), patients experience occasional relapses



followed by periods of complete or partial recovery [1]. Disease diagnosis typically occurs during prime career- and family-building years, with an inevitable disease progression over time for most patients [2]. Patients with MS experience a reduction in working hours and productivity, unemployment, and early retirement as a consequence of their physical and cognitive disabilities, fatigue and pain [3–7]. Diminished independence and productivity are associated with increased healthcare resource usage, reduction in patient health-related quality of life (HRQoL), and substantial economic burden to patients, caregivers, society and the healthcare system [8,9].

Treatment optimization for RRMS includes the use of disease-modifying therapies (DMTs) to reduce relapse severity and frequency, and delay disability [1,10]. There are 16 DMTs indicated for patients with RRMS in Canada, with treatment selection dependent upon the level of disease activity, drug efficacy, safety and tolerability and adherence [11]. Treatments approved for initial therapy (base therapies), as well as fingolimod, are generally considered to have moderate efficacy (average relapse reduction of 30–50%) [11,12]. Due to the greater risk of adverse events (AEs), some higher efficacy DMTs, such as monoclonal antibodies natalizumab and alemtuzumab are generally prescribed for patients with high initial disease activity or persistent disease activity due to a suboptimal response to other DMTs [13]. However, evidence suggests an improvement in disease outcomes (i.e., a reduction in disease progression and long-term disability) when higher efficacy DMTs are used within 2 years of disease onset [14].

Treatment with monoclonal antibodies that selectively deplete B cells have shown improved treatment outcomes in MS [15]. In Canada, ofatumumab is the first fully human monoclonal anti-CD20 antibody approved for initial therapy for RRMS with active disease. A network meta-analysis (NMA) demonstrated that ofatumumab had similar effectiveness to other highly efficacious monoclonal antibody therapies with respect to reducing relapse rates and disability progression [12], as well as a favorable safety profile [16]. This positive benefit-risk profile helps to fill the gap of higher efficacy DMTs that can be initiated in the early phase of RRMS. Furthermore, a 2021 study using two different approaches to classify the efficacy of DMTs in MS found that higher efficacy (average relapse reduction >50%) DMTs included ofatumumab, cladribine, and natalizumab, as well as ocrelizumab depending on the approach used [11].

Given that patients with RRMS are faced with deteriorating physical and mental wellbeing, as well as economic instability, the current study evaluated the costs and consequences of treatment with ofatumumab versus other first-line and second-line DMTs and best supportive care (BSC; i.e., no active therapy) in patients with RRMS with active disease from a Canadian healthcare system perspective. A scenario analysis also examined the impact of administering ofatumumab as a first-line therapy versus delaying ofatumumab until after treatment with commonly administered first-line therapies.

Methods

Model structure

A cohort multi-state Markov transition model was developed in Microsoft[®] Excel[®] for Microsoft 365 MSO (Build 16.0.14931.20652) 64-bit Version 2202 (Build 14931.20660 Click-to Run) to predict the costs and consequences of DMTs with a first- and second-line indication in adults with RRMS from a Canadian healthcare system perspective. The base case used a time horizon of 10 years, an annual cycle length, a half-cycle correction (for costs) and a 1.5% annual discount rate [17]. The base case evaluated ofatumumab versus other first-line and second-line DMTs, as well as BSC, with no treatment switching. Once patients reach an EDSS of 7 or higher, while on treatment, they would discontinue treatment and receive BSC. A sensitivity analysis examined the impact of a 15-year time horizon. Time horizons were chosen based on clinician input, which assumed that treatment is typically discontinued after 10 years; however, some patients may remain on treatment for a longer timeframe, which was examined in the sensitivity analysis. To assess the costs and consequences of initiating ofatumumab early in the disease course compared with after a patient had been previously treated with another first-line DMT, a scenario analysis examined the impact of administering ofatumumab as a first-line therapy versus administering ofatumumab after 3 and 5 years of treatment with teriflunomide, dimethyl fumarate, glatiramer acetate and interferon beta-1a (Rebif 44) (e.g., ofatumumab given initially was compared against teriflunomide [3 years] plus ofatumumab [7 years] etc.). Based on clinician inputs, these four treatments were chosen as the most commonly administered first-line DMTs that would be expected to be used prior to treatment switching to ofatumumab.

At model entry, the cohort was assigned to baseline Expanded Disability Status Scale (EDSS) state distributions based on a pooled analysis of the ASCLEPIOS trials for patients with RRMS with active disease [16]. A detailed description of baseline patient characteristics from this trial has been previously published elsewhere [16]. In the

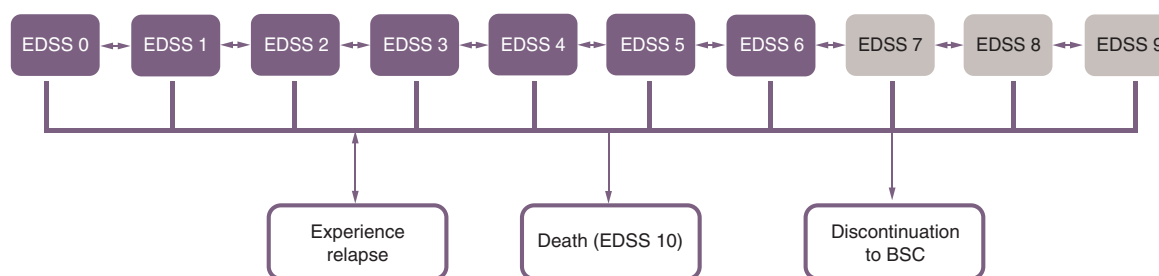


Figure 1. Model structure. Rounded rectangles on top represent health states and rounded rectangles on the bottom represent events that patients could experience at any time. Patients who reached an EDSS score of ≥ 7 (denoted by grey boxes) while on treatment would discontinue treatment and receive BSC. BSC: Best supportive care; EDSS: Expanded disability status scale.

model, patients moved between EDSS states 0 (normal neurological examination) through 9, and 10 (death state) (Figure 1). Each cycle, patients could move to a higher or lower EDSS state (i.e., worsen or improve, respectively), remain at their current EDSS state, or die; natural history transition probabilities between EDSS states for BSC were informed from the British Columbia MS (BCMS) database (Supplementary Table 1).

Consistent with previous economic models, EDSS-dependent natural history annualized relapse rates (ARR) were informed by data from Mauskopf *et al.* [18], Orme *et al.* [19] and Patzold and Pocklington [20]. Relapse categorization by hospitalization status was sourced from a prospective cohort of patients with RRMS, which classified relapses as mild, moderate, or severe. As relapses could occur continually throughout the model, second event relapse severity data were used [21]. Patients with severe relapses (i.e., 18%) were assumed to require hospitalization, whereas patients not requiring hospitalization were considered to have a mild or moderate relapse (i.e., 82%).

Mortality and life expectancy data were based on age- and sex-specific all-cause mortality rates for the Canadian general population [22], and were adjusted for the MS population using an EDSS-dependent MS-specific hazard ratio (HR) (Supplementary Table 2) [23]. MS-specific disability weights were based on a survey of MS experts, using trade-off procedures per EDSS categories (2, 4, 6, 7 and 9), with disability weights of the remaining EDSS scores assigned by linear interpolation (Supplementary Table 2) [24]. Hospitalization days per year were EDSS-dependent and based on assumptions validated by clinician input (Supplementary Table 2).

