The Value of Economic Modeling Studies in the Evaluation of Treatment Strategies for Multiple Sclerosis

Bruno Detournay, MBA, MD
Cemka-Eval Team, Bourg la Reine, France

Multiple Sclerosis (MS) is a chronic inflammatory disease of the central nervous system characterized by successive exacerbations over its course.

Epidemiological studies have established that the prevalence of MS varies considerably across geographic areas. Prevalence estimates vary from 20 to 180 per 100,000 inhabitants in studies of northern developed countries. Reasons for these differences are not known. The prevalence of MS is highest in northern Europe, southern Australia, and the middle part of North America [1]. Estimates suggest that there are currently 250,000 to 350,000 MS patients in the United States.

MS generates many physical and social impairments of varying severities. Physical symptoms and limitations are often associated with social ones in connection with loss of productivity at work, long periods off work, and an important burden for families. These features are accentuated by the relatively young average age of onset of the disease, at 30 years.

The recent availability of interferon beta and glatiramer acetate for treatment of MS has raised concerns among medical decision makers and payers with regard to their efficacy, the magnitude of side effects, public expectations for their widespread use, and the high expected cost of such treatments [2]. Therefore there is an urgent need for cost-effectiveness data to provide guidelines for the optimal choice of available treatment strategies. Such data are particularly useful in the case of MS, where opinions about appropriate medical management vary greatly among clinicians based on the specific clinical characteristics and medical history of each patient [1,3,4].

In the last decade, several cost-of-illness studies of MS have been published in the international literature [5–7]. The results have been consistent in underscoring the importance of indirect costs in MS patients. However, these studies have also demonstrated the methodological difficulties in evaluating indirect costs in a credible and generally accepted manner. The quantification or valuation of indirect costs is one of the areas of great controversy in health economics. Furthermore, the generally accepted methods for evaluation of indirect costs have not gained widespread acceptance among decision makers and other practitioners.

Regarding direct costs, previous studies have shown that the clinical category (relapsing-remitting and secondary progressive MS) and extent of the physical disability are highly predictive of the medical costs. Direct costs are highly heterogeneous, however, of the course of the disease. Initially, costs are primarily related to routine treatment and inpatient care for relapses; as the disease progresses, the loss of functional autonomy becomes the main determinant of care.

More recently, a number of cost-effectiveness studies of treatment, mainly with interferon beta, have been published [8,9], and this issue of Value in Health presents an important new study on this topic by Mark Nuijten and John Hutton. These studies appear at a time when the efficacy of all registered drugs has been demonstrated in phase III clinical trials.

The clinical data currently available for treatment efficacy are sufficiently well documented to allow for economic evaluations. Nevertheless, important questions that challenge the development of pharmacoeconomic evaluations of MS treatment strategies remain unanswered. We will discuss some of these questions below.

Ideally, economic modeling of treatment strategies should include the entire treatment time frame. In the case of MS, long-term effectiveness and safety data for treatments are not available. In existing clinical trials, the follow-up period does not exceed 3 to 5 years, which is considerably shorter than the expected survival of patients with MS (typically, more than 30 years). Economic models provide tools for extrapolating from the observed data, which makes the exercise somewhat speculative, especially over longer periods of time. In addition, the choice of an appropriate time frame often presents unique challenges. The recent debate [10] surrounding the UK-NICE committee’s conclusions on the use of interferon beta and glatiramer acetate in MS illustrates the problems that can arise regarding the choice of a relevant time frame: Should it be 10 years, 20 years, or a lifetime, as in the paper presented in this issue?
The choice is not merely scientific because it relates to several different domains discussed below.

Extrapolating from short-term efficacy, as measured in clinical trials, to long-term effectiveness is particularly complicated for MS, a disease of unknown etiology with variable pathophysiologic features and a highly unpredictable evolution. The primary outcome measures in clinical studies (degree of disability, relapse rate, time to progression) may not be predictive of long-term evolution.

Another set of issues relates to discounting. At the moment, there is no general consensus among international economists regarding the use of discounting. Controversy exists as to whether discounting should be applied to both costs and benefits or only to costs, and what discount rate is appropriate. Discounting tends to greatly diminish long-term costs and benefits, especially when a discount rate of 6% is applied, as is recommended in the United Kingdom. It seems paradoxical, although understandable from an academic perspective, to simultaneously apply high discount rates to the cost benefits of a long-term treatment rather than to consider a short-term treatment horizon without discounting when the long-term effects of the treatment occur at the time of treatment delivery.

Furthermore, therapeutic innovations are likely to emerge and compete with current experimental treatments, which may weaken the case for considering a very lengthy time frame for economic analyses of treatment strategies. This may be particularly true for MS, which is an area of active medical research. Finally, there is also controversy regarding the effect of treatment after its discontinuation.

One area of uncertainty relates to the natural history of MS. In the absence of data from large cohort studies, modeling of the temporal evolution of MS is often based on information from clinical trials. However, such data may not be representative of the evolution of MS in the general population. Furthermore, while the Expanded Disability Status Scale (EDSS) introduced by Kurtzke in 1983 allowed for standardization of handicap assessment by clinicians and is now universally used, it has certain limitations. The scale has been criticized for its large interrater variability [11], its ordinal nature, and its unnecessary focus on certain categories of functional impairment. Its use for economic modeling seems unavoidable but its limitations raise issues regarding the validity of results. Another uncertainty concerns the assumptions used for modeling of disease progression. Most models assume only stabilization or progressive worsening of the disease over time. However, improvement as well as sudden major deterioration may also occur and must therefore be incorporated in the models.

In the field of outcomes research, economic modeling is increasingly used for the assessment of expensive treatments in various settings. The case of interferon beta in MS is an interesting example of the different challenges that analysts face in such an exercise. An important and difficult task is to improve the communicability of such studies. Even trained professionals often find it difficult to fully understand the inner workings of economic models, which inevitably appear to be “black boxes.” Hence, readers often have to trust the quality of the work based on the reputations of the authors, the reviewers, and the journals. At the same time, the ultimate role of modeling is to provide a synthesis of all relevant information and serve as a guideline for decision making. The challenge then becomes finding the appropriate compromise between simplicity and scientific credibility in this exercise.

References