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COMMENTARY

Cost-Effectiveness Modeling in Multiple Sclerosis: Playing Around with Non-Healthcare Costs?

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1 Introduction

Multiple sclerosis (MS) is a chronic disabling neurological disorder that affects more than two million people worldwide [1]. Accounting for more than half of the total population diagnosed with MS in the world, Europe is considered a high-prevalence region [1]. Patients with MS experience a wide range of signs and symptoms [2], which impair their capacity to perform day-to-day activities and thus quality of life [2, 3]. The onset of MS at an early age implies a substantial burden in terms of both healthcare and societal costs [2].

The drugs currently used to treat MS aim to alleviate symptoms, delay disease progression and, ultimately, disability. Steroidal anti-inflammatory drugs are traditionally used to inhibit the inflammatory process of MS, then various types of drugs can be used to alleviate the different symptoms (e.g., visual, motor, cognitive). However, the most important therapeutic group is the disease-modifying drugs (DMDs); drugs designed to delay the progression and the development of long-term disability. DMD prescription is still mainly restricted to patients with relapsing-remitting MS (RRMS), although there are some DMDs indicated for specific conditions of secondary progressive MS [4].

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The two beta interferons (IFNβ-1a and 1b) and glatiramer acetate (GA) have been the first-line DMDs for years. Indicated in patients with at least two relapses in the previous 2 years, they are all injectable (IFN β-1b and GA subcutaneous, IFN β-1a subcutaneous or intramuscular) [4]. More recently, other DMDs have been approved as second-line treatments: (1) natalizumab, a monoclonal antibody injected intravenously; (2) alemtuzumab, another monoclonal antibody for intravenous injection (initially marketed as an anticancer drug) that has recently proved to benefit MS patients, and (3) fingolimod, an oral drug that prevents lymphocyte migration to the central nervous system. Finally, the European Medicines Agency has very recently approved two oral first-line DMDs with different mechanisms of action [5]: teriflunomide and dimethyl fumarate.

The pharmaceutical costs of MS have risen steeply over the previous few years, mainly owing to the introduction of new DMDs. Although medical evidence on the most dated DMDs is quite well established, the economic literature on these drugs is still controversial [6–9], casting doubts on their cost effectiveness. In this commentary, we assess the potential contribution of cost-effectiveness analyses to pricing and reimbursement decisions in Europe. In particular, we analyze the credibility of the major assumptions contained within the analyses.

2 Economic Evaluations in the European Union

We searched the PubMed international database to select full economic evaluations on first-generation DMDs (the two IFNβs and GA) conducted in European Union (EU)

countries and published in English from January 2009 until December 2014.[1]

The seven studies finally selected [10–16] came from only four countries (Germany, Italy, Spain, and Sweden) (Table 1); three focused on clinically isolated syndrome (CIS)[2] (comparing DMD vs. 'do nothing' or early vs. delayed regimens of the same DMD) and the other four on RRMS patients (comparing the two IFNβs and GA). Three studies included a cost-utility analysis, two a cost-effectiveness analysis, and the others both. Only one study adopted exclusively the third-party payer's perspective [14]; the others took the societal viewpoint (together with the third-party payer's perspective in two studies). Five studies were based on Markov models with a long-term horizon and two on 'decision trees' [12, 16], only one of them with a short-term horizon [16]. All studies used virtual cohorts of patients, only three referring to samples of clinical trials to define the virtual cohorts [10, 11, 16]. Extrapolation of short-term efficacy to long-term time horizons was performed in all studies but one [16]. Six studies sourced most costs from short-term, domestic, prevalence-based cost-of-illness (CoI) studies (all sponsored by DMD manufacturers), which all estimated a wide range of items including indirect and direct non-medical costs. To adapt this information and generate the data lacking to fully populate models, all studies relied on assumptions, three on anonymous experts [10, 11, 15], and two even on non-European [14] or unpublished data [16] to estimate relapse costs. Non-healthcare costs were a substantial proportion of total costs in all the six studies that adopted the societal perspective. All studies were sponsored by the pharmaceutical industry and six were even co-authored by company employees. All studies concluded in favor of the sponsored DMD, their results conflicting depending on the sponsor in the studies on RRMS. Unsurprisingly, time horizons and discount rates were the most influential variables in sensitivity analyses in four of the six studies [10–12, 15] with a long-term horizon.

[1] For the search, we used the MeSH terms 'multiple sclerosis' and 'costs and cost analysis'. We retrieved 202 articles and 174 were discarded, being: (1) epidemiological or clinical articles (101); (2) partial economic evaluations and literature reviews (61); and (3) editorials, letters, and comments (12). Because 21 studies did not concern the EU setting, we finally selected seven articles and screened them to assess their main methodologic features, using a common checklist based on the one used to abstract studies in the EURONHEED database.

