Cost-utility analysis of interferon beta-1a (Avonex and Cinnovex) for relapsing remitting multiple sclerosis

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ABSTRACT

Background: Cinnovex is a biosimilar form of intramuscular (IM) interferon beta-1a (IFNβ-1a) manufactured in Iran for management of multiple sclerosis (MS). The present study aimed to determine the cost-utility of Cinnovex versus Avonex for patients with relapsing-remitting MS (RRMS) from Iranian health ministry perspective.

Methods: A Markov model was developed to determine 10-year cost and quality-adjusted life-years (QALYs) of patients with transition through health states based on Kurtzke Expanded Disability Status Scale (EDSS). To estimate the cost of each method, we inquired the subsidies allocated to Avonex and Cinnovex by Iran's health ministry. Moreover, to estimate the quality of life (QOL) of patients in each group, a cross-sectional study was conducted among two groups of patients who had used Avonex and Cinnovex (n = 50 and n = 50, respectively), using the multiple sclerosis quality of life-54 (MSQOL-54) questionnaire. Finally, one-way sensitivity analysis (tornado diagram) was performed in order to examine the strength of the results.

Results: According to results, the estimated 10-year discounted cost per patient for Avonex and Cinnovex were 21346.5 international dollar ($Int) and 47436.6 $Int, respectively; while the estimated total discounted QALYs per person were 3.76 and 3.89, respectively. The incremental cost per QALY for Cinnovex compared with Avonex was 162718.55 $Int.

Conclusion: It is concluded that Cinnovex in patients with progressive relapsing MS is cost-effective associated with increased benefits compared with Avonex.

Keywords: Multiple sclerosis; Interferon beta-1a; Economic evaluation; Cost-utility analysis

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1. Introduction

Multiple Sclerosis (MS) is a chronic, inflammatory disease which degenerates the central nervous system, and is identified by destruction of myelin in the brain and spinal cord [1,2].

Globally, the median estimated prevalence of MS is 112.0 per 100000 people, and the median estimated incidence of MS is 5.2 per 100000 individuals [3]. Greatest prevalence observed in North America and Europe (140 and 108 per 100000, respectively) [4]. Iran is considered as a country with high MS prevalence (51.52 per 100000) in Middle East [5]. The study for prevalence estimation of MS in Iran in 2013 indicated a high prevalence rate in Isfahan (89 per 100000 population) and Tehran, situated at the central part of Iran (88 per 100000 people) [6]. The point prevalence of MS was 101.39 per 100000 population in 2014 [7].

In general, MS is classified into three categories of relapsing-remitting MS (RRMS), secondary progressive MS (SPMS), and progressive relapsing MS (PRMS) [1]. At the beginning of the disease, 80$-85% of the patients are diagnosed with RRMS [8,9]. Interferon beta (IFNβ) is widely used in this group of patients for immunomodulation [10]. In 1992, for the first time, some researchers showed that IFN could reduce the attacks and the number of plaques in magnetic resonance imaging (MRI). in the patients suffering from MS [11].

In general, IFNβs utilized for treatment of MS include intramuscular (IM) IFNβ-1a (Avonex), subcutaneous IM IFNβ-1a (Rebif), and subcutaneous IM IFNβ-1b (betaseron) [1].

Considering the large number of patients with this type of MS and high expenses of IFNβs due to the challenges regarding medicine import and foreign exchange, since a few years ago, various studies have been performed in Iran in order to achieve the technology of IFNβ production, leading to production of Cinnovex in 2005, which is a type of IFNβ-1a. This medicine is a biosimilar form of Avonex which is supplied from other countries in order to treat MS. Cinnovex was investigated in the laboratories of the Iranian Health Ministry as well as some reliable laboratories around the world, and after confirmation of its effectiveness, it was distributed in the Iranian market [12].

Nowadays, almost 40 percent of patients with MS receive

IM injection of Avonex or Cinnovex through 30 mcg vials once a week [13]. The subsidies of these two medicines are not equivalent in order to support national products, and this has led to an increase in the cost of Avonex. On the other hand, some patients have experienced complications after consumption of Cinnovex and need to use Avonex instead [13]. Thus, proper decision making has to be performed regarding the best treatment method for MS.

Economic evaluation, particularly cost-utility analysis, has become a constant instrument for policymaking in health finance. Therefore, we designed this study to determine the cost-utility of Cinnovex versus Avonex.

