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PEER-REVIEW REPORT

Name of journal: World Journal of Clinical Cases

Manuscript NO: 62693

Title: Liver injury associated with the use of selective androgen receptor modulators and post-cycle therapy, a case series

Reviewer's code: 02916643
Position: Peer Reviewer
Academic degree: MD
Professional title: Professor
Reviewer's Country/Territory: Spain
Author's Country/Territory: Slovakia

Manuscript submission date: 2021-01-22
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Reviewer accepted review: 2021-01-22 07:35
Reviewer performed review: 2021-01-26 15:14
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Scientific quality	[ ] Grade A: Excellent [ ] Grade B: Very good [Y] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [ ] Accept (General priority) [Y] Minor revision [ ] Major revision [ ] Rejection
Re-review	[Y] Yes [ ] No
Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous Conflicts-of-Interest: [ ] Yes [Y] No

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SPECIFIC COMMENTS TO AUTHORS

In this manuscript the authors present two cases of liver injury potentially associated with the use of ligandrol. The manuscript focuses on an important issue, the hepatotoxicity potential of muscle enhancing products, and it is important to publish this kind of case reports to increase the awareness of this type of liver injury. However, the exact role of ligandrol in the reported cases is difficult to determine due to additional treatments taken by both of the patients and this should be more emphasized as not to mislead the reader. Furthermore, the discussion section mentioning similar cases previously published is somewhat disappointing and could be improved. Suggestions for improvements to the manuscript that should be considered are outlined below: 1. I agree with the authors in that the two presented cases are drug-induced liver injury. However, to determine the causative agent is more difficult. Both cases took ligandrol followed by PCTs, which are not described in detail. In addition, the second patient is said to have taken a second SARM (ostarine). As all these products were initiated prior to the liver episodes it is very difficult to determine a single causative agent for the two presented cases. Hence, describing these cases as SARM toxicity is in my opinion not completely correct. The PCT products should also be considered, but their hepatotoxicity potential is of course dependent on the ingredients. In fact, the temporal sequence between drug intake and liver injury onset is more compatible with the PCT as "In both cases, patients did not develop symptoms or clinical signs while using ligandrol and those signs only appeared after stopping the drug and taking substances for so-called "post cycle therapy" (discussion page 8). I suggest that the author should discuss this issue in more details. I assume that the authors is referring to this problem in their final sentence of the abstract "Among amateur athletes, other hepatotoxic substances are often involved". However, this sentence is not very specific and the message is not very clear.

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This sentence should be reworded so that it conveys a clearer message. 2. Case presentation 1: Based on the biochemical data provided for this case, it does not fulfil the latest consensus biochemical criteria for clinically significant hepatotoxicity according to Aithal et al (Clin Pharmacol Ther 2011;89:806-815). This does not mean that the liver damage cannot be caused by a drug/dietary supplement. However, the authors should mention this fact, to demonstrate that they are aware of it. If the patient in fact had an ALT value above 3 xULN at any time point (not indicated in Table 1) this should be stated as if this is the case the patient did in fact fulfil the DILI criteria. In addition, determining liver injury pattern using R value should be based on the earliest identified liver chemistry elevations that qualify as DILI (Aithal et al, 2011). Furthermore, the use of the R value to determine the type of liver injury when ALT and ALP values are low is questionable. Both patients described had ALP values within the normal range on admission (Table 1). Hence, as these cases do not have elevated ALP they do not reflect cholestatic injury biochemically, i.e. the cases should automatically be considered as hepatocellular cases based on biochemical values. Histological findings can also determine type of liver injury and do not always coincide with R value determinations. This can be discussed or the authors may simply concentrate on one way of determining the type of liver injury, preferably histological findings as you provide more details here. 3. Discussion: I find the discussion dealing with previously reported cases of ligandrol hepatotoxicity cases poor. The authors describe two cases from references 12 and 13, however there is no comparing or contrasting with the cases described in the current manuscript. Such an analysis is clearly missing and should be included, rather than simply describing the external cases. 4. In line with the previous comment, I think the wording “and review” should be omitted from the title. 5. Possible mechanisms of hepatotoxicity, page 11. The authors state “Also, low HDL cholesterol levels in both reported cases likely indicate the shift of cholesterol transport towards bile acid

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synthesis." Is this related to the mechanism of hepatoxicity or is it simply a consequence of ligandrol use independent of hepatotoxicity? Minor comments 1. The word "icterus" is used in the abstract, while "jaundice" is used in other parts of the manuscript. Please be consistent. I suggest to use jaundice throughout the manuscript. 2. Introduction, page 5: "….the widespread use SARMs…" should be "the widespread use of SARMs" 3. Reference 14 is not correct. Lewis et al did not develop the RUCAM scale. Reference 14 is simply an article in which Lewis et al have applied this scale to cases to assess potential DILI. The RUCAM scale was first published by Danan and Benichou (J Clin Epidemiol 1993) as correctly stated by Lewis et al in reference 14. 4. Case presentation 1, page 6: "A transcutaneous liver biopsy has been performed…" is better said as "…was performed.." 5. Case presentation 2: The RUCAM category is said to be "likely". What does this mean? What was the total score? The RUCAM scale classifies the likelihood of DILI into 5 categories: excluded, unlikely, possible, probable and highly probable. Likely is not a category in this scale. 6. Last sentence on page 12: What do the authors mean with "….prevent their ultimate disqualification…."?

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RE-REVIEW REPORT OF REVISED MANUSCRIPT

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Position: Peer Reviewer
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Reviewer's Country/Territory: Spain

Author's Country/Territory: Slovakia

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Reviewer chosen by: Chen-Chen Gao

Reviewer accepted review: 2021-03-01 10:46

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Scientific quality	[ ] Grade A: Excellent [ ] Grade B: Very good [Y] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
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I approve of the revised version of the manuscript and have no further comments.