Cost-Effectiveness of Peginterferon Beta-1a and Alemtuzumab in Relapsing-Remitting Multiple Sclerosis

Ankur A. Dashputre, BPharm; Khalid M. Kamal, MPharm, PhD; and Gauri Pawar, MD

ABSTRACT

BACKGROUND: Multiple sclerosis (MS) is a chronic inflammatory disorder of the central nervous system, affecting 2.5 million people globally and 400,000 people in the United States. While no cure exists for MS, the goal is to manage the disease using disease-modifying therapies (DMTs), which have been shown to slow disease progression and prevent relapses. Relapsing-remitting MS (RRMS) is the most common form of MS at the time of diagnosis. Peginterferon beta-1a (PEG) and alemtuzumab (ALT) were recently approved and have demonstrated good clinical outcomes, including reduced relapse rates in clinical trials. High costs associated with these DMTs necessitates cost-effectiveness analyses to understand their overall value in RRMS management.

OBJECTIVES: To assess the cost-effectiveness of (a) Model 1: PEG relative to intramuscular interferon beta-1a (IM IFN), subcutaneous interferon beta-1b (SC IFN), glatiramer acetate 20 mg per mL (GA), fingolimod (FIN), natalizumab (NAT), and dimethyl fumarate (DMF), and (b) Model 2: ALT relative to subcutaneous interferon beta-1a 44 µg (IFN beta-1a 44 µg). Both analyses were conducted from a U.S. third-party payer perspective.

METHODS: Two static decision models were used to compare the cost-effectiveness of PEG and ALT over a 1-year and a 2-year time horizon, respectively. Model inputs were drug acquisition costs (wholesale acquisition cost from RED BOOK); drug administration and monitoring costs (package inserts and Centers for Medicare & Medicaid Services 2015 Physician Fee Schedule); relapse rates and relapse rate reduction (clinical trials); and cost of managing relapses (published literature). All costs were adjusted to 2015 U.S. dollars using the medical care component of the Consumer Price Index. Outcomes measured were total cost of therapy per patient, cost per relapse avoided, and incremental cost-effectiveness ratios (ICERs) calculated as cost per relapse avoided. Sensitivity analysis was conducted to test model robustness given the uncertainty of model inputs and study assumptions.

RESULTS: Model 1 results showed that PEG dominated IM IFN and GA, compared with SC IFN; PEG had an ICER of $1,978,000 per relapse avoided. Compared with FIN, NAT, and DMF, PEG was less expensive and less effective. Model 2 showed that ALT had an ICER of $25,276 per relapse avoided relative to IFN beta-1a 44 µg.

CONCLUSIONS: In patients with RRMS, PEG is a viable alternative when compared with the DMTs in our model. Deciding whether to choose PEG over other DMTs would depend on multiple factors. On the other hand, ALT had an ICER of $25,276 cost per relapse avoided relative to IFN beta-1a 44 µg. The study results will assist payers in evaluating different medication choices for effective therapy.

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What is already known about this subject

- Peginterferon beta-1a (PEG) and alemtuzumab (ALT) were approved by the U.S. Food and Drug Administration in 2014.
- In previous studies conducted over a 10-year time frame, PEG has been shown to dominate subcutaneous interferon (IFN) beta-1a 44 µg and glatiramer acetate (GA).
- In the only previous U.S. study, which was conducted over a 2-year time frame, ALT had an incremental cost-effectiveness ratio (ICER) of $43,826 per quality-adjusted life-years (QALY) relative to subcutaneous IFN beta-1a 44 µg.

What this study adds

- Static decision models were used to compare the cost-effectiveness of PEG and ALT over 1-year and 2-year time frames, respectively, in patients with relapsing-remitting multiple sclerosis.
- ICER values were measured as cost per relapse avoided as compared with cost per QALY, which was reported in earlier studies.
- This study included oral and injectable disease-modifying therapies and found that PEG dominated intramuscular IFN beta-1a and GA; was more expensive but had comparable effectiveness when compared with subcutaneous IFN beta-1b; and was less expensive and less effective when compared with natalizumab, fingolimod, and dimethyl fumarate.

Multiple sclerosis (MS) is a progressive, debilitating autoimmune disorder that affects the central nervous system. It is characterized by the destruction of the myelin sheath and inhibition of nerve impulses, eventually resulting in loss of motor function and a high level of disability. In addition to being associated with impaired mobility, MS affects quality of life, causing fatigue, pain, swallowing and breathing problems, cognitive impairment, hearing and vision problems, and sexual dysfunction. The Multiple Sclerosis Foundation reports an estimated prevalence of 400,000 people in the United States, with over 2.5 million people affected globally.[1] MS is typically diagnosed between the ages of 20-40 years, and women are twice as likely as men to be affected by the disease.[1] The National Multiple Sclerosis Society reports an estimated total cost of $28 billion annually for individuals with MS in the United States, with an average annual cost of $69,000 per person, including direct and indirect costs.[2]

