Author's response to reviews

Title: Monthly i.v. methylprednisolone in relapsing-remitting MS - Reduction of enhancing lesions, T2 lesion volume and plasma prolactin concentrations

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Author's response to reviews: see over
Manuscript ID 1854764528926011
“Monthly intravenous methylprednisolone in relapsing-remitting multiple sclerosis - Reduction of enhancing lesions, T2 lesion volume and plasma prolactin concentrations” by F. Then Bergh, T. Kümpfel et al.

Dear Dr Norton,

thank you for your email as of April 04, 2006, informing us about the results of the reviewers’ and your own editorial considerations. We appreciate the time and effort taken by all those involved in constructive criticism, and the willingness to have their identity communicated. We feel that the suggested additions and revisions, which we have addressed as detailed below, have improved and clarified the manuscript. Please find enclosed a revised version of the manuscript.

The following changes have been made, according to the reviewers’ comments:

Dr. M. Zorzon:
- **Historical comparison group:** The reviewer obviously raises a valid point, inherent in all analyses comparing experimental subjects to a historical control group. In order to make the paper most informative to readers, we have included more information about the imaging data included in the Sylvia Lawry Center database. In this respect, two points deserve mentioning: 1. The experimental data provide, by themselves, statistically sound evidence of an effect of time, coincident with treatment initiation. 2. As the reviewer correctly points out, the comparison to patients from the SLC database is provided as a supporting piece of information, and we have deliberately labelled these data a “comparison” rather than a “control” group.
- **Appropriate sample of patients:** Judging from imaging data, our patients do appear to exhibit more inflammatory activity than an unselected group of MS patients. It may be of interest that our MRI inclusion criteria applied to 40% of patients first selected on fairly standard, and representative clinical criteria. Our data, and potential future research, may best apply to a certain group of MS patients, and we have strengthened this point in the discussion, subheading “Clinical prospects of...”
- **Side effects:** The recently published analysis of side effects (or rather lack of side effects) of repeated glucocorticoids was included in the “Discussion” section, subheading “Clinical prospects...”
- **Figure designation:** Figure 1 is now referred to in the “Subjects and Methods” section, subheading “Patients”. The designation of figure 2 was corrected in the first paragraph of the “Results” section.
Dr. H. P. Hartung:
- Relation of Gd+ MRI to clinical efficacy: The suggested additional information on clinical characteristics and course were included in the text and tables, where available. Since it was clear that trial duration and sample size would not allow even preliminary conclusions about clinical efficacy, the MSFC and other detailed clinical tests were not performed. While the reviewer is right in stressing clinical effects over MRI measures, this particular trial was designed to provide initial information on the effects of pulsed IVMP on inflammatory activity. This approach appears relatively common in the development of new therapeutic strategies in MS. We have pointed out this aspect again in the discussion.
- T2 lesion load: Total T2 lesion load, expressed as T2 lesion volume [ml], is given in table 2. The number of individual T2 lesions was not determined, taking into account the known difficulties in reliable segmentation of, e.g., large individual vs. confluent lesions.
- MRI protocols: We are grateful for the reviewer’s hint; more detailed information, now given as requested, is obviously helpful for readers. Post-contrast T1 weighted images were acquired at a standardized interval of 6 minutes after injection of Gd-DTPA. In that respect, these trial scans were performed in a different fashion than routine clinical protocols. The respective parameters for imaging data included in the SLC database are largely equivalent and have been added in the “Subjects and Methods” section, subheading “Comparison group.”
- Diurnal variations: Patients were seen at the clinic, and blood was drawn, in the afternoon, between 15:00 and 18:00. MRI was performed after blood sampling. Endocrine stimulation tests were performed at standardized hours (8:00 for the ACTH test; 15:00 for the dexamethasone/CRH test, as outlined in the cited reference). These additional pieces of information have been added in the “Subjects and Methods” section, subheadings “Serum cytokine and...” and “Safety.”
- Combination therapy: We have deleted the comment about combination therapy altogether (“Discussion” section). It was not our intention to suggest combination therapy with the approach we studied; rather, we wanted to point out that a similar kind of combination has been suggested, and independent effects may apply.
- The bad link to the the SLC website’s list of data donors has been updated.

Name change:
Dr. Michaela Schwan has married and prefers to be listed under her new surname (maiden name Gottschalk). We would like to ask to grant the exceptional permission for a change of an author’s name due to this circumstance.

Formatting:
- A “Competing interests” section has been added after the Conclusions.
- Title: The acronyms have been replaced by the appropriate words fully spelled out.
- Formatting instructions: The entire manuscript has been formatted according to the template provided.

Files:
We are uploading three files: This cover letter (ThenBCoR.doc), the revised manuscript as it should be used for further processing (ThenBergh_Revision.doc) and, as “additional material file”, with changes highlighted using MSWord’s change tracking feature (ThenBergh_RevisionMarked.doc). The figure files are unchanged. We hope this will facilitate editing.

We hope that in the current form, the manuscript will be suitable for publication in BMC Neurology. Again, we would like to thank the reviewers and editorial staff for their contributions.

Sincerely,

Dr. Florian Then Bergh
Neuroimmunology