Turin, 28/05/2018

Dear Referees of World Journal of Transplantation,

I am pleased to resubmit for publication the revised version of Manuscript 39671 entitled "Treatment with Plasmapheresis, Immunoglobulins and Rituximab for chronic-active antibody-mediated rejection in kidney transplantation: clinical, immunological and pathological results" for publication in World Journal of Transplantation.
Below you will find my response for the constructive criticism of the reviewers. I do hope that all points raised by the reviewers are properly addressed and the new version of the manuscript will be suitable for publication in your journal.

Your sincerely,
Luigi Biancone, MD, PhD

Reviewer # 02844701 Comment 1: Authors have evaluate effect of PE-IVIG-RTX for c AMR vs control group Please include other confounding variables such as DGF , SCD vs ECD deceased donor , surgical details (anastomosis time warm and cold ischemia time) CDC cross match,Flow cross match,DSA status before transplant, ABO compatible transplant , Induction therapy , levels of CNI , compliance to drugs /CNI in 2 groups

Answer: We appreciate reviewer's suggestions, and we include all these variables in text and tables with appropriate comments. In detail:

- perceantage of delayed graft function (dialysis within the first 72 hours after transplantation) is slightly higher in control group but without statistical significance (0/9 in PE-IVIG-RTX group vs 4/12 in control group, p=0.060) (see Page 8 and Table 1);
- number of standard or extended criteria donor (according to Crystal City criteria) and cold ischemia time are similar in both groups (see Page 8 and Table 1);
- data about the warm ischemia time associated with vascular anastomosis are not routinaly recorded by our surgical team; however, the surgical operations were reported as uneventful either in PE-IVIG-RTX and in the control groups; cold ischemia times are also reported in Table 1;

- complement-dependent cytotoxicity (CDC) crossmatch was performed in all patients prior transplantation, and a negative result was necessary in order to proceed to transplant. Flow cytometry crossmatch was not available until 2017, so none of our patients in this study has been evaluated with this approach (see Page 7). As reported in Page 7, patients were also tested repeatedly pre-transplantation for anti-HLA antibodies by the panel reactive lymphocytotoxicity assay (PRA), and were investigated with Luminex assay only after transplantation;
- no ABO incompatible transplantation was included in this study (see Page 6);
- informations about induction therapy are highlighted in text and tables (see page 8 and table 1);
- maintenance CNI through levels at diagnosis are similar in both groups: for Cyclosporin A C0 80-150 ng/ml, C2 600-800 ng/ml; for Tacrolimus 5-7 ng/ml (in monotherapy or in association with MMF 1 gr/day with or without steroids), 2-4 ng/ml when used in combination with an mTor inhibitor or MMF 1.5-2 gr/day with or without steroids. Correct drug intake has been assessed with periodical through level monitoring, a good compliance in both groups was reported (see Page 6).

Reviewer # 02844701 Comment 2. What are study limitations why outcome was same in 2 groups ? PE-IVIG-RTX therapy is expected to show better outcome for c AMR than control group ACE inhibitor ARB for proteinuria ? add study limitations DSA monitoring was not done routinely affect of abrogation of DSA was not evaluated

Answer: As reported in discussion, we are aware of some limitations in our analysis: the low numerosity, the retrospective design and the absence of protocol biopsies in the control group. However, some studies with similar characteristics showed an improvement or a GFR stabilization in patients treated with IVIG and RTX (*Billing H et al Transplantation 2008; Billing H et al Transpl Int 2012*). Our analysis, in our opinion, added some important informations, because no difference in graft survival and renal functional tests was noted at 24 months despite a reduction in microvascular inflammation score on protocol biopsies. We appreciate reviewer's comment about DSA monitoring, which is now part of routinary panel of test in transplanted patients, and we include this comment in the discussion (see Page 14).

As it is reported in result and discussion, a lowering effect in DSA titer was not obtained in all patients (the median value was unchanged after treatment). In two patients DSA titer was abrogated after treatment, although in association with highly different functional data (stabilization of GFR in one patient, graft failure in the other one), so we are unable to formulate definitive conclusions about patients with DSA disappearance after treatment.

Reviewer # 02855928 Comment 1. In other transplant field, pretransplant management for donor specific antibodies (DSA) well worked. This point should be clearly mentioned in the Introduction or Discussion section, with related papers (Surgery 2010;147[6]:840-4.).

Answer: We include these informations in introduction (Page 5) also mentioning DSA management in discussion (Page 14).

Reviewer # 02855928 Comment 2. Their data was informative, even if data seemed to be negative. Especially from the viewpoint of cost, IVIG, Rituximab and PE are so expensive. Hence, these treatment should be removed if they have no effect. This point should be clearly mentioned.

Answer: We include an appropriate comment about cost-effectiveness of PE-IVIG-RTX in discussion (Page 13).

Reviewer # 02855928 Comment 3. Important paper in other transplant field should be listed, as the reference. Does a positive lymphocyte cross-match contraindicate living-donor liver transplantation? Surgery 2010;147(6):840-4.

Anwer: We list this study in references.