Based on the clinical course, MS can be classified into 3 subtypes: relapsing-remitting MS (RRMS), secondary-progressive MS (SPMS), and primary-progressive MS (PPMS).[3] RRMS is the most common disease course and is seen in 85% of all cases at initial diagnosis. RRMS is characterized by clearly defined relapses followed by remissions, during which there is no apparent disease progression.[3] Individuals diagnosed with RRMS transition to SPMS, with 50% transitioning within 10 years and 90% transitioning within 25 years of RRMS diagnosis.[3] PPMS is seen in 15% of individuals diagnosed with MS.[3]

Disease-modifying therapies (DMTs) are used to manage MS to modify the disease course, reduce the number of relapses, and improve patient quality of life. Over the years, a number of DMTs have been approved by the U.S. Food and Drug Administration (FDA) for the management of MS. These approved DMTs include 4 beta interferon products, branded and generic forms of glatiramer acetate, teriflunomide, fingolimod, dimethyl fumarate, mitoxantrone, and natalizumab. In 2014, peginterferon beta-1a (Plegridy), a pegylated form of beta interferon, and alemtuzumab (Lemtrada), a CD52-directed cytolytic antibody were approved by the FDA.

Compared with earlier beta interferons, peginterferon beta-1a has a lower dosing frequency, with 26 doses per year, and alemtuzumab has a dosing frequency split over 2 years (year 1 = 5 doses on consecutive days; year 2 = 3 doses on consecutive days) and is reserved for patients who have inadequately responded to 2 or more earlier DMTs. Phase 3 clinical trials of peginterferon beta-1a (ADVANCE) and alemtuzumab (CARE-MS I and II) have shown significant reduction in annual relapse rates in patients using these DMTs (36% reduction vs. placebo and 49%-55% reduction vs. subcutaneous interferon beta-1a, respectively).[4-6] Although these treatments have demonstrated better efficacy rates and offer new treatment alternatives to patients with MS, the estimated costs are $65,442 for 1 year of peginterferon beta-1a treatment and $158,000 for 2 years of alemtuzumab treatment. Given the high cost of therapy, it is important to evaluate the value of these new treatments with respect to their outcomes, compared with existing DMTs.

Several studies have assessed the cost-effectiveness of these new treatments. Studies on peginterferon beta-1a have been conducted in the United States, Italy, Ireland, and Scotland and have compared peginterferon beta-1a to multiple comparators over 10 years to lifetime analytic time frames using societal and payer perspectives.[7-11] Studies on alemtuzumab have been conducted in the Unites States, Ireland, and the United Kingdom using societal and payer perspectives and have used 2- to 10-year analytic time frames.[12-14] Both U.S.-based studies on peginteferon beta-1a used a payer perspective and an analytical time frame of 10 years.[7,8] The U.S.-based alemtuzumab study used a 2-year time frame and was conducted from a societal perspective.[14] Although several studies on the newly approved DMTs have been conducted in the United States, no study has looked at their cost-effectiveness from a payer perspective over a shorter time horizon.

The objectives of this study were (a) to estimate the incremental cost-effectiveness of peginteferon beta-1a (PEG) relative to intramuscular interferon (IM IFN) beta-1a, subcutaneous interferon (SC IFN) beta-1b, glatiramer acetate 20 mg per mL (GA), fingolimod (FIN), natalizumab (NAT), and dimethyl fumarate (DMF) and (b) to estimate the incremental cost-effectiveness of alemtuzumab (ALT) relative to subcutaneous interferon beta-1a 44 μg (IFN beta-1a 44 μg).

■ Methods

Model Characteristics

Model Design. Two separate static decision models were developed using Microsoft Excel (Microsoft Corp, Redmond, WA) to evaluate the cost-effectiveness of PEG and ALT in a hypothetical RRMS population. Static models were used because the evaluation involved shorter time horizons. Also, since RRMS was being studied, and its transition to SPMS occurs over 10 years, a static model with robust data from randomized controlled trials was sufficient to demonstrate the cost-effectiveness of these treatments.[3] Dynamic models, on the other hand, need time-dependent transition probabilities and long-term outcomes and invariably include assumptions that may introduce uncertainty in the models. For this study, Model 1 compared PEG with multiple comparators—IM IFN, SC IFN, GA, FIN, NAT, and DMF—and Model 2 compared ALT with IFN beta-1a 44 μg.

Patient Population and Perspective. The hypothetical patient population for both models were RRMS patients, and demographic and clinical characteristics were based on clinical trial data of the 2 treatments.

Both models were analyzed from a U.S. third-party payer perspective. As a result, only direct costs such as drug acquisition costs, drug administration and monitoring costs, health care provider visit costs, and relapse treatment costs were included in the analysis.

