PND39

THE IMPACT OF ADHERENCE AND DEVELOPMENT OF NEUTRALIZING ANTIBODIES TO INTERFERONS β ON TREATMENT OF MULTIPLE SCLEROSIS IN THE CZECH REPUBLIC

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OBJECTIVE

Interferon beta can be effective first-line therapy for clinically isolated syndrome (CIS) and of the clinically definite multiple sclerosis (MS). Their effectiveness may be reduced by neutralizing antibodies (NAb) against interferon beta as well as by patient non-adherence, resulting in increased relapses.[1-6]

Particular types of interferon beta drugs differ in level of adherence to MS treatment and risk of NAb development. Intramuscular (IM) interferon beta-1a dosed once-weekly has been characterized as a regimen with by high adherence rates[7] and a low rate of NAb development[8].

The objective of this analysis was to compare clinical outcomes (reduction in the number of relapses) and costs associated with MS treatment with different interferon beta treatment options available in the Czech Republic over a five-year period from payer's perspective taking into consideration development of NAb and patient adherence.

Table 1. Input parameters of the model (1)

Intervention	Adherence	Risk of NAb	$RR_{ARR,intervention:ARR,placebo}$	Annual costs
IM interferon beta-1a	85.0%[7]	0.033[8]	0.678[9]	€ 9,088[16]
SC interferon beta-1a	73.0%[7]	0.278[8]	0.676[10]	€ 9,088[16]
SC interferon beta-1b	70.0%[7]	0.321[8]	0.696[11]	€ 9,088[16]
Glatiramer acetate	66.0%[7]	-	0.702[12]	€ 9,088[16]
Fingolimod	-	-	0.460[12]	€ 18,759[16]
Natalizumab	-	-	0.321[14]	€ 18,987[16]

(ARR - annual relapse rates, IM - intramuscular, NAb - neutralizing antibodies, RR - rate ratio, SC - subcutaneous)

Table 2. Input parameters of the model (2)

Parameter	Value
$ARR_{untreated\ patients}$	0.928[15]
$RR_{non\text{-}adherent\ patients}$	1.188[1]
Proportion patients switch to fingolimod after glatiramer acetate/ interferons β	16.6%[21]
Cost of relapse	€ 680[17]
Annual MS treatment costs w/o DMT	€ 1,950[19]
Cost on switch	€ 6[20]
Increase of MS costs due to non-adherence	28.6%[18]

(ARR - annual relapse rates, DMT - disease-modifying therapy, MS - multiple sclerosis, RR - rate ratio)

METHODS

A Markov cohort model was developed using MS Excel 2010 with one-year cycle length. The model simulates the treatment pathway of patients with MS (Figure 1), taking into account the risk of NAb development, levels of adherence to MS treatment and their impact on relapse rate (Figure 2).

In the Czech Republic, majority of patients start their MS treatments with one of the approved interferon beta drugs. NAb-positive patients are switched/escalated to a different disease modifying therapies (DMT) such as glatiramer acetate/fingolimod or natalizumab. Simultaneously, if patients experience two or more relapses during one year of treatment, they are escalated to fingolimod or natalizumab.

Adherence rates, incidence of NAb development, relapse rates and associated costs used in the model were sourced from the literature.

Relapses rates used in the model were based on pivotal phase III clinical trial data[9-14] and were affected by the absence/presence of NAb and levels of adherence.

The risk of non-adherence used in the model was derived from Devonshire et al.[7], which found that the level of adherence is linked to the frequency of administration. As a result, IM interferon beta-1a have the highest probability of treatment adherence among the first-line DMTs.[7] According to Steinberg et al.[1], patients who are non-adherent to treatment have an increased risk of relapse.

According to Hegen et al.[8], IM interferon beta-1a is also associated with a lower risk of NAb development than the other interferon beta. It was assumed/modelled that NAb could be detected/occurred during the second year of interferon beta treatment. Once NAb occur, there is a complete loss of modelled benefit (in terms of relapse rate) for a particular interferon beta. In such case relapse rate NAb is identical to untreated patients according to Tappenden et al.[15].

