

Sunday, 12 January 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 7682-review.doc).

Title: Immune Monitoring Post Liver Transplant

Author: Siddharth Sood, Adam G Testro

Name of Journal: *World Journal of Transplantation*

ESPS Manuscript NO: 7682

Thank you for considering to publish our manuscript on immune monitoring post liver transplant. We appreciate the helpful comments of the reviewers, and have endeavoured to improve the manuscript according to their suggestions:

1 Format has been updated, with a running title, abstract and core tip now provided.

2 The response to each of the 6 reviewers are listed individually below:

Reviewer 2438890

In the article "Immune monitoring post liver transplant" the author reviewed the current available methods for the monitoring of the immune system after liver transplantation. This paper is a very comprehensive work discussing the many aspects of immune monitoring including clinically widely used and experimental methods of immune monitoring. I believe that this review deserves publishing in the World Journal of Transplantation. My only suggestion is to correct typing errors (Introduction section second paragraph: minimizeside, Other drugs section: futureimmune, Biopsies section: andprotocol etc.

We appreciate the reviewers positive comments regarding the manuscript. The above spelling issues have been reviewed and prior to re-submission we have repeated a spell-checker.

Reviewer 00011087

This is a very interesting and well performed review evaluating the current available options for monitoring the immune system after liver transplantation. The authors accurately described different methods and assays and highlighted pros and cons for each. The interesting conclusion of the review was that no single method is able to meet the diagnostic requirements and that multiple assays may be needed in the same patient to trace an accurate immunological profile. The review is well designed and well written with clinical relevant conclusions and appropriate examination of published data.

We thank the reviewer for their positive commentary regarding the manuscript.

Reviewer 2439579

1.The authors stated all the methods used in clinic to monitor immune function post liver transplant, and gave out the differences in them 2.The authors did not give some direction for future development of immune monitoring post liver transplant. 3.The authors did not indicate some useful combination for immune monitoring post liver transplant in clinic. 4.The paragraph of "Dendritic Cells" is inadequate supported by the references

We thank the reviewer for their helpful comments and suggestions. In the conclusion we have added a statement suggesting that a combination of assays that comprise parts of both the innate and adaptive immune systems may offer a useful combination for immune monitoring. We believe this addresses the reviewer's points 2 and 3.

In regards to point 4, we have added an additional reference (Tokita et al, Transplantation, 2008) which documents the increased ratio of plasmacytoid to myeloid dendritic cells.

Reviewer 00068914

The authors have reviewed the field of immune monitoring in patients who have received a liver transplant. It is an important subject and the authors have emphasized the need of monitoring and intervening in the immunomodulatory response of the organ recipients so that chances of successful engraftment can be improved and/or long and short term graft rejection by the recipient can be minimized. While the other molecular methods have been described well application of cell based immune

modulation particularly by generating donor-recipient hematopoietic chimerism and specially using Treg cells or hematopoietic stem cell transplantation has not been sufficiently emphasized. The quality of the review improve considerably if these aspects are further highlighted in the review. The scientific language of the review is good and the references are up to date.

We appreciate the reviewers suggestions and positive feedback. We have taken their suggestion to improve the manuscript by reviewing haematopoietic chimerism in a new paragraph. Stem cell transplantation remains out of the scope of this review on immune monitoring given its therapeutic nature and is therefore not discussed in this manuscript.

Reviewer 522743

The review reports all relevant issue in the immunological monitoring after organ transplantation. However, the Authors performed a descriptive review. Nevertheless, studies are not cited according to their relevance, nor the degree of evidence and the strength of recommendation are reported. In addition, the large parte of evidences reported by Authors are not specifically related to liver transplantation, being obtained in studies on kidney transplant patients. Nevertheless, the manuscript can be ameliorated. I suggest: 1. The peculiarity of the liver transplant setting should be identified and reported in the introduction (low risk of rejection, high risk postoperative course, complexity of identification of rejection among other cause of liver dysfunction, ...). The immunological differences versus kidney, heart, intestine transplant should be discussed. Alternatively, the Authors can modify the title in "Immuno monitoring in organ transplantation" and summarize in a table the tests used in the different organs transplanted. 2. The clinical application(s) of immunological tests should be reported in a dedicated table. The sensitivity and specificity of most relevant tests should be specified according to the literature. 3. Among all reported immunological tests, Authors should identify (new table) those performed in the past (old tests), those currently used in the clinics, those potentially available in the near future in order to be very informative for the readers. 4. The histopathology of liver rejection should be reported according to most used scores. 5. A limitation paragraph with identification of shadows should be hopefully included before the conclusion paragraph. 6. A 5-6 point take-home message should be reassumed in a separate table or in the conclusion paragraph.

We thank the reviewer for the above comments and attempt to address them individually below:

- 1) In writing this review we have tried to focus on immune function monitoring after liver transplantation. We agree with the reviewer that liver transplant presents a unique situation post-transplant and have emphasized this in the introduction.*

2+3) *Most of the tests mentioned in this review remain research tools, with very few used in current clinical practice. We have added an additional table (now Table 1) to summarise this.*

4) *We appreciate the reviewer bringing this oversight to our attention, and have added a sentence explaining that the Branff criteria is used to diagnose rejection following liver transplant.*

5) *The rejection cascade is complex, and as suggested by the reviewer, we have added a sentence to the last concluding paragraph.*

6) *We have added a core tip as suggested by the Editor and believe this core tip also addresses the reviewer's suggestion.*

Reviewer 722339

Liver transplant immune suppressors used because it is vital dose adjustment. This review has examined an important issue in the article. Comparative tables with additional topics can be presented more dramatically. English spelling errors should be corrected. Published with minor revisions

We appreciate the reviewers comments and have corrected spelling errors when found. We have prepared the table as per World Journal of Transplant guidelines and added an additional table as suggested (now Table 1).

3 References and typesetting were corrected

Thank you again for publishing our manuscript in the *World Journal of Transplantation*. Please feel free

Sincerely yours,

Dr Siddharth Sood

LTU Fellow

Liver Transplant Unit Victoria,

Austin Health, University of Melbourne,

Melbourne, Australia

soodsiddharth@hotmail.com