Peer Review File

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Reviewer A

This study compares numerous cytokine responses in a group of 11 autologous vs. 6 allogenic islet transplant recipients. In general, the increases in cytokines were more prominent immediately after induction of anesthesia and during surgery, and the trend of the data indicated greater cytokine responses in allogenic transplant group.

Comment 1: This study is somewhat limited because of the small number of recipients in both transplant groups, although in some instances the numbers were sufficient were detect statistically significant differences. The conclusion is valid, although not surprising since a general cytokine response would be expected during the stress of surgery and an allograft procedure would be expected to have greater responses than an autograft procedure. Nonetheless, from a purely descriptive point of view, the data do add relevant information for scientists interested in this field.
Reply 1: Many thanks. We do appreciate with your positive comments.

Comment 2: The information starting on line 143 of the manuscript indicates a lower success rate following autologous transplantation than most centers report for 5 and 8 years post-transplant. The publication the authors cite, number 15, is not yet published, so this statement is not possible to verify.
Reply 2: Reference number 15 is published in the British Journal of Surgery 2012; 99:761-766.
Changes in the text: I made changes on line 567, reference number 15.

Comment 3: In Table 1a it is not clear how the outcomes re insulin dependent and insulin free were determined. It seems this is simply historic and anecdotal information rather than any formal testing of insulin dependency by repeated measurements of fasting glucose or HbA1c levels under insulin withdrawal protocols. The table also does not provide post-transplant times for the values given.
Reply 3: Outcomes re insulin dependent and insulin free in Table 1a and 1b is 1 year after autologous or allogenic islet transplantation that either patient is insulin dependent or insulin free.
Changes in the text: Table 1a and 1b outcomes had added to outcomes (1 year) in both tables.

Reviewer B

The authors performed a comparison of the inflammatory response following autologous compared with allogenic islet cell transplantation. However, concerns remain about the research design, novelty of the manuscript and overall interpretation.
The following suggestions are provided in the interest of enhancing the manuscript.

Comment 1. The importance of the current study has not been adequately explained. What hypotheses did you formulate and how did you define the endpoints? It seems that the perioperative blood collection during islet transplantation was performed to capture only a superficial phenomenon.
Reply 1: The purpose of this study was to demonstrate and compare the initial phase of cytokine profiles following allogenic and autologous islet cell transplantation and examine the mode of induction therapy. The inflammation response associated with islets has been recognized for the early damage to islets and graft loss after transplantation. This study will contribute to more understanding all the contributory components and to develop strategies which will abrogate the response and maximize islet cell survival.
Changes in the text: NO changes.

Comment 2. The authors have done a multicenter study, but what is the significance of it?
Reply 2: As mentioned from reply 1 above, it is important to find therapeutic strategy. Many several potent anti-inflammatory strategies have been implied in different centers. Therefore, it is very important to compare the difference between vary of strategies. I think interesting questions that we can ask include the effect of ATG on inflammatory markers and to see the differential effect of Etenercept and the IL1-beta blockade on the cytokine profiles. Baylor recently shows that the use of IL-1beta and TNF-alpha with reduction of inflammation at transplantation and with better engraft function (Onaca et al., 2020)
Changes in the text: Onaca et al., paper is added to the references number 42..

Comment 3. Because it is a multicenter study, it may be difficult to make an accurate comparison because the protocols for surgery and transplantation are not uniform. In particular, differences in immunosuppressive protocols for allogenic islet transplantation and differences in islet isolating enzymes can make a significant difference in outcomes. If there are too many variables, it will be difficult to achieve the original purpose of comparing Allo and Auto.
In addition, the number of N is too small to be sufficient for the analysis.
Reply 3: I agree with the comment. This study is somewhat limited because of the small number of recipients in both transplant groups, but the numbers were sufficient to detect statistically significant differences. Nonetheless, from a purely descriptive point of view, the data do add relevant information for scientists interested in this field (Comment from Reviewer A). We provide the novel data regarding the cytokine profiles of islet allograft recipients treated with two different induction regimes. The present data provides further supporting evidence for the reduction of inflammation by the addition of agents producing IL-1ra and TNF-alpha antagonism.
Changes in the text: NO.