Annual drug acquisition costs were calculated in accordance with the Summary of Product Characteristics drug dosing scheme and with the drug's reimbursed price[16]. The cost of relapses in the Czech Republic was sourced from Vocelka et al.[17]. MS treatment costs, which are increased due to non-adherence according to Tan et al.[18], were sourced from the COMS study (i.e. Czech MS costs based on disease severity according to Expanded Disability Status Scale)[19]. Moreover, drug switches were associated with the use of additional resources; costs linked to switches were derived from the current pricing list[20].

Table 1 and Table 2 show details of all model inputs.

Costs and outcomes discounting was not performed for a short time period and the nature of the model that was designed to be used more as a calculator tool.

One-way sensitivity analysis and scenario analysis were performed; inputs into the sensitivity analysis (SA) are presented in Table 3.

Figure 1. Treatment scheme

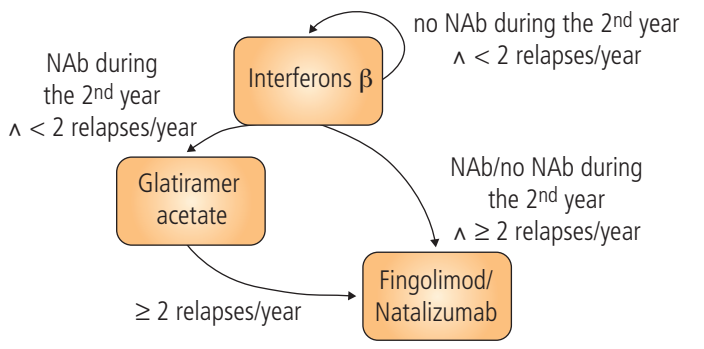
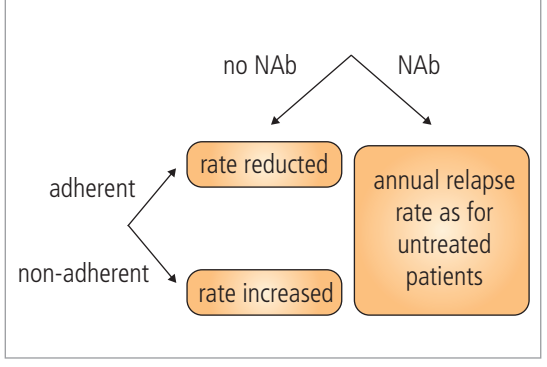


Figure 2. Determinants of annual relapse rate



RESULTS

The main results of the analysis are presented in Table 4.

A cohort of one hundred patients, who initiated treatment with IM interferon beta-1a once-weekly, experienced 287 relapses over 5 years. Those who started treatment with subcutaneous (SC) interferon beta-1a and interferon beta-1b experienced 15 and 19 relapses more than those treated with IM IFN beta-1a.

In the cohort of one hundred patients, the total cost of treatment with IM interferon beta-1a was 6.4 million €. This cost was by €139,000-€200,000 less than treatment with SC interferon beta-1a and interferon beta-1b due to lower acquisition cost of drugs after switch, lower number of switches and relapses and higher adherence which not associated with generation of additional MS costs.

The incremental cost-effectiveness ratio was -€9,600/relapse avoided and -€10,400/relapse avoided, respectively.

The results of the SA are presented in Figure 3 and Figure 4, where it is apparent that the relapse rate and the adherence parameter are the most sensitive inputs into the model with the largest effect on base-case results of the analysis. In spite of this, the tornado diagrams show that IM interferon beta-1a is the dominant (i.e. more efficacious and costs less) intervention in all modelled scenarios.

