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Letter to the editor

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Letter to the editor

Re: Cost-effectiveness analysis of disease modifying drugs (β-interferons and glatiramer acetate) as first line treatments in remitting-relapsing multiple sclerosis patients. Sánchez-de la Rosa R, Sabater E, Casado MA, Arroyo R. JME 2012;15(3):424–33.

Dear Editor,

We would like to address some concerns regarding the manuscript published by Sanchez-de la Rosa *et al.*[1]. We have thoroughly read the article 'Cost-effectiveness analysis of disease modifiying drugs (β-interferons and glatiramer acetate) as first line treatments in remitting-relapsing multiple sclerosis patients' recently published in JME. We would like to point out some issues, regarding the efficacy, discontinuation, neutralizing antibodies data, and cost estimates.

One of the limitations is the absence of evidence to support some of the assumptions related to estimation of transition probabilities, and both direct and indirect costs. Furthermore, this model has been built up on the basis of a previous article[2], reproducing the same weaknesses.

Regarding the transition probabilities and according to the Spanish recommendations on economic evaluation of health technologies, the use of different efficacy sources must be justified and clearly defined[3]. The inclusion of a table summing up the efficacy data considered for each therapeutic alternative, as well as a detailed explanation for efficacy studies selection, would be recommended to facilitate model understanding.

Treatment discontinuation has been considered for each therapy, although the authors have not referenced this assumption nor have they specified proportion of treatment dropouts for each drug or the way this impacts on final transition probabilities.

Another important issue related to transition probabilities relies on the incidence of neutralizing antibodies (NAbs) which is assumed to decrease interferon β efficacy in favor of glatiramer acetate (GA). Sanchez-de la Rosa *et al.* used the percentage of NAbs observed among a sample of 571 patients without specifying the lack of efficacy attributable to each interferon β. In this sense, Curtiss[4] also questioned this decline in patient response due to NAbs titers in the previous model by Bell *et al.*[2].

The authors have fitted treatment effectiveness data using log-linear regression curves. This fit has been made for all transition probabilities except for transition probabilities from health status EDSS (Expanded Disability Status Scale) 6.0–7.5 to EDSS 8.0–9.5 without justifying this lack of data.

Regarding the drug costs estimations, we could not replicate the sc IFN β-1b estimated costs reported in the article, according to the methodology described by the authors, when we quantified this difference in a 7% of added costs for sc IFN β-1b.

Indirect costs estimations, expressed as 'loss of productivity', relies on some weak evidence. The supporting reference for these data (Lage *et al.*[5]) have some important limitations. First, the number of patients receiving treatment with any of the drugs assessed is quite small compared to the whole sample, and more important is the fact that Lage *et al.* are estimating lost worker productivity considering 'absenteeism', which includes vacation time combined with sick leave. This lost work time has nothing to do with multiple sclerosis (MS). These comments were also pointed out by Curtiss[4] on his editorial letter, accompanying the Bell *et al.*[2] model publication. Besides the weaknesses of these data, the authors have extrapolated interferon β-1a im reduction on sick leave data to sc interferon β-1a (which was not assessed in the Lage *et al.* study) without justifying this assumption.

It is important to point out that lost worker productivity due to MS depends on EDSS status and progression. In a Spanish study carried out over 200 MS patients, the indirect cost were estimated according to EDSS[6], which is a better approach for MS patients.

The results described by the author show that patients treated with GA progress further and spend less time free of exacerbations when compared to those with the other drugs assessed. This is reflected in the shortest number of life years gained and QALYs gained (quality-adjusted life years).

Regarding the sensitivity analysis, the deterministic approach performed to assess model uncertainty also has some important limitations. Deterministic analysis only provides results for one point estimation, which might under-estimate model parameters uncertainty[7]. The use of probabilistic sensitivity analysis offers the opportunity to make statistical statements about the impact of parameter uncertainty for cost-effectiveness estimates[8]. It is possible to perform these analyses by Monte Carlo simulations, thus generating a joint distribution in the incremental costs and effects that represents the consequences of the input parameter uncertainty[7]. This distribution allows the creation of acceptability curves in order to determine the percentage of simulations in which the cost-effectiveness ratio is below the threshold commonly accepted in Spain. In sight of the extraordinarily high cost per QALY described by the authors (between −1,005,194

and 117,914 Euros per QALY for the comparison among different therapies), a probabilistic analysis would represent a more accurate approach to model uncertainty. The sensitivity analysis performed by the authors does not provide enough information related to model uncertainty due to this deterministic approach.

