

PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 56760

Title: Effects of denosumab treatment in chronic liver disease patients with osteoporosis

Reviewer's code: 03260101

Position: Peer Reviewer

Academic degree: MBChB

Professional title: Surgeon, Surgical Oncologist

Reviewer's Country/Territory: United Kingdom

Author's Country/Territory: Japan

Manuscript submission date: 2020-05-19

Reviewer chosen by: Jia-Ping Yan

Reviewer accepted review: 2020-06-07 14:29

Reviewer performed review: 2020-06-11 13:06

Review time: 3 Days and 22 Hours

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input checked="" type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
Peer-reviewer statements	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

comments passed on to the editorial office

PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 56760

Title: Effects of denosumab treatment in chronic liver disease patients with osteoporosis

Reviewer's code: 04105237

Position: Peer Reviewer

Academic degree: MD

Professional title: Doctor

Reviewer's Country/Territory: Mexico

Author's Country/Territory: Japan

Manuscript submission date: 2020-05-19

Reviewer chosen by: Jia-Ping Yan

Reviewer accepted review: 2020-06-10 01:51

Reviewer performed review: 2020-06-15 04:33

Review time: 5 Days and 2 Hours

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input checked="" type="checkbox"/> Rejection
Re-review	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
Peer-reviewer statements	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

This is an interesting study, aiming to evaluate the effect of denosumab in patients with CLD and osteoporosis, however, the study has several major issues that must be improved to better sustain the conclusions stated by the authors: 1) Design of the study: this is a quasi-experimental study, not including a proper control study, rendering the main findings difficult to fully sustain. Even though an improvement in BMD and markers of bone turnover and quality was seen, there is no a fair point of comparison, as had been done with a different analysis. The same is true for occurrence of adverse events. 2) Description of patients with CLD is rather poorly addressed throughout the manuscript. None of the patients with autoimmune CLD were receiving steroids during the study? Were these autoimmune liver diseases only PBC and PSC, or was AIH also included? The basic characteristics of patients with cirrhosis are not shown (i.e. MELD and Child-Pugh scores). 3) Regarding safety of the drug, there are no biochemical tests at follow up, which would be the most appropriate given that the effect of the drug in chronic liver diseases (specially in cirrhosis), has been scarcely studied. 4) Due to the design of the study, it is difficult to reach those conclusions, mainly because there is no comparison group nor a sample size estimation. 5) How many patients were diagnosed as postmenopausal osteoporosis? And how many had CLD-related osteoporosis? There is no description of this point, and together with the more detailed characteristics of CLD (and specially cirrhosis) is extremely important in order to provide to the reader with sufficient information to implement this intervention in clinical practice.

PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 56760

Title: Effects of denosumab treatment in chronic liver disease patients with osteoporosis

Reviewer's code: 02439211

Position: Peer Reviewer

Academic degree: PhD

Professional title: Professor

Reviewer's Country/Territory: China

Author's Country/Territory: Japan

Manuscript submission date: 2020-05-19

Reviewer chosen by: Jia-Ping Yan

Reviewer accepted review: 2020-06-08 06:13

Reviewer performed review: 2020-06-19 09:22

Review time: 11 Days and 3 Hours

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input checked="" type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
Peer-reviewer statements	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No



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SPECIFIC COMMENTS TO AUTHORS

Minor revisions comments: In the manuscript, Saeki C et al. were devoted to evaluate the effect of denosumab in chronic liver disease (CLD), which had already been verified to increase bone mineral density (BMD) and decrease the risk of osteoporotic fracture in general population. According to the parameters, such as BMD, serum TRACP-5b and P1NP levels, they gave the conclusions that denosumab treatment was safety and increased BMD, suppressed bone turnover, and improved bone quality marker levels in CLD patients with osteoporosis, irrespective of differences in baseline characteristics. Honestly, the results is not surprised, but the logic is straight, and data are kind of solid. I personally support the publication of this manuscript in the world journal of gastroenterology. However, there still exist some doubts: 1. The main idea of this paper aimed to investigate the effect and safety of denosumab in CLD patients, but denosumab was used to cure osteoporosis, while the osteoporosis is a common complication in patients with CLD. The necessity or connection need to specifically address to stand as the background if there do exist correlations. 2. As the authors mentioned in the manuscript, the sample size was a drawback as it displayed.

PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 56760

Title: Effects of denosumab treatment in chronic liver disease patients with osteoporosis

Reviewer's code: 03700188

Position: Editorial Board

Academic degree: MD, PhD

Professional title: Assistant Professor, Attending Doctor

Reviewer's Country/Territory: Brazil

Author's Country/Territory: Japan

Manuscript submission date: 2020-05-19

Reviewer chosen by: Jia-Ping Yan

Reviewer accepted review: 2020-06-18 15:55

Reviewer performed review: 2020-06-22 01:46

Review time: 3 Days and 9 Hours

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input checked="" type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input checked="" type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
Peer-reviewer statements	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

This article is well written, points to a therapeutic possibility for osteoporosis in chronic hepatitis. The sample is small, but it opens up the possibility of larger studies to better assess the risk and benefit of long-term use of the medication. Denosumab appears to be better tolerated than bisphosphonates and appears safe. Answers that may come from larger studies and with longer follow-up.

RE-REVIEW REPORT OF REVISED MANUSCRIPT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 56760

Title: Effects of denosumab treatment in chronic liver disease patients with osteoporosis

Reviewer's code: 04105237

Position: Peer Reviewer

Academic degree: MD

Professional title: Doctor

Reviewer's Country/Territory: Mexico

Author's Country/Territory: Japan

Manuscript submission date: 2020-05-19

Reviewer chosen by: Le Zhang

Reviewer accepted review: 2020-08-05 13:24

Reviewer performed review: 2020-08-05 19:28

Review time: 6 Hours

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input checked="" type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Peer-reviewer statements	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

Thank you for the responses. Additional comments: 1) Please specify others in the

footnote in Table 1 (which specific disease had the patients, v.gr. AIH=x, etc.) 2) Please use a current calculator to obtain the median MELD score (the numbers provided are too low). 3) Please check for typos. In the abstract in the conclusion it should be safe, instead of safety.

RE-REVIEW REPORT OF REVISED MANUSCRIPT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 56760

Title: Effects of denosumab treatment in chronic liver disease patients with osteoporosis

Reviewer's code: 03700188

Position: Editorial Board

Academic degree: MD, PhD

Professional title: Assistant Professor, Attending Doctor

Reviewer's Country/Territory: Brazil

Author's Country/Territory: Japan

Manuscript submission date: 2020-05-19

Reviewer chosen by: Le Zhang

Reviewer accepted review: 2020-08-07 12:59

Reviewer performed review: 2020-08-07 14:53

Review time: 1 Hour

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input checked="" type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input checked="" type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Peer-reviewer statements	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

1 Title. The title reflects the main subject. 2 Abstract. The abstract summarizes and



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reflect the work described in the manuscript 3 Key words. The key words reflect the focus of the manuscript 4 Background. The manuscript was adequately described 5 Methods. The manuscript described methods well, but I had a doubt about statistic. Why did the authors use the Mann-Whiney test for all continuous variables? 6 Results. The research objectives were achieved by the experiments used in this study and they showed that the drug is save and it helps improve the bone disease. 7 Discussion. The manuscript interpreted the findings adequately and appropriately and highlighted the key points logically. 8 Illustrations and tables. They were of good quality and illustrative 9 Biostatistics. I only had one doubt about continuous variables. 10 Units. It met the requirements of use of SI units. 11 References. The manuscript cited appropriately the latest, important and authoritative references in the introduction and discussion sections (12 of them had < 3 years). The author self-cited once. 12 Quality of manuscript organization and presentation. The manuscript was well written.