Review of the pharmacoeconomics of early treatment of multiple sclerosis using interferon beta

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Abstract: Multiple sclerosis (MS) is a common neurological disease with increasing incidence and prevalence. Onset of disease is most frequently in young adulthood when productivity is usually highest; it is of chronic nature and, in the majority of patients, it will result in accumulation of disability. Due to loss of productivity in patients and caregivers as well as high expenses for medical treatment, MS is considered a disease with high economic burden for patients and society. Several drugs have been approved for treatment of MS. While treatment ameliorates the course of the disease, it is very costly; therefore, pharmacoeconomics, evaluating costs and effects of disease-modifying treatment in MS, has become an important issue. Here, we review the economic impact and treatment strategies of MS and discuss recent studies on pharmacoeconomics of early treatment with interferon beta.

Keywords: MS, pharmacoeconomics, disease-modifying therapy, interferon beta, CIS

Introduction

Multiple sclerosis (MS) is considered a chronic inflammatory disease of the central nervous system of autoimmune origin. Onset of disease is most frequently in young adulthood, between 20 to 40 years of age.1 Although many aspects of MS pathogenesis have been elucidated, the exact causal mechanisms are still not fully understood. An interplay between environmental factors in genetically susceptible individuals is assumed.2 This concept is supported by a wealth of research findings.3–5 Unambiguously, once the disease has developed, it continues lifelong, and there is still no cure. The course of the disease can be relapsing–remitting, which means that episodes with exacerbation of neurological symptoms alternate with periods of remission.6 Over time, these relapses often do not fully resolve, leading to a stepwise accumulation of disability. Moreover, after 10–15 years, one-half of patients with initial relapsing–remitting disease course will develop a secondary progressive disease7 that is characterized by a progressive increase of disability, independent of relapses and predominantly caused by deterioration of walking ability. Only about 10%–15% of patients exhibit a primary progressive disease course, which is defined by at least one year disease progression from onset on.8 A clinically isolated syndrome (CIS) is diagnosed in patients with a first clinical event suggestive of MS and evidence of disease dissemination in space, but not yet evidence of dissemination in time, thus chronicity of disease.

One of the hallmarks of MS is a high variability of the natural disease course. While some patients, apart from relapses, never experience any handicap, the majority of patients will ultimately develop disability to a variable degree and after a variable time...
interval after onset of disease. As first shown by Confavreux et al and based on a concept of a two-stage disease with focal inflammation in the early stage and diffuse inflammation and neurodegeneration in a second-disease stage, Leray et al recently confirmed highly interesting data on time to disability accumulation in MS, while duration of the first stage from onset of disease until reaching a milestone of Kurtzke Disability Status Scale (DSS) 3 (corresponding to moderate disability) ranged from less than 3 years to more than 15 years, duration of Phase II (Kurtzke DSS 3 to DSS 6, the latter is defined by requiring unilateral assistance to walk 100 meters) remained nearly identical in all patients with 6–9 years, irrespective of the duration of Phase I. This observation suggests that, once a clinical threshold of irreversible disability is reached, further progression of disability becomes inevitable. Support of this hypothesis can be derived from two typical findings of the chronic progressive phase of MS. Even in the absence of new or contrast-enhancing magnetic resonance imaging (MRI) lesions, disability usually increases in the chronic progressive phase of the disease, and once the chronic progressive phase is reached, efficacy of disease-modifying therapies often declines.

Although relapse rate and progression of the Expanded Disability Status Score (EDSS) are widespread parameters of disease activity, many patients with MS do not only suffer from physical disability; they also suffer from neurocognitive decline, fatigue, or depression. Hence, the diagnosis of MS is a life-changing event with a significant impact on family, society, and the social welfare system. Fortunately, during the last decades, several disease-modifying therapies (DMT) have been licensed that ameliorate the course of the disease. The aim of these DMT is to reduce inflammation, disease activity as measured by MRI, and relapse rate. Thereby, a delay of transition into the secondary progressive phase and prevention of permanent disability ought to be achieved. Due to the chronic nature of MS, DMTs are usually applied continuously over many years, or even decades. To keep in mind, DMTs are applied in a preventive manner, since neuronal damage cannot be reversed.

Epidemiology and economic impact of MS

MS is the most frequent nontraumatic cause for disability among young adults in North America and Europe. Worldwide, about 2.5 million people are affected by MS; although traditionally, the incidence is supposed to vary by geographical latitude. The highest prevalence with more than 30 MS patients per 100,000 inhabitants can be found in northern Europe and North America. A medium prevalence of 5–30 per 100,000 is observed in southern Europe and the southern United States; whereas, a low prevalence of fewer than 5 per 100,000 has been reported for Asia and South America. Population genetics, the geographically determined physical environment, and socioeconomic structures have been proposed as possible reasons for continental differences in MS prevalence. In the United States alone, about 400,000 individuals suffer from MS; each week, more than 200 persons are newly diagnosed with the disease. According to estimates for 2010, MS has been diagnosed in 540,000 subjects of the European population. However, recent epidemiological studies found an increasing incidence and prevalence of MS, especially in women. This seems to be the case also in areas of the world that were formerly classified as low-prevalence regions. For example, MS prevalence was recently reported as 31–55 per 100,000 inhabitants in the Arabian Gulf Region and 0.83–21.5 per 100,000 individuals in Latin America and the Caribbean. Factors contributing to an increasing incidence of MS have not been fully elucidated. Earlier MS diagnosis, due to revised diagnostic criteria; better ascertainment of diagnosis; less sunlight exposure; higher standards in hygiene; and cigarette smoking, have all been proposed as likely candidates.

The economic impact of MS can be divided into direct costs and indirect costs. Direct costs account for health care costs, such as pharmaceuticals, inpatient care costs, outpatient care costs, additional treatments like physiotherapy, and medical aids. In contrast, indirect costs are caused by productivity loss of patients and caregivers. This might be due to sick leave, reduced daily working time, unemployment, or premature retirement. In Europe, mean annual cost per person with MS is estimated to be around €27,000, ranging from €7,227 in Bulgaria to €44,565 in Luxembourg. On average, about two-thirds of the totals are caused by direct costs, while approximately one-third are derived from indirect costs. In 1998, all-over costs of MS in the United States were US$6.8–$11.9 billion annually, which averages about US$34,000 per patient, per year. In a survey among patients receiving DMT in the United States in 2004, total average costs per patient and year were estimated as high as US$47,000. Of these, 63% accounted for direct costs, including 34% of total costs (US$16,000) for DMT. Of note, patients having suffered a relapse were found to have higher costs than patients without relapse. Furthermore, several studies have shown that total costs rise with increasing disability. In line with this result, a secondary and primary progressive disease course was found to be more costly than a relapsing–remitting one,
due to a rise of indirect costs. Besides degree of physical disability, age, depression, and fatigue have been identified as independent factors of an increase of costs. Quality of life remarkably and constantly declines with advancing stages of disability, and the occurrence of relapses negatively affects quality of life measures.

**Efficacy of early initiation of DMT in MS using interferon beta**

It was in 1993 that interferon beta-1b was introduced as the first DMT of MS. Still, it represents a very common first-line treatment that is widely used. Interferon beta is approved for the treatment of CIS, relapsing–remitting MS, and secondary progressive MS with superimposed relapses.

There are three different recombinant interferon beta preparations on the market. Interferon beta-1b (Betaferon®, Bayer HealthCare Pharmaceuticals, Berlin, Germany; Betaseron®, Bayer HealthCare Pharmaceuticals, Berlin, Germany; Extavia®, Novartis, Basel, Switzerland) is recombinantly expressed in Escherichia coli and is subcutaneously injected every other day. Interferon beta-1a is recombinantly expressed in Chinese hamster ovary cells and is identical to the human interferon beta. There are two preparations of interferon beta-1a. Rebif® (Merck Serono, Geneva, Switzerland) is subcutaneously administered three times a week. Avonex® (Biogen Idec, Cambridge, MA, USA) is applied once weekly as an intramuscular injection. Placebo-controlled trials have demonstrated a significant reduction of disease activity for all three interferon beta preparations.