Productivity loss due to disability was EDSS-dependent (Supplementary Table 3). The percentage of patients who were employed and working full time for EDSS states 1 to 6 were obtained from Grima *et al.* [8], with remaining health states based on extrapolations and clinician input. The percentage of patients retiring early and the number of informal care days per year (calculated based on the number of informal care hours per patient per year divided by an 8 h work day) were sourced from Karampampa *et al.* [25] and modified based on clinician input. Retirement age was assumed to be 65 years, with the number of full-time working days assumed to be 260 days per year [26].

Treatment-specific inputs

For both the base case and scenario analyses in the treatment-adjusted model, natural history transition probabilities were adjusted by a treatment effect derived from an NMA [12]. The NMA estimated the comparative efficacy of DMTs versus placebo for 6-month confirmed disability progression (CDP-6) and ARR (Supplementary Table 4). Discontinuation rates for each DMT were calculated using the relative effect estimates from the NMA [12], using the annualized all-cause discontinuation probability of ofatumumab from ASCLEPIOS [16] as a reference arm (Supplementary Table 4). To capture real-world management of patients with RRMS, all analyses assumed constant discontinuation for 9 years, followed by 100% discontinuation for all treatments at 10 years based on clinician opinion.

Cost inputs

Total direct medical costs per patient (Supplementary Table 5) were sourced from Grima *et al.* [8], Patwardhan *et al.* [27] and Karampampa *et al.* [25]. Costs for mild and moderate relapses (\$7275) were informed by Karampampa *et al.* [25]; severe relapse cost (\$17,459) was calculated based on the systematic review that suggested a severe relapse in RRMS costs 240% more than a mild or moderate relapse [27].

Treatment-related costs were comprised of administration and monitoring costs (Supplementary Table 6), while adverse event (AE) costs were considered as part of non-DMT costs. Drug costs were not included as this study aimed to analyze the subsequent costs and resource consequences associated with the use and maintenance of ofatumumab and comparators beyond treatment acquisition. The accrual of costs were assumed to apply for the amount of time that patients received treatment in the model. Annual administration (Supplementary Table 7) and monitoring costs (Supplementary Table 8) were calculated by multiplying the annual resource use (informed by Health Canada product monographs) by the respective unit cost and were sourced from the Ontario Schedule of Benefits, Ontario Case Costing (OCC) Costing Analysis Tool, formularies, published literature and clinician opinion [28–34]. Non-serious AE costs were assumed to be a physician visit cost of \$84 [30], while serious AE costs were assumed to be an MS Day Case admission cost of \$363 (ambulatory care, 18–69 years, Most Responsible Diagnosis Code G35) [28]. All cost inputs were converted to 2021 CAD (Canadian dollars), if applicable.

Outcomes

Clinical outcomes included patient distribution and time spent in each EDSS health state, number of relapse events and risk of wheelchair use or confinement to bed (% patients progressing to EDSS 7 or higher over time). The overall burden of disease was assessed using the disability-adjusted life year (DALY), which combines years of life lost due to premature mortality (YLLs) and years of life lost due to disability or due to living in states of less than full health (YLDs). One DALY represents the loss of the equivalent of 1 year of full health. For economic outcomes, administration and monitoring and non-DMT costs (direct medical, relapse, and AE) are presented. Productivity outputs included the percentage of patients employed and working full time.

Sensitivity analyses

Univariate sensitivity analyses were performed to determine the impact of varying several key parameters by $\pm 10\%$ of the base case value on incremental costs: drug acquisition costs of ofatumumab at Year 1, 2 and from Year 2 onwards, ofatumumab CDP-6 hazard ratio, cohort size, discount rates, annual relapse costs, percent relapses and ofatumumab drug monitoring costs at Year 1.

Model validation

To ensure the predictions from this model were accurate for the MS population, the model underwent a validation assessment of the model scope, structure, assumptions, calculations and data inputs. Since the cost-consequence model structure has many similarities to previous cost-effectiveness models used in Canadian Health Technology Assessment agencies, it was assumed that the structure and approach were valid within the Canadian landscape. In addition, the appropriateness of Canadian-specific data inputs and clinical assumptions were validated by three Canadian clinical experts from across Canada (Nova Scotia, Ontario and British Columbia). Model inputs were reviewed by the clinicians during two rounds of advisory meetings and discussed until consensus was reached.

Results

Base case results

Clinical outcomes

Over a 10-year time horizon, patients treated with ofatumumab or another high-efficacy DMT (i.e., ocrelizumab, cladribine and natalizumab) had a similar degree of disability, as indicated by a greater percentage of patient time (64.09–67.47%) spent in the mild disability health states (EDSS 0–3) versus moderate-efficacy DMTs or BSC (54.13–61.21%). Ofatumumab and other high-efficacy drugs had a lower percentage of patient time (6.70–8.06%) spent in the health states associated with greater disability (EDSS 7–9) versus moderate efficacy DMTs or BSC (9.3–13.0%) (Figure 2A). The average percent of patient time spent in health states over 10 years for all high-efficacy and moderate-efficacy DMTs and BSC is shown in Figure 2B. The majority of patients treated with ofatumumab or another high-efficacy DMT (52.01–57.26%) spent more time (6.35–6.68 years) in the mild disability health states (EDSS 0–3) versus patients treated with moderate-efficacy DMTs or BSC (40.30–49.04%; 5.36–6.06 years). A lower proportion of patients treated with ofatumumab or another high-efficacy DMT (14.63–17.47%) spent less time (0.66–0.80 years) in the health states associated with greater disability (EDSS 7–9) versus patients treated with moderate-efficacy DMTs (19.39–25.84%; 0.92 to 1.28 years) (Figure 2C; Supplementary Figure 1). The average percent of patient distribution in health states over 10 years for all high-efficacy and moderate-efficacy DMTs and BSC is shown in Figure 2D.

