Reviewer's report

Title: Analysis of treatment persistence with Glatiramer Acetate in treatment-naive patients and after treatment failure with Interferons.

Version: 1 Date: 5 January 2015

Reviewer: Tomas Kalincik

Reviewer's report:

The manuscript by Dr Mireya Fernandez-Fournier and colleagues reports the outcomes of a retrospective single-centre analysis of treatment persistence among patients with relapsing-remitting multiple sclerosis treated with glatiramer acetate (GA) with either no previous exposure to disease modifying drugs or after previous exposure to interferon beta (IFN). This is an interesting topic, as our knowledge of the effect of various factors on treatment persistence is limited. However, there are several methodological issues which need to be addressed, in particular the lack of adjustment of the statistical analysis, exclusion of the patients lost to follow-up and the reporting of various patient proportions without a clear indication of time relative to treatment initiation. In addition, only a relatively limited description of the studied cohort is provided, and the Results section would benefit from a better structure (in particular concerning the various reported proportions of various sub-cohorts). Finally, some of the conclusions are not supported by the presented data (e.g. the proportion of patients with break-through activity and the average time on GA for those escalating therapy).

Major revisions

1) The description of the used statistical methodology is rather brief (p.6-7, l.143-150). Given that the study describes treatment persistence in a retrospective analysis of observational data, which also comprises a comparative component, a great attention should be paid to the elimination of potential confounders. To my understanding and based on the provided description, the proportional hazards model was only adjusted for age; however, numerous other confounders, including demographic and clinical information, should have been taken into account and adjusted for. Also the lack of statistical significance of the described difference in the sex ratio between the groups (with females being more likely to initiate GA as their first disease modifying therapy) does not justify the lack of the adjustment for sex, as the lack of statistically significant difference could also be due to the lack of power for the purpose of comparison of sex ratios between the groups. The authors indicate that a value “lost to follow-up” was allowed as a reason for treatment discontinuation. Figure 1 indicates that those lost to follow-up while treated with GA were excluded from the analysis (this should be stated explicitly in the Methods); however, it would be appropriate to include these patients in the analysis, indicating their censoring as per survival analysis. The same applies to the trend for the EDSS to be lower in the treatment-naïve cohort. On page 7 lines 155-156, the authors report average
patient age in October 2013. However, if age is considered as a potential confounder of treatment persistence, it should be reported at the time of treatment initiation and summary statistics for both groups should be shown.

2) The authors should clearly indicate the criteria for previous treatment with GA. Was any pre-GA exposure to IFN considered or were only patients immediately switching therapy from IFN to GA included? If the latter is the case, what was the definition of treatment switch and was a maximum “inter-treatment gap” defined for this purpose?

3) The authors should provide the descriptive statistics of the available on-study follow-up (from GA initiation to the end of the available follow-up regardless of treatment status).

4) What was the fate of the patients who discontinued therapy? The authors should provide information about the further treatment status for the entire cohort as well as for the treatment groups.

5) p.7, l.162-163: Reporting the proportion of patients who discontinued therapy at a particular date (as of study end-point) does not provide the reader with any useful information. The proportions of discontinuees should be reported in relation to the time on-treatment (i.e. at defined time points post treatment initiation, e.g. using visualisation with Kaplan-Meier curves for the evaluation of total treatment persistence).

6) p.8, l.172-176: The break-down of patients who stopped therapy provides information about 51 patients, which is not in agreement with the 50+3 patients reported on p.7, l.163-164. According to the break-down, 4 patients stopped their therapy and 47 switched to other agents, whereas the break-down of the switchers by the reason for switching adds-up to 50 patients. This information should be rectified and should also be provided per treatment group (naïve vs. post-IFN); e.g. it can only be assumed that the 14 patients switching from GA to IFN were presumably from the treatment-naïve cohort. Finally, the information about the reason for switching therapy from GA would more logically follow after the overview of the number of patients undergoing the switch.

7) p.8-9, l.194-196: Treatment persistence among 1113 patients in relation to several examined potential predictors, including the pre-treatment status and the preparation (incl. GA) was reported by Jokubaitis et al. 2013, PLoS One 8:e59694.

8) p.9, l.219: It is unclear where the proportion of patients (17.4%) with break-through activity is derived from. I assume that this is the sum of the patients who switched from GA to another drug due to previously identified relapses, progression of disability or MRI activity (p.7, l.167-168). However, this is most probably an underestimation of the real break-through activity, as it does not include the patients who remained on GA despite break-through activity. Also, reporting of on-treatment disease activity should always be related to treatment duration (see above).

9) p.10, l.225: Is the reported average time on GA for those escalating therapy (29.2 months) merely the time on GA for those who discontinued therapy due to the lack of treatment efficacy (l.177-178) or was this calculated specifically for
those who escalated therapy?

10) The Discussion of study limitations should be more comprehensive and should discuss some of the issues raised above, as well as the limitations concerning the cohort size and the statistical power, and the generalizability of the observations.

Minor and discretionary revisions

11) p.5, l.120: Were also patients who received therapy other than IFN or GA after discontinuing GA excluded from the study?

12) p.5, l.127-128: How were the criteria of MRI activity defined?

13) p.7, l.162: While Figure 1 states that 74 patients who continued therapy were included in the analysis, the text reports 75 patients.

14) p.8, l.177-183: The incidence of reasons for treatment discontinuation seems to vary with treatment duration (e.g. serious adverse events tend to occur earlier than injection-site reactions). It would be of interest to show whether these differences reach the level of statistical significance in the survival analysis and visualise these in survival curves.

15) p.8, l.186-189: What are the interval estimators for hazard ratios provided? Why do authors report the unadjusted hazard ratio, which is very similar to the age-adjusted hazard ratio?

16) In the Introduction (p.4, l.81-83), the authors state that there is a need to carefully evaluate the reasons for treatment failure, including adherence, neutralising antibodies or adverse events. This statement is somewhat out of the context of the reported analysis, as of the three given reasons for treatment failure, the study only evaluates one - the serious adverse events.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:

The reviewer received research support from National Health and Medical Research Council, Multiple Sclerosis Research Australia and University of Melbourne, and conference travel support and consultancy/speaker honoraria from Genzyme, Novartis, Biogen Idec, Sanofi Aventis, Teva, BioCSL and Merck Serono.