The pivotal trial on efficacy of interferon beta-1b in MS, which led to the initial approval of the drug for treatment of MS, demonstrated an annual relapse rate of 1.27 for placebo and 0.84 for 250 µg interferon beta-1b. Similar results were observed for interferon beta-1a. In the Prevention of Relapses and Disability by Interferon beta-1a Subcutaneously in Multiple Sclerosis (PRISMS) trial on subcutaneous interferon beta-1a, the annual relapse rate was 1.28 for placebo, 0.91 for 22 µg, and 0.87 for 44 µg. Intramuscular interferon beta-1a reduced the annual relapse rate to 0.61, compared with 0.90 in the placebo group. These findings are supported by significant reduction of MRI disease activity in all three trials, while only in the latter two trials, a beneficial effect on disability progression was recorded during this 2-year study period.

While these therapies have been introduced, a better understanding of MS pathophysiology – especially the knowledge of unrecoverable axonal loss already in early stages of the disease – has prompted a fundamental shift in the MS treatment approach and provided the rational for early MS treatment. Based on this consideration, DMTs are initiated early in the course of the disease and before irreversible neuronal damage and disability have occurred. Following the concept of early MS treatment, interferon beta treatment has been investigated in patients with CIS and has shown a beneficial effect in terms of conversion to definite MS, EDSS progression, and MRI disease activity.

In the Betaferon®/Betaseron® in Newly Emerging Multiple Sclerosis for Initial Treatment (BENEFIT) trial, patients with CIS were randomized to receive interferon beta-1b or placebo for 2 years, or until clinically definite multiple sclerosis (CDMS) was diagnosed, according to the Poser et al criteria. Within the 2-year study period, 45% of patients in the placebo group versus 28% of the interferon beta group progressed to CDMS, according to the McDonald criteria of 2001. Both results reached statistically significant difference. Results of these clinical primary endpoints were supported by the MRI data. These data revealed a significant lower number of newly active lesions, cumulative number of new T2-weighted MRI lesions and gadolinium-enhancing lesions, as well as cumulative volume of gadolinium-enhancing lesions in the interferon beta-treated patients group. Of note, there was no change of health-related quality of life observed during the 2 years. No difference of health-related quality of life was found between groups. After having finished the placebo-controlled core study, patients were offered to enroll in an open-label interferon beta-1b 250 µg follow-up trial to investigate effects of early treatment in CIS, versus delayed treatment after diagnosis of CDMS or after 2 years on study. Three years after initial randomization, 37% of the early treatment group versus 51% of the delayed-treatment group have developed CDMS (risk reduction of 41%); 16% of the early treatment group versus 24% of the delayed-treatment group experienced confirmed EDSS progression (risk reduction 40%). A subgroup analysis revealed lower treatment effects in patients with less clinical or MRI activity at the time of the first event; patients with initial multifocal presentation and high lesion load would benefit more from early treatment. In the 5-year active treatment extension follow-up study, risk reduction of CDMS remained 37% in the early treatment group; whereas, no statistically significant difference in confirmed disability progression was observed any more between early and delayed interferon beta treatment. In both treatment groups, median EDSS remained 1.5 during the 5-year study period. Finally, in the BENEFIT...
extension trial, a long-term international observational study of patients having completed the initial placebo-controlled core study, data on follow-up for more than 8 years are available. At the discretion of the physician and according to local standards, patients were treated with any of the disease-modifying drugs or received no treatment. During the study periods, 5.1% of patients received no treatment; 77.6% received no other drug than interferon beta-1b; 6%, interferon beta-1a; 5.8%, glatiramer acetate; and 6.6% of patients received any escalation therapy. In the overall study population, disability – as quantified by the EDSS – changed only slightly over 8 years, with the median EDSS remaining 1.5 at year 8. However, 55.5% of patients, who had received early interferon beta treatment in the core study, developed clinically definite MS, while clinically definite MS was diagnosed in 65.8% of patients with delayed interferon beta treatment. Moreover, a difference of the overall annualized relapse rate was still observed over the 8-year period – 0.20 early treatment versus 0.26 delayed treatment. Placebo-controlled clinical trials on interferon beta-1a in CIS have yielded very similar results, suggesting a class effect of interferon beta treatment in early MS and CIS.

