Reviewer's report

Title: Prognostic implications of a carefully performed neurological assessment in patients with a first event suggestive of multiple sclerosis

Version: 3 Date: 27 October 2008

Reviewer: Corree Laule

Reviewer's report:

Overall, this is an interesting paper which investigates if one can identify which patients with a clinically isolated syndrome suggestive of MS have the highest risk of going on to develop clinically definite MS. The findings are potentially very useful and with some modifications to the manuscript, I feel this work is definitely worth publishing.

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Major Compulsory Revisions (The author must respond to these before a decision on publication can be reached)

1. The current manuscript expands and builds substantially on a minor finding reported in a previous publication which the authors have not referenced (Subgroups of the BENEFIT study: risk of developing MS and treatment effect of interferon beta-1b. Polman C, Kappos L, Freedman MS, Edan G, Hartung HP, Miller DH, Montalbán X, Barkhof F, Selmaj K, Uitdehaag BM, Dahms S, Bauer L, Pohl C, Sandbrink R; BENEFIT investigators. J Neurol. 2008 Apr;255(4):480-7). The previous publication specifically states “the risk of CDMS in monofocal placebo-treated patients with ≥ 9 T2-lesions was 55% and 31% in patients with < 9 T2-lesions. The risk of CDMS in patients with Gd-lesions at screening was 63%, and 36% in patients without Gd-lesions. The risk of CDMS was highest in monofocal patients with ≥ 9 T2-lesions and ≥ 1 Gd-lesion (75 %).” The authors later go on to say “Of note, neither the risk of CDMS nor the treatment effect was increased in multifocal patients with ≥ 9 T2-lesions and/or at least 1 Gd-lesion at screening (data not shown)”. So, essentially, one of the main points of the current manuscript (that the risk for CDMS was highest in monofocal CIS patients with ≥ 9 T2-lesions and ≥ 1 Gd-lesion at screen, while MRI findings were not predictive of risk for multifocal patients) has already been suggested in this previous publication. This is indeed a minor portion of this previous publication and it is perfectly appropriate for the authors to expand on this finding in the form of a new, far more detailed manuscript. However, the previous work needs to be referenced.

2. Abstract: The conclusion of the Abstract states that “a carefully performed neurological assessment of symptoms and signs is important for defining the risk of conversion to CDMS”, when in fact the results of the study show that time to CDMS was similar for monofocal and multifocal patients. Therefore, the neurological assessment alone is not sufficient for defining the risk of conversion.
to CDMS, and it is only when the assessment is combined with MRI (in particular for the monofocal patients), that one may be able to better define the risk of conversion to CDMS. Please reword the conclusion.

3. Patients and Methods: Please include a sentence about what MRI sequences were collected for the study. Also, was Gd by weight or some standard dose?

4. Patients and Methods: What software was used for statistical analysis?

5. Results: Table 1 shows that there was no difference in the number of mono and multifocal patients presenting with at least 1 Gd lesion. Was there any difference in the average number of enhancing lesions between the 2 groups at baseline? Likewise for the average number of T1 lesions.

6. Results: The first 2 paragraphs/sentences under the section entitled “Comparison of the impact of MRI findings at screening, month 3, and month 6 on time to CDMS within the monofocal and multifocal group separately (placebo patients)” are somewhat difficult to read. When one first reads it, it is unclear what the p-values are referring to, as the comparison isn’t made until the end of the very long sentence. Perhaps it can be reworded to something like “The risk of CDMS in monofocal placebo patients was significantly higher if # 9 T2 hyperintense lesions were present at screening (p=0.032), etc…”

7. Results: Table 4 seems to be missing from my version of the manuscript. Perhaps it was not included as it is labeled “supplemental”? I would like to see it if possible.

8. Discussion, 4th paragraph: The authors suggest in the last sentence of this paragraph that a trend exists for more multifocal patients by symptoms to show at least one Gd lesion (p=0.3376) and for more multifocal patients by signs to show at least one T1 lesion (p=0.7627). While I can appreciate the authors are trying to further support their hypothesis, I was under the impression the use of the word “trend” applies when the p-value is within a range considered close to but does not achieve statistical significance. I would not consider p=0.3376 or p=0.7627 to be close to p=0.05 (which the authors have set as their cutoff for significance). I have typically observed p-values between 0.06 to 0.12 referred to as trends in the literature…

9. I feel the current title of the manuscript “Prognostic implications of a neurological assessment in clinically isolated syndrome patients” does not accurately convey the potential importance of the findings within the manuscript (especially if one were to interpret the words “neurological assessment” as based on clinical characteristics (signs & symptoms) alone, as the clinical findings show that time to CDMS was similar for monofocal and multifocal patients). I would encourage the authors to come up with a more descriptive title which highlights the main findings of the study. A few possible starting points based directly on sentences from the discussion that come to mind are “…In monofocal, but in not multifocal patients, the risk for CDMS depends on MRI findings” or “…only in CIS patients with monofocal clinical presentation do MRI findings have prognostic
Minor Essential Revisions (The author can be trusted to make these. For example, missing labels on figures, the wrong use of a term, spelling mistakes)

ABSTRACT
-Background; first sentence: as both dissemination in space and time is required to make a diagnosis of MS, please revise to include “and time”.
-Methods; third sentence: in all other portions of the manuscript the authors refer to “mono” and then “multi” focal, whereas here it is the reverse. Please be consistent.

INTRODUCTION
-page 5, reference (2) should not be superscripted. (page 5)
-last sentence: please reword to “…period of the BENEFIT study.” (page 6)

PATIENTS AND METHODS
Study design, patients and procedures
-second paragraph, third sentence: you mention “MRI” and then “MRI findings”. What is the difference between the two? Please clarify or remove one. (page 7)
-third paragraph, first sentence: you have previously defined International Panel as IP in the introduction. Either then use it throughout or remove the original definition. (page 7)
-fourth paragraph, first sentence: should read “In the case of…” (page 8)

Statistical analysis
-first paragraph, first sentence: change to “…versus by symptoms only.” (page 8)

RESULTS
-first paragraph, third sentence: this sentence is currently incomplete. Please reword to “…and 176 received placebo.” Or “…and 176 were in the placebo arm.” (page 10)
-reference to Figure 1 – in the text you refer to the figures as 1a,b but the caption is 1A, B. Be consistent. (page 11 and 12)
-section entitled “Comparison of key baseline characteristics…”, the first sentence is incomplete and should read “…symptoms, while 100 (45%) presented by signs…”

Level of interest: An article of importance in its field

Quality of written English: Needs some language corrections before being published
**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests.