Cost- Effectiveness Analysis of Interferon βeta-1a versus Interferon βeta-1b In the Treatment of Relapsing- Remitting Multiple Sclerosis (RRMS) in Iran

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Abstract

The primary objective of this analysis was to evaluate the cost-effectiveness analysis of two Disease-modifying drugs (DMD) used as first-line treatment of Relapsing Remitting Multiple Sclerosis (RRMS): interferon IFNβ-1a IM injection (Avonex®) and IFN β-1b SC injection (Betaferon®) from Iranian Ministry of Health perspective. The outcome of interest was number of relapses avoided. Costs were reported in 2011 USD. Costs and outcomes were discounted at 5%. The time horizon was two years. All uncertainties were tested via one-way sensitivity analyses. Total costs per patient over the time horizon of a study were estimated at 39923, 47670 and 52045 USD for symptom management, IM IFNβ-1a and SC IFNβ-1b, respectively. The incremental cost per relapse avoided was 25823 and 14965 USD for IM IFNβ-1a and SC IFNβ-1b, respectively, compared with no active treatment (symptom management).Results were sensitive to the discount rate, frequency of relapse and cost of DMDs. The cost-effectiveness analysis determined that INFβ-1b SC (Betaferon®) was the best strategy of the two immunomodulatory therapies used to treatment of patients experiencing a relapsing-remitting multiple sclerosis (RRMS) and resulted in better outcomes than symptom management alone. Sensitivity analyses indicated that the model was sensitive to changes in a number of key parameters.

Keywords: Cost-Effectiveness, INFβ 1-a, INFβ-1b, Relapsing-Remitting Multiple Sclerosis, Iran

1. Introduction

Multiple sclerosis (MS) is the second most common cause of neurologic disability in young and middle-aged adults [Hauser SL 1998; Isselbacher KJ et al 1998]. Population studies have reported that females are more susceptible by a factor of almost 2:1, but this varies among surveys [Hauser SL 1998].Males are more likely to have progressive disease from the onset [Noseworthy JH, 2000].The mean age of onset of MS is during the third and fourth decades of life, with a peak incidence during the late twenties and early thirties [Weinshenker BG et al 1989; Rieumont MJ, DeLuca SA , 1993].

Initially, most patients (~65%) have relapsing remitting MS (RRMS), with a variable frequency of exacerbations (mean, 1–2 per year) [Noseworthy JH, 2000; Weinshenker BG et al 1989; Rieumont MJ, DeLuca SA, 1993]. Eventually, most patients with RRMS develop secondary progressive MS (SPMS). In this stage, there are fewer exacerbations, although recovery from these exacerbations is always incomplete. In addition, there is a chronic and slow increase in neurologic deficits. Thus, the patient has increasingly severe disability, with no recovery [Hibberd PL, 1994; Clark W, 1996; Goodkin DE et al, 1989; Weatherall DJ et al, 1987].

MS can dramatically affect the quality of life (QoL) of patients and their families. Family life, economic status, and social interaction may be affected by somatic symptoms of the disease [Weinshenker BG, 1995]. Cognitive dysfunction affects 43% to 65% of patients with MS, also negatively affecting QoL. Cognitively impaired patients with MS are less likely to be professionally active, are more dependent, report more sexual dysfunction, and tend to be less socially engaged than cognitively intact patients with MS [Rudick RA et al, 1992].

In the absence of a cure, MS therapy for many years consisted of supportive care and symptomatic management. However, the introduction of disease-modifying drugs (DMDs) potentially changed the evolution of MS by reducing the number of disease exacerbations. In early clinical trials in patients with RRMS, recombinant interferon-beta (IFNβ-1a or IFNβ-1b) was found to significantly reduce rates of relapse and disease progression [PRISMS, 1998; The IFNB Multiple Sclerosis Group, 1993; European Study Group on Interferon Beta-1b in Secondary Progressive MS, 1998]. Currently available first-line agents for the treatment of RRMS are IFNβ-1a 44 μg SC (Rebif) and 30 μg IM (Avonex) IFNβ-1b (Betaferon) and glatiramer acetate (Copaxone). In addition, natalizumab (Tysabri) a monoclonal antibody that affects the actions of the immunosystem, is indicated for second-line therapy.