Analytical Time Frame. Model 1 (PEG) and Model 2 (ALT) were analyzed over a 1-year and 2-year time horizon, respectively, from the point of initiation of therapy, and incremental cost-effectiveness ratios (ICERs) of the treatments were assessed. Different time frames were selected based on the frequency of drug administration. In Model 1, PEG had a time frame of 1 year, since it is administered once every 14 days, while a longer time frame was selected for ALT, in Model 2, since ALT is prescribed over 2 treatment courses, which are 12 months apart. Short time frames were chosen because (a) they reflect the length of phase 3 clinical trials and outcomes assessed in these clinical trials, and (b) most U.S. third-party payers prefer shorter time periods (1-3 years) when conducting economic analyses.[4-6,15-22]

TABLE 1 Number of Relapses Avoided per Patient over Respective Horizons for Models 1 and 2

Model 1: PEG

DMT	Number of Relapses (Placebo)	Number of Patients (Placebo)	Relative Relapse Rate Reduction (%)	Number of Relapses Avoided per Patient	Number of Relapses per Patient
PEG[5]	0.40	500	36	0.20	0.35
IM IFN beta-1a[17]	0.82	143	18	0.10	0.45
SC IFN beta-1b[18]	1.27	123	34	0.19	0.36
GA[19]	0.84	126	29	0.16	0.39
FIN[20]	0.40	418	54	0.30	0.25
NAT[21]	0.73	315	65	0.36	0.19
DMF[22]	0.36	408	53	0.29	0.26

Model 2: ALT

DMT	Number of Relapses at Baseline	Number of Patients	Number of Relapses at 2 Years	Relative Relapse Rate Reduction (%)	Number of Relapses Avoided per Patient
ALT[6]	1.7	426	0.52	69.41	1.18
IFN beta-1a 44 μg[23]	1.5	202	1.04	30.67	0.46

ALT = alemtuzumab; DMF = dimethyl fumarate; DMT = disease-modifying therapy; FIN = fingolimod; GA = glatiramer acetate; IFN = interferon; IM = intramuscular; NAT = natalizumab; PEG = peginterferon beta-1a; SC = subcutaneous.

Outcome Measures. Outcomes of interest for both models were total cost of therapy per patient, cost per relapse avoided, and ICERs. Incremental ratios were calculated as additional cost per patient to avoid 1 relapse. The ICERs were calculated as follows:

$$\text{ICER} = \text{Cost}_A - \text{Cost}_B \div \text{Number of relapse avoided per patient}_A - \text{Number of relapse avoided per patient}_B$$

For Model 1, A = PEG; B = IM IFN, SC IFN, GA, FIN, NAT, and DMF. For Model 2, A = ALT; B = IFN beta-1a 44 μg

Sensitivity Analysis. Since this study involved estimations and there were uncertainty in some variables, univariate sensitivity analyses were conducted to determine the effect of varying the model inputs on the cost-effectiveness of PEG and ALT. Drug acquisition costs, cost of relapse management, and number of relapses per patient before treatment were varied over a range of estimates (±20%) to test the robustness of the results. The literature supports the use of ±20%-25% as variations in the base case wherever the range was not available.[15,23-25]

Efficacy Input

Annualized relapse rate (except for IFN beta-1a 44 μg, mean number of relapses over 2 years) was used as the efficacy input in the models, since it was commonly reported in the phase 3 clinical trials of the DMTs.[4,5,16-22] These relapse rates were used to calculate the number of relapses per patient and number of relapses avoided per patient after treatment with DMTs over their respective time horizons. The model calculations are shown as follows.

Model 1 (PEG)

A weighted average of annualized relapses was calculated for patients in the placebo group (untreated patients) using published phase 3 clinical trial data for the DMTs. The relative reduction in relapse rates was taken from the phase 3 clinical trials (PEG, 36%,[4] IM IFN beta-1a 18%,[16] SC IFN beta-1b 34%,[17] GA 29%,[18] FIN 54%,[19] NAT 65%,[20] and DMF 53%[21]). The number of relapses avoided per patient was calculated as the product of weighted average of annualized relapse rate and relative rate of reduction for each DMT. The number of relapses per patient was calculated by subtracting number of relapses avoided per patient from the weighted average of annualized relapse rate:

Weighted annualized relapse rate = Σ (Annual relapses × Number of patients in placebo group) ÷ Σ Number of patients in placebo group

Number of relapses avoided/patient = Weighted annualized relapse rate × Relative rate of reduction

Number of relapses/patient = Weighted annualized relapse rate – Number of relapses avoided per patient

Model 2 (ALT)

Since Model 2 had a 2-year time frame, the following formula was used to first calculate the relative reduction in relapse, and then the number of relapse avoided per patient was calculated.

