Assessing the Cost-Effectiveness of Immunomodulatory Therapies for Relapsing-Remitting Multiple Sclerosis Based on Long-Term Data

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BACKGROUND

- Multiple sclerosis (MS) is a chronic, neurodegenerative inflammatory disease of the central nervous system that has been diagnosed in approximately 400,000 people in the US.
- In approximately 70% of patients, the onset of MS occurs during early adulthood, making MS one of the most common causes of neurological disability among young and middle-aged adults.
- Three main types of MS are generally recognized:
  - Relapsing-remitting MS (RRMS) (most prevalent)
  - Secondary progressive MS (SPMS)
  - Primary progressive/relapsing MS (PPMS or PRMS)

MS TREATMENT OPTIONS

- Prior to the introduction of the immunomodulatory therapies for MS, treatment options consisted of symptom management (SM), such as physical therapy and drug therapy to manage symptoms.
- SM has been supplemented by two new classes of immunomodulatory therapies approved for first-line treatment of RRMS:
  - Subcutaneous glatiramer acetate (SCGA)
  - The ß-interferons:
    - Intramuscular interferon beta-1a (IM-IFNß-1a)
    - Subcutaneous interferon beta-1a (SC-IFNß-1a)
    - Subcutaneous interferon beta-1b (SC-IFNß-1b)

ECONOMIC MODELS IN MS

- A number of economic models in MS have been published, resulting in scenarios ranging from cost-saving to incremental cost-effectiveness ratios (ICERs) exceeding $2 million per quality-adjusted life year (QALY).
- Differences among the models with respect to modeling approaches, perspectives, and assumptions make comparison of results across the multiple models difficult.
- Previously published models have utilized only short-term clinical trial data (e.g., 1-2 years) and have not included longer-term data from follow-up studies of patients initially enrolled in clinical trials. In addition, these models have not fully assessed the impact of neutralizing antibodies (NAbs).
- Given the chronic nature of MS, the use of long-term follow-up data in an economic model presents an excellent opportunity to assess the clinical and economic benefits of the various immunomodulatory therapies approved for the treatment of RRMS.

OBJECTIVES

- To assess the cost-effectiveness of five MS treatment strategies (SM alone and SM in combination with one of the following: SCGA, IM-IFNß-1a, SC-IFNß-1a, and SC-IFNß-1b) used to manage a hypothetical cohort of patients diagnosed with RRMS in the US using long-term follow-up data from clinical trials.

METHODS

- Literature-based Markov model, where the clinical course of RRMS was modeled in terms of Kurtzke expanded disability status scale (EDSS)-based health states (Figure 1).
- Lifetime time horizon with 1-month transitions between health states.
- Per product labeling, only RRMS patients (i.e., EDSS<6.0) were eligible for immunomodulatory therapy.
- Relapse and disease progression probabilities for SMA were obtained from published natural history studies as reported in a previous model (Table 1).[1]
- To account for the inherent differences between the immunomodulatory therapy clinical trials, a percent reduction for relapse (73%) and disease progression (70%) in the first 2 years of therapy was assumed to be similar for all therapies.[2]
- In subsequent years of the model, relapse and disease progression rates were abstracted from the pivotal, randomized clinical trials and continuous, prospective extensions of the pivotal trials[3-10] and mapped and fitted to prediction curves over time to estimate long-term treatment effects (Figures 2-4).
- Rates of discontinuation were obtained from clinical trials and long-term follow-up studies, and a relative 3% annual discontinuation rate was assumed if data were not available.
- To account for the effect of NAbs, the probabilities of relapse for patients taking ß-interferon were subsequently adjusted to reflect a weighted average of NAb-positive and NAb-negative patients (incidence of NAbs: IM-IFNß-1a = 2.2%; SC-IFNß-1a = 17.4%; SC-IFNß-1b = 36.4%).[11]
- Patient mortality occurred at either the age-specific, all-cause mortality rates or after patients progressed through all EDSS health states (e.g., EDSS 10 = death).
- Costs and utilities were obtained from the published literature (Table 1). Costs (reported in 2005US$) and outcomes were discounted at 3% per annum.
- Sensitivity analyses were conducted to test the robustness of the model.

Figure 1. Schematic Representation of the Markov Model

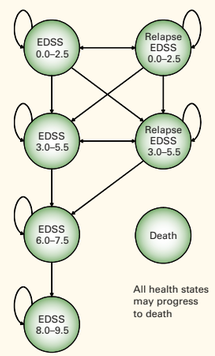

Figure 2. Prediction Curve of the Long-Term Probability of Relapse While on Immunomodulatory Therapy

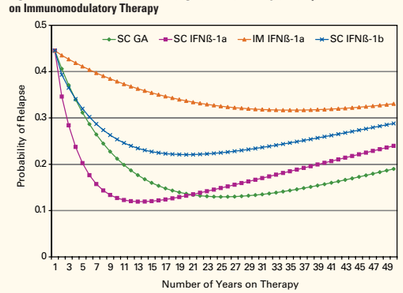

Figure 3. Prediction Curve of the Long-Term Probability of Disease Progression (EDSS 0.0–2.5 to EDSS 3.0–5.5) While on Immunomodulatory Therapy