The full economic burden of MS on society and on the individuals concerned is not known, but considering that patients with MS experience disruption in their daily activities and that MS affects mainly young (age 25–40 years) people whose professional activities are interrupted either temporarily or permanently [Catanzaro M, Weinert C, 1992] the cost is likely to be substantial. In patients with MS, a positive correlation has been reported between total health care costs and scores on the Expanded Disability Status Scale (EDSS). EDSS scores range from 0 to 10, with higher scores indicating greater disability. Above an EDSS score of 5.5 (needs aid to walk), costs have been reported to increase particularly rapidly.

Although discussion usually focuses on the total mean annual cost of MS drugs, DMDs account for only 20% of all costs [Kobelt G et al, 2006]. Indirect costs tend to be the largest contributors to the overall cost burden of MS. Taking into account employment history, medical insurance, amount and source of family income, and disease progression, MS can cost up to 40% of an individual's lifetime earnings [Catanzaro M, Weinert C, 1992; Weinfeld FD, Baum HM,1984; Weinshenker BG et al, 1996]. It has been reported that 50% to 80% of patients with MS are unemployed within 10 years of disease onset, with 39% of men and 19% of women with MS retiring early due to disability, frequently citing MS-related fatigue [PRISMS, 1998; LaRocca N et al, 1982]. Cognitive impairment, spasticity, problems of coordination, disturbances of bladder and bowel function, a non- remitting disease course, heavy physical work, and age >30 years have been reported as factors contributing to early retirement or unemployment [Bauer HJ et al, 1965; Grönning M et al, 1990].

Cost-effectiveness and cost-utility analyses (CEA/CUAs) are useful tools to assess the trade-off between the added costs and potential benefits (e.g., improved patient outcomes) of new therapies. In the current environment of cost-consciousness and limited health care resources, CEA/CUA affords decision makers an opportunity to evaluate new therapies from an economic perspective and quantify the budgetary implications of adopting such therapies.

The objective of this study was to assess the cost-effectiveness of IFNβ-1a 30 µg IM (Avonex) compared with IFNβ-1b 250 µg SC (Betaferon) from the Iranian Ministry of Health (MoH) perspective in 2011.

In this regard, we examine the cost-effectiveness of two treatment strategies in patients diagnosed with RRMS. Cost-effectiveness results were reported in terms of cost per relapse avoided as well as cost per outcome achieved (e.g., cost per year spent relapse free or cost per year spent in less severe disease health states), thus providing decision makers relevant data with which to evaluate the cost-effectiveness of the two immunomodulatory therapies in treating RRMS.

2. Research Method

A cost-effectiveness analysis conducted to estimate the cost-effectiveness of the two first-line Interferon βetas available in Iran—IFNβ-1a 30 µg IM given once weekly and IFNβ-1b 250 µg SC given every other day —in a hypothetical cohort of patients with RRMS in the Iranian health care setting in 2011. Data derived from the published literature, clinical trials, official Iran price/tariff lists, and national population statistics. The time horizon of the analysis was two years. The foreign exchange rate used in the analysis was 10720 Iranian Rial =1USD (Sep, 2011).

2.1. Effectiveness Outcomes

Because pharmacoeconomic evaluations should employ end points that are oriented toward patient benefit, a reduction in the number of relapses chosen as the most relevant effectiveness outcome. As a consequence, the cost-effectiveness of each treatment option will be defined as the cost per relapse avoided. All input data used in the study are reported in Table 1.

Table1. Clinical Trial and Effectiveness Measures Used in the Study

First Author/Year	Treatment	No. of Clinical Relapses, Mean (1-2 years)	Mean Baseline Relapse Rate, EDSS	N (Placebo, Treatment)	2-Year Relapse Rates (Placebo, Treatment [Absolute Difference, Percent Difference])
Jacobs et al 23	IFNβ-1a 30 µg IM	1.34	1.2, 2.4	143, 158	1.64,1.34[0.30, 18.3%]
	Placebo	1.64			
	Absolute Reduction	0.30			
IFNB Multiple Sclerosis Study24,25	IFNβ-1b 250 µg SC	1.81	3.4, 3.0	123, 124	2.62, 1.81 [0.81, 30.9%]
	Placebo	2.62			
	Absolute Reduction	0.81			

2.2. Model Calculations

The study estimated the following outcomes: average number of years spent relapse free; and total costs and costs by component (i.e., DMDs drugs, MS-related medical costs, and lost worker productivity costs). Incremental cost-effectiveness ratios (ICERs) assessed in the study by comparing each of the individual DMDs with symptom management alone. The ICERs were calculated as the difference in costs between two treatments divided by the difference in effectiveness: (Cost Drug A – Cost Drug B) / (Effectiveness Drug A – Effectiveness Drug B). The resulting ICERs described the relative cost of purchasing one additional unit of relative effectiveness (e.g., cost of one additional year spent in the lower relapse rate).

