Thank you for the opportunity to review this manuscript to the World Journal of Gastroenterology. I apologize for the delay in submitting the comments. I have reviewed the manuscript titled, "Management of Immunosuppressant Agents Following Liver Transplantation: Less is more" by Mustafa S Ascha, Mona L Ascha, Ibrahim A Hanouneh of the Department of Gastroenterology and Hepatology, Cleveland Clinic, Cleveland, Ohio, United States, and the comments are provided below:

The topic is very relevant and timely because liver transplantation is increasing in developed and developing countries and one of the key determinant of successful liver transplantation next to the mastery in the art of surgery is the science and art of immunosuppression in all allogenic/xeno grafts. One of the important message conveyed by this review is about the importance of appropriate tailoring of immunosuppressant drugs to patient needs- 'personalized liver transplant medicine'.

1) The authors have ignored biologicals such as rituximab, natalizumab etc although their use in current transplantation practice is limited (for example natalizumab is liver toxic for very interesting reasons). Currently small molecules such as tacrolimus are dominating the field. However, we should see the advantages of biologicals in terms of specificity. Yes, it is true that in future, we will see more precision in medicine, pharmacology as better small molecules emerge. ABO incompatable liver transplantation is an area which is of interest. Humanized livers and human livers grown in primates are also on the horizon (Refer: PMID: 21990949). You may also discuss about emerging drugs/drugs in pipeline, a note on cancer management in liver transplants.

Thank you for this input. We have expanded discussion of biological drugs, and present this discussion in light of ABO incompatible liver transplantation on page 8. We also wrote about the interesting article that you referred regarding the future of liver transplantation.

3) Mycophenolate mofetil is a prodrug of mycophenolic acid. This compound is an inhibitor of inosine monophosphate dehydrogenase (IMPDH- the rate-limiting enzyme in de novo synthesis of guanosine nucleotides. What is more important is the fact that T- and B-lymphocytes are more dependent on this pathway than other cell types are. This idea is not clear/missing in your review.

Thank you for this input. We have included more detail regarding the mechanism of action of mycophenolate on pages 6 and 7.

4) Besides anti-tumor activity and minimal impact on kidneys, mTOR inhibitors such as serolimus delay ageing in worms and rodents. Several animal studies have shown that it increases longevity by slowing down the ageing process.

Thank you, we have furthered our discussion of mTOR inhibitors on page 7.

5) Please explain why: "However, there was no difference in mortality or graft loss between patients on SIR monotherapy compared to CNI therapies."

Thank you for noting this point. We have clarified our writing to indicate that there are fewer side effects associated with SIR compared to CNIs, while the two achieve similar outcomes. This is on page 11.

6) Obesity is a heterogeneous trait. *The fact is that obesity may be actually protective*. It is important to actually look into the quality of adipocytes and fat distribution. BMI does not point to the quality or distribution of adipose tissue (Refer: PMID: 19046821, PMID: 18240340).

Thank you for this input. We have included more information regarding adipocyte qualities on pages 13 and 14. We referred to the interesting articles that you mentioned.

7) Components of metabolic syndrome may be listed as subheadings below that.
Thank you, the headings have been reformatted to reflect this.

8) It is important to explain the uniqueness of liver from the point of immunology. The largest reticuloendothelial cell network in the human body is in liver. Again, liver contains the single largest population resident macrophages, it also has the greatest concentrations of NK cells and NKT cells, network in the body.

This is an excellent point, and was included on page 4.

9) The diagram may be revised. There nothing the text (body of the review) about migration of APCs to lymph nodes and migration of effector T cells from lymph nodes to liver. This may be explained in the main text.

Thank you for this input. Information describing Figure 1 was added to page 6, and a caption was added to the diagram.

10) You may add more cartoons/diagrams on the mode of action of the drugs discussed, tables condensing the positive versus negative points of current drugs.

Thank you for raising this point. A table explaining the benefits and risks of different immunosuppressant classes was added as a second appendix.

Hopefully, the reviewer comments will assist you in improving this manuscript.

These comments were extremely helpful, thank you very much for your help.