[2] Frequently, MS begins with isolated neurologic episodes, defined as CIS, which last at least 24 h and are caused by inflammation and demyelization in focal sites of the central nervous system. CIS can be either monofocal or multifocal and people who experience CIS will not necessarily develop MS.

3 Policy Implications

Our review of the most recent economic evaluations conducted in the EU setting on first-generation DMDs confirms the widespread concern raised in previous wider reviews [6–9]. First, most studies were based on long-term modeling and they all had to rely on weak sources to populate them [8]. The need for extensive reliance on assumptions is an intrinsic limit of long-term models dealing with clinical efficacy and cost evaluation where only short-term experimental data are available. This is likely to lead to great within- and between-study variability generated by authors' choices of sources of information and assumptions. Then too, the societal viewpoint adopted by most studies seems to play a large role in determining the cost-effectiveness ratio. In fact, almost all the studies sourced costs from CoIs that estimated a substantial proportion of non-healthcare costs in MS, whose evaluation and monetization is open to the authors' discretion [7]. All these CoIs used the 'human capital approach' to assess indirect cost, a controversial method that is likely to lead to overestimates and implies a state of full employment in the long run [17], which is hardly the case in the EU countries in this period of unprecedented economic crisis. Last but not least, all the studies gave the clear impression of being part of the manufacturers' marketing strategies, trying to highlight high social costs for MS to demonstrate the value of their product [7–9].

To sum up, we feel the studies reviewed can be considered no more than mere forecasting exercises, in which short-term information is projected into the future on the basis of heterogeneous estimates and non-healthcare costs are included to enhance the chances of DMDs being cost effective. Because we are reasonably sure that companies will manage to show an acceptable incremental cost-effectiveness ratio for each of the new expensive DMDs despite their high prices, we wonder whether future similar studies will really add any value for public decision making. We would really prefer economic evaluations in this field to be more pragmatic, i.e., conducted from the third-party payer's perspective and excluding non-healthcare costs to make their results more plausible, as repeatedly suggested by the National Institute for Health and Care Excellence starting from its very first guidance on DMDs [18–21]. We are also convinced that simpler short-term analyses could be more useful for public decision making to assess the different healthcare costs for new and old DMDs, which all have different mechanisms of action and can be grouped only by form (oral or injectable). Surely, there could be scope for referring more often to 'budget impact analyses' [22] in this field too, to assess whether the new DMDs induce some trade-offs on other healthcare

Table 1 Main characteristics of the studies reviewed

	CIS			RRMS			
	Fredrikson [10] (Sweden, 2013)	Caloyeras [11] (Sweden, 2012)	Lazzaro [12] (Italia 2009)	Dembek [13] (Spain, 2014)	Darbà [14] (Spain, 2014)	Sánchez-de la Rosa [15] (Spain, 2012)	Nuijten [16] (Germany, 2010)
Study type (perspective)	CEA and CUA (society)	CUA (society)	CUA (society, third payer)	CUA (society)	CEA (third payer)	CEA and CUA (society)	CEA (society, third payer)
Model (time horizon, discount rate)	Markov (40 years, 3 %)	Markov (50 years, 3 %)	Decision tree (25 years, 3 %)	Markov (30 years, 3 %)	Markov (10 years, 3 %)	Markov (10 years, 3 %)	Decision tree (4 years, 5 %)
Alternatives	sc IFNβ-1a vs. do nothing	Early IFNβ-1b vs. delayed IFNβ-1b	Early vs. delayed IFNβ-1b	im IFNβ-1a vs. sc IFNβ-1a vs. IFNβ-1b vs. GA vs. BSC	GA vs. im IFNβ-1a vs. GA + im IFNβ-1a	GA vs. im IFNβ-1a vs. sc IFNβ-1a vs. IFNβ-1b	im IFNβ-1a vs. sc IFNβ-1a vs. IFNβ-1b vs. GA vs. do nothing
Sources for costing	CoI, expert opinions, assumptions	CoI, expert opinions, assumptions	CoI, assumptions	CoI, assumptions	BIA, US costs for relapse, assumptions	CoI, expert panel, assumptions	CoI, manufacturer's data on file for relapse, assumptions
Non-healthcare cost as % of total[a]	72	72	85	64		64	57
Most influential variables in SA	MS risk, discount rate	Time horizon	DMD cost, discount rate	DMD cost	DMD cost	Indirect costs, time horizon	Relapse rate

BIA budget impact analysis, *BSC* best supportive care, *CEA* cost-effectiveness analysis, *CUA* cost-utility analysis, *CIS* clinically isolated syndrome, *CoI* cost of illness, *DMD* disease-modifying drug, *GA* glatiramer acetate, *IFN* interferon, *im* intramuscular, *RRMS* relapsing-remitting multiple sclerosis, *SA* sensitivity analysis, *sc* subcutaneous

[a] Sourced from the CoI studies referenced in each article

resources (e.g., specialist consultations and nursing interventions) to somehow compensate the extra costs due to their higher prices.

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