Reviewer 1:

Comment:

However I experience the need of a section that clarifies the hypothetical worsening effects in terms of post-transplant infections and neoplasms and also the risks for patients that will experience PNF.

Replied Addendum:

The risk of infection post Lymphocyte depletion, as described, would be similar to current existing strategies used in high risk renal transplant programmes as well as lymphoablative therapies used in Lymphoma. Paradoxiclly, the risk of infetion would be rather reduced following the cycle of lymphocyte depletion strategy as mentioned, because the strategy is time limitted. This therapy would be followed by rather a reduced and dual immunosuppressive low CNI trough level therapy to maintain the renal graft. In practical situations of Lymphoma treatment, infection and recurrent malignancies are rather infrequent. In our case and several other similar sitautions, recurrent malignancies and infections were not of frequent impediments.

Reviewer 2 comment:

The opinion review “Tolerance Protocol of Living Kidney Transplant For Developing Countries Through Basic Strategy of Lymphocyte Depletion” suggest a stagey to induce Partial or Prope tolerance in LKT recipients: giving R-CHOP chemotherapy prior to transplantation. The opinion is interesting. 1, Although the protocols of MGH, Stanford and Northwestern include rituximab, high dose CTX and other potent lymphocyte deletion treatments, tolerance still failed in part of recipients. Considering the authors have only 1 case experience in PTLD patient, the effects of R-CHOP chemotherapy on tolerance need more data to have conclusion. In fact, many PTLD recipients have received R-CHOP chemotherapy. After cure, they still need receive maintenance immunosuppressive therapy to avoid rejection. 2, The authors suggest “Target neutrophil and lymphocyte counts are 1 × 109/L and 0.5 × 109/L”. How to evaluate the risk of infection and the safety? 3, Does the status of “a half dose dual immunosuppressive therapy” mean “Partial or Prope tolerance”? How to test the status of “Partial or Prope tolerance”? The opinion review “Tolerance Protocol of Living Kidney Transplant For Developing Countries Through Basic Strategy of Lymphocyte Depletion” suggest a stagey to induce Partial or Prope tolerance in LKT recipients: giving R-CHOP chemotherapy prior to transplantation. The opinion is interesting. 1, Although the protocols of MGH, Stanford and Northwestern include rituximab, high dose CTX and other potent lymphocyte deletion treatments, tolerance still failed in part of recipients. Considering the authors have only 1 case experience in PTLD patient, the effects of R-CHOP chemotherapy

on tolerance need more data to have conclusion. In fact, many PTLD recipients have received R-CHOP chemotherapy. After cure, they still need receive maintenance immunosuppressive therapy to avoid rejection. 2, The authors suggest “Target neutrophil and lymphocyte counts are 1 × 109/L and 0.5 × 109/L”. How to evaluate the risk of infection and the safety? 3, Does the status of “a half dose dual immunosuppressive therapy” mean “Partial or Prope tolerance”? How to test the status of “Partial or Prope tolerance”? 4, A stagey to induce Partial or Prope tolerance will benefit the recipient world-wide. I don’t think it is necessary to focus on developing Countries. 5, The abstract gives too much background introduction. Should focus on the authors’ strategy.

Reply:

Thank you for appreciating this proposition for a Prope tolerance as interesting. With deep respect to the valuable comments, I would do the following addendum to the revised manuscript.

Addendum:

Comment 1&2.

We aimed at a sequential Lymphocyte depletion therapy rather than an ablative therapy. The sequence starts with B lymphocyte depletion with cycles of R-CHOP therapy to achieve the target Neutrophil and Lymphocyte levels, pre-transplant. Following LKD transplant with a low immunogenic donor-recipient risk-relation, standard tripple immunosuppressive protocol with CNI, MMF and prednisolone will resume for achieving stable graft function. This will be followed by step wise and monitored reduction of immunosuppression to a half trough level CNI and minimum alternate day Prednisolone regimen. Thus, episodes of immediate acute rejections are minimised and a prope or partial tolerance with low dose dual immunosuppressive startegy is achieved.

Commnet 3.

The strategy of CNI half trough level as described, and alternate day low dose prednisolone is described as Prope or partial tolerance. The monitoring of this tolerance would be the regular monitoring of graft function by serum Creatinine levels and hematuria and proteinuria levels. In essence, is the equivant monitoring of a standard graft kidney.

Commentt 4.

This strategy to induce Partial or Prope tolerance, even though is meant for facilitating low risk LKD transplant is developing countries for reasons explained in the epilog, in fact, it will

benefit the recipient world-wide. I would rather think that developed countries are better equipped with ancilliary supportive infrastructure to consider this proposed protocol.

Comment 5.

In the abstract, a detailed background introduction, was mentioned in order to simplify the understanding of issues related to scope of transplant needs, specially in developing countries with marked limitaions in infrastructure, finance, and scarcity of dialysis facilities for an increasing population of endstage kidney disease. To maintain an universal understanding of different stakeholders of chronic kidney disease, the article did a little elaboration before focusing on the strategy of partial tolerance.