By numerous investigational trials and the clinical experience in interferon beta for two decades, safety and tolerability profile of this drug is well-known and has proven favorable, also, in long-term application. Side effects mainly include injection site reactions, flu-like symptoms, leukopenia, and liver-enzyme elevation. Moreover, up to 40% of patients develop antibodies against interferon beta, which antagonize bioactivity in a significant proportion of patients. If neutralizing antibodies against interferon beta persistently occur, therapeutic efficacy of the drug is reduced or abolished.

Besides interferon beta glatiramer acetate ([GA], Copaxone®, Teva, Petah Tikva, Israel) represents a common first-line therapy with daily subcutaneous injections, which is approved for treatment of patients with relapsing–remitting MS, as well as for patients with CIS and typical MRI features of MS. The PreCISe (early glatiramer acetate treatment in delaying conversion to clinically definite multiple sclerosis in subjects Presenting with a Clinically Isolated Syndrome) study demonstrated that GA reduced the risk of developing clinically definite multiple sclerosis by 45%, compared with placebo during a 3-year study period.

Interferon beta and GA are the only agents that are licensed for treatment of CIS. However, for the sake of completeness, it needs to be mentioned that there are several other therapeutics licensed for baseline and escalation therapy in definite MS, and more agents are likely to enter the market. Approval of all these agents is usually based on efficacy and safety data of a 2-year clinical trial. In MS Phase II and Phase III interventional clinical trials, a duration of about 6 months to a few years has become common, since demonstration of efficacy usually needs several months of treatment. On the other hand, duration of clinical trials longer than 2 years will make a well-controlled trial less feasible to accomplish and might hold back an effective treatment from MS patient care. Given an increasing number of available DMT in MS, trials investigating the long-term efficacy are needed.

Methodological aspects of pharmacoeconomic analyses

Pharmacoeconomic analyses evaluate costs and consequences of pharmacological health interventions. A wide range of methodological approaches are used in this field. This is to briefly summarize the terms and types of pharmacoeconomic evaluations used in the studies reviewed here (adapted from Clifford Goodman unless cited otherwise). Cost-effectiveness analyses (CEA) measure costs in monetary units and consequences in natural units, such as life-years gained, or relapses avoided. In cost-utility analyses (CUA), a variant of CEA, consequences are measured in terms of preference-based measures of health, most commonly based on quality-adjusted life-years (QALY). A QALY is a unit that adjusts gained or lost life-years subsequent to an intervention by the quality of life during those years. Gained or lost life-years are multiplied by a weighting factor (utilities) ranging from 0.00 (representing death) to 1.00 (representing a perfect health state). CEA and CUA always involve comparison of alternative interventions, expressed as incremental cost-effectiveness ratio (ICER) and incremental cost-utility ratio (ICUR), respectively. Therefore, incremental costs are divided by the change of effectiveness or utility (eg, QALY’s gained). Depending on the perspective of pharmacoeconomic evaluations (eg, society overall, third-party payers, patients), different types of costs are of interest. Costs need to be corrected for effects of inflation; both costs and outcomes should be discounted. Discounting reflects the fact that costs and benefits tend to have less value in the future than in present.

Pharmacoeconomic analyses are based on primary data methods or integrative methods. The former approach involves collection of original data (eg, randomized controlled studies). The latter combines data from existing resources. Integrative methods comprise meta-analyses, reviews, and model-based analyses. Quantitative modeling-based
pharmacoeconomic analyses simulate costs and consequences of pharmacological interventions, based on existing data and estimates of key variables where there are no data available. In this type of analysis, the Markov model is frequently applied. It is based on predefined sets of health states (eg, EDSS levels). Its time horizon is divided into equal increments of time, referred to as Markov cycles. For each cycle, costs, outcomes, and transition probabilities of moving from one state to another or of remaining in the same state are estimated. Finally, sensitivity analyses determine robustness of results of model-based analyses by varying the estimates of key variables within plausible ranges (eg, by applying a multivariate approach).

**Literature search and quality assessment**

We conducted a systematic literature search in MEDLINE (PubMed) on December 14, 2012, applying the medical subject headings (MeSH) terms “multiple sclerosis” and “costs and cost analysis.” We deliberately chose the comprehensive MeSH term “costs and cost analysis” to cover all potentially relevant studies. Four hundred fourteen publications met our search criteria, including 40 non-English publications, which were excluded; titles and abstracts of the resulting 347 publications were reviewed by FC and DB.

