

OPEN PEER REVIEW REPORT 1

Name of journal: Neural Regeneration Research

Manuscript NO: NRR-D-21-00473

Title: Is there a window of opportunity for therapeutic use of vitamin D in multiple sclerosis?

Reviewer's Name: Anne L. Astier

Reviewer's country: France

COMMENTS TO AUTHORS

This review presents updated data on the role of vitamin D in MS pathogenesis. It is well written, reads well, with nice illustrations of the pathogenesis of MS/EAE. It has a very detailed introduction encompassing the molecular and cellular mechanisms involved in the disease, and describing the immunology of MS. This is followed by a section of the immunomodulatory role of VitD, and its role in neuroprotection. The review then highlights the different trials supplementing patients with VitD, which have given mixed outcomes, and this is well summarized in a Table. A last part is back to the EAE model and finishes with a summary of the work of the team. This includes some raw data on the potential of oral vitamin D given very early in disease (d1 after induction) or later (day 7), showing better improvement of disease when given at the earlier time point and with no effect of circulating calcium levels. Please address why the 200ng dose is not given in the early phase?

This highlights the beneficial role of vitamin D in the early phase, before the clinical signs. The authors could maybe modulate this by mentioning how identifying MS in the prodromal phase remains challenging.

Some minor comments:

I would suggest making it clearer whether the studies relate to mice, humans or both.

To add subsections in the immunomodulatory sections for ease of reading.

Sakaguchi probably not the right ref in this sentence. "the contribution of B cells, mitochondrial dysfunction, oxidative stress and inflammasome activation have been characterized as pivotal players and potential therapeutic targets in this disease'

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Reviewer's Name: T H

Reviewer's country: NORWAY

Date sent for review: 2021-7-7

Date reviewed: 2021-7-7

Review time: 1 Days

1. Is there any content which has been previously presented in a review??

Yes, there has been very many reviews on vit D in EAE/MS

2. Do you consider this paper is hotspots or important areas in the research field related to neural regeneration?

No

3. Is it a balanced and unbiased overview of current understanding?

No

4. Is the interpretation and presentation of results of previous studies accurate and precise?

No, the use of references is quite selective and sometimes misleading

5. Is the manuscript presented in an intelligible fashion and written in standard English?

Yes

6. Your peer review comments will be published as an open peer review report. Do you agree to have your name included with the published article?

No

Manuscript Rating Question(s):	Scale	Rating
The subject addressed in this article is worthy of investigation. (3 as the best score)	[1-3]	3
The information presented was new. (5 as the best score)	[1-5]	2

COMMENTS TO AUTHORS

This paper reviews some current concepts on the immunopathogenesis of EAA and MS, and in particular the potential role of vitamin D. The scope is therefore quite wide, and the first part of the paper is not sufficiently focused on the main topic, which is the role of vitamin D.

Although much knowledge is included, I find the use of references somewhat selective and sometimes misleading. For example, it is not mentioned that neither the SOLAR nor CHOLINE study reached their primary endpoint, and is therefore per definition negative. This is not acceptable. Another example is the reference to the impact of interferon beta treatment on the association between vitamin D levels and disease activity in MS patients. This was not the case in the OFAMS study, where more than 80 patients were followed closely with clinical assessments, MRI and inflammation markers before and during interferon beta therapy. On the contrary, associations with vitamin D was only present before interferon beta. PMID: 22700809 PMID: 25773151.



In the table of intervention an observational studies, an observational study of the association with vitamin D is included. This is misleading. One of the major RCT studies, performed by M Kampman et al, is not included. This was another negative study. Even though the impact is somewhat reduced by the low relapse frequency at baseline and the lack of MRI, it definitely should be mentioned, along with the (also negative) substudy of the effect on neurofilament by Røsjø et al PMID: 30317548