Relative reduction in relapse = (Number of relapses at the end of 2 years of clinical trial – Number of relapses at baseline) × 100 ÷ Number of relapses at baseline

TABLE 2	DMT Dosing and Acquisition Cost				
DMT	Dose, Frequency, Route	Doses per Pack	Packs per Year	Wholesale Acquisition Price per Package (2015 U.S. $)	Wholesale Acquisition Price per Year (2015 U.S. $)
Model 1: PEG					
PEG[24]	125 µg Every 14 days Subcutaneous	2	13	5,034.00	65,442.00
IM IFN beta-1a[25]	30 µg Once a week Intramuscular	4	13	5,034.00	5,034.00
SC IFN beta-1b[26]	0.25 mg Every other day Subcutaneous	15	12.2	3,740.75	45,637.00
GA[27]	20 mg/mL Every day Subcutaneous	30	12.2	6,110.50	6,110.50
FIN[28]	0.5 mg Every day Oral	30	12.2	5,831.22	5,831.22
NAT[29]	300 mg Every 4 weeks Intravenous infusion	1	13	4,960.00	64,480.00
DMF[30]	SD: 120 mg Twice daily for 7 days MD: 240 mg Twice daily after 7 days Oral	SD: 14 MD: 60	12.9	SD: 1,274.00 MD: 5,460.00	66,248.00
Model 2: ALT					
ALT[31]	Year 1:12 mg/day 5 consecutive days Year 2:12 mg/day 3 consecutive days Intravenous infusion	1	Year 1: 5 Year 2: 3	19,750.00	Year 1: 98,750.00 Year 2: 59,250.00
IFN beta-1a 44 µg[32]	44 µg 3 times per week Subcutaneous	12	13	5,433.70	70,638.00

ALT = alemtuzumab; DMF = dimethyl fumarate; DMT = disease-modifying therapy; FIN = fingolimod; GA = glatiramer acetate; IFN = interferon; IM = intramuscular; MD = maintenance dose; NAT = natalizumab; PEG = peginterferon beta-1a; SC = subcutaneous; SD = starting dose.

The number of relapses avoided was calculated as a product of relative reduction in relapse and number of relapses at baseline for ALT and IFN beta-1a 44 µg. Baseline relapses were taken from phase 3 clinical trials.[5,22] The number of relapses avoided per patient for models 1 and 2 are presented in Table 1.

Cost Input

Drug Acquisition Costs. Drug acquisition costs were calculated using the wholesale acquisition cost from the 2015 RED BOOK. Dosage information from published FDA package inserts and number of doses per package from RED BOOK were used to calculate the number of packages per year per patient. For both models, the drug acquisition cost was calculated as the product of the monthly cost of drug acquisition and the number of packages required per year over the respective time horizon. Both

models did not take into account product rebates, discounts, copays, or coinsurance. DMT dose, frequency, route of administration, and acquisition cost are presented in Table 2.

Drug Administration and Monitoring. The drug administration and monitoring schedules used in both models were taken from the DMT package inserts.

Model 1 (PEG)

Each DMT has a different route of administration, so the cost of administration was accounted for in the model. Unlike PEG (subcutaneous), IFN beta products (subcutaneous, intramuscular), GA (subcutaneous), FIN (oral), and DMF (oral), NAT is an intravenous infusion and is administered over a 1-hour period under the supervision of a health care provider, followed by an observation period of 1 hour.[26-32] As such, our analysis included administration costs for NAT.

TABLE 3 DMT Administration and Monitoring Frequency and Health Care Provider Utilization for Models 1 and 2

	Model 1: PEG							Model 2: ALT	
	PEG	IM IFN beta-1a	SC IFN beta-1b	GA	FIN	NAT	DMF	ALT	IFN beta-1a 44 µg
Drug administration									
Frequency	26	52	183	365	365	13	730	8	312
Monitoring									
Complete blood count[24-30]	3	2	3	1	2	1	3	25	6
Liver function test[24-29]	3	2	3	1	1	1	0	N/A	6
Magnetic resonance imaging[29]	0	0	0	0	0	1	0	9	N/A
Electrocardiogram[28]	0	0	0	0	2	0	0	25	N/A
Macular edema testing[28]	0	0	0	0	2	0	0	25	N/A
Thyroid function test[25]	0	2	0	0	0	0	0	9	N/A
Serum creatinine level	N/A	N/A	N/A	N/A	N/A	N/A	N/A	25	N/A
Urineanalysis	N/A	N/A	N/A	N/A	N/A	N/A	N/A	25	N/A
Skin test for melanoma	N/A	N/A	N/A	N/A	N/A	N/A	N/A	3	N/A
Health care provider visit									
Neurologist[33]	3	3	3	3	3	4	3	7	6

ALT = alemtuzumab; DMF = dimethyl fumarate; DMT = disease-modifying therapy; FIN = fingolimod; GA = glatiramer acetate; IFN = interferon; IM = intramuscular; N/A = not applicable; NAT = natalizumab; PEG = peginterferon beta-1a; SC = subcutaneous.

