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LETTER

Authors' Response to the Letter to the Editor Regarding: A Comprehensive Review on Copemyl®

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We read with interest the letter by Comi et al. [1] in response to our review [2]. In the still complex therapeutic landscape of multiple sclerosis (MS), more complexity was added by the controversy following the commercialization of Copemyl®, at times perplexing neurologists in their clinical practice. We thank Comi et al. for having provided additional information on the intricate question of possible differences between glatiramer acetate (GA) and glatiramoids. Indeed some references were not included in our review, e.g., some abstracts and papers not available as the full text.

The appropriateness of the definition of Copemyl as a generic of GA has been already evaluated and solved by regulatory agencies. We would like to focus here on the statistical issues raised by Comi et al. These issues are mainly related to the interpretation of the results of the GATE trial, indicating some apparent inconsistency between these results and those of the pivotal trial of GA.

Comi et al., in comparing the results of the two trials, considered only the point estimates

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of the treatment effect estimates, without taking into account their confidence limits. This is incorrect and can be misleading.

The first objection is that in the pivotal study of GA, GA reduced relapses vs placebo with a rate ratio (RR) of 0.71, while in the GATE trial there were no differences between GA and placebo in terms of relapses and the RR was 1.05. However, for the GATE trial it is easy to calculate that the confidence intervals of this RR of 1.05 are 0.42–1.68, largely containing the point estimate of the pivotal GA trial. Therefore we must say that the results of the two trials are not significantly different or, in other words, that there is no evidence of any difference between the results of the two trials. The large confidence limits are a consequence of the low power of the study to detect a difference, if any, based on relapses.

Second, in the GATE trial there is a reduction in the number of new T2 lesions of 40% in the GA arm vs placebo, while there is no effect on relapses. This is claimed to violate what Comi et al. call "Sormani's equation". As the author of that equation is in the author list, we had the opportunity to examine it thoroughly. From the equation, the expected effect on relapses according to the effect seen on magnetic resonance in this study would be an RR of 0.74 (95% prediction interval 0.47–1.17) [3]; again, the observed RR of 1.05 is largely contained in the 95% prediction interval and thus the equation is not violated.

Finally Comi et al. claim a "rebound" of lesions in the placebo group switching to Copemyl, but this is due to a misinterpretation of some summary measures. The placebo group has a mean value of 2.8 gadolinium-enhancing lesions at baseline (and a median of 1). The value reported in the month 7–9 period is not a mean value of the counted lesions but, as described in the notes to the table, is a value derived from a mixed effect negative binomial model. This value (that is the exponential of a mean of log-transformed values, representing a geometric mean of predicted values) is closer to the median of the original values rather than to the mean. Therefore, the value of 0.8 cannot be compared to the mean baseline value. The mean number of lesions is not reported at month 7–9, but the value of 0.8 is very similar to the baseline median value of 1. The mean number of lesions decreased after 3 months of Copemyl to 1.7 at month 12 and further decreased to 0.9 at 2 years. Bearing in mind the mixed effect negative binomial model, no rebound is observed.

More generally, our position is in line with that of the Italian Neurological Society that recently expressed a position paper on the topic of generic/biosimilar drugs for MS [4]. This states that drugs sharing the same active ingredient at the same dosage should have the same cost, thus strongly supporting MS-expert neurologist autonomy in prescribing, bearing in mind the patient's therapeutic continuity and disabling therapeutic choices based merely on economic considerations.

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Compliance with Ethics Guidelines. This letter is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

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