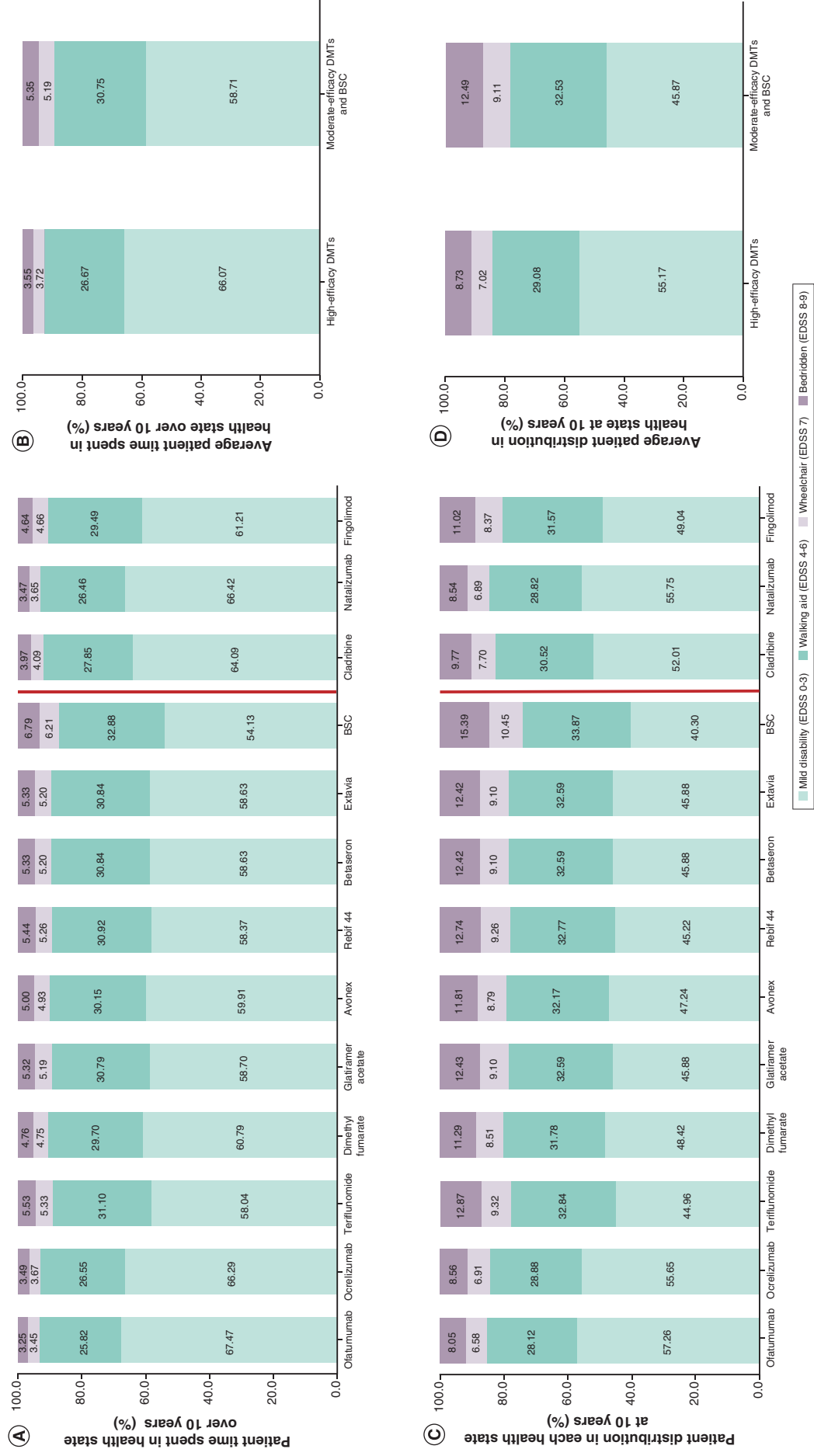


Figure 2. Base case clinical outcomes. (A) Percent of patient time spent in each health state over a 10-year horizon for first-line and second-line treatments without treatment switching or delay. **(B)** Average percent of patient time spent in each health state over a 10-year time horizon for high-efficacy versus moderate-efficacy DMTs and BSC. **(C)** Percent of patient distribution in each EDSS health state at 10 years for first-line and second-line treatments without treatment switching or delay. **(D)** Average percent of patient distribution in each EDSS health state at 10 years for high-efficacy versus moderate-efficacy DMTs and BSC. **(E)** Number of relapse events over a 10-year time horizon for first-line and second-line treatments without treatment switching or delay. **(F)** Average number of relapse events over a 10-year time horizon for high-efficacy versus moderate-efficacy DMTs and BSC. High-efficacy DMTs include ofatumumab, ocrelizumab, cladribine, and natalizumab. Moderate-efficacy DMTs include teriflunomide, dimethyl fumarate, glatiramer acetate, Avonex, Rebif 44, Betaseron, Exavia, and fingolimod. Bars to the left and right of the red line represent first-line and second-line therapies, respectively **(A, C, E, G)**. Values in red text above bars show percent change versus ofatumumab **(E & G)**. BSC: Best supportive care; DALY: Disability-adjusted life years, DMT: Disease-modifying therapies, EDSS: Expanded Disability Status Scale, EDSS 7+: Expanded Disability Status Scale 7 or above.

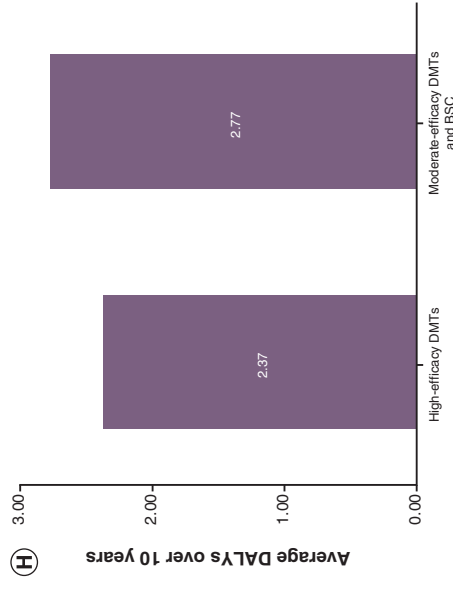
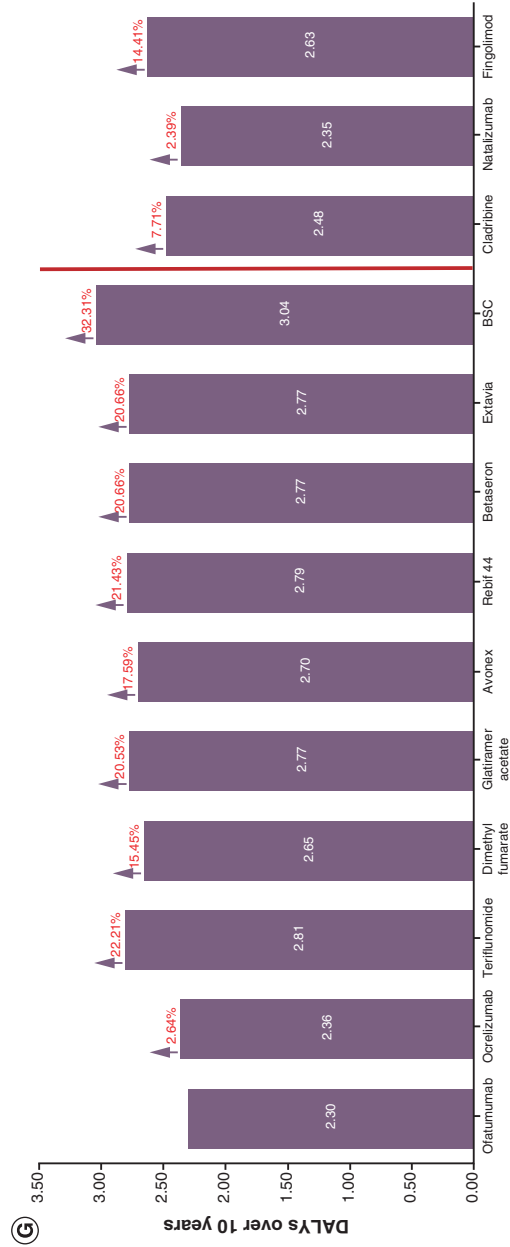
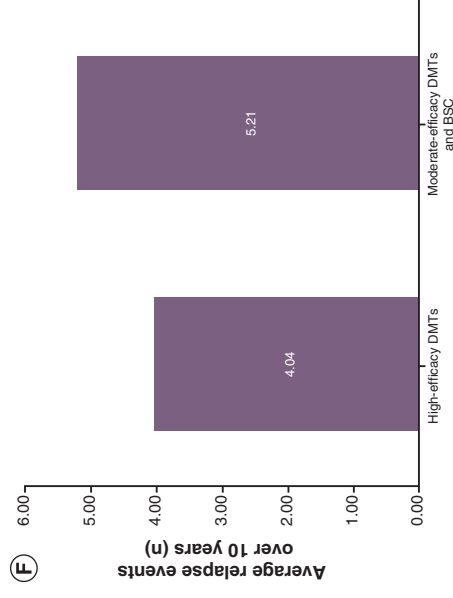
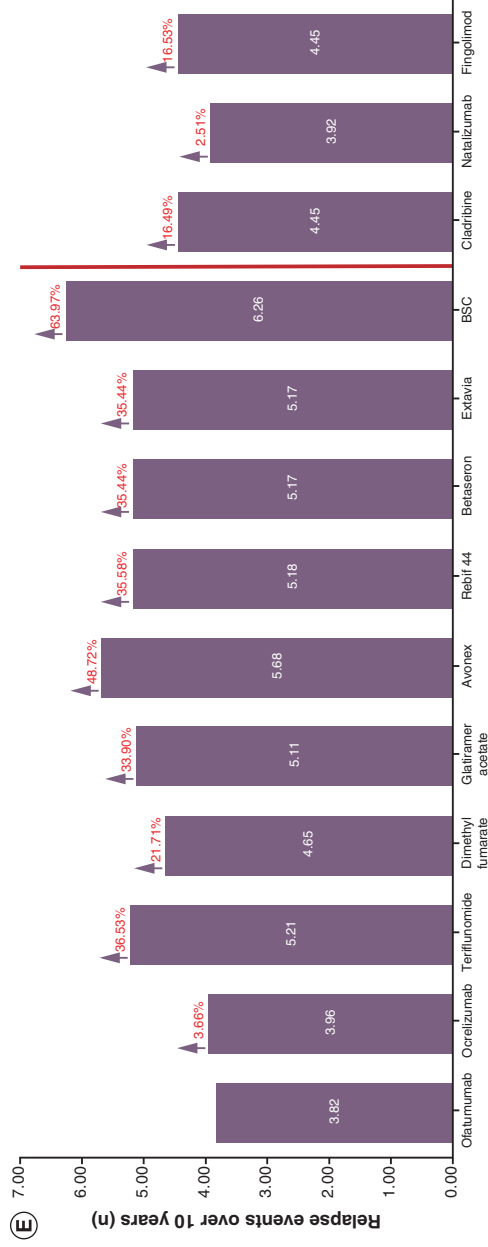


