Dear editors, dear reviewers,

Thank you very much for your peer review and consideration of the manuscript entitled **Liver Regeneration as Treatment Target for Severe Alcoholic Hepatitis** for publishing in the World Journal of Gastroenterology.

We have carefully read and considered the reviewers comments, and revised the manuscript accordingly.

In response to the reviewers' specific comments:

Reviewer #1:
Scientific Quality: Grade B (Very good)
Language Quality: Grade A (Priority publishing)
Conclusion: Accept (General priority)
Specific Comments to Authors: This is a very good and objective overview of the liver regeneration problem in decompensated ALD and in particular in AH. The topic is well presented and the data as well. Such a comprehensive review on this important topic is welcome. One comment, however: I suggest the authors should insist more on alcohol relapse in the period following AH (a quite frequent situation) with a considerable negative impact on liver regeneration with regards on the effect of ethanol itself on cellular proliferation cycles.

Thank you very much for this comment. At the end of the Discussion section, we have added a paragraph addressing the problem of alcohol relapse in the period following an episode of AH, as a possible explanation for the lack of efficacy of liver regeneration therapies in the clinical practice due to its negative impact on liver regeneration.

The explanation of this paradox and lack of evidence for clinical efficacy of SC therapy for the treatment of AH is still not completely understood. One of the possible explanations might be a relapse of alcohol use in the follow-up period, which is common in clinical practice. In the STOPAH trial, only 45% of patients with AH abstained from alcohol at six months and 37% at 12 months, meaning that relapse of alcohol use occurred in two thirds of patients surviving an episode of AH after a one-year follow-up period[7]. In a study from Barcelona investigating alcohol abstinence in patients surviving an episode of AH, the investigators also report complete abstinence in only 39% of patients after a median follow-up period of 55 months, and showed that it had positive impact on long-term survival[97]. Similar results were obtained in a study from the United Kingdom, where 65% of patients surviving an episode of AH experienced alcohol relapse, and abstinence was shown to be the only predictor of long-term survival in these patients[98]. Indeed, in a previously mentioned randomized study investigating bone marrow mononuclear cell transplantation with G-CSF in patients with decompensated ALD, 81% of whom met the histological criteria for AH, alcohol abstinence was achieved in 67% of patients during 12-week follow-up period, while almost one-third returned to moderate alcohol drinking [66]. The study failed to show benefit of such therapy compared to standard medical treatment, and alcohol relapse in 31% of study patients might be one possible explanation for such results. Another possible explanation is that the effects of SC and other treatments aimed to stimulate liver regeneration depend on the etiology of the liver disease. It has been shown that in ALD related cirrhosis, acute and chronic exposure to alcohol interferes with liver regeneration

capacity and may actually impair hepatic progenitor cell response to injury, as mentioned previously, resulting in poor outcomes[14,23,99,100].

The issue on the effect of ethanol to liver regeneration has also been partially addressed in the section Pathophysiology of liver injury and liver regeneration.

The limitations are clearly presented, due to the small number of good quality clinical data, and the heterogeneous protocols of proregenerative strategies administration. This publication will be important for basic scientists and clinicians who want to have a good overview of the problem

Reviewer #2:
Scientific Quality: Grade C (Good)
Language Quality: Grade A (Priority publishing)
Conclusion: Minor revision
Specific Comments to Authors: A good review of the literature, with a focus on G-CSF and stem cells. I only have minor comments. Structurally, I would be tempted to discuss G-CSF and stem cells first, as these are discussed in detail, and are the focus of the review, then mention the other experimental treatments which are covered superficially with far less detail.

Thank you very much for your comment. Originally, we wanted to mention other experimental treatment options as a part of introduction into the topic, especially since some of these therapies are sometimes being used in clinical practice (e.g. pentoxifillyine or N-acetylcysteine), depending on the specific guidelines of the medical societies and clinicians' preferences, while liver regeneration therapies are experimental and in the early phases of development. However, we accepted your suggestion and discussed G-CSF and stem cells first, since they are the topic of the review, and mentioned other treatments to complete the information on other experimental approaches for the treatment of AH.

Otherwise, in the introduction, I would not say that AH is usually accompanied by ascites and HE, as although it can be it is certainly not always accompanied by these. AH is also a spectrum - non-severe AH with a mDF <32 is much less likely to be accompanied by additional symptoms of hepatic decompensation.

Thank you very much for this comment. The original sentence was true for severe AH, so we have corrected the statement to: Alcoholic hepatitis (AH) is a distinct clinical manifestation of ALD, characterized by jaundice and sometimes accompanied with other signs of hepatic decompensation and liver failure…

AH usually occurs in patients with advanced fibrosis or cirrhosis, those without significant fibrosis are a minority. Consequently, I am not sure I would say 'sometimes in occur in the presence of fibrosis or cirrhosis'.

Thank you for your comment, we have corrected the statement to: Underlying this clinical condition are histological changes including steatosis, hepatocyte injury with ballooning degeneration and lobular neutrophil infiltration, which are characteristic of alcoholic steatohepatitis, and which usually occur in the presence of advanced fibrosis or cirrhosis[3].

In the conclusion I think it is important to note that the results of the G-CSF trials in ACLF cannot be directly extrapolated to AH given the hetrogenuity in the ACLF cohorts.

Thank you very much for this comment. This is very much true, of course. We have therefore added a comment at the end of the third paragraph in the Discussion section, addressing this issue in more detail.

Still, it is important to note that the results of G-CSF for the treatment of ACLF cannot be directly extrapolated to AH due to great heterogeneity of ACLF cohorts regarding the cause of the underlying liver disease and the precipitating event for ACLF. In the previously mentioned German (GRAFT) study, alcohol abuse was the precipitating event in approximately half of the patients in both treatment groups, while bacterial infections and gastrointestinal bleeding were triggers for ACLF in the majority of the remaining cases [39]. However, the authors did not prove benefit of G-CSF over standard medical treatment in a cohort of patients with alcohol-related ACLF, which probably comprised mostly patients with AH.

According to the Journal's requirements, a professional English language editor has edited the revised version of the manuscript.

I hope that the revisions made according to the peer reviewers' comments have improved the manuscript and that the revised version will meet the high standards of the World Journal of Gastroenterology.

Kind regards,

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