2. Methods

Model Description: A Markov model was developed to determine the cost-utility of Avonex compared to Cinnovex. The clinical course of RRMS was modeled in terms of Kurtzke Expanded Disability Status Scale (EDSS) [14]. Specifically, 7 EDSS health states were modeled (Figure 1):

1. EDSS 0.0-2.5: no or few limitations in mobility
2. EDSS 3.0-5.5: moderate limitations in mobility
3. EDSS 6.0-7.5: walking aid or wheelchair required
4. EDSS 8.0-9.5: restricted to bed
5. Death (natural causes or EDSS 10)
6. Relapse EDSS 0.0-2.5: relapse with a change in disability within EDSS 0.0-2.5
7. Relapse EDSS 3.0-5.5: relapse with a change in disability within EDSS 3.0-5.5

We assumed that transitions between health states occurred in 1-month cycles. The baseline time horizon of the model was assumed 10 years. Costs and outcomes were estimated from the Iran's health ministry perspective and were discounted at 5% per annum. Relapse and disease progression transition probabilities were derived from the published literature (Table 1), and due to the lack of long-term clinical trials investigating the effect of Cinnovex in Iran as well

as the similar effectiveness of the two medicines [12,15-17], these probabilities were used for Cinnovex as well.
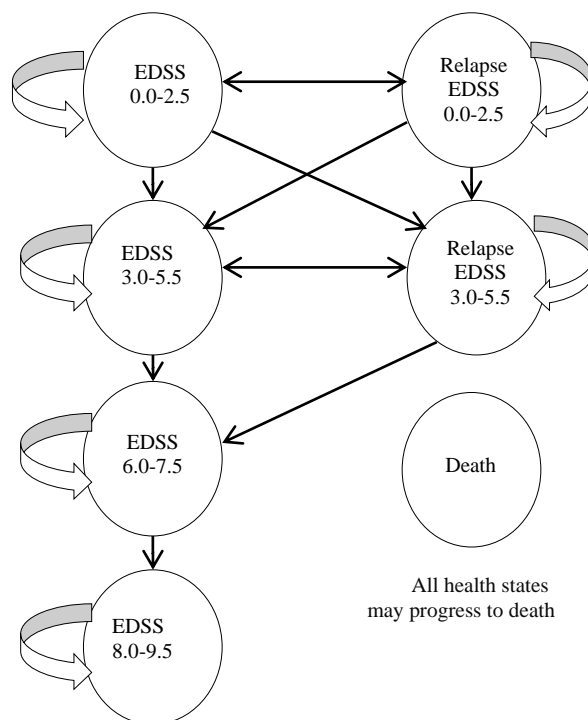

Figure 1. Structure of Markov model [1]
EDSS: Expanded Disability Status Scale

The model calculated the following outcomes: average number of years spent in EDSS 0.0-5.5; average number of years spent relapse-free; quality-adjusted life-years (QALYs); 10-year costs; and incremental cost-effectiveness ratios (ICERs) comparing Cinnovex with Avonex. Model parameters varied in sensitivity analyses.

Table 1. Base-case values for the model variables

Parameter description	Estimate for base-case model	Reference
Initial patient distribution among EDSS health states (%)		Bell et al. [1]
EDSS 0.0-2.5	26.4	
EDSS 3.0-5.5	58.7	
EDSS 6.0-7.5	13.8	
EDSS 8.0-9.5	1.1	
Monthly probability of disease progression (symptom management)		Bell et al. [1]
EDSS 0.0-2.5 to 3.0-5.5	0.004438	
EDSS 3.0-5.5 to 6.0-7.5	0.009189	
EDSS 6.0-7.5 to 8.0-9.5	0.003583	
EDSS 8.0-9.5 to 10 (death)	0.000952	
Monthly probability of relapse (symptom management)	0.075500	Bell et al. [1]
Treatment effects of SC GA and β-interferons, percent of reduction in:		Bell et al. [1]
Probability of disease progression	30	
Probability of relapse	27	
Monthly drug acquisition costs (subsidies) ($Int):		calculated
Avonex	164	
Cinnovex	364	
Utility values (mean + utility)		calculated
Avonex	(63.92 + 16.76)	
Cinnovex	(62.32 + 17.81)	

EDSS: Expanded Disability Status Scale; Sc: Subcutaneous, GA: Glatiramer acetate; $Int: International dollar

The underlying assumptions of Markov model were as follows:

1. All the patients with EDSS of 0-2.5 were put into the model.

2. In each month (length of each cycle), a patient can remain in the previous disability status or move to the next one.

3. It has been assumed in the model that the EDSS scores which are not related to relapses do not improve over time. Thus, such patients move to a more severe disease status. Moreover, each patient may experience disease relapse during the disease period. According to other studies, each relapse lasts for one month [11,18].

4. Transfers among various health states occur in one-month cycles [1,19].

5. Based on age-specific mortality rates, deaths resulting from natural factors may occur in any of the model cycles for any reason. However, MS-related deaths only take place after the patients passed all the health states based on EDSS, i.e. being transferred to the 10th EDSS [1,19].