Table 3. Inputs parameters of sensitivity analysis

Parameters of OWSA	Scenario/Range of value	
Adherence, scenario[22,23]		
IM interferon beta-1a	62.3%[22]	79.0%[23]
SC interferon beta-1a	58.5%[22]	68.0%[23]
SC interferon beta-1b	52.2%[22]	49.0%[23]
glatiramer acetate	55.4%[22]	49.0%[23]
Risk of NAb, scenario[24,25]		
IM interferon beta-1a	0.022[24]	0.000[25]
SC interferon beta-1a	0.096[24]	0.320[25]
SC interferon beta-1b	0.094[24]	0.530[25]
RR, scenario[26]		
$ARR_{IM\ interferon\ beta\text{-}1a}$:$ARR_{placebo}$	-	0.696[26]
$ARR_{SC\ interferon\ beta\text{-}1a}$:$ARR_{placebo}$	-	0.696[26]
$ARR_{SC\ interferon\ beta\text{-}1b}$:$ARR_{placebo}$	-	0.696[26]
$ARR_{glatiramer\ acetate}$:$ARR_{placebo}$	-	0.665[26]
$ARR_{fingolimod}$:$ARR_{placebo}$	-	0.444[26]
$ARR_{natalizumab}$:$ARR_{placebo}$	-	0.343[26]
$ARR_{untreated\ patients}$, range ± 20%	0.312	1.545
$RR_{non\text{-}adherent\ patients}$, range ± 20%	1.000	1.426
Proportion patients switch to fingolimod after glatiramer acetate/interferons β, scenario	8.3%	24.9%
Cost of relapse, range ± 20%	€ 544	€ 816
Annual MS treatment costs w/o DMT, range ± 20%	€ 1,560	€ 2,340
Cost on switch, range ± 20%	€ 5	€ 7
Increase of MS costs due to non-adherence, scenario	14.3%	42.9%

(ARR - annual relapse rates, DMT - disease-modifying therapy, IM - intramuscular, MS - multiple sclerosis, NAb - neutralizing antibodies, OWSA - one-way sensitivity analyses, RR - rate ratio, SC - subcutaneous)

Table 4. Results of the deterministic analysis (undiscounted)

CEA, group of 100 patients	IM interferon beta-1a	SC interferon beta-1a	SC interferon beta-1b	IM INF β-1a - SC INF β-1a	IM INF β-1a - SC INF β-1b
Costs, total	€ 6,441,940	€ 6,581,329	€ 6,642,130	€ -139,389	€ -200,190
Costs of drug	€ 5,742,854	€ 5,859,618	€ 5,915,167	€ -116,764	€ -172,313
Costs of drug, intervention/comparator	€ 3,344,703	€ 2,656,185	€ 2,532,360	€ 688,519	€ 812,343
Costs of drug, glatiramer acetate after switch	€ 94,518	€ 675,520	€ 748,184	€ -581,002	€ -653,665
Costs of drug, fingolimod/natalizumab after switch	€ 2,303,632	€ 2,527,913	€ 2,634,623	€ -224,281	€ -330,991
Costs of switch	€ 322	€ 352	€ 361	€ -30	€ -39
Costs of relapses	€ 194,950	€ 204,876	€ 208,056	€ -9,926	€ -13,105
Other MS treatment costs	€ 503,813	€ 516,484	€ 518,546	€ -12,670	€ -14,733
Number of relapses	286.671	301.266	305.942	-14.595	-19.271
ICER	-	-	-	dominant* (€ -9,550/relapse avoided)	dominant* (€ -10,388/relapse avoided)

(CEA - cost-effectiveness analysis, ICER - incremental cost-effectiveness ratio, IM - intramuscular, MS - multiple sclerosis, SC - subcutaneous)
* dominant = more efficacious and costs less

CONCLUSIONS

Intramuscular interferon beta-1a represents the dominant intervention in the Czech Republic for first-line MS treatment in terms of our health economic evaluation. IM interferon beta-1a appears to be a cost-saving intervention from the payer's perspective (perspective of health insurance funds) and, simultaneously, a more efficacious intervention in terms of relapses number reduction due to higher patient adherence and lower incidence of Nab development when compared to the other interferon beta drugs available in the Czech Republic.

The SA showed that results are the most sensitive to relapse rate and the adherence parameter.