Accordingly the potential economical benefits attributed to GA rely on methodologically poor estimations, and therefore the findings described in this article need to be interpreted with caution.

We hope you find this discussion of value for professionals in charge of making decisions in relation to cost-effectiveness of MS therapies.

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Author's response to Letter to the Editor

Re: Cost-effectiveness analysis of disease modifying drugs (β-interferons and glatiramer acetate) as first line treatments in remitting-relapsing multiple sclerosis patients. Sánchez-de la Rosa R, Sabater E, Casado MA, Arroyo R. JME 2012;15(3):424–33.

Dear Editor,

We would like to acknowledge Dr Granda and colleagues for their comments regarding 'Cost-effectiveness analysis of disease modifying drugs (β-interferons and glatiramer acetate) as first line treatments in remitting-relapsing multiple sclerosis patients'[1].

Economical modeling uses assumptions to simplify the complexity of real world events and procedures. In the case of multiple sclerosis, the heterogeneous aspects of randomized clinical trials of different therapies require the use of several assumptions, each of which affects the results of the model[2]. In the manuscript, we have explained every assumption made in the model in detail to achieve the objective of the study, which is to provide insights that can help health decision-making[1].

In the following sections, we will address the issues that Dr Sanz and colleagues raised in their letter:

(1) All of the inputs and assumptions are clearly identified and referred to in the Methods section of the manuscript: transition probabilities (Table 1), efficacy sources (transition probabilities section), and direct and indirect costs (Table 2 and the resource use and costs estimation section). We would like to clarify that, as we reported in treatment section of the manuscript, patients who progress to an Expanded Disability Status Scale (EDSS) score over 5.5 will discontinue disease-modifying drug (DMD) therapy. Therefore, it is not necessary to consider DMD treatment effectiveness data for EDSS 6.0–7.5 and EDSS 8.0–9.5 because these patients do not receive DMD treatment. This assumption was also made in the validated Bell *et al.*[3] model.

(2) The wholesale price of subcutaneous interferon β-1b was changed during the preparation of the manuscript and was not updated in the model. We have updated the price of interferon β-1b in the model and confirmed that the conclusions of the study do not change substantially (Table 1).

(3) Our model considers that neutralizng antibodies affect the incidence of relapse only after the second year of the simulation, as we report in the neutralizing antibodies section of the paper. Moreover, sensitivity analysis of this parameter showed that this variable did not have a major influence on the results of the study.

(4) We decided to use the same work productivity loss values considered by Bell *et al.*[3] in their previously validated model. When sensitivity analysis was performed and the same work productivity loss value was

Table 1. Cost-utility results (price of interferon β-1b updated).

	Cost/outcome			
Reference scenario	IM IFNβ-1a	SC IFNβ-1a	SC IFNβ-1b	SC GA
Drug costs per patient (€, 2010)	€47,531.94	€65,474.67	€45,359.71	€42,453.89
Total costs (€, 2010)	€329,595.43	€348,208.20	€330,533.56	€322,509.96€
QALY per patient	4.176,996,27	4.158,479,68	4.157,614,31	4.116,906,617
Incremental cost-utility ratio (cost €/QALY) IM IFNβ-1a vs (SC IFNβ-1a *or* SC IFNβ-1b or SC GA)	NA	Dominant	Dominant	117,914
Incremental cost-utility ratio (cost €/QALY) SC IFNβ-1a vs (SC IFNβ-1b or SC GA)	NA	NA	20,424,379	618,146
Incremental cost-utility ratio (cost €/QALY) SC IFNβ-1b vs SC GA	NA	NA	NA	197,103

IFN, interferon; GA, glatiramer acetate; IM, intramuscular; SC, subcutaneous; QALY, quality-adjusted life year.

considered for all DMD, this parameter did not have a significant influence on the outcomes of the analysis.

(5) We agree that a probabilistic sensitivity analysis (PSA) would have provided valuable information. To overcome the lack of a PSA in our study, we used extensive deterministic sensitivity analyses to assess the model robustness.

After reviewing all of the issues raised by Dr Sanz *et al.*, we reaffirm our conclusion that first-line treatment with glatiramer acetate is the less costly strategy for the treatment of patients with remitting-relapsing multiple sclerosis. Moreover, treatment with intramuscular interferon β-1a is a dominant strategy compared with subcutaneous interferon β-1a and subcutaneous interferon β-1b. In addition, intramuscular interferon β-1a is not considered a cost-effective strategy compared to glatiramer acetate because the incremental cost per quality-adjusted life year gained with intramuscular interferon β-1a is well above the cost per quality-adjusted life year threshold commonly accepted in Spain.

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