Costs: In this study, the subsidies allocated to Cinnovex and Avonex was considered and inquired from the Iran's health ministry. To have an international perspective, the costs (subsidies) were converted from Iranian Rials (IRR) into international dollars ($Int), which is a method of measuring the relative purchasing power of the currencies of different countries over the same types of goods and services, by eliminating the differences in price levels between countries.

Utility: To determine the utility, multiple sclerosis quality of life-54 (MSQOL-54) questionnaire which is specified for patients with MS, was utilized [20]. This questionnaire, which was designed in the United States (U.S.) in 1995, focuses on the patient in order to investigate various dimensions of health status. The reliability and validity of the Persian version of the questionnaire was confirmed in a study by Ghaem et al. [21].

MSQOL-54 consists of 52 items in 12 scales, and 2 separate items. It has two main areas of Physical Health (PH) and Mental Health (MH). The core of this questionnaire includes 36 short-answer items for assessing the overall health status which facilitates the comparison with other patient populations as well as the total population. Besides, the questionnaire includes 18 items related to discomforts about health.

The mean weight of the scales of these two areas is calculated in order to compute the utility scores. The scores of each area range from 0 to 100 and higher scores represent higher health related quality of life (QOL).

Statistical Analysis: The mean estimates of the MSQOL-54 questionnaire responses were compared between two groups using sample t-test. The Markov model was built using TreeAge software. The Markov chain analysis was performed, using microsimulation trials with 1000 hypothetical patients.

Finally, we conducted a deterministic one-way sensitivity analysis to determine the strength of the results that are presented by a tornado diagram.

3. Findings

Base-case Analysis: The main characteristics of the subjects, recruited to estimate the utility, were as follows in the Avonex and Cinnovex groups, respectively:

Approximately 80-90% were women, the (mean ± SD) ages were (33.94 ± 9.75) and (34.72 ± 7.68), and all the patients were married.

The mean utility of patients who received Avonex and Cinnovex were (63.92 ± 16.76) and (62.32 ± 17.81), respectively; and the results of T-test revealed no significant difference between the two groups regarding their utility scores (P > 0.05).

The subsidies allocated to each vial of Avonex and Cinnovex were 41$Int and 91$Int, respectively. Since each patient uses one vial of the medicine every week, the cost of each one was calculated in 52 weeks in 1 year in order to compute the medication costs imposed on the Iran health ministry for 1-year consumption of each medicine by each patient. According to the results, the cost of 1 year consumption of Avonex (2134.65$Int) was lower than that of Cinnovex (4743.65$Int).

Table 1 shows the mean utility and annual costs per patient for each strategy.

Our base-case analysis showed that the estimated total 10-year costs of using Avonex and Cinnovex per patient were 21346.5$Int and 47436.6$Int, respectively; while the estimated total discounted QALYs per person were 3.76 and 3.89, respectively (Table 2). The mean years of life passed in EDSS of 0-5.5, and that passed without relapse were 7.40 and 7.38 for both drugs. The ICER results (162718.55$Int) showed that Cinnovex in patients with RRMS was associated with increased benefits compared to Avonex, albeit at higher costs.

Sensitivity Analysis: One-way sensitivity analysis results are shown in figure 2. The mean and utility of Avonex and Cinnovex were changed in a sequence to the upper and lower limits at 95% CI. Moreover, the discount rate of cost and effectiveness was changed from 0 to 6, and 20% change in the costs was tested, while the other variables were held constant.

Table 2. Results of base-case analysis

Outcome measure	Cinnovex	Avonex	Difference
QALYs			
Not discounted	4.620	4.470	0.150
Discounted	3.890	3.760	0.130
Mean years of life passed in EDSS of 0-5.5			
Not discounted	7.400	7.400	0.000
Discounted	6.690	6.690	0.000
Mean years of life passed without relapse			
Not discounted	7.380	7.380	0.000
Discounted	6.670	6.670	0.000
Discounted costs ($Int)	38460.749	17307.340	21153.409
Total	47436.600	21346.500	26090.100
ICER Cinnovex vs. Avonex (ΔCost/ΔQALY)		162718.550	

QUALYs: Quality-adjusted life-years; EDSS: Expanded Disability Status Scale; ICER: Incremental cost-effectiveness ratio
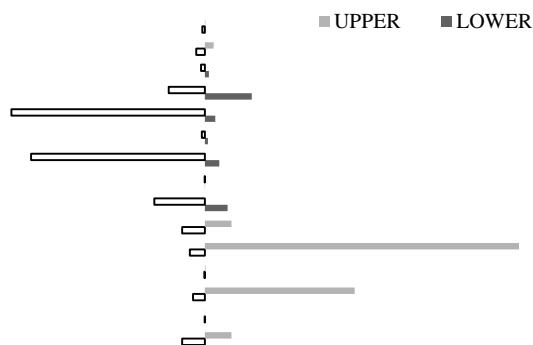
Figure 2. Results of one-way sensitivity analysis (tornado diagram)

The results showed that the ICER was relatively insensitive to changes in QOL variables in Cinnovex and Anovex at 6-7.5 and 3-5.5 scores. On the other hand, the changes in other variables had no significant effects on the final output probability in the two strategies.