Figure 2. Base case clinical outcomes (cont.). (A) Percent of patient time spent in each health state over a 10-year horizon for first-line and second-line treatments without treatment switching or delay. (B) Average percent of patient time spent in each health state over a 10-year horizon for high-efficacy versus moderate-efficacy DMTs and BSC. (C) Percent of patient distribution in each EDSS health state at 10 years for first-line and second-line treatments without treatment switching or delay. (D) Average percent of patient distribution in each EDSS health state at 10 years for high-efficacy versus moderate-efficacy DMTs and BSC. (E) Number of relapse events over a 10-year time horizon for first-line and second-line treatments without treatment switching or delay. (F) Average number of relapse events over a 10-year time horizon for high-efficacy versus moderate-efficacy DMTs and BSC. (G) Number of DALYs over a 10-year horizon for first-line and second-line treatments without treatment switching or delay. (H) Average number of DALYs over a 10-year time horizon for high-efficacy versus moderate-efficacy DMTs and BSC. High-efficacy DMTs include ofatumumab, ocrelizumab, cladribine, and natalizumab. Moderate-efficacy DMTs include teriflunomide, dimethyl fumarate, glatiramer acetate, Avonex, Rebif 44, Betaseron, Exavia, and fingolimod. Bars to the left and right of the red line represent first-line and second-line therapies, respectively (A, C, E, G). Values in red text above bars show percent change versus ofatumumab (E & G). BSC: Best supportive care; DALY: Disability-adjusted life years, DMT: Disease-modifying therapies, EDSS: Expanded Disability Status Scale, EDSS 7+: Expanded Disability Status Scale 7 or above.

Table 1. Costs per patient over the 10-year time horizon.

Treatment	Administration & monitoring		Non-disease modifying therapy costs	
	Absolute cost	Incremental cost of ofatumumab vs comparator	Absolute cost	Incremental cost of ofatumumab vs comparator
First-line therapies				
Ofatumumab	\$1246	–	\$99,332	–
Ocrelizumab	\$10,179	\$8934	\$102,938	\$3606
Teriflunomide	\$1263	\$18	\$131,610	\$32,279
Dimethyl fumarate	\$1371	\$126	\$120,561	\$21,230
Glatiramer acetate	\$1218	-\$27	\$129,275	\$29,943
Avonex	\$1501	\$256	\$131,427	\$32,096
Rebif 44	\$1460	\$215	\$130,595	\$31,263
Betaseron	\$1848	\$602	\$129,950	\$30,619
Extavia	\$1848	\$602	\$129,950	\$30,619
BSC	–	–	\$150,018	\$50,686
Second-line therapies				
Cladribine	\$1188	-\$58	\$111,623	\$12,291
Natalizumab	\$22,078	\$20,833	\$102,356	\$3025
Fingolimod	\$1938	\$693	\$117,927	\$18,595

BSC: Best supportive care.

Patients receiving ofatumumab or another high-efficacy DMT had a similar number of relapse events (3.82–4.45 over 10 years) that were lower versus patients receiving a moderate-efficacy DMT or BSC (4.45–6.26); the number of relapses for comparators ranged from a 2.51% increase for natalizumab to a 63.97% increase for BSC versus ofatumumab (Figure 2E). The average number of relapse events at 10 years for all high-efficacy and moderate-efficacy DMTs and BSC is shown in Figure 2F. Patients receiving ofatumumab or another high-efficacy DMT had similar YLL (0.92–0.94) and YLD (1.38–1.54) that were lower versus patients receiving a moderate-efficacy DMT or BSC (YLL: 0.96 to 1.03; YLD: 1.67–2.02) (Supplementary Figure 2). Patients receiving ofatumumab or another high-efficacy DMT had less DALYs (2.30–2.48) versus moderate-efficacy DMTs or BSC (2.63–3.04) (Figure 2G). The average DALYs at 10 years for all high-efficacy and moderate-efficacy DMTs and BSC are shown in Figure 2H.

Costs

Table 1 presents the absolute and incremental costs over the 10-year time horizon. Treatment with a comparator resulted in greater incremental administration and monitoring costs compared with ofatumumab, except for glatiramer acetate (-\$27) and cladribine (-\$58). Incremental non-DMT costs were greater for all comparators versus ofatumumab and ranged from \$3606 (ocrelizumab) to \$32,096 (Avonex).

Productivity outputs

Patients treated with ofatumumab or another high-efficacy DMT resulted in a greater percent of patients employed (32.70–35.60%) and working full time (23.90–26.40%) at 10 years versus patients initially treated with a moderate-efficacy comparator (26.40–31.10% employed; 18.80–22.60% working full time) (Figure 3A). Both percent employed (range: 2.25% decrease for natalizumab to 25.84% decrease for BSC) and working full time (range: 2.65% decrease for natalizumab to 28.79% decrease for BSC) were reduced for all comparators versus ofatumumab. The average percent of individuals working (employed and working full time) at 10 years for all high-efficacy and moderate-efficacy DMTs and BSC is shown in Figure 3B.

