Author’s response to reviews

Title: Administration of Anti-receptor Activator of Nuclear Factor-kappa B Ligand (RANKL) Antibody for the Treatment of Osteoporosis was Associated with Amelioration of Hepatitis in a Female Patient with Growth Hormone Deficiency: A Case Report

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Version: 1 Date: 02 Nov 2016

Author’s response to reviews:

November 3, 2016

Dear Editor of BMC endocrine disorders

We thank you and the reviewers for the comments on our manuscript (Manuscript ID: BEND-D-16-00156) entitled “Improvement of Elevated Liver Enzymes by an Anti-receptor activator of nuclear factor-kappa B ligand (RANKL) Antibody for Treatment of Osteoporosis in a Female Patient with Growth Hormone Deficiency: A Case Report”. Herewith we are sending the manuscript revised according to the revisers' corrections. Please find the points of revision and responses to the reviewer's suggestions in the following pages. We are very grateful if the revised manuscript is now suitable for publication of “BMC endocrine disorders”.

Yours sincerely,

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Reviewer’s comment:

Takeno and colleagues report a case where they observed an improvement in liver function tests in association with administration of denosumab. They propose that there may be a causal link between anti RANKL therapy and improvements in liver enzymes in non-alcoholic steatohepatitis (NASH).

1. Hydrocortisone was administered at a very low dose. Why was this?

Furthermore, a very small dose of levothyroxine was administered after a number of months. Why was this?

Response:

Thank you very much for your practical comments. Five mg/day glucocorticoid is sufficient dose for her to avoid adrenal insufficiency because her build is very small. The low dose of levothyroxine (25 μg) seems to be suitable to keep her thyroid function at that time.

Reviewer’s comment:

2. The patient was only 47 years of age and the overall risk of fracture was relatively low. Why was denosumab therapy initiated? Why were no other forms of anti-fracture therapy considered? Was she administered HRT?

Response:

Thank you very much for your practical comments. Estrogen and its analog agent interfere in the action of GH and reduce IGF-1 production. These effects are not beneficial for patients with GH deficiency.

The effect of denosumab disappears in a shorter period (within six months) than bisphosphonate, which seems to be a good point of denosumab when atypical femoral fracture is occurred or
when we can use new anti-osteoporotic agents. Therefore, we chose denosumab to treat her osteoporosis.

Reviewer’s comment:

3. There does appear to be a temporal association between the administration of denosumab and an improvement in liver enzymes. Causality can not automatically be inferred and thus the language and terminology used needs to be softened throughout the manuscript.

a. I think the word ‘associated’ rather than caused or improved should be used throughout. The conclusion states that was that anti-RANKL antibody… improved elevated liver enzymes. Instead it would be more appropriate to state that administration of anti-RANKL antibody… was associated with an improvement in elevated liver enzymes.

Response:

Thank you very much for your precious comments and recommendations.

According your comment, we have edited manuscript title in page 1, lines 1-3, running head in page 2, line 5, and several sentences in page 4, line 20 to page 5, line 1, page 7, line 7, and page 8, lines 8-9 which you mentioned above. We had changed the word “improvement” to “amelioration” in page 3, line 9, and page 8 line 1, “improved” to “decreased” in page 6, line 13, “improve” to ”associated with” in page 7, lines 11-12, “cause” to “associated with” in page 7, lines 6, and “crucial causes” to “potential pathogenesis” in page 7, line 9. We have added the word 'may' in page 8 line and page 8, line 11.

Reviewer’s comment:

4. Message could be conveyed in a much shorter, succinct document and whole script could be reduced by at least 30% in length.

Response:

Thank you for your comments. We shortened our manuscripts as much as possible.