The limitation of this analysis may be that no quality life measurement was included. However, we assume that the results would be even more in favor of IM interferon beta-1a if utility (quality of life data) were included. Another possible limitation of this study is the omission of disability progression data in our model. Assumptions about the time period of NAb development and their persistence represent another limitation. If NAb are develop earlier, patients may experience more relapses and differences in clinical outcomes between analyzed DMTs will be even more pronounced. Finally where the development of NAb does not completely prevent the activity of interferon beta (i.e. relapse rate reduction) or if the presence of NAb was transitory, a lower difference in efficacy and lower saving for IM interferon beta-1a would be observed.

Figure 3. Result of Sensitivity Analysis (for group of 100 patients), IM INF β-1a vs. SC INF β-1a

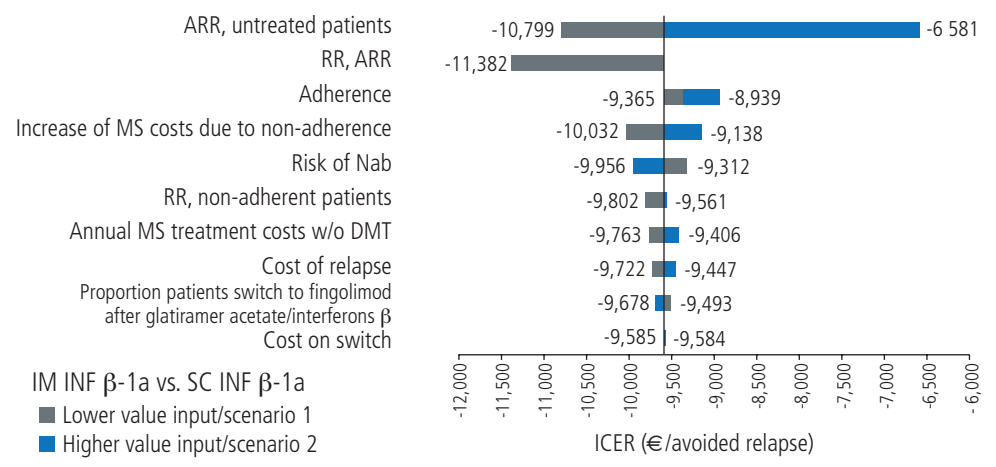
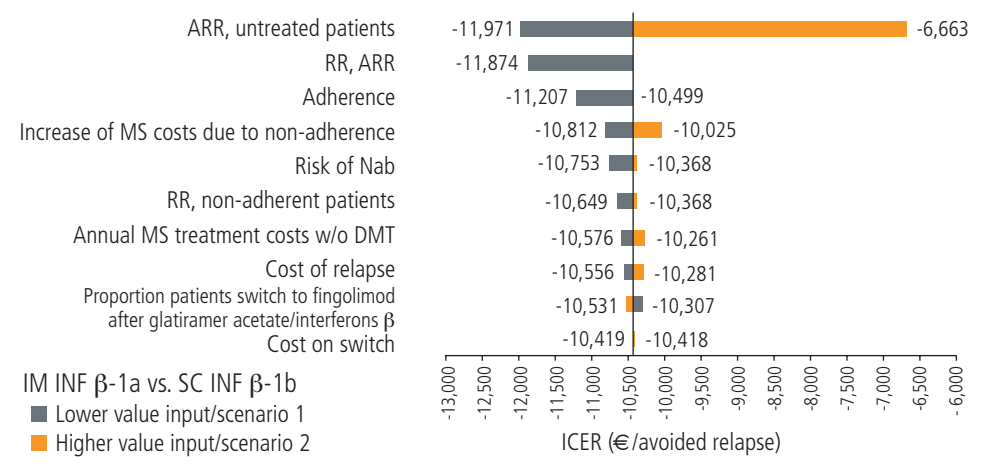


Figure 4. Result of Sensitivity Analysis (for group of 100 patients), IM INF β-1a vs. SC INF β-1a



(ARR - annual relapse rates, DMT - disease-modifying therapy, ICER - incremental cost-effectiveness ratio, IM - intramuscular, INF - interferon, MS - multiple sclerosis, NAb - neutralizing antibodies, RR - rate ratio, SC - subcutaneous)

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