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2.3. Data Sources

2.3.1. Clinical Data

Data sources in this study included the published literature, clinical trials, and national population statistics. The probabilities of relapse were based on data from pivotal trials of DMDs [Jacobs LD et al, 1996; The IFNB Multiple Sclerosis Study Group, 1993; The IFNB Multiple Sclerosis Study Group and the University of British Columbia MS/MRI Analysis Group, 1995].

2.3.1. Economic Data

Two cost categories were considered in this review. Direct costs referred to the resources consumed by MS-related interventions and any associated events. Direct costs could fall on the healthcare system and comprised items such as DMDs, other drugs, Hospitalization, outpatient care, radiology tests, laboratory tests and transport which were classified as direct costs. Indirect costs comprised items such as mobility aids, other aids (car), adaptations (home and work), services (nursing, child care), short-term sickness absence and change in status over last year. We reported all costs in USD, year 2011 values. Historical currency exchange rates were used to convert estimates reported in foreign currencies into USD. Annual drug costs will be calculated from the Iranian Ministry of health (MoH) perspective, based on Sep 2011 information from the National FDA database. Costs of adverse events will not be included, as these assumed to be similar across treatment groups. Official Iranian price/tariff lists were used for the pricing of resources.

2.4. Sensitivity analysis

To test the robustness of the model assumptions and specific parameters, univariate sensitivity analyses were performed by increasing and decreasing values for key parameters in the model. Plausible ranges of values were obtained from the published literature or by varying the estimates by up to 25% in each direction. One way sensitivity analyses were performed with the discount rate, frequency of relapse and cost of DMDs, which were varied to test the robustness of the analysis.

3. Research Results

Tables 2 and 3 present the results of cost analysis for patients with Relapsing-Remitting Multiple Sclerosis (RRMS), including average direct costs and average indirect costs with each treatment option from the Iranian Ministry of Health perspective. The direct costs make higher proportion of total costs of the treatment of RRMS relative to the indirect costs. Total costs per patient over the time horizon of a study were estimated at 39923, 47670 and 52045 USD for symptom management, IM IFNβ-1a and SC IFNβ-1b, respectively.

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Table2. Average direct costs per patient treated for Relapsing-Remitting Multiple Sclerosis (RRMS) over one year (Sep 2011 USD)

Treatment Group Cost category	INFβ-1a 30mcg IM 3 times weekly	INFβ-1b 250mcg SC every other day
Disease-modifying drugs	8955	10914
Drugs :other	2985	3638
Hospitalization	4011	4757
Outpatient care	10448	9515
Radiology tests	820	911
Laboratory tests	113	122
Transport	65	54
Total Direct Costs	27397	29911

Table3. Average indirect costs per patient treated for Relapsing-Remitting Multiple Sclerosis (RRMS) over one year (Sep 2011 USD)

Treatment Group Cost category	INFβ-1a 30mcg IM 3 times weekly	INFβ-1b 250mcg SC every other day
Mobility aids	6487	7083
Other aids (car)	60	66
Adaptation (home, work)	1157	1262
Services (nursing, child care)	7096	7747
Short-term sickness absence	4257	4648
Change in status over last year	1216	1328
Total Direct Costs	20273	22134

To compare the cost-effectiveness of one treatment over another is to calculate the Incremental Cost-Effectiveness Ratio (ICER). In general, ICER means the cost of obtaining an incremental effectiveness unit (e.g. an incremental QALY). This is represented by the formula:

ICER= (Cost T1 – Cost T2) / (Effectiveness T1 – Effectiveness T2)

Table 4 summarizes the incremental cost-effectiveness outcomes for each treatment option compared with no active treatment (symptom management). The incremental cost per relapse avoided was 25823 and 14965 USD for IM IFNβ-1a and SC IFNβ-1b, respectively, compared with no active treatment (symptom management).