Laboratory tests and imaging procedures, such as magnetic resonance imaging (MRI) during DMT therapy, were taken from package inserts. For those DMTs with no explicit requirements for complete blood count (CBC) and liver function test (LFT), it was assumed that each of these tests were conducted at least once before the initiation of therapy. For PEG, since the frequency of CBC and LFT was not stated in the package insert, both tests were assumed to have been provided 3 times in 1 year. The model assumed 1 MRI for NAT conducted before initiation of therapy as per the recommendation in the NAT package insert.[31] The model assumed 3 neurologist visits for all drugs (except NAT) based on an MS health care utilization study that reported a mean of 3.4 visits per patient for 12 months.[33] The model also assumed an extra visit for patients on NAT, since the drug is distributed through a restricted program, with a recommendation that prescribers evaluate patients after 3 and 6 months of initiation of therapy and then 6 months after that.[31]

Model 2 (ALT)

ALT is an intravenous infusion that needs to be administered over 4 hours under the supervision of a health care provider, followed by a 2-hour observation period.[34] IFN beta-1a 44 µg is self-administered subcutaneously and does not include a cost for administration.[35] Laboratory tests were taken from package inserts. Three neurologist visits were assumed per year for IFN beta-1a 44 µg, and 1 extra visit was assumed for ALT because of restricted prescribing.[34,35] The model assumed an extra visit for patients on ALT, since it is distributed through a restricted program in which

prescribers are advised to assess patients before baseline infusion, at 6 months after first infusion, and every 6 months thereafter.[36]

Neither model accounted for costs associated with serious adverse events. The comparators—NAT, FIN, and DMF—are associated with serious adverse events, such as progressive multifocal leukoencephalopathy (PML). However, the occurrence of PML is 1 in 1,000, with a mean occurrence of 17.9 months in patients on NAT and 2.5 years and 4 years for patients on FIN and DMF, respectively.[30,32,37] Model 1 (PEG) had a 1-year horizon, so it was assumed that there would be no expected incidence of PML within the analytical time frame. For Model 2, ALT is associated with immune thrombocytopenia (ITP) and antiglomerular basement membrane disease (AGBMD). However, these adverse events were not included in the model, since their occurrence is low (<1%-1%).[34]

Relapse Management Cost. Cost for relapse management was acquired from Bozkaya et al. (2015).[7] The cost per relapse was calculated as the product of relapse per patient and cost of relapse management.

The costs for laboratory and monitoring tests was extracted from the Centers for Medicare & Medicaid Services 2015 Physician Fee Schedule using the Current Procedural Terminology codes for each test.[38] Costs for neurologist visits were taken from the U.S. Bureau of Labor Statistics.[39] DMT administration and monitoring frequency and health care provider utilization for both models are presented in Table 3. All costs were adjusted to 2015 U.S. dollars using the medical care component of the Consumer Price Index.[40]

TABLE 4 Total Cost per Patient, Relapses Avoided, Cost per Relapse Avoided and ICERs for Models 1 and 2

| | Model 1: PEG | | | | | | | Model: 2 ALT | |
	PEG	IM IFN beta-1a	SC IFN beta-1b	GA	FIN	NAT	DMF	ALT	IFN beta-1a 44 µg
DMT cost ($)	65,442	65,442	45,637	74,548	71,141	64,480	66,248	158,000	141,276
Administration + monitoring + utilization cost ($)	340	364	340	296	802	2,331	307	3,438	810
Treatment of relapses ($)[a]	776	998	798	865	554	421	576	1,153	2,306
Total cost ($)	66,558	66,804	46,775	75,710	72,761	67,232	67,131	162,591	144,392
Relapse avoided per patient	0.20	0.10	0.19	0.16	0.30	0.36	0.29	1.18	0.46
Cost per relapse avoided ($)	332,790	668,040	246,184	473,188	242,537	186,756	231,486	137,789	313,896
ICER ($)[b] Cost$_A$−Cost$_B$÷Number of relapses avoided$_A$−Number of relapses avoided$_B$	–	PEG dominated	PEG vs. SC IFN beta-1b: $1,978,000	PEG dominated	FIN vs. PEG: 62,030[c]	NAT vs. PEG: 4,213[c]	DMF vs. PEG: 6,367[c]	–	ALT vs. IFN beta-1a 44 µg: $25,276

Note: All costs are reported per person in 2015 U.S. dollars.

[a]Cost for relapse treatment was calculated as a product of number of relapses elapses after DMT treatment and cost of treating 1 relapse. Cost of treating relapse was extracted from literature (inflated to 2015 dollars: $2,217).[7]

[b]Cost$_A$ and Cost$_B$ for Model 1: A = PEG; B = IM IFN, SC IFN, GA, FIN, NAT, and DMF; for Model 2, A = ALT; B = IFN beta-1a 44 µg.

[c]ICERs for FIN, NAT, and DMF are compared with PEG, since these 3 DMTs cost more and were more effective than PEG.

ALT = alemtuzumab; DMF = dimethyl fumarate; DMT = disease-modifying therapy; FIN = fingolimod; GA = glatiramer acetate; ICER = incremental cost-effectiveness ratio; IFN = interferon; IM = intramuscular; NAT = natalizumab; PEG = peginterferon beta-1a; SC = subcutaneous.