Inclusion criteria were as follows: (1) original research on the pharmacoeconomics of DMT in MS; (2) comparative study; and (3) comparators (initiation of DMT at the time of the first demyelinating event versus treatment after CDMS). Because our search strategy resulted in no more than four relevant studies, we did not exclude the study by Cukendall et al, although the authors only report on costs and not on health-outcome measures of DMT in CIS. The remaining three studies were rated for quality of health-economic analyses, based on the quantitative scoring system that has been proposed by Chiou et al (range 0–100; 0 representing the lowest; 100 representing the highest quality). The 16-item weighted scoring system was independently applied by FC and DB. Our scoring results were in accordance with the results reported by Yamamoto and Campbell, who chose the same approach (Table 1).

**Early treatment with interferon beta from a pharmacoeconomic perspective**

As outlined before, early initiation of DMT with interferon beta or GA has been proven to reduce time to CDMS, relapse rate, and disease progression. This observation led to the approval of interferon beta and GA for treatment of relapsing–remitting MS, as well as CIS. Therefore, initiation of DMT may be started even before definite diagnosis of MS is established.

To date, four studies have been published that address the economic impact of starting DMT at the time of the incident CIS versus after conversion to CDMS (Table 1). The Swedish study by Caloyer et al estimated cost-effectiveness of interferon beta-1b if initiated in CIS compared with delayed treatment after the diagnosis of CDMS has been made. The authors applied a Markov model analysis, based on twelve health states defined by EDSS scores, the assigned diagnosis (ie, CIS versus CDMS), and the course of disease (ie, relapsing or nonrelapsing forms of MS, and death). Transition probabilities after 6-month cycles were estimated for a lifetime time horizon of 50 years. The authors assumed that treatment discontinuation rates would not differ between both treatment arms; all hypothetical patients would discontinue DMT after roughly 25 years. Switching to another DMT and therapeutic escalations were not taken into account. The core input data for the statistical model were derived from the BENEFIT trial. Moreover, extrapolations of BENEFIT data and best available data from the published literature were used as model parameters. All costs were reported in 2009 Swedish kronor (SEK). Results of the CUA demonstrate that, during a 50-year time horizon, patients assigned to the early treatment group gained 12.9 QUALYs, as compared with 12.4 QUALYs in the delayed-treatment group. On average, patients in the delayed-treatment group progressed 2 years earlier to CDMS (estimated conversion rate 99.54%), compared with patients in the early treatment group (estimated conversion rate 99.31%). Direct medical costs (ie, interferon beta-1b drug costs, costs for inpatient and outpatient care, and costs related to testing, other drugs, and relapse events) were higher in the early treatment arm, whereas indirect costs (ie, costs related to early retirement and short-term absence) and direct nonmedical costs (ie, informal care, services, investments) in the delayed-treatment group exceeded those in the early treatment group. When all costs were summed up over the 50-year time horizon, total costs in the delayed-treatment arm were higher than those in the early treatment arm (difference of approximately 344,000 SEK per patient).

In summary, the Markov model-based estimation revealed that early interferon beta-1b treatment may decrease total costs and increase QUALYs. However, sensitivity analyses revealed that costs per QUALY gained were very high for short time horizons. In fact, only for time horizons longer than 10
Table 1  Pharmacoeconomic analyses of disease-modifying therapies of CIS

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<td>1. DMT initiated after CIS</td>
<td>QALY</td>
<td>1. 12.9 QALYs gained, 10.567 million SEK1 2. 12.4 QALYs gained, 10.911 million SEK1</td>
<td>Higher iCUR for shorter time horizons</td>
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Notes: 1 total costs (direct and indirect), 2 no model-based analysis, 3 no health outcome measures reported, 4 only cost-utility analysis shown.

