

Format for ANSWERING REVIEWERS



January 11, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: AJE_Edited_4F4B2XPB_Manuscript-ESPS-7605_World_j_Transplant_edited_finalME.doc.doc).

Title: Coronary Microvasculopathy in Heart Transplantation: Consequences and Therapeutic Implications

Author: Alessandra Vecchiati, Sara Tellatin, Annalisa Angelini, Sabino Iliceto, Francesco Tona

Name of Journal: *World Journal of Transplantation*

ESPS Manuscript NO: 7605

The manuscript has been improved according to the suggestions of reviewers:

1 Format has been updated

2 Revision has been made according to the suggestions of the reviewer

(1) #00225286: In this review paper the authors summarize data on the pathophysiology, detection and treatment of coronary microvasculopathy after heart transplantation. The paper is of appropriate length, with updated references. Major comments: 1. The section on the role of endothelial function is quite large and uninterrupted. Please divide with subheadings, such as immune responses, non-immune mechanisms, NO pathway, CMV etc.

Authors' reply: changed as suggested

Minor comments: 1. The authors may consider to add refs for the non-HLA antibodies with possible effect development of microvasculopathy, such as by Reinsmoen NL and Hiemann NE from Transplantation 2013 and 2012 respectively.

Authors' reply: We thank the reviewer for this important advice, we included a short discussion about non-HLA antibodies and we added references (page 5, lines 26-30).

2. page 2, l 3: consists of, instead of in

Authors' reply: changed as suggested

3. P 2, l 13: ...they are not enough..., you mean they are not sensitive enough?

Authors' reply: changed as suggested

4. P 4, l 9: stimulus instead of stimuli?

Authors' reply: changed as suggested

5. P 7, l 8: The authors may elaborate briefly on the potential implications endothelial chimerism may have on the development and treatment of microvasculopathy.

Authors' reply: We agree with the reviewer and have briefly wrote about endothelial chimerism (page 8; lines 9-11).

6. P 7, l 11: EPCs instead of ECPs?

Authors' reply: changed as suggested

7. P 8, l 6: vasodilator instead of vasodilatator?

Authors' reply: changed as suggested

8. P 8, para 2, l 3: Similar to DSE ... instead of as well as DSE?

Authors' reply: changed as suggested

(2) #00214301: Comments the above mentioned manuscript is a well written paper which gives an excellent overview of the immunosuppressive treatment in microvascular coronary disease. The current literature in this field is thoroughly summarized. The paper is well structured. Endothelial function, histopathological features and techniques of diagnosis of microvasculopathy as well as pharmacologic interventions are broadly discussed. The paper is provided to be published in the World Journal of Transplantation. Probably the readers are to some extent familiar with rejection processes after heart transplantation. However, the paper is not easy to read for non-experts. To facilitate understanding I would suggest to reduce the excessive numbers of abbreviations. Furthermore the authors should inform more about malignancies which are an important cause of death after transplantation. They normally occur years after transplantation and are most likely due to the immunosuppressive treatment. Because this is a very important side-effect of immunosuppressive agents, it is worthwhile to emphasize this topic. Side-effects of immunosuppressive treatment are a limitation of survival. In all this is a well written paper which gives a very good overview of the current literature in addition. It is written in good English and I would recommend it for publication in the World Journal of Transplantation, however, I would enlarge a chapter about malignancies in response to immunosuppressive therapy. In detail: Reference 7: There is a misspelling: A. Muegge (instead of Mogge)

Authors` reply: Regarding reference n 7 we apologize for the misspelling and we corrected it as suggested. Regarding malignancies, we thank the reviewer for this important comment and agree with this observation. We think that an entire chapter about malignancies would fall off the topic of the review. However, like suggested, we briefly discussed about them in "Medical treatment" section (page 11, lines 4-11).

(3) #02628618: Some issues should be addressed:

- The authors should discuss the difference of pathological finding, mechanism, and prognostic impact between epicardial vasculopathy and microvasculopathy in patients receiving heart transplant.

Authors' reply: We thank the reviewer for this important remark. The literature data show that epicardial- and micro- vasculopathy after heart transplantation are due to endothelial dysfunction, caused by both immunological and non-immunological mechanisms (like we discussed in "The endothelial function" chapter). Regarding the pathological findings, they are constituted by a typically

concentric intimal thickening of both the major epicardial vessels and the intramyocardial vessels, with comparable severity from proximal to distal in the epicardial coronary tree. A real comparison between epicardial- and micro-vasculopathy is lacking. Hiemann et al. proposed a classification of microvasculopathy that we summarized in the paragraph "Histopathological Features". Prognostic impact of cardiac allograft vasculopathy has been analyzed in the Registry of the International Society for Heart and Lung Transplantation: Thirtieth Official Adult Heart Transplant Report (Reference n 2 in our review) and it is recognized as a leading factor to graft failure and death. The main issue, still open, is to define how much microvasculopathy affect long-term prognosis in transplanted heart.

- Is endothelial dysfunction associated with poor outcome in heart transplant patients?

Authors' reply: We thank the reviewer for this important question. An endothelial damage promote and initiate both microvasculopathy and epicardial vessels disease, leading to myocardial ischemia, graft failure and death (like we discussed in the "Endothelial function" chapter).

- Could the authors provide the target LDL-cholesterol level for heart transplant patients receiving statin therapy?

Authors' reply: We thank the reviewer for this important question. However, actually, it is not established in the literature a LDL-cholesterol target level in heart transplant recipients.

- Please provide the detail of invasive diagnostic tools and criteria of microvasculopathy.

Authors' reply: We thank the reviewer for this important remark. Regarding the invasive diagnostic tools able to detect microvasculopathy, we discussed in "Diagnostic tools" chapter the assessment of Coronary Flow Reserve (CFR), that can be performed during coronary angiography (but its use is not widely instituted) or with transthoracic echocardiography. Another invasive index of microvascular disease, but still not validated, is index of microcirculatory resistance (IMR), proposed by Fearon et al. It is calculated by dividing distal coronary pressure by the inverse of the hyperemic mean transit time. Actually, it has been performed in patients with coronary artery disease, and there are several studies demonstrating that microcirculatory resistance is dependent on epicardial stenosis severity.

In the literature data, there is not a consensus about microvasculopathy classification. We summarized in Table 1 the different definitions of microvasculopathy.

3 References and typesetting were corrected

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

Sincerely yours,



Francesco Tona, MD, PhD
Department of Cardiac, Thoracic and Vascular Sciences
Padova University Hospital, via Giustiniani 2
35128 Padova, Italy
francesco.tona@unipd.it
Telephone: +3949 8211844
Fax: +3949 8211802