Reviewer's report

Title: Vitamin D supplementation for patients with Multiple Sclerosis treated with Interferon-beta: a randomized controlled trial assessing the immunomodulator properties and the effect on flu-like symptoms

Version: 1 Date: 5 February 2013

Reviewer: Trygve Holmoy

Reviewer's report:

Although small, this study has interest as it addresses a relevant question; the effect of high dose vitamin D on flu-like symptoms in multiple sclerosis patients treated with interferon beta.

Major Compulsory Revisions:
1) please provide data on the timing of inclusion of patients in the study - was this distributed throughout the year or biased towards any particular month or season?

2) p-values should be given in a consistent way: Thus, in table 1, exact p values are given for each comparison, whereas the term "non significant" is used in table 2. Moreover, a level of significance should be defined and used throughout. For example, the p value for reduction in PTH in the high dose group is 0.06, which is usually not considered significant. Nevertheless, it is stated that the PTH level was reduced.

3) Please provide data on coefficient of variations (CV) for each analyte. Moreover, please state clearly whether all measurements of each analyte from each patient was performed in the same assay (preferentially also in the same ELISA plate), or in separate assays at different time points. Inter- or intra assay CV should be stated as appropriate.

4) Figure 4, showing the proportion of patients with either increased or decreased levels of IL17 is not clear (how small changes are defined as increase/decrease?), and should preferentially be replaced by a figure showing coupled data for baseline and month 3 in each individual patients (for example data points connected with a line). This will allow the reader to see the magnitude of the increase or decrease. Moreover, the least difference needed to be deemed as an increase or decrease should be defined.

5) Please state how compliance was obtained. Could lack of compliance explain why the increase in 25(OH)D levels was not maintained in the low dose group? (Seasonal fluctuation, as suggested by the authors, is not necessarily a good explanation, as baseline and baseline and month 12 is expected to be quite similar).

6) Please provide data on vitamin D supplementation at baseline. This is
important, as I assume that patients were not allowed to continue this supplementation after entering the study (please correct me if I am wrong). Thus, it might well be that patients in the low dose group actually reduced (or at least did not change) their vitamin supplementation. Could this have contributed to the lack of persistent increase in 25(OH)D levels in the low dose group?

7) Please comment on the increase in mean levels of IL17 in the low dose group.

8) There are some typos that need to be corrected (including Scandinavian names in the reference list)

9) Please provide additional details on the study drug (brand name, manufacturer). Was the vitamin D3 content of the study drug checked?

Minor Essential Revisions

1) What was the rationale for the selected high dose vitamin D dose? Was the increase as expected?

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

Quality of written English: Needs some language corrections before being published

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests:

I am in the steering committee of a randomised clinical trial of high dose vitamin D as add-on treatment to interferon beta in multiple sclerosis