Abbreviations: DMT, disease-modifying therapy; QHES, Quality of Health Economic Studies; CIS, clinically isolated syndrome; CDMS, clinically definite multiple sclerosis; QALY, quality-adjusted life-years; INHS, Italian National Health Service; €, Euro; SEK, Swedish krona; MoH, Ministry of Health; ICUR, incremental cost-utility ratio; CA$, Canadian dollars; QAMLY, quality-adjusted monosymptomatic life-years; MPS, methylprednisolone therapy of index event/relapses; NA, not applicable.
years, early treatment was less costly and more effective with respect to QALYs gained. This study reached the highest Quality of Health Economic Studies (QHES) score of the articles reviewed here (99 points).

Curkendall et al applied a different approach to assess the pharmacoeconomics of early DMT. Their analysis was based on insurance claims data in the United States for the years 2000–2008, extracted from the Thomson Reuters MarketScan Commercial and Medicare Supplemental databases; therefore, only health care expenditures and utilizations were analyzed. All costs were reported in 2008 US dollars. Health outcome measures were not included in the analysis. The core inclusion and exclusion criteria were as follows: (1) no diagnosis of MS during 12 months before and at the time of a cerebral MRI; this MRI scan was defined as start date of the 12-months observation period; (2) at least one symptom that was documented 6 months before or 1 month after the index date and that was likely to be attributable to MS; (3) initiation of treatment with interferon beta-1a, interferon beta-1b, or GA sometime during the follow-up period. Thus, CIS patients who may have received DMT after the follow-up period were not included. Patients were categorized into two groups – an early DMT and a delayed DMT group – depending on whether they received DMT before or after the diagnosis of MS. MS diagnosis was defined as one inpatient claim or two outpatient claims coded with ICD-9-CM diagnosis code 340. Three thousand nine hundred fifty one patients were enrolled; 227 and 3,724 were assigned to the early and delayed-treatment cohort, respectively. The mean follow-up was approximately 3 years in both groups, yet the pharmacoeconomic analysis was restricted to the first year after the index MRI. The mean time interval between index MRI and initiation of DMT was, as expected, significantly shorter in the early treatment group than in the delayed-treatment group (122 days versus 184 days). However, this difference was small, and more than 90% of the patients assigned to the delayed-treatment group received DMT within the first year after index MRI. Within the observation period, the early DMT cohort had significantly fewer hospitalizations compared with the delayed DMT cohort (0.20 versus 0.33). Total drug expenditures were higher in the early DMT cohort; whereas, total MS-related expenditures were significantly lower in the early DMT group, compared with the delayed DMT group after taking out costs for DMT. Both all-cause and MS-related total financial expenditures were not significantly different between the two groups (all-cause total expenditures US$331,184 in the early DMT group, US$330,051 in the delayed DMT group). The authors conclude that the high drug costs of early DMT might be compensated by savings in other medical expenditures. However, the observation period was short, and the analysis was conducted from a third-party payer’s perspective alone. The QHES quality score could not be applied to this study, as it does not report on outcome measures, thus not fulfilling the criteria of pharmacoeconomic analyses. In contrast to the other articles reviewed here, the strength of this study lies in the analysis of real costs, albeit restricted to health care expenditures.

Lazzaro et al applied an open cohort epidemiological model from an Italian perspective. Two treatment arms were analyzed. One group of patients received interferon beta-1b after diagnosis of CIS; the other group was treated with interferon beta-1b after diagnosis of CDMS. The “virtual” observation period lasted 25 years with 2,000 CIS patients being added to each treatment arm every year, resulting in two cohorts of 50,000 patients each. The model was based on several assumptions. Conversion to CDMS should not occur within 12 months after the first clinical event. The conversion rates for years 1–2 were based on the BENEFIT data, while the conversion rates for the remaining 22 years were assumed to decline asymptotically. The annual treatment dis-continuation rate was estimated to be 17.7%. Nineteen years after CDMS diagnosis, approximately 50% of the patients would progress to secondary progressive MS. Moreover, the observation period was arbitrarily divided into four periods (year 0; years 1–10; years 11–20; and years 21–24). Based on the report by Kobelt et al, EDSS scores were converted into utility parameters, which were assumed to stay constant within each period. Costs were adopted from both the Italian National Health Service (INHS) and the societal viewpoints. Most of the cost estimates were based on the Italian cost-of-illness study by Amato et al; all costs were reported in 2006 Euro. According to this analysis, patients gained 7.84 and 7.49 QALYs in the early and delayed treatment arm, respectively; the difference of 0.35 QALYs reached the level of significance. The CUA showed that, from the INHS perspective (ie, only health care resources were considered), the ICUR for early versus delayed interferon treatment was €2,575 per QUALY gained and lay considerably below a recently proposed Italian willingness to pay of €12,000–€60,000 per QALY. When patient and family resources (ie, the societal perspective) were additionally taken into account, early treatment would be even less costly than delayed treatment (€220,416 versus €226,022 per patient for early versus delayed treatment, respectively). A sensitivity analysis confirmed robustness of results. The authors conclude that, from the health service and societal perspective, early treatment with interferon beta-1b may be cost-effective, compared with treatment initiation after CDMS. However, this interpretation did not hold true for
short time horizons as there was a sharp decline in ICUR estimates over the first years; eg, from the societal perspective, the ICUR started from approximately €135,000 per QUALY gained at year 1, decreased below €60,000 after year 3, and, finally, became negative after year 6 onward. The QHES score of this study reached 75 points and lay considerably below the quality score of the Swedish study reviewed here.

