

January 29, 2020

Dr. Ruo-Yu Ma
Science Editor
World Journal of Transplantation

Dear Dr. Ma:

We would like to thank you for reviewing our manuscript titled, “Novel alternative transplantation therapy for orthotopic liver transplantation in liver failure: A systematic review,” (Manuscript No. 53098), submitted to the *World Journal of Transplantation*.

We also thank all the reviewers for their time and insightful comments, which helped improve the manuscript. We have revised the manuscript as per the reviewers’ comments. We hope the revised manuscript is satisfactory and meets the expectations of the reviewers and editors. We have highlighted the modifications in the revised manuscript.

Reviewer 1; 2019-12-05

Dear Editor Thank you for asking me to review the paper. It is well structured. However, the topic is so wide and searching of only one database is not enough. The authors should search and other bibliographic databases e.g EMBASE etc

Response

We thank the reviewers for the comments on our manuscript. We agree with the reviewer’s comments and thus increased the number of databases to three by including the Cochrane Library and EMBASE in our study. We also increased the number of searched and cited articles. We hope this approach would meet your advice satisfactorily.

Reviewer 2; 2019-12-06

1) Alternatives to liver transplantation such as liver support systems, including bioartificial livers, and hepatocyte transplantation are important therapies to overcome the problem of liver shortage. 2) The review is too superficial and lack of in-depth discussion on each method

Response

We thank the reviewer for the critical review of our manuscript. Our point-by-point responses to the reviewer’s comments are as below:

1) Firstly, the reviewer raised important points regarding the alternative therapies for liver transplantation. As pointed out, bioartificial livers are among the established treatments in regenerative medicine for the liver. Although bioartificial livers have been used for clinical trials, they were evaluated only for short-term follow-ups. They are considered useful as a bridge while waiting for a transplantation; thus, they are not radical treatments for liver failure. In this review, we

did not discuss bioartificial livers since our focus was on radical transplantation treatments as alternatives to organ transplantation. Thus, our searches were limited to articles that presented transplantations cases.

Secondly, hepatocyte transplantation is a type of cell transplantation therapy that has been applied clinically. However, the effects were limited, and it had limitation regarding quantity and quality. Without overcoming these shortcomings, it is challenging to use hepatocyte transplantation for clinical application. Therefore, we discussed the research on various cell sources and modalities and summarized the current status of *in vivo* transplantation. We hope that our study will contribute to the future of transplantation research.

2) We agree with the reviewer's comments. Therefore, we included two more databases i.e. the Cochrane Library and EMBASE, to increase the number of searched articles. This approach widened the scope of discussion on cell types and their advantages, disadvantages, and the future possibilities for each cell type. We hope that this change would increase the depth of our discussion and address your questions.

Reviewer 3; 2019-12-06

The idea of this review is good. However, it is too simple and lacks depth. It is recommended that the authors increase the database size and have a deeper discussion.

Response

We thank the reviewer for reviewing our manuscript. We agree with your comment and modified our manuscript accordingly. We increased our search to three databases by including the Cochrane Library and EMBASE, and increased the database size from 1311 to 2821. We checked each article and subsequently increased the number of citations from 44 to 91. We expanded the discussion on cell types by talking about the benefits, disadvantages, challenges, and future prospects. We sincerely hope that this approach satisfactorily addresses your concerns .

We thank you all for giving us an opportunity to improve our manuscript. We hope these changes would satisfy you to accept our manuscript for publication in the World Journal of Stem Cells.

Sincerely yours,

Yun-Wen Zheng, Ph.D.

Department of Gastrointestinal and Hepato-Biliary-Pancreatic Surgery

Faculty of Medicine

University of Tsukuba

1-1-1 Tennodai, Tsukuba-shi, Ibaraki 305-8575, Japan

Telephone: +81-29-851-3221

Fax: +81-29-851-3222

E-mail: ywzheng@md.tsukuba.ac.jp