Author’s response to reviews

Title: Outcome of MS relapses in the era of disease-modifying therapy

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Author’s response to reviews:

Dear Dr Lou,

thank you for the email message as of Apr 11, 2017. We appreciate the time and effort put into the manuscript by the reviewers, Drs Monson and Chan. We were happy to see that we met the first reviewer’s requests, and were also happy to address the second reviewer’s suggestions.

Please find enclosed a revised version of the manuscript. We would like to list our modifications according to the second reviewer’s suggestions.

(Reviewer #2): This manuscript covers an interesting scientific question and the study is generally well performed. Drawbacks are an overall small and somewhat heterogeneous patient population reflecting clinical practice and lack of longer term follow up.

Other issues are listed below:
- Please specify the definitions of complete, partial, no response and worsening within your method section (EDSS-based, FS based definition?).

Authors’ response: The following details were added in the Methods section (lines 109-117 of the revised version):

"Recovery was defined based on both subjective symptoms and objective findings on neurological examination related to the current relapse (scored by Kurtzke Functional System and EDSS ratings). “Complete recovery” denotes complete resolution of symptoms and a neurological examination as documented pre-relapse (or, in first episodes, a normal neurological examination, EDSS 0). Accordingly, “partial response” refers to improvement in symptoms or/and FS score not returning to pre-relapse score, “no response” to unchanged symptoms and neurological findings, and “worsening” to an increase in the FS score relevant to the current relapse (which was always paralleled by an increase in symptoms)."

- There is an ongoing discussion regarding late effects of methylprednisolone therapy on relapse symptoms. Thus the correct time point for re-evaluation of relapse symptoms and initiation of an escalated relapse therapy is yet not well defined. Because the follow up visit of the presented study was performed in median 14 (IQR 7-38 days) after relapse treatment it might be possible to search for difference in treatment response in regard to time of follow up. I would therefore kindly ask the authors to stratify their patient population into those with early versus late follow up visit and compare treatment responses. Likewise, do the authors have any data on late recovery, e.g. during routine controls 3 and 6 months afterwards?

Authors’ response: Thank you for this suggestion for an additional point of view. We analyzed outcomes and treatment decisions based on time to follow-up, yielding remarkably similar results in the two groups. This information was added in the Results section (lines 252-257):

"To address the question on optimal timing of the follow-up visit, we analysed outcome and treatment decision in the patients seen early (within 14 days) or late (15-42 days) after primary relapse treatment, based on the median time to follow-up. This revealed full remission in 24 and 28%, partial remission in 46 and 43%, no response in 19 and 23%, and worsening in 8.7 and 2.3%, respectively. Escalation treatment was indicated in 24 and 21%, respectively."
We commented on this finding in the discussion as follows (lines 327-337):

"With respect to optimal timing of the follow-up visit, longer follow-up (2-6 weeks) yielded a slightly higher proportion of “full recovery” while “worsening” was stated more often when follow-up was shorter (up to 2 weeks). Interestingly, however, the indication for escalating relapse treatment was confirmed in a remarkably similar proportion. Thus, patients recovering, but also those requiring escalation treatment can be identified early after primary relapse treatment. Given that some patients require second escalation treatment which should be started within a reasonable time from relapse onset, this argues for a follow-up visit at around two weeks after primary treatment, to allow for an equivalent period to evaluate the effect of escalated therapy."

- When was response to escalating relapse therapy assessed

Authors´ response: A follow-up visit was scheduled after each (primary or escalation) treatment at a 10-14 day interval. We added this detail in the Methods section (line 105-106).

- Could the overrepresentation of sensory relapses impact their results?

Authors´ response: While this is, of course, a valid concern, we believe that defining response by both subjective and examiner-rated findings prevented a major bias in the conclusion. We feel that after adding the details of response assessment, readers will be able to appreciate this point and did not specifically comment on this point; should the reviewer prefer a specific discussion, we will of course be happy to add it.

- Given that this was a prospective study the authors should provide information on ethics or a statement/waiver, why a vote/ICF was not necessary.

Authors´ response: Upon admission to this hospital, patients are requested to consent to statistical analyses of anonymous diagnostic and treatment information for scientific and quality assurance purposes. We included only anonymous data from patients who consented to this request. This information was added in the Methods section (lines 92-96).
- How about the patients who were also part of another study? Is this covered by the other study protocol/ICF?

Authors´ response: The protocol and ICF of the other study did not object to using data for observational purposes.

Again, we thank the reviewers for their input which has certainly contributed to improving our manuscript. We hope that the adaptations outlined above will be sufficient to enable publication. Otherwise, please let us know, and we will be happy to adjust the manuscript further.

Sincerely,

Prof. Dr. Florian Then Bergh
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