BAISHIDENG PUBLISHING GROUP INC
8226 Regency Drive, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242 Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com http://www.wjgnet.com

Name of Journal: ***World Journal of Transplantation***

ESPS Manuscript NO: 26566

Manuscript type: Review

Friday, July 1, 2016

Dr. Shui Qiu
Science Editor, Editorial Office
World Journal of Transplantation
Baishideng Publishing Group, Inc.
E-mail: s.qiu@wjgnet.com

Dear Journal Editor and Reviewers:

Thank you very much for reviewing the manuscript and providing excellent feedback on the content. I appreciate that you all understand that this is a very complex disease, and that it is a challenge to cover every nuance of the symptoms, etiology and biology of this condition in one article.

Below is a point-by-point response to the comments from each of the 7 reviewers. In each case the page number in the R1 version is referenced where the revised text can be found, highlighted in yellow. With regard to Reviewer 5 (code **5029), I included most of his/her suggestions on the immunological aspects. However, since this is a transplantation journal, I feel that including all of the complex nuances of the immunobiology might lose some of the prospective readership- which will include transplantation experts as well as GVHD researchers and clinicians, as well as some immunologists. Hence, I tried to strike a reasonable balance (or compromise) in terms of what R5 requested and what I felt was appropriate for the journal.

Reviewer 1

I disagree that Figure 1 is irrelevant to the review: it relates to the text discussed on pages 5 and 9, where I discuss causes of death as a result of allo-HSCT. Mortality (and its origins) is an important issue in allo-HSCT and fits well in the section on Risk Factors. The figure also emphasizes the point that HLA disparity does not much affect

GVHD incidence (which might be a surprise to some people)—HLA disparity is an important issue with regard to GVHD risk, but not for mortality.

The grammatical error on p. 9 has been corrected (the word "is" has been removed).

The majority of the references are post-2000, with many post-2006. There is some earlier literature that is relevant, such as the research characterizing animal models. The NIH consensus group published their first set of reports in 2005-06, and this work is important to cite- but I also include the updated reports that were published quite recently (2015), Jagasia et al. (ref. 13) and Paczesny et al. (ref. 73).

Reviewer 2

Thank you for your nice comment.

Reviewer 3

1. I have changed the title to reflect the importance I have placed on the immunobiology of the disease (i.e. role of T- and B-cells) and the work identifying biomarkers. The new title is:

   "The Biology of Chronic Graft-versus-Host Disease: Immune Mechanisms and Progress in Biomarker Discovery".

   I think the new title should better target readers who are clinicians/researchers in this field.

2. The Introduction was only meant to be the very first section (<2 pages); the sections "Clinical Features" and "Risk Factors" were not actually part of the introduction. I apologize for the confusion. I have uncapitalized the title of the introduction.

3. I disagree that the sections you list are not part of the consideration of Pathobiology (better described as Biology, now reflected in the new title). All of the elements contained in the paper are relevant. The study of animal models and biomarkers are very relevant to an understanding of this disease- models provide insight into the immune mediators of the disease, as well as providing a platform for pre-clinical testing of new drugs. The biomarker discovery and validation is relevant from the biological standpoint (per the new title of the article)- as it confirms the important of CD8 cells and B-cells (for example) in the disease etiology and biology. Hence, the biomarker studies are closely tied to understanding the disease. The next frontier with cGVHD biomarkers is in patient diagnosis and prognosis- but this is yet to be realized.

Reviewer 4

1. Introduction, p.4- I have replaced the old text with "hematological malignancies".

2. Clinical features- I have removed the term "de novo" as an alternative way of thinking about Classic cGVHD. I just use the terms classic and overlap when explaining the subtypes (p. 6).

3. I have removed the sentence about cellular epithelial apoptosis.

4. I have changed the sentence on p. 9 to say "early NRM".

5. I have rewritten the short section about T-regs on p. 13 to be more balanced (highlighted) and added the reference by Martelli et al. (ref. 51).

6. p. 15, I changed the text discussing Rituximab to read "clinical observations".

7. Regarding the comment about France's Cryostem Project, I thought this discussion would fit better in "Concluding Remarks", which is now significantly expanded (p. 22-23). The new (second) paragraph mentions the Cryostem project, and the latest NIH biomarker report recommendations (Paczesny et al., 2014; ref. 73) relating to biomarker priorities. I thought this was a good way to conclude the manuscript.

8. I have fixed the reference.

Reviewer 5

1. I have removed the term 'de novo cGVHD', which was also requested by Reviewer 4 (p. 6). The terms classic and overlap cGVHD are used through the manuscript, per the current NIH guidelines.

2. Skin manifestations. I have rewritten this section to distinguish between diagnostic, distinctive and common signs (p. 6). This information is also summarized in Table 1.

3. I agree with you that both allo- and auto-antibodies can be present in cGVHD patients. I have renamed this edited section 'Antibodies' and avoided the use of the term autoantibodies. I have been more specific with my discussion of this topic, referring to antibodies to HY and nuclear antigens, for example in the abstract (p. 2), and on p. 14.

4. I have tried to address many of the points you raised here. Here is a list of changes I have made to the manuscript:

    a) Lichenoid vs. schlerodermatous cutaneous cGVHD. Please see new paragraph p. 7, with a reference (#15).
    b) I have expanded the discussion about B-cells, highlighting changes in B-cell subsets (p. 14 and 21). I have also added information to Table 2 on this topic.
    c) I have added some information about regulatory B-cells (p. 14) and added two references. Regulatory B-cells are also included now in Table 2, as are the other B-cell subsets.

5. The 2014 consensus update is mentioned and referenced on p. 23.

6. The impact of immunosuppressive drugs on biomarker levels is discussed on p. 19-20 (new paragraph).

7. Cellular biomarkers are discussed in a separate section on p. 21. Some of these cellular biomarkers are also listed in Table 2, as indicated.
8. A reference for cGVHD incidence has been added (p. 4).

9. I added ref. 10, in relation to treatment strategies (Wolff et al., 2010)(bottom of p. 5). This article was a summary of the last consensus conference on treatment strategies for cGVHD, especially second-line therapies.

10. Oral mucoceles is not included under diagnostic criteria for oral disease (Table 1 and p. 7).

11. The sentence has been corrected (p. 8).

12. The word "immature" has been removed in relation to B-cells (p. 15).

13. The studies with Ruxolitinib in a BMT mouse model have been added, with two references (p. 16).

Reviewer 6

Thank you for the nice comment.

Reviewer 7

Cellular biomarkers are now discussed on p. 21, as part of the Biomarker section. The discussion is cross-referenced to Table 2, where some cell types and key relevant markers (secreted and/or cell surface) are listed.

Lastly, I have added quite a few references to the article. Reference 89 is the reference recommended for Fig. 1, in addition to the included URL link.

With my sincere thanks and regards,

Richard B. Presland, PhD
University of Washington
Seattle, WA, USA