Sensitivity analyses results

Using a 15-year time horizon, overall results generally aligned with the base case for clinical and productivity outcomes (Table 2), as well as costs (Table 3). Patients treated with ofatumumab or another high-efficacy DMT had a similar degree of disability (i.e., 57.52 to 61.18% of patient time was spent in the mild disability health state and 11.57 to 13.47% of patient time was spent in health states associated with greater disability (EDSS 7–9)), a lower number of relapse events (6.79 to 7.37 over 15 years), less DALYs (4.34 to 4.68), and slower progression to EDSS 7 or higher at 10 years (26.05 to 29.09%). In comparison, patients treated with moderate-efficacy DMTs or BSC

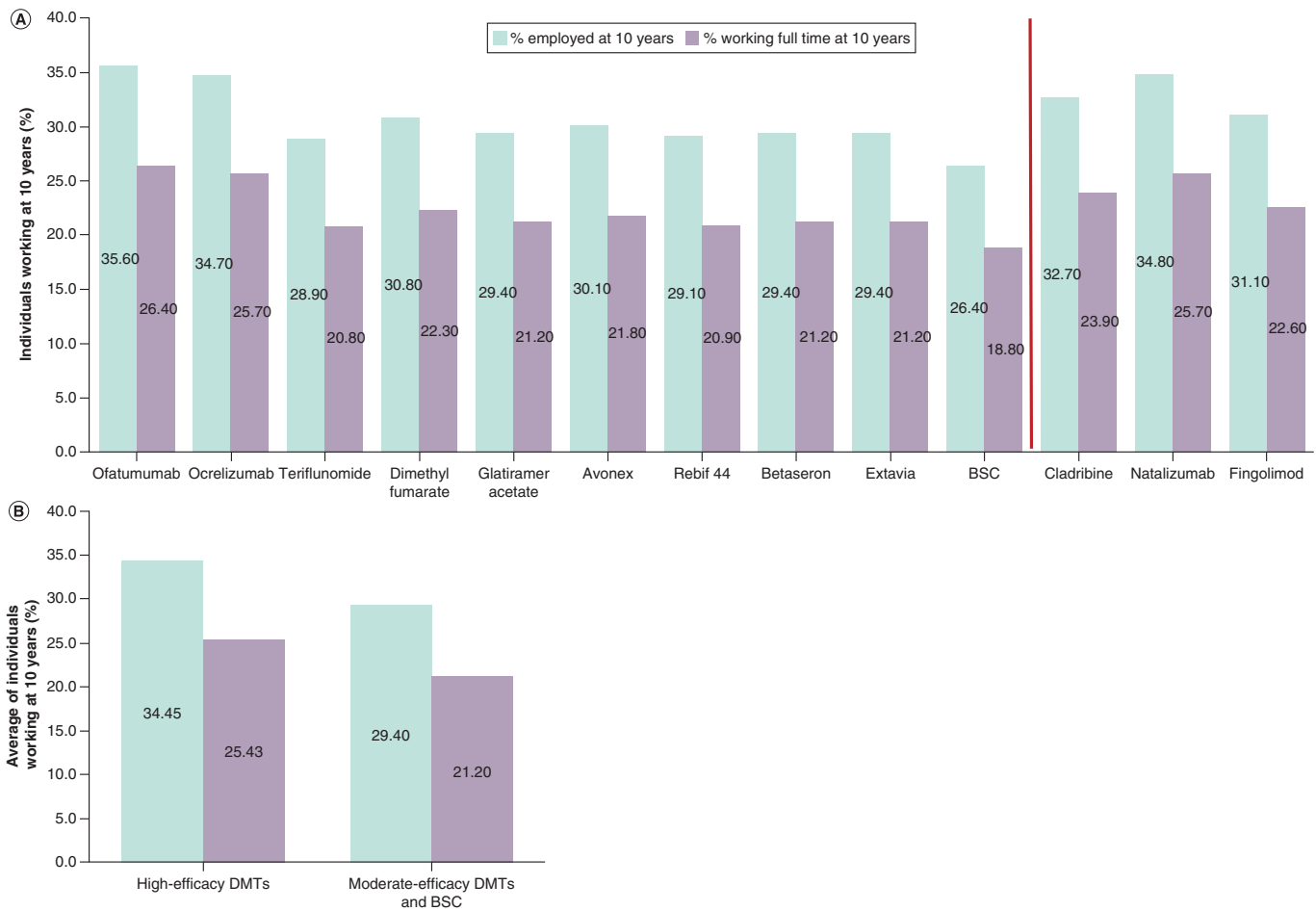


Figure 3. Base case productivity outcomes. (A) Percent of individuals employed and working full time at 10 years for first-line and second-line treatments without treatment switching or delay. High-efficacy DMTs include ofatumumab, ocrelizumab, cladribine and natalizumab. Moderate-efficacy DMTs include teriflunomide, dimethyl fumarate, glatiramer acetate, Avonex, Rebif 44, Betaseron, Extavia and fingolimod. Bars to the left and right of the red line are first-line and second-line therapies, respectively. **(B)** Average percent of individuals employed and working full time at 10 years for high-efficacy versus moderate-efficacy DMTs and BSC. BSC: Best supportive care, DMT: Disease-modifying therapy.

showed worse disability outcomes. Since treatment was discontinued at 10 years, extending the time horizon did not impact administration and monitoring costs (as such, values remain the same as the base case; [Supplementary Table 6](#)); however, while non-DMT costs were slightly increased over the extended time horizon, incremental results versus ofatumumab were reduced compared with the base case. Overall, incremental productivity was slightly reduced (i.e., less patients employed or working full time) compared with the base case for all comparators.

Univariate sensitivity analyses showed that incremental costs were primarily influenced by DMT costs from the second year onwards, as well as ofatumumab CDP-6 ratio, and cohort size ([Supplementary Figures 3–14](#)). Variations in annual relapse costs as well as percent of relapses requiring hospitalization, and discount rates did not impact the results substantially.

Scenario analyses results

Patients initially treated with ofatumumab versus switching to ofatumumab after 3 or 5 years with another commonly used first-line DMT had a lower degree of disability, a lower number of relapse events, less DALYs, slower progression to EDSS 7 or higher, and higher percent of patients employed at 10 years ([Figure 4A–E](#)); switching to ofatumumab later (i.e., after 5 vs 3 years) resulted in poorer clinical outcomes. Incremental differences in administration and monitoring costs between initial versus delayed treatment over the 10 years were minimal. While administration and monitoring costs were generally greater in patients who switched to ofatumumab after 5