4. Discussion

Various studies have been conducted to achieve the technology of IFNβ production in Iran since several years ago. Finally, Cinnovex which is a kind of IFNβ-1a was produced in Iran in 2005. After the production of Cinnovex, the subsidies allocated to Avonex were reduced in order to support the internal production, resulting in an increase in the price of Avonex. However, some patients experience complications after consumption of Cinnovex and need to continue their treatment with Avonex [13].

The findings of the present study, i.e. cost-utility analysis of Avonex and Cinnovex using Markov model for a 10-year time horizon, showed that from the Iran's health ministry point of view, the total costs of treatment with Avonex and Cinnovex were 21346.5$Int and 47436.6$Int, respectively.

The study by Jankovic et al. showed that a patient's consumption of Avonex for his/her life years in Balkan imposed 16.5 million Serbian dinars (171848$) on the society. In addition, Bell et al. estimated this cost as 82635$US in the U.S. Yet, this cost has been estimated 17307$US for 10 years in Iran. The difference between the results of these studies might be due to the difference in the selected viewpoints in the studies and the time horizon considered for the Markov model. Moreover, since Avonex is produced in the U.S. [1], it is quite natural that the cost of this medicine in this country is lower than other countries. Moreover, since the prices of medicine vary in different years, the difference of price in the years these studies were performed can be effective in the results obtained in these studies.

In general, in cost-utility analyses, improvement in the health status is assessed through QALY. In this study, the discounted QALYs related to the interventions by Avonex and Cinnovex were measured 3.76 and 3.89, respectively, using Markov model.

In the study by Jankovic et al., the QALYs of symptoms control, glatiramer acetate, IM IFNβ-1a (Avonex), subcutaneous IFNβ-1a (Rebif), and subcutaneous IM IFNβ-1b (betaseron) were respectively reported to be 9.3, 9.7, 9.7, 9.7, and 9.7 in a patient's mean years of life (40 years) [22].

In addition, Bell et al. reported QALYs of 9.03, 9.30, 9.30, and 9.30 for symptoms control, glatiramer acetate, IM IFNβ-1a, subcutaneous IM IFNβ-1a, and subcutaneous IM IFNβ-1b, respectively in a patient's mean years of life (40 years) [1].

The results of economic evaluation of comparison of Avonex and Cinnovex for 10 years showed that from health ministry point of view, Cinnovex had higher utility (0.13 QALY higher) and higher costs (26090.1$Int higher) per patient.with RRMS. Besides, the cost of each extra QALY using Cinnovex (ICER compared to Anovex) was equal to (162718.55$Int).

Jankovic et al. reported high cost of each extra QALY using the immunomodulation medication. In addition, ICER of using glatiramer acetate, IM IFNβ-1a, subcutaneous IM IFNβ-1a, and subcutaneous IM IFNβ-1b compared to symptoms control was respectively computed as 1240, 4520, 4527, and 4022 million Serbian dinars per QALY. Finally, symptoms control was determined as the most cost-effective intervention for treating MS [22].

Furthermore, the results of the study by Bell et al. showed that in comparison to symptoms control, using glatiramer acetate, IM IFNβ-1a, subcutaneous IM IFNβ-1a, and subcutaneous IM IFNβ-1b during 40 years (a patient's mean years of life) led to 0.222, 0.204, 0.198, and 0.203 extra QALYs as well as 57174, 68681, 82410, and 62923$US extra cost per patient, respectively. In addition, compared to symptoms control, ICER of consuming glatiramer acetate, IM IFNβ-1a, subcutaneous IM IFNβ-1a, and subcutaneous IM IFNβ-1b was respectively calculated as 257541, 336672, 416212, and 309966$ per QALY. Finally, glatiramer acetate was identified as the most cost-effective medicine in treatment of RRMS [1].

5. Conclusion

In conclusion, although the cost of Cinnovex for treatment of RRMS was quite higher than Avonex, little difference was found between the two medicines regarding their effectiveness. Thus, using Cinnovex imposes high costs on the ministry of health per QALY.

6. Conflict of Interests

Authors have no conflict of interests.

7. Acknowledgments

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