Model Assumptions

Published real-world adherence data for PEG and ALT were not available at the time of model development. Although adherence rates for comparators were available, adherence was assumed to be 100% to provide a fair comparison and avoid preference of any DMT. Patients were assumed to be maintained on the assigned DMTs throughout the duration of the model. Clinical inputs (annualized relapse rates and relative relapse rate reduction) taken from published phase 3 clinical trials were assumed to be highly reliable and valid. Both models had a short analytic frame, so it was assumed that the disease condition of the patient remained the same and that the patient did not transition into a higher level of disease severity. The cost for a neurologist visit was assumed to be the same for each visit, and the model did not account for any potential differences in the intensity of the visits. The number of CBC and LFT tests conducted for PEG per year was assumed to be 3, and this was based on expert opinion. An extra visit was assumed for patients on NAT and ALT because of their restricted prescribing.[31,36]

Results

Base-Case Analysis

For a hypothetical RRMS population, Table 4 describes the total cost per patient, number of relapses avoided per patient, cost per relapse avoided per patient, and ICERs for each DMT analyzed in the 2 models.

Model 1 (PEG)

Total cost of therapy per person for 1 year was $66,558 for PEG, which was lower compared with all DMTs except SC IFN beta-1b ($46,775). PEG avoided a greater number of relapses (0.20) compared with IM IFN beta-1a (0.10) and GA (0.16) but avoided fewer relapses compared with FIN (0.30), NAT (0.36), and DMF (0.29). For the number of relapses avoided, SC IFN beta-1b was almost comparable to PEG (PEG 0.20 vs. SC IFN beta-1b 0.19). The cost per relapse avoided was lowest for NAT ($186,756), followed by DMF ($231,486), FIN ($242,537), and SC IFN beta-1b ($246,184). PEG ($332,790) fared better than GA ($473,188) and IM IFN beta-1a ($668,040) only. The ICER values show that PEG dominated (less costly and more effective) IM IFN and GA. PEG had an ICER of $1,978,000 per relapse avoided compared with SC IFN beta-1b. This might be due to the comparable efficacy between the 2 comparators. However, when compared with NAT, DMF, and FIN, PEG was less costly and less effective. The ICERs for FIN, NAT, and DMF, compared with PEG, were $62,040, $4,213, and $6,267 per relapse avoided, respectively (Table 4).

Model 2 (ALT)

Total cost of therapy per patient for ALT was higher than IFN beta-1a 44 µg ($162,591 vs. $144,392). However, the number of relapses avoided was higher for ALT compared with IFN beta-1a 44 µg (1.18 vs. 0.46). Thus, the cost per relapse avoided per patient was significantly lower for ALT compared with IFN beta-1a 44 µg ($137,789 vs. $313,896). ALT had an ICER of $25,276 per relapse avoided compared with IFN beta-1a 44 µg (Table 4).

| TABLE 5 | Univariate Sensitivity Analysis of ICERs (Cost per Relapse Avoided) for Models 1 and 2 |

| | Input Variable | | | | | |
| | Drug Acquisition Cost | | Number of Relapses Before Treatment | | Cost for Relapse Treatment | |
	(+)	(-)	(+)	(-)	(+)	(-)
Model 1: PEG ICERS						
IM IFN beta-1a	PEG dominated	PEG dominated	PEG dominated	PEG dominated	PEG dominated	PEG dominated
SC IFN beta-1b	PEG vs. SC IFN beta-1b: $2,374,400	PEG vs. SC IFN beta-1b: $1,582,200	PEG vs. SC IFN beta-1b: $1,976,100	PEG vs. SC IFN beta-1b: $1,978,300	PEG vs. SC IFN beta-1b: $1,977,800	PEG vs. SC IFN beta-1b: $1,978,800
GA	PEG dominated	PEG dominated	PEG dominated	PEG dominated	PEG dominated	PEG dominated
FIN	FIN vs. PEG: $70,790	FIN vs. PEG: $47,990	FIN vs. PEG: $49,308	FIN vs. PEG: $74,788	FIN vs. PEG: $58,950	FIN vs. PEG: $59,830
NAT	NAT vs. PEG: $3,015	NAT vs. PEG: $5,415	NAT vs. PEG: $3,200	NAT vs. PEG: $5,700	NAT vs. PEG: $3,375	NAT vs. PEG: $4,656
DMF	DMF vs. PEG: $8,160	DMF vs. PEG: $4,560	DMF vs. PEG: $4,809	DMF vs. PEG: $8,814	DMF vs. PEG: $5,922	DMF vs. PEG: $6,811
Model 2: ALT ICERs						
IFN beta-1a 44 µg	ALT vs. IFN beta-1a 44 µg: $29,922	ALT vs. IFN beta-1a 44 µg: $20,631	ALT vs. IFN beta-1a 44 µg: $23,384	ALT vs. IFN beta-1a 44 µg: $32,356	ALT vs. IFN beta-1a 44 µg: $24,957	ALT vs. IFN beta-1a 44 µg: $25,576

ALT = alemtuzumab; DMF = dimethyl fumarate; FIN = fingolimod; GA = glatiramer acetate; ICER = incremental cost-effectiveness ratio; IFN = interferon; IM = intramuscular; NAT = natalizumab; PEG = peginterferon beta-1a; SC = subcutaneous.

