Author's response to reviews

Title: High-dose vitamin D supplementation and Plaquesnil treats refractory immune thrombocytopenia: two case reports

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Author's response to reviews: see over
To: Dr. Michael Kidd, Editor-in-Chief, Journal of Medical Case Reports

Thank you for the thorough review of this manuscript. We have made the requested formatting changes. We appreciate the reviewers’ comments, which will improve the quality of the manuscript. Please see our point-by-point response to each reviewer below.

Best wishes,

Barry Bockow, MD, FACP

Point-by-point responses to reviewers

Reviewer 1

Thank you for the positive review.

Comments to authors:

Page 3 and 4. What was the role of the oncologist in the management of these patients?
Did these patients have an underlying malignancy?

The oncologist was initially consulted because of the serious life threatening hematologic condition. However, when they were unsuccessful in treating this condition they consulted the
Page 3 and 5. For both patients, what rheumatological criteria were used to classify these patients as having SLE and Sjögren’s Syndrome?

We used the full composite of clinical data, including positive ANA and SSA levels as well as a very strong history of sicca complex with multiple joint complaints and cytopenia. We clarified this in the manuscript (page 5, third paragraph; page 7, third paragraph).

Pages 3-5. Were there significant calcium, phosphate, and creatinine levels during vitamin D therapy.

There were no significant changes during therapy with vitamin D and this has been added to the text (page 7, second paragraph).

Page 4. Vitamin D levels were not low but normal, although borderline low. Is it customary to give high-dose vitamin D to patients with borderline low vitamin D levels?

This is a very important question. In our experience almost all of our patients respond better after their vitamin D levels are increased to 40-50 ng/ml or above.

With our newly diagnosed rheumatoid arthritis patients we have noticed enhanced response to our usual treatment regimens after treatment with high dose vitamin D.
We have added this comment to the manuscript (page 5, last paragraph, continued on page 6).

Page 4. What was the rationale to increase Vitamin D doses after 1 week of treatment?

The patient’s platelet count had not responded significantly, and clinically it was felt that a higher dose would be more effective.

Page 4. What do you mean with “In response to this 100-fold decrease”? 100-fold decrease of what? The platelet count fell from 140,000 to 18,000, a less than 8-fold decrease.

Thank you for pointing out this mistake. We have corrected the text.

Page 5. What were the baseline 25-OH vitamin D levels of this patient? Her initial 25-OH vitamin D level was 17 ng/ml.

Page 6. The sentence “While ITP is commonly idiopathic, several treatments are currently in use...” is not logically consequential. Remove the initial part “While ITP is commonly idiopathic”.

Thank you for pointing out this mistake. We have corrected the text.
Page 7. Can the authors discuss the potential side effects of plaquenil and high-dose vitamin D. What monitoring strategy of these side effects do they recommend?

Plaquenil has been used clinically for over 50 years and has an exceptional safety record. It is probably the safest among the disease-modifying agents that rheumatologist prescribe. Retinopathy is extremely rare, and the few reported cases were in patients taking the drug for more than 5 years. Baseline and annual eye exams are recommended. Other less common side effects include rash, tinnitus and muscle aches. It should not be prescribed to patients with G6PD deficiency.

We have added this discussion to the manuscript (page 11, last paragraph, continued on page 12) and included the reference: Marmor MF, et al. Recommendations on screening for chloroquine and hydroxychloroquine retinopathy: a report by the American Academy of Ophthalmology. *Ophthalmology*. 2002 Jul;109(7):1377-82.

Page 7. Could Vitamin D produce a platelet response irrespective of plaquenil?

Please discuss.

This is a good question. We believe there is a synergism between the two drugs based on our clinical experience. It would be of interest to study what effect high dose vitamin D alone has on increasing platelet counts.
Since patient 1 had normal vitamin D levels, one can speculate that high-dose vitamin D is beneficial in patients with ITP. You may also want to discuss that vitamin D deficiency is an extremely prevalent condition, affecting as many as half of adults and children in the U.S.

We agree with the reviewer that this is an important public health concern and many children and adults probably should be taking supplements to at least achieve normal levels. We have added point to the text (page 12, first full paragraph).

Reviewer 2

Thank you for the positive review.

Comments to authors:

Autoimmune thrombocytopenia (ITP) is classified in primary and secondary forms. The former form is characterized by an isolated thrombocytopenia without any association with other diseases. In contrast, the secondary form occurs in association with underlying diseases, i.e. infections, autoimmune diseases, and lymphoma. A successful treatment of the causative underlying disease usually results in an improvement or recovery of ITP. I think, these cases worth
reporting.

The authors describe two patients with secondary ITP. Both patients seem to have SLE/Sjörgen Syndrome, which may successfully be treated with hydroxychloroquine, and presumably with high-dose vitamin D alone. Ultimately, vitamin D is involved in wide variety of biological processes including bone metabolism, immune system and cell proliferation and differentiation. Thus, I do not wonder whether both drugs may have a synergetic effect. It is highly interesting to know whether the authors have also tried to treat patients with primary ITP.

We appreciate this question. We have not treated any patients with primary ITP.