Iskedjian et al performed a pharmacoeconomic analysis of treatment with interferon beta-1a administered intramuscularly once weekly in CIS patients; the study was conducted from a Canadian perspective.54 The aim of this study was to investigate: (1) cost-effectiveness of interferon beta-1a treatment based on the gain of additional monosymptomatic life-years (MLYs); and (2) cost-utility of long-term interferon beta treatment based on the gain of quality-adjusted monosymptomatic life-years (QALYs). Monosymptomatic life-years were defined as years after diagnosis of CIS and before diagnosis of CDMS. For CIS patients, the model comprised two treatment arms. High-dose intravenous steroid pulse therapy (plus tapering) for the index event (current treatment) and high dose intravenous steroid pulse therapy (plus tapering) for the index event plus interferon beta-1a. Once the diagnosis of CDMS was established, all patients received the same treatment regime with interferon and high dose steroids for treatment of relapse. The time horizon of the CEA and CUA was 12 and 15 years, respectively, starting from diagnosis of CIS and extending to various EDSS stages of CDMS. For the CEA and CUA, two Markov models were developed: the state of CIS and various EDSS states defined the Markov cycles (cycle length, 1 year). The conversion rate to CDMS was derived from the efficacy results of the Controlled High Risk Avonex Multiple Sclerosis Study (CHAMPS) study.38 Transition probabilities through the various stages of EDSS were derived from a Canadian MS study by Weinshenker et al.7 Cost analyses, including unemployment rates and the average hospital length of stay within each EDSS level, were based on data from the literature70–72 and Canadian health authorities. Costs were reported in 2002 Canadian dollars (CAS); total costs were estimated from the perspective of the Canadian Ministry of Health (MoH) and from the Canadian societal perspective. The former perspective was limited to direct medical costs; the latter additionally covered direct nonmedical and indirect costs. The input parameters tested in the sensitivity analyses comprised the progression rate to CDMS, the indirect costs associated with the duration from CIS diagnosis to CDMS, the time horizon, the discount rate, and the utilities. The CEA demonstrates that the incremental cost-effectiveness ratio (ICER) of interferon beta per MLY gained was CA$53,110 and CA$44,789 from the MoH and societal perspectives, respectively. As opposed to the MOH perspective, interferon beta treatment was considered cost-effective from the societal perspective, as costs of current treatment per MLY gained were higher (CA$75,444) than the ICER of interferon beta treatment. The CUA was conducted, based on the utility estimates derived from both a Canadian and a Swedish study.50,70 From the MoH perspective, incremental cost of interferon beta per QAMLY gained (ICUR) was CA$227,586 (CA$116,071 for the Swedish utility estimates); whereas, from the societal perspective, incremental cost of interferon beta reached CA$189,286 (CA$91,228, Swedish utility estimates). The sensitivity analyses showed that both the CEA and CUA were sensitive to variations of the time horizon with shorter horizons producing higher ICER/UCER and vice versa. The multivariate sensitivity analysis of the CEA showed that in 87% and 6% of the resulting scenarios the ICER of interferon beta therapy would be lower than the costs of current treatment per MLY gained from the societal and MOH perspective, respectively. Therefore, the authors conclude that interferon beta treatment in CIS may be cost-effective. However, this conclusion could be drawn from the CEA of the societal perspective, only. Moreover, concerning the results of the cost-utility analysis, the authors omit to address the issue of decision makers’ willingness to pay. Of the three pharmacoeconomic studies reviewed here, this study got the lowest quality rating (69 of 100 points).