Sensitivity Analysis

For Model 1, drug acquisition costs, cost of relapse management, and average number of relapses per patient before treatment were varied by ± 20% of the base-case estimates (Table 5). Sensitivity analysis results demonstrated that PEG dominated IM IFN and GA after varying all 3 parameters. On varying drug acquisition cost, PEG had an ICER that ranged from $1,582,200 to $2,374,400, compared with SC IFN. When NAT, FIN, and DMF were compared with PEG, NAT had the lowest ICERs, followed by DMF and FIN. Average number of relapses per patient before treatment and cost of relapse management when increased by 20% of base-case results showed better ICERs (lower) compared with decreasing these inputs by 20%.

As with Model 1, base-case estimates were varied by ±20% in Model 2 (Table 5). Results showed that ALT had an ICER of $20,631 (-20% base case) and $29,922 (+20% base case) compared with IFN beta-1a 44 µg. As observed in Model 1, number of relapses per patient at baseline and cost of relapse management when increased by 20% of base-case results showed better ICERs ($23,824 and $24,957, respectively) compared with decreasing these inputs by 20% (ICERs $32,356 and $25,596, respectively).

■ Discussion

Results from Model 1, which evaluated the cost-effectiveness of PEG, indicated that PEG dominated IM IFN beta-1a and GA. However, when compared with SC IFN beta-1b, PEG was more expensive and had comparable effectiveness, resulting in a high ICER (base case $1,978,000 per relapse avoided). On the other hand, when compared with NAT, FIN, and DMF, PEG was less expensive and also less effective, showing that results are mixed for PEG as treatment for RRMS.

Results from Model 2, which evaluated the cost-effectiveness of ALT, indicated that ALT had a higher cost per patient ($162,591) but was more effective (relapse avoided 1.18) compared with IFN beta-1a 44 µg ($144,392; relapse avoided 0.46). Thus, the average cost-effectiveness ratio for ALT ($137,789 per relapse avoided) was lower than IFN beta-1a 44 µg ($313,896 per relapse avoided). The ICER of ALT compared with IFN beta-1a 44 µg was $25,276 per relapse avoided.

This study was conducted from a payer perspective, so only direct medical costs were included in the analysis. Also, since most payers prefer a shorter analytical time frame, relapses avoided was used as an outcome instead of quality-adjusted life-year (QALY), which seems to be a preferred outcome measure for a chronic condition with a longer analytical time frame. As previously discussed, our study results are consistent with the findings of other published studies that evaluated the cost-effectiveness of PEG and ALT.

In the U.S. study by Hernandez et al. (2016),[8] PEG dominated IFN beta-1a 44 µg (cost savings of $22,070 and additional 0.06 QALYs gained) and GA (cost savings of $19,163 and 0.07 QALYs gained). In another U.S. study by Bozkaya et al.,[7] PEG dominated IFN beta-1a 44 µg. Studies based in Ireland and Scotland by Hernandez et al. (both 2015) showed that—in comparison with IFN beta-1a 22 µg, IFN beta-1a 30 µg, IFN beta-1a 44 µg, IFN beta-1b 250 µg, and GA—PEG treatment resulted in greater benefits and cost savings (Ireland) and greater benefits and cost savings compared with IFN beta-1a

22 µg and 30 µg, IFN beta-1b 250 µg, and ICERs of £17,821 and £4,121 when compared with GA and IFN beta-1a 44 µg, respectively (Scotland).[9,10] Study results from Iannazzo et al. (2015) in Italy show that PEG had ICERs of €11,112, €12,604, €10,580, €16,702, and €21,536 per QALY when compared with IFN beta-1a 30 µg, IFN beta-1a 22 µg, IFN beta-1b 250 µg (2 different suppliers), and GA, respectively, and dominated IFN beta-1a 44 µg (cost savings of €21,456 and 0.52 QALYs gained).[11]

For ALT, Kohn et al. (2013) conducted a U.S.-based study that had an ICER of $43,826 per QALY compared with IFN beta-1a 44 µg.[14] Diaz et al. (2014) conducted a study in the United Kingdom and concluded that ALT dominated SC IFN beta-1b, FIN, and NAT and had a probabilistic and deterministic ICER of £7,017 per QALY and £8,924 per QALY, respectively, compared with GA.[12] In the study by the National Center for Pharmacoeconomics in Ireland (2014), ALT had an ICER of €4,166 per QALY and dominated all other DMT comparators.[13] Our study findings for ALT reflect findings from these studies when compared with IFN beta-1a 44 µg.

