Author's response to reviews

Title: Differential glatiramer acetate treatment persistence in treatment-naive patients compared to patients previously treated with interferon.

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Article title: Differential glatiramer acetate treatment persistence in treatment-naive patients compared to patients previously treated with interferon.

Former article title: Differential glatiramer acetate treatment persistence in treatment-naive patients compared to switchers from interferon.

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Dear Mr Jhonell De Los Santos and Dr Roberto Bergamaschi,

Please find enclosed our modified manuscript entitled “Differential glatiramer acetate treatment persistence in treatment-naive patients compared to patients previously treated with interferon.” by Fernandez-Fournier et al, currently under consideration for publication as a Research article in BMC Neurology.

We are very grateful to you for the opportunity to send back this revised version of the manuscript, with the requested modifications, as they improve the text. We are providing, as requested, a revised manuscript and a full covering letter with a point-by-point response to the requested additional modifications.

We look forward to hearing from you at your earliest convenience. We are willing to make further revisions if deemed necessary. Please address all correspondence to: fernandezfournier@hotmail.com

Yours faithfully,

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The manuscript has been revised and edited for the following:

Editor’s comment: "Minor essential revisions"

We want to thank the reviewers and the editors for their helpful comments in ameliorating the quality of this manuscript.

1) L.97-99: I have some reservations as to whether any exposure to interferons prior to glatiramer acetate, irrespective of its recency, can be termed “treatment switch?. There are multiple possible scenarios (e.g. recommencing therapy after pregnancy, a “treatment holiday” of several years in those with inactive disease or lack of compliance etc.) which would fulfil the relatively broad definition of treatment switch used here. The authors should either restrict the analysis to the true switchers (defined by a maximum “intertreatment gap”) or adjust the terminology to reflect the relatively broad rules for previous exposure to interferons.

We agree, as suggested, that the term “previous exposure to interferons” may be a more correct term than “treatment switch or switchers” to describe the group of patients that are not treatment-naive in this study. We have not restricted the analysis to patients switching therapies with a maximum inter-treatment gap as we have aimed to analyse, as truly as possible, our real-life situation, and have therefore maintained these two treatment groups: treatment-naive patients prior to GA exposure vs. patients who had been previously treated with interferon.

We have thus adjusted the terminology in the manuscript as follows:

Lines 1 - 3: The new title now reads: “Differential glatiramer acetate treatment persistence in treatment-naive patients compared to patients previously treated with interferon.”

Lines 26 - 30: In the Abstract’s Background sub-section we no longer talk about studying the effects of switching therapies but of studying the effects of use of previous therapies. This section now reads: “Although disease modifying drugs’ (DMD) efficacy and side effects have been fully analysed in clinical trials, the effects of previous therapy use are less well studied. We aimed to study medication persistence with glatiramer acetate in treatment-naive patients and in patients previously treated with interferon.”

Lines 81 – 88: Similarly, the last paragraph in the Background section now reads: “Although DMD efficacy and side effects have been fully studied in clinical trials, the effects of use of previous therapies are less well known. Analysing experience gathered from ‘real-world’ clinical practice can help make rational individualised treatment decisions. Treatment persistence with GA when used after treatment failure with IFNs is not well characterized. The aim of this pilot exploratory study was to describe GA use and treatment persistence, measured as time to GA treatment discontinuation, in a group of Relapsing Remitting MS (RRMS) treatment-naive patients and in a group of RRMS patients previously treated with IFNs.”

Lines 96 - 99: In the Methods section we specify how we define our two groups: “Patients were included according to their clinical history in one of the following two groups: treatment-naive patients and patients previously treated with IFN. All RRMS patients who had been exposed to IFN before initiating treatment with GA were included.”
The term “interferon-switcher” has been changed to “previously treated with interferon” or “previous exposure to IFN” throughout the manuscript.

Figure 3 and Table 1 have been similarly modified.

The second and third lines of the first paragraph of the Discussion now read: “Little is known on how the use of previous DMDs affects treatment outcome. This is the second published study that aims to describe differences in treatment persistence with GA in treatment-naïve patients with respect to patients previously treated with IFNs, and the first to do so in Europe.”

The Abstract’s conclusion now reads: “Patients who had been previously treated with interferons presented a lower probability of glatiramer acetate discontinuation than treatment-naïve patients.”

The manuscript’s conclusion now reads: “patients with previous exposure to IFN presented a significantly lower probability of GA treatment discontinuation than treatment-naïve patients.”

As part of the limitations subsection of the Discussion (p 12), the authors should state that the analysis was not adjusted for disability, which is known to be associated with the probability of treatment discontinuation, and therefore the results could be biased if the levels of disability differed between the cohorts (which is not possible to assess objectively, as this information was only available for 55% of the studied cohort).

As suggested, we state in the limitations subsection of the Discussion that the lack of adjustment for disability could be a potential source of bias. The following sentence has been incorporated: “We were not able to eliminate potential bias by adjusting for disability which can influence treatment persistence [22, 25].”

This has been modified as suggested, giving the break-down as a proportion of the patients who stopped GA within each subgroup:

“…all patients with previous IFN exposure escalated therapy to second line drugs, while those in the treatment-naïve group followed a variety of pathways, including switching to second-line drugs (60.4% patients), but also to IFN (29.2%) and immunosuppressive drugs (4.2%), as well as stopping treatment altogether following patients’ demands (4.2%) or conversion to secondary progressive MS (2.1%).”

In the Methods, the authors state that they used both logrank test as well as the proportional hazards model to compare discontinuation rates between the cohorts. While this may seem as a duplicity (where the adjusted Cox model is the superior model), in fact, the authors (correctly) only report the results of the Cox model to compare the two groups.

We thank the editors/reviewers for the comment. We have corrected this error:
Lines 37 – 38: The Abstract’s methods subsection now reads: “The Kaplan Meier method and Cox regression model were used to estimate time to and risk of treatment discontinuation.”

Lines 141 - 142: In the Methods section, the following sentence has been deleted: The Logrank test was used to test for differences between groups.

5) l.121: I assume that the ?increased T2 lesion load? refers to both new and enlarging T2 lesions.”

Lines 121 - 122: This assumption is correct. We have added the words “including both new and enlarging T2-lesions” to clarify this point.