Conclusion

MS is a chronic disease with high economic burden on patients, families, the health system, and society. Worldwide incidence and prevalence seems to be increasing with a total of about 2.5 million individuals currently being affected by MS. As reviewed here, several studies have demonstrated that progression of disease severity is accompanied by a rise of total costs as well as a change in the distribution of costs. During early stages of the disease, direct costs, which are mainly caused by DMT, dominate the total costs; whereas, with accumulation of disability during later stages of the disease especially indirect costs significantly increase.73 Moreover, occurrence of relapses has been associated with a peak of costs. Noteworthy, quality of life is substantially reduced with increase of disability and during relapse. Due to a better understanding of MS pathogenesis and the experience that efficacy of available DMT is high in early stages of MS but declines in the progressive phase of the
disease, the concept of early MS treatment has been established. Therefore, DMTs are usually initiated after diagnosis of relapsing–remitting MS or even before definite diagnosis of MS is made at the stage of CIS.

Since DMTs are, in general, considered as rather expensive treatments, there has been much debate whether it is economically justifiable to widely prescribe these drugs. A major concern is that clinical trials for approval of DMT – even though they have clearly demonstrated efficacy on parameters such as relapses, MRI activity, and sometimes also on EDSS progression during the trial – have hardly addressed long-term disability.

Numerous studies have investigated the pharmacoeconomics of DMT in MS, though only few have explicitly analyzed the pharmacoeconomic effect of early initiation of DMT in CIS.61–64 These studies indicate that early versus delayed treatment with interferon beta may be overall cost-effective in the long term. Reduction of relapses, hospitalization, and indirect costs and a gain of QALYs seem to outweigh the costs of DMTs. However, to keep in mind, all these analyses and models highly depend on estimates of the applied input parameters. For instance, Becker et al74 recently demonstrated the impact of cohort selection by replicating a previously published model-based analysis75 on the cost-effectiveness of interferon beta in MS. Based on a different patient cohort with longer follow-up, costs per relapse avoided turned out to be approximately 45% lower than in the original model. In their study reviewed here, Iskedjian et al showed that, from the Canadian societal perspective, estimated incremental costs of early interferon beta treatment would be 189,286 CAD per QAMLY gained. When applying different utility estimates, the same analysis resulted in 91,228 CAD, which is less than 50% of the former result.64 However, it seems to be ambiguous which of the applied utility estimates may be more valid than the other. Thus, results of pharmacoeconomic studies and inferences that may be drawn by decision makers largely depend on the analysis approach, the applied simulations and estimations, the perspective of the analysis, and particularly on the quality of the pharmacoeconomic analysis. As shown in our review and for instance in the recent work by Yamamoto et al, the latter has turned out to be considerably variable.66 We believe that this is especially critical in a chronic, heterogeneous, and complex disease, such as MS. In this context, one should note, that several pharmacoeconomic studies in MS, including the four studies reviewed here, have been funded by manufacturers of DMT (Table 1). Obviously, the results of all four reviewed studies cannot be readily generalized to other national settings as several key input data (eg, costs) were country-specific.66

Besides interferon beta and GA, new DMTs have been introduced, which are used as baseline and/or escalation therapy. The wider range of DMTs, as well as escalation strategies, needs to be taken into account in future pharmacoeconomic studies, which will be even more challenging.

Given limited resources to allocate pharmacoeconomics will remain of high importance. Therefore, we need more data on long-term efficacy of DMT and costs in MS in the real-life setting. Biomarkers, which will help to stratify patients at early stages with respect to severity of the disease course and response to therapy, are of great need from an economic point of view and even more so for patient care.

Disclosure

The authors report no conflicts of interest in this work.

References