Limitations

This study has several limitations that need to be considered. First, the models assumed 100% adherence to therapies, since adherence data for PEG and ALT were not available at the time of model development, and varied adherence rates were reported in the literature for different DMTs.[42-45] Considering the lower dosing frequency for PEG compared with the DMTs in our model (except NAT), adherence to PEG can be expected to be higher. For ALT, dosing frequency was very low compared with IFN beta-1a 44 µg.

Although ALT is associated with serious adverse effects, the low dosing frequency may lead to better adherence. Studies have reported adherence rates for DMTs, and a review by Menzin et al. (2013) showed that the overall adherence rate for IM IFN beta-1a, SC IFN beta-1b, GA, and SC IFN beta-1a ranged from 41% to 88% with a weighted mean adherence of 69.4%, 58.4%, 56.8%, and 63.8%, respectively.[41] Bergvall et al. (2014) showed that adherence to FIN, any IFN therapy, GA, and NAT were 93.8%, 88.1%, 88.1%, and 88.7%, respectively.[42] Polson et al. (2015) observed the adherence rate for fingolimod and dimethyl fumarate to be 82% and 77%, respectively.[43] Finally, a study by Hansen et al., conducted in Germany, reported the adherence rates for IM IFN beta-1a, SC IFN beta-1b, SC IFN beta-1a, and GA to be 34.2%, 33.4%, 31.7%, and 29.8%, respectively, which was by far the lowest reported adherence rates.[44]

Second, there was no head-to-head clinical trial data in the PEG model, so pretreatment relapse rate was calculated based on the weighted average of relapse rates from the placebo groups from different phase 3 clinical trials of all DMTs. It is plausible that differences in study designs, procedures, or baseline characteristics may have an impact on these rates. However, the sensitivity analysis showed that the model was robust to the changes in the relapse rate input.

Third, univariate sensitivity analyses were conducted to test for uncertainty in model parameters. A multiway sensitivity might have shown an effect because of the combination of study variables but was not used, given the short study time horizon and small number of study variables.

Fourth, the outcome of interest was relapse avoided rather than sustained disability progression or other outcome such as QALY. Although relapse avoided is an important outcome, it did not fully represent the disease burden, since RRMS is a progressive disease. Because of the short analytic frame, relapse avoided was considered to be best suited for this study.

Finally, costs associated with adverse events were not included in the model, since these adverse events occurred over a longer period of time, which would not be captured in a short-term model. Earnshaw et al. (2009) estimated the cost of a 1-time PML treatment at $22,995 (2007 U.S. dollars).[45] Given the low incidence for PML, it was not expected to drastically affect the ICER.[30,32,37] A cost-of-illness study by Saleh et al. (2009) estimated the annual cost of ITP treatment at around $7,000 per person (year when cost was taken not specified).[46] Also, the burden of AGBMD (reported as mean hospital costs) was estimated from national hospital discharge data and was around $47,405 (2014 U.S. dollars).[47] As with PML, the prevalence of these adverse events is very low and did not affect the ICERs in our short-term analyses. However, future long-term studies may need to capture the effect of these adverse events in order to see their effect on the DMT cost-effectiveness ratios.

■ Conclusions

In patients with RRMS, PEG dominated GA and IM IFN beta-1a and had comparable effectiveness with SC IFN beta-1b but was more expensive. When compared with NAT, DMF, and FIN, PEG was less expensive but had lower effectiveness. Overall, PEG is a viable alternative compared with the DMTs in our model over a short-term horizon. The decision to choose PEG over other DMTs is influenced by multiple factors, including adverse event profile, ease of administration, clinical outcomes, and health plan coverage issues.

On the other hand, ALT is a cost-effective alternative when compared with SC IFN beta-1a 44 µg over a short time horizon. ALT had an ICER of $25,276 per relapse avoided

compared with SC IFN beta-1a 44 μg over a 2-year time horizon. However, caution should be exercised if the ICER is calculated over a longer time period, since serious adverse events associated with ALT may be a factor in influencing the overall cost. The results of this study will assist payers in making better decisions about choosing between PEG and ALT over a short-term horizon for patients with RRMS.

Authors

ANKUR A. DASHPUTRE, BPharm, and KHALID M. KAMAL, MPharm, PhD, Department of Pharmacy Administration, Mylan School of Pharmacy, Duquesne University, Pittsburgh, Pennsylvania. GAURI PAWAR, MD, Robert C. Byrd Health Sciences Center, West Virginia University, Morgantown.

AUTHOR CORRESPONDENCE: Khalid M. Kamal, MPharm, PhD, Department of Pharmacy Administration, 418 B Mellon Hall, Duquesne University, Mylan School of Pharmacy, 600 Forbes Ave., Pittsburgh PA 15282. Tel.: 412.396.1926; E-mail: kamalk@duq.edu.

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