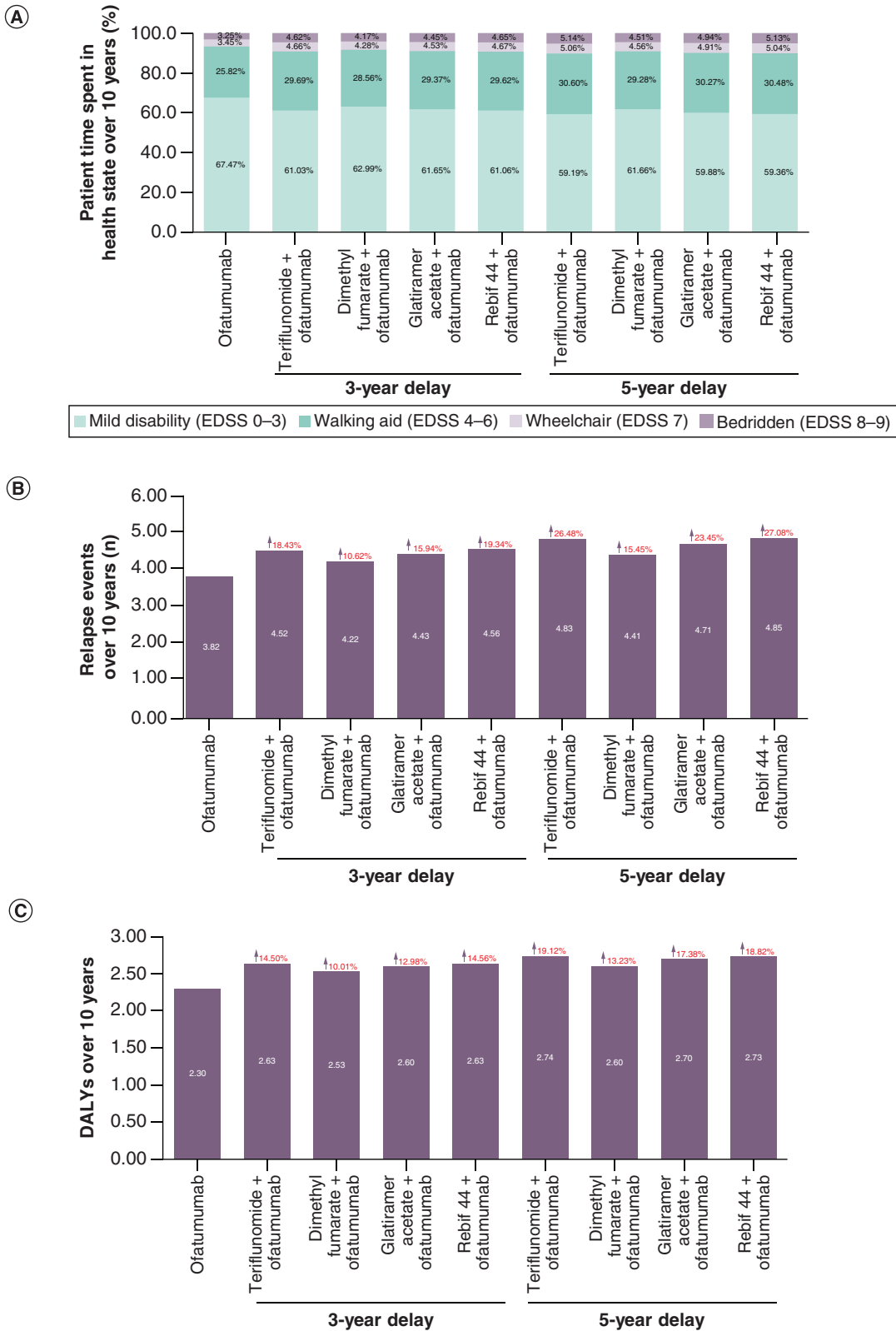


Figure 4. Delayed treatment scenario results over a 10-year time horizon for ofatumumab provided initially versus switching to ofatumumab after 3 and 5 years of treatment with another commonly used first-line disease-modifying therapy. (A) Percent of patient time spent in each health state over a 10-year time horizon. **(B)** Number of relapse events over a 10-year time horizon. **(C)** Number of DALYs over a 10-year time horizon. **(D)** Percent of patients at EDSS 7+ at 10 years. **(E)** Percent of individuals employed at 10 years. Values in red text above bars show percent change versus ofatumumab **(B–E)**.

DALY: Disability-adjusted life years; DMT: Disease-modifying therapy; EDSS: Expanded Disability Status Scale; EDSS 7+ -: Expanded Disability Status Scale 7 or above.

Table 2. Sensitivity analysis results for clinical outcomes over a 15-year time horizon for all first-line and second-line treatments without treatment switching or delay.

Treatment	% Patient time spent in health state over 15 years				Relapse events over 15 years	DALY over 15 years	% Patients at EDSS 7+ at 15 years	% Employed at 15 years
	Mild Disability (EDSS 0–3)	Walking Aid (EDSS 4–6)	Wheelchair (EDSS 7)	Bedridden (EDSS 8–9)				
First-line therapies								
Ofatumumab	61.18%	27.25%	5.14%	6.43%	6.79	4.34	26.05%	27.70%
Ocrelizumab	59.96%	27.87%	5.38%	6.79%	6.91	4.45	26.98%	27.10%
Teriflunomide	51.64%	31.49%	7.12%	9.75%	8.07	5.23	33.58%	23.30%
Dimethyl fumarate	54.38%	30.42%	6.53%	8.68%	7.54	4.97	31.34%	24.50%
Glatiramer acetate	52.32%	31.25%	6.97%	9.46%	7.98	5.16	32.97%	23.60%
Avonex	53.49%	30.77%	6.72%	9.02%	8.56	5.05	32.10%	24.10%
Rebif 44	51.93%	31.36%	7.06%	9.65%	8.04	5.20	33.41%	23.40%
Betaseron	52.28%	31.28%	6.98%	9.46%	8.04	5.17	32.97%	23.60%
Extavia	52.28%	31.28%	6.98%	9.46%	8.04	5.17	32.97%	23.60%
BSC	47.82%	32.76%	7.98%	11.44%	9.08	5.62	36.78%	21.60%
Second-line therapies								
Cladribine	57.52%	29.01%	5.88%	7.59%	7.37	4.68	29.09%	25.80%
Natalizumab	60.08%	27.79%	5.36%	6.77%	6.87	4.44	26.93%	27.20%
Fingolimod	54.82%	30.25%	6.43%	8.50%	7.35	4.92	30.95%	24.70%

BSC: Best supportive care; DALY: Disability-adjusted life years; EDSS 7+: Expanded Disability Status Scale 7 or above.

Table 3. Sensitivity analysis results for costs per patient over a 15-year time horizon for all first-line and second-line treatments without treatment switching or delay.

Treatment	Non-disease modifying therapy costs [†]	
	Absolute cost	Incremental cost of ofatumumab vs comparator
First-line therapies		
Ofatumumab	\$177,808	–
Ocrelizumab	\$182,956	\$5148
Teriflunomide	\$222,578	\$44,770
Dimethyl fumarate	\$207,828	\$30,020
Glatiramer acetate	\$219,234	\$41,427
Avonex	\$219,945	\$42,137
Rebif 44	\$221,279	\$43,471
Betaseron	\$219,907	\$42,099
Extavia	\$219,907	\$42,099
BSC	\$246,279	\$68,471
Second-line therapies		
Cladribine	\$195,163	\$17,355
Natalizumab	\$182,289	\$4482
Fingolimod	\$204,538	\$26,730

[†] Results for administration and monitoring costs are not presented for the 15-year analysis as they do not change from the 10-year results.
BSC: Best supportive care.

versus 3 years, patients starting on glatiramer acetate had marginally lower costs than those starting on ofatumumab (Table 4). Over 10 years, non-DMT costs were greater in patients who switched to ofatumumab after 5 versus 3 years; both treatment delay scenarios resulted in greater non-DMT costs than patients initially treated with ofatumumab. Finally, productivity was higher (i.e., more patients employed and working full time) in patients initially starting on ofatumumab versus patients switching to ofatumumab, with an earlier switch (3 years) to ofatumumab resulting in higher productivity than a delayed switch (5 years).