The sensitivity analyses performed show that results were sensitive to a number of variables including the discount rate, frequency of relapse and cost of DMDs. Sensitivity analysis indicated that the study was sensitive to changes in a number of key parameters, and thus changes in these key parameters would likely influence the estimated cost-effectiveness results.

Table4. Base-case Analysis: Cost-effectiveness analysis

Variable	No. of Clinical Relapses, Mean	Total MS-related Costs USD	Incremental Cost(ΔC) USD	Incremental Effect(ΔE)	ICER (ΔC/ ΔE) USD
No active treatment	INFβ-1-a:1.64 INFβ-1-b:2.62	39923	-	-	-
INFβ-1a, 30 µg IM	1.34	47670	7747	0.30	25823
INFβ-1b, 250 µg SC	1.81	52045	12122	0.81	14965

4. Discussion

The aim of this study was to conduct a cost-effectiveness analysis to estimate the cost-effectiveness of the two first-line Interferon βetas available in Iran—IFNβ-1a 30 µg IM given once weekly and IFNβ-1b 250 µg SC given every other day —in a hypothetical cohort of patients with RRMS in the Iranian health care setting in 2011. The study indicated that, of the two immunomodulatory therapies used to manage MS and in comparison with symptom management, IFNβ-1b 250 µg SC was the best strategy in terms of outcome and costs.

To our knowledge, this is the first attempt to undertake a cost-effectiveness analysis of the two first-line Interferon βetas available in Iran—IFNβ-1a 30 µg IM given once weekly and IFNβ-1b 250 µg SC given every other day in an Iranian clinical setting.

All two immunomodulatory therapies used in the treatment of RRMS patients are associated with increased benefits compared with symptom management alone, albeit at higher costs. The CEA indicated that, of the two immunomodulatory therapies used to manage MS and in comparison with symptom management, INFβ 1-b SC was the best strategy. Sensitivity analysis indicated that the model was sensitive to changes in a number of key parameters, and thus changes in these key parameters would likely influence the estimated cost-effectiveness results.

5. Conclusions

The 2002 study by Nuijten [26] used clinical data to evaluate the cost-effectiveness of both IFNβ-1a and IFNβ-1b in the treatment of MS versus standard care. The authors concluded that using IFN as preventative treatment "may not be fully justified from a health-economic perspective", but they acknowledged that it is "associated with an improved effectiveness compared with no preventative treatment."

Parkin et al [27] evaluated the cost-effectiveness of IFNβ-1b in patients with RRMS. The clinical data was taken from 2 trials by the IFBN Multiple Sclerosis Study Group with patient, cost and quality of life data collected from questionnaires administered (EQ-5D and MSQOL). When discounted at 6%, IFNβ-1b was shown to reduce relapse by 1.52 per patient (over 5 years) giving a cost-effectiveness ratio of £28,700 (US$44,428) per relapse avoided.

Kendrick et al's 2000 study [28] examined the CE of long term IFNβ-1a to estimating the rate of disability progression in the RRMS patients receiving either IFNβ-1a or standard care (ie, without DMDs). Results of the model showed high disease progression within the placebo arm compared to patients receiving IFNβ-1a. The authors conclude that treatment of RRMS with IFNβ-1a could provide "substantial" cost savings to society, increasing with treatment duration.

The current analysis supplements the pivotal clinical trials with data from patients initially enrolled in the pivotal trials and followed over time. While both approaches have limitations (pivotal trials in MS are based on a 2-year snapshot of a chronic, lifelong condition, and the follow up studies are nonrandomized), they represent alternative methods for modeling MS outcomes.

First and foremost among the limitations of this study is its reliance on clinical trial data. While clinical trial data are considered the preferred source for the basis of parameter inputs used in cost-effectiveness analyses, the MS clinical trials have been criticized for a number of methodological issues. Second, our economic analyses did not include the impact of adverse events (e.g., cost and disutility) except to the extent that these might be captured indirectly in the proportion of patients.

While the results of this analysis provide decision makers with health economic information supporting the use of the immunomodulatory therapies, MS is a heterogeneous disease and physicians must select the most appropriate treatment based on the disease characteristics of individual patients.

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