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**AUTHORS' REPLY TO COMMENTS**

We express sincere thanks to the editor and the reviewers for your thorough comments and suggestions. We have enclosed below a point-by-point response to each of the comments raised. Corrections on the final text are tracked in yellow.

**REVIEWERS' COMMENTS:**

**Reviewer: 1**

*The author has made a systematic review of chronic rejection (CR) of liver allograft, and comprehensively summarized the current knowledge and research on CR. Overall, the article reviews the current issues that need to be solved in the field of CR of liver transplantation, such as non-invasive predictive tools, personalized management of immunosuppressants, etc. I believe this article will be more useful to readers of WJG. My suggestion for this article is minor revision.*

*I have one major comment:In Figure 1, the author summarizes all the risk factors of CR in the first column, but in fact, the risk factors that affect TCMCR and AMCR are not the same. Therefore, it is recommended to separate the risk factors of TCMCR and AMCR in Figure 1, and use arrows to indicate clearly, so as not to mislead readers.*

**Authors' reply:**

Thank you for this useful comment. We have indeed modified Figure 1, clearly separating risk factors for TCMCR and AMCR as suggested.

**Reviewer: 2**

*This is a well written review covering chronic rejection and would be of interest to the readers of WJG. I have only a few minor comments:*

*- It would be of interest to expand on the concept of the liver 'being immune-privileged' compared to other organs*

**Authors' reply:**

Thank you for your suggestion. The liver is undoubtedly a uniquely immunologically privileged organ and this concept is important in the process of chronic rejection. A paragraph describing the immune privileges of the liver allograft has been added in the revisited manuscript.

*- Page 4 – presumably the authors mean arterial stenosis and biliary strictures?*

**Authors' reply:**

Yes indeed, the word "stenosis" has been added. Thank you for pointing out the type error.

*- Page 5 – clarification of the time periods that the incidences quoted in the last two paragraphs is*

**Authors' reply:**

Thank you for this precious consideration. The incidence quoted refer to 5-years time frame and this has been clarified in the text.

*- There is continuous referral to inadequate or adequate IS throughout the review – an approach to determine this should be discussed early in the review*

**Authors' reply:**

The IS drugs play a crucial role in influencing the onset of CR. Yet, different strategies of IS regimens are currently adopted depending of a large number of variables (such as recipient's renal function, cardiovascular disease, risk of infections and tumours, recurrence of underling liver

disease); therefore, there is not a unique definition for the optimal IS regimen, but IS should be tailored to each recipient. After LT, the "adequate" IS is considered as this which maintains a viable graft and healthy patients, balancing the risk of rejection (by maintaining the target drugs' blood trough levels) and the risk of IS-associated side effects. For the complexity of this scenario, we devoted a complete section to IS management after LT and how it may influence the occurrence of chronic rejection. As suggested, we included a definition of the concept of adequate IS in the introduction section of the revisited manuscript.

- *There is repetition regarding DSA's throughout the review – one section addressing both class I and II should be sufficient*

**Authors' reply:**

As suggested, we summarized all principal data on DSAs in one section and deleted the repetitions. Though, DSAs are part of the definition of AMCR and therefore are inevitably referred to in the text, as much as we refer to AMCR. Thank you for your comment.

- *Page 10 – presumably Untreated HCV is what is meant in regard to lowering immunosuppression?*

**Authors' reply:**

Yes, we were referring to patients whose HCV infection has not been eradicated yet. This has been specified in the revisited article.

- *An approach to immunosuppression post redo transplant for CR plus the use of induction agents such as basiliximab would be of interest*

**Authors' reply:**

Thank you for your comment. This is an extremely interesting subject, yet no data exists on this specific topic. We discussed this possibility in the revisited manuscript.

**Reviewer: 3**

*Baiocchi et al. presented an overview of the current knowledge and research on CR, focusing on early detection, identification of non-invasive biomarkers, immunosuppressive management, re-transplantation and future perspectives of CR in this article. The article has a very fluent language and gives very important information about CT and CR follow up. Thank you for giving opportunity to review this article*

**Authors' reply:**

Thank you for reviewing our manuscript and for your positive comments.