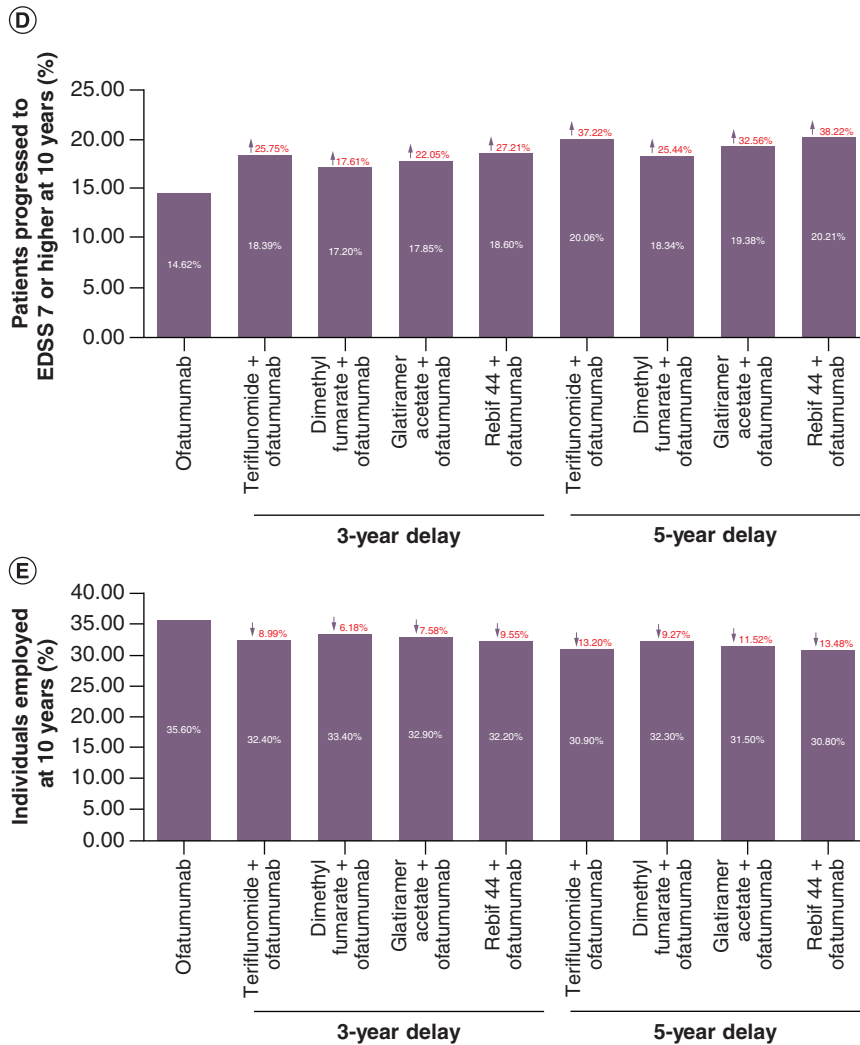


Figure 4. Delayed treatment scenario results over a 10-year time horizon for ofatumumab provided initially versus switching to ofatumumab after 3 and 5 years of treatment with another commonly used first-line disease-modifying therapy (cont.). (A) Percent of patient time spent in each health state over a 10-year time horizon. (B) Number of relapse events over a 10-year time horizon. (C) Number of DALYs over a 10-year time horizon. (D) Percent of patients at EDSS 7+ at 10 years. (E) Percent of individuals employed at 10 years. Values in red text above bars show percent change versus ofatumumab (B–E).

DALY: Disability-adjusted life years; DMT: Disease-modifying therapy; EDSS: Expanded Disability Status Scale; EDSS 7+ -: Expanded Disability Status Scale 7 or above.

Discussion

This study demonstrated that patients treated with ofatumumab over a 10-year period had improved clinical outcomes (i.e., a lower degree of disability, less relapses, slower time to disease worsening, and less DALYs) and productivity outcomes (i.e., more patients employed and working full time) than moderate-efficacy DMTs and BSC; outcomes with ofatumumab were comparable to other high-efficacy DMTs approved for RRMS from a Canadian public healthcare system perspective. Relative to all other DMTs, ofatumumab resulted in low administration and monitoring costs, as well as the lowest non-DMT costs. Earlier treatment with ofatumumab may also be associated with better clinical, economic and productivity outcomes compared with delayed treatment with ofatumumab.

We previously showed that ofatumumab was cost effective against all currently approved and reimbursed first-line and second-line indicated therapies for RRMS from a Canadian public healthcare system perspective [35]. The current model provides additional information on the clinical and productivity outcomes of ofatumumab and comparators. However, while there are multiple cost-effectiveness analyses in MS, to our knowledge only

Table 4. Delayed treatment scenario results for costs per patient over a 10-year time horizon for ofatumumab provided initially versus switching to ofatumumab after 3 and 5 years of treatment with select first-line comparators.

Treatment	Administration and monitoring		Non-disease modifying therapy costs	
	Absolute cost	Incremental cost of ofatumumab vs comparator	Absolute cost	Incremental cost of ofatumumab vs comparator
Ofatumumab (initially)	\$1246	–	\$99,332	–
3-year delay				
Teriflunomide + ofatumumab	\$1273	\$27	\$118,871	\$19,539
Dimethyl fumarate + ofatumumab	\$1285	\$39	\$112,118	\$12,786
Glatiramer acetate + ofatumumab	\$1223	-\$22	\$116,693	\$17,361
Rebif 44 + ofatumumab	\$1376	\$131	\$119,196	\$19,865
5-year delay				
Teriflunomide + ofatumumab	\$1267	\$22	\$125,681	\$26,350
Dimethyl fumarate + ofatumumab	\$1320	\$75	\$116,606	\$17,274
Glatiramer acetate + ofatumumab	\$1220	-\$25	\$123,149	\$23,817
Rebif 44 + ofatumumab	\$1412	\$166	\$125,572	\$26,241

one cost-consequence model study has been conducted in MS. The current results are aligned with a German cost-consequence analysis comparing the long-term clinical and economic impact of ofatumumab versus dimethyl fumarate and glatiramer acetate in patients with relapsing MS [36]. Both cost-consequence models emphasize that immediate treatment with ofatumumab and an early switch improves clinical and productivity outcomes [36]. Although both models used a time horizon of 10 years, other economic models with longer time horizons suggest that the beneficial effects from DMTs will increase over time [37–39].

Studies have indicated an inverse correlation between EDSS scores and HRQoL (as measured by EQ-5D utility scores) and the positive association that receiving high efficacy treatment early in the course of the disease have on such outcomes [40,41]. As the disease progresses, informal and inpatient care become more involved and burdensome due to the physical disabilities that patients often face. In the present study, treatment with high-efficacy DMTs, including ofatumumab, resulted in patients spending the most time in mild disability health states, with a reduction in the proportion of patients with disease progression to the health states associated with greater disability (EDSS 7+) compared with moderate-efficacy DMTs. Avoiding progression to the higher EDSS states helps to promote greater patient independence, reduce declines in patients' HRQoL, reduce caregiver burden and reduce the healthcare resource costs required for management of the disease. Patients who received ofatumumab also had a reduction in the total number of relapses over both 10- (base case) and 15-years (sensitivity) compared with moderate-efficacy DMTs, which may have a positive impact on the HRQoL of patients and costs to the healthcare system associated with hospitalizations for patients with severe relapses.