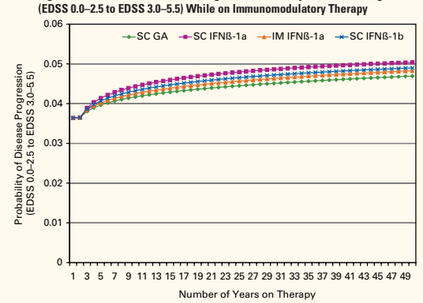

Figure 4. Prediction Curve of the Long-Term Probability of Disease Progression (EDSS 3.0–5.5 to EDSS 6.0–7.5) While on Immunomodulatory Therapy

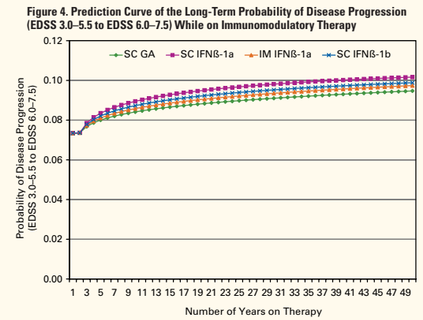

Table 1. Summary of Parameters and Values Used in Base Case Model

Parameter Description	EDSS 0.0–2.5	EDSS 3.0–5.5	Relapse EDSS 0.0–2.5	Relapse EDSS 3.0–5.5	EDSS 6.0–7.5	EDSS 8.0–9.5
Initial patient distribution[12]	26.4%	58.7%	0.0%	0.0%	13.8%	1.1%
Monthly probability of disease progression for SMA (to next EDSS health state)	0.0044	0.0092	0.0044	0.0092	0.0036	0.0010
Monthly probability of relapse for SMA	0.0755	0.0755	0.0000	0.0000	0.0000	0.0000
Health state-specific MS-related monthly costs[12]	$433.26	$838.83	$427.98	$1,094.80	$1,990.02	$3,499.59
Utility weights[1,13]	0.824	0.679	0.730	0.585	0.533	0.491
Monthly drug acquisition costs (WAC)[14]	SCGA = $1,258.20 IM IFNß-1a = $1,275.00 SC IFNß-1a = $1,469.64 SC IFNß-1b = $1,264.85			Immunomodulatory therapy not administered		

EDSS = expanded disability status scale; GA = glatiramer acetate; IFNß-1a = interferon beta 1a; IFNß-1b = interferon beta 1b; IM = intramuscular; MS = multiple sclerosis; SC = subcutaneous; SMA = symptomatic management alone; WAC = wholesale acquisition cost.

Table 2. Summary of Model Results

Model Result	SMA	SCGA	IM-IFNß-1a	SC-IFNß-1a	SC-IFNß-1b
Total cost	$295,586	$352,760	$377,996	$364,267	$358,509
QALYs	9.08145	9.30265	9.27940	9.28466	9.28397
Average number of years spent in EDSS < 6.0	12.28411	14.92281	14.29373	14.71157	14.54264
Cost per QALY	-	$258,465	$416,301	$337,968	$310,691
Cost per additional year spent in EDSS < 6.0	-	$21,668	$41,008	$28,293	$27,860

EDSS = expanded disability status scale; GA = glatiramer acetate; IFNß-1a = interferon beta 1a; IFNß-1b = interferon beta 1b; IM = intramuscular; QALY = quality-adjusted life-year; SC = subcutaneous; SMA = symptomatic management alone.

RESULTS

- Base case model results indicated that the immunomodulatory therapies were both more effective and more costly than SM alone in treating RRMS (Table 2).
- The incremental cost per QALY (immunomodulatory therapy vs. SM alone) was $258,465, $416,301, $337,968, and $310,691 for SCGA, IM-IFNß-1a, SC-IFNß-1a, and SC-IFNß-1b, respectively.
- Sensitivity analyses showed that results were sensitive to changes in utilities, disease progression rates, time horizon, and immunomodulatory therapy cost.

CONCLUSIONS

- The present analysis is the first economic model in MS to (1) incorporate long-term data on treatment effects, (2) include the effect of NAbs, and (3) account for the inherent differences in clinical trial design.
- The immunomodulatory therapies were more effective and more costly than SM alone in treating RRMS and SCGA was the most cost-effective of the immunomodulatory therapies (vs. SM alone).
- While the results of this analysis and other economic evaluations in MS have resulted in ICERs well above the commonly referenced and arbitrary benchmark of $50,000 per QALY, the cost-effectiveness literature reveals that not all economic evaluations are bounded by this threshold and that numerous interventions with ICERs above this threshold are deemed valuable by patients, healthcare decision-makers, and society.

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