Reviewer's report

Title: Use of glatiramer acetate between 2010-2015: effectiveness, safety and reasons to start GA as first or second line treatment in Swiss multiple sclerosis patients

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Reviewer: Ingo Kleiter

Reviewer's report:

The authors examined a cohort of MS patients treated with GA to report real-world data on reasons to choose GA, efficacy, side effects and factors associated with a change in ARR and EDSS. Design of the study was multicenter, observational, with 2 pre-defined visits 12 months apart.

While real-world studies on the efficacy and adverse events of DMTs for MS are welcome, particularly when comparative evaluations between DMTs are done, this study has several shortcomings. Most importantly, the research question (hypothesis and/or goals) and the methods to assess this question are not well defined or described. It does not become clear how clinical assessments were done and each set of data was obtained. By questionnaire from the patient, a physician assistant, or from a neurologist? From chart review? At which time points? Moreover, it is not described how often and by which means adverse events and relapses were captured. Were patients instructed to report these, were extra visits done upon relapses to clinically confirm them? Since this study is reported to be "prospective", it is expected that all these issues were defined prior to start of the study.

Both, the reported incidence of adverse events (total n=28 in 194 patients followed-up for 1 year) and of relapses (0.0 (0.0-0.0); 4 relapses reported as adverse events) are much lower than would be expected from the pivotal studies leading to GA approval or recent RCTs, e.g. GALA (expected ARR during GA is 0.3-0.4, expected injection site reactions appr. 70 per 100 patient years). Thus, the methods used most likely were inappropriate to reliably assess ARR (efficacy) and safety of GA, as claimed in the title.

Further points:

* Title: Given the limited population examined, I recommend to add in the title that Swiss MS patients were analyzed.

* Abstract: I recommend to add the aim of the study (rather than stating "Several other treatment options have been subsequently introduced", which is not needed here).

* Abstract, Methods: please describe primary (and if applicable) secondary endpoints and methods to measure these endpoints as it would be expected for a prospective study.
Abstract, Conclusion: it is not clear whether "previous studies in this population" refers to GA studies or to the MS population in Southern Switzerland.

Background, line 10: "Neuroprotection" as mechanism of GLAT is more than questionable. To my knowledge there is no clinical study unequivocally showing that GA is neuroprotective. If at all, this seems to be an effect of immune modulation (and subsequently less brain inflammation), as seen with many other MS drugs.

Background or Discussion: I was missing information about biosimilars of GA, which are available since several years and have shown equal efficacy and side effects as GA.

Methods, Ethics: Was written informed consent obtained?

Results, Table 1: The sex distribution with 73% male in switchers and 70% male in naïve patients is rather unusual for a MS population, in particular considering pregnancy issues, which might be an additional reason for women to start GA.

Results, Table 2: Please specify which "comorbidities" were factors motivating to start GA. What is the difference to "depression/fatigue/cognitive problems", some of which rather are MS symptoms than comorbidities.

Results, Table 3: correct spelling "ARR annualized relapse rate"

Results, Table 4 is hard to assess for me because of confusing track changes.

Results, page 9, line 29. It would be of interest to know when during pregnancy GA was stopped (time of exposure) and the pregnancy outcomes.

Discussion, page 10, line 10. The claim "We found that GA was prescribed twice more frequently in naïve than in switcher patients" can only be made, if all GA-treated patients of the 45 participating centers were included in the study. How was this assured?
Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

No

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Yes

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

No

Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

I am able to assess the statistics

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