MS is associated with a considerable economic burden related to presenteeism and absenteeism (time away from work caused by health problems) [7,9], with unemployment rates increasing with age, disability, duration of disease, and measures of disease activity [8,42,43]. Moreover, employed individuals with RRMS often report higher HRQoL and lower depression when compared with unemployed individuals [44]. Herein, patients who received ofatumumab and other high-efficacy DMTs had higher rates of employment and a greater proportion of individuals working full time at both 10- (base case) and 15-years (sensitivity) versus moderate-efficacy comparators. Thus, the present results suggest the potential value of initiating a high-efficacy therapy such as ofatumumab as an early or first-line treatment to help reduce both the economic and societal burden of RRMS through improved productivity.

An additional advantage of ofatumumab is that it provides a high-efficacy first-line option and can also be self-administered through subcutaneous injection at home in contrast to other monoclonal antibodies (i.e., ocrelizumab) that are given intravenously. This feature offers more flexibility and convenience for patients compared with intravenous administration, which is of particular importance for the treatment of chronic disease; this promotes patient independence, reduces healthcare resource utilization, and decreases the burden of travelling to infusion clinics, while allowing treatment in areas without appropriate infusion facilities [45]. While administration and monitoring costs were the lowest for glatiramer acetate (first-line) and cladribine (second-line), the cost differences between these DMTs and ofatumumab was nominal (\$27 and \$58 over 10-years, respectively). Of note, ofatumumab had substantially lower administration and monitoring costs compared with ocrelizumab (first-line) and natalizumab

(second-line) (\$8,934 and \$20,833 over 10-years, respectively), both of which require intravenous administration. As such, these results indicate that patients receiving ofatumumab are treated with a highly efficacious DMT with administration and monitoring costs that are similar to other commonly prescribed DMTs available via subcutaneous injection.

As disease severity increases, the need for inpatient care in a registered nursing facility can also substantially contribute to the economic burden [46]. In Canada, living with MS is estimated to cost between \$34,168 and \$86,408 (2021 CAD\$) per patient per year, with higher costs occurring as disease severity increase [25,47]. In the present study, non-DMT costs over both 10- (base case) and 15-years (sensitivity) were lowest for ofatumumab, and were driven by lower disease management, relapse and AE costs compared with all other comparators. Moreover, non-DMT costs were greater for patients who delayed treatment with ofatumumab (by up to 3- or 5-years) compared with those who were treated with ofatumumab initially. These results suggest that a high-efficacy DMT, like ofatumumab, provided early in treatment, may reduce the economic burden associated for caring for a patient with RRMS.

The analyses conducted in this study effectively highlights and strengthens the real-world clinical setting, as ofatumumab was compared with the currently approved and reimbursed DMTs with a first- and second-line indication. Current practices suggest patients who initially receive highly effective treatments had a longer time to progression and a smaller increase in EDSS over time [48]. This study confirmed first-line treatment with ofatumumab was associated with outcomes that were comparable to other high-efficacy DMTs. However, there are limitations to consider. First, the clinical data used in this study were informed by an NMA, which are limited by incomplete evidence networks and between-trial heterogeneity [12,49]. However, for health technology assessments, NMAs are the gold standard for indirect treatment comparisons when only summary-level data are available [50]. Of note, the NMA was previously used in two recently published economic models in MS: in a German-adapted version of the same cost-consequence model [36] and in our previous cost-effectiveness model in RRMS in Canada [35]. Furthermore, productivity loss data were sourced from older datasets, prior to the introduction of higher efficacy DMTs and therefore may not accurately reflect the current employment status for patients with RRMS. In the same way, hospitalization data were based on assumptions and Canadian clinical opinions and may not reflect other regions where MS is treated in more outpatient settings. Lastly, as Canadian-specific disability weights were not available, published data from Cho *et al.* [24] with data from South Korea were used.

Conclusion

Overall, the base case and sensitivity analyses found similar or better clinical, productivity, and economic outcomes for ofatumumab versus other DMTs approved for RRMS in Canada. In addition to its high efficacy, ofatumumab has a favorable safety profile that does not require restriction to patients with higher disease activity, as well as the ability for patients to self-administer treatment at home. Therefore, ofatumumab may be a valuable treatment option to beneficially affect the treatment paradigm toward early high-efficacy treatment for patients with RRMS.

Summary points

- Ofatumumab is a high-efficacy disease-modifying therapy (DMT) approved for first-line treatment of relapsing-remitting multiple sclerosis (RRMS) with active disease in Canada.
- Using a Markov cohort model, this study evaluated the costs and consequences of ofatumumab as an initial therapy versus other first-line and second-line DMTs and best supportive care (BSC), as well as the impact of delayed treatment initiation with ofatumumab.
- Over 10 years, ofatumumab resulted in favorable clinical outcomes similar to other high efficacy comparators.
- Over 10 years, ofatumumab had lower non-drug costs versus comparators.
- Over 10 years, ofatumumab resulted in productivity outcomes similar to other high efficacy comparators.
- Sensitivity analysis over 15-years generated similar result trends as the 10-year analysis.
- Switching to ofatumumab early (e.g., 3 vs 5 years) may result in better outcomes compared with delayed treatment initiation.

Given its high efficacy and favorable safety profile as a first-line treatment option, ofatumumab may shift the treatment paradigm toward early high-efficacy treatment for patients with RRMS.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: <https://bpl-prod.literatumonline.com/doi/10.57264/ce-2022-0175>

Author contributions

V Bhan: Validation, writing – review & editing. F Clift: Validation, writing – review & editing. M Baharnoori: Validation, writing – review & editing. K Thomas: Conceptualization, methodology, formal analysis, data curation, writing - original draft, writing – review & editing, supervision. B Patel: Methodology, formal analysis, data curation, writing - original draft, writing – review & editing. F Blanchette: Conceptualization, methodology, writing – review & editing. N Adlard: Conceptualization, writing – review & editing. U Vudumula: Software, writing – review & editing. K Gudala: Software, writing – review & editing. N Dutta: Writing - original draft, writing – review & editing. D Grima: Writing – review & editing, supervision. S Mouallif: Conceptualization, writing – review & editing, Funding acquisition. F Farhane: project administration, methodology, writing – review & editing.

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No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

The current cost-consequence model did not require institutional review board oversight or approval. The ASCLEPIOS I and II trials (NCT02792218 and NCT02792231) on which the clinical efficacy of ofatumumab was based was conducted in accordance with the International Conference on Harmonization guidelines for Good Clinical Practice and the principles of the Declaration of Helsinki. The protocol was approved by an institutional review board or ethics committee at each trial site. The protocol ID nuo. was COMB157G2301 for ASCLEPIOS I and COMB157G2302 for ASCLEPIOS II. All the patients or their legal representatives provided written informed consent before beginning any trial-related procedures.

Availability of data & material

The economic model employed in this study is not available for public dissemination due to the presence of proprietary information. Other data sources used to inform model parameters are publicly available and have been referenced accordingly throughout the manuscript.

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