Dear Editors-in-Chief,

Re: Manuscript ID BNEP-D-19-00663

We are very much thankful to the reviewers for the deep and thorough review. Your comments were highly insightful and enabled us to greatly improve the quality of our manuscript.
The manuscript had been revised extensively, addressing all of the issues raised by the editors and reviewers. In the following pages are our point-by-point responses to each of the reviewer’s comments.

Response to comment from Reviewer 1

The paper tries to explain differences of the graft and patient outcomes with regard of the 2 different treatment policy retrospectively. The following items as the major and minor considerations should be reevaluated before publishing:

The major considerations:

1- What is the conservative treatment? How did measure and how did monitor those? Which variables treated? By which drug or maneuver?

Response: Thanks for your perceptive comment. Conservative (supportive) treatment involved a medical care for general chronic kidney disease patients, including ideal blood pressure control, blood sugar control, hyperuricemia control, and preventing further kidney damage by avoiding drugs such as nonsteroidal anti-inflammatory drugs (NSAIDs). Antihypertensive agents (ACEI or ARB), oral hypoglycemic agents or insulin, and urate-lowering therapy (allopurinol/febuxostat) were prescribed according to each patient’s clinical condition. Oral sodium bicarbonate were prescribed if the patient had metabolic acidosis (serum bicarbonate less than 22 mEq/L). We monitor each patient’s blood pressure by self-reporting record, and check serum creatinine, uric acid, blood sugar regularly. The above description had been added to our “Materials and Methods” section.

2- As the patients in the group 2 (who did not receive aggressive treatment) it was not randomly selected (it would be secondarily that the therapy would not be effective from the outset [for example cg score in this group is more than the treated group in the table 1 (p=0.052)], or proteinuria was heavier in the group, although without a high p value (probably because the small sample size?) it is not a desirable control group. In the other word your aggressive or conservative treatment may be influenced by the severity of the CABMR primarily.
Response: Thanks for your valuable and important comment. It is possible that aggressive or conservative treatment may be influenced by the severity of the CABMR. A receiver operating characteristic (ROC) curve had been created for using proteinuria to predict treatment response. We found that at a threshold of 1.73 g/d, there was an AUC of 0.679 in discriminating treatment responsive group from non-responsive group. We therefore conducted a Kaplan-Meier analysis of graft survival in patients with proteinuria < 1.73 g/d and ≥ 1.73g/d. Aggressive treatment resulted in better graft survival in patients with proteinuria < 1.73 g/d (p = 0.016 by log rank analysis), but not in patients with proteinuria ≥ 1.73g/d (p = 0.215 by log rank analysis) (figure 4; figure 5). In the subgroup analysis which included proteinuria < 1.73 g/d (table 4), there was no significant difference between aggressive treatment and supportive treatment group in terms of proteinuria, creatinine, banff scores, etc. In summary, in patients with proteinuria < 1.73 g/d, aggressive treatment was associated with better graft survival regardless of proteinuria level or cg scores. This result reminds the primary care physicians that early diagnosis and early treatment are very crucial for CAMR. The above findings had been added to our “Results” section.

3- What is the definition of graft loss? Going back to dialysis of doubling of serum Cr?

Response: Thanks for your kindly comment. The definition of graft loss includes:

returned to dialysis, re-transplant or patient death. The above statement had been added to our “Materials and Methods” section.

4- Sample size is smaller than to reach a conclusive results.

Response: Thanks for your important comment. A total of 82 graft biopsies with diagnosis of chronic active antibody mediated rejection were identified in our study from February 2009 to December 2017. It is true that sample size was relatively small. However, it is our limitation due to the retrospective nature of the study design. Despite of the small sample size, aggressive treatment was still associated with better graft survival and higher incidence of adverse events.

5- Blood pressure, hyperlipidemia, and the drugs were used for, are very important forgotten issues.
Response: Thanks for your valuable comment. All of our colleagues are familiar with the care for chronic kidney disease patients. The control of lipids with statin/fibrate and blood pressure with ACEI/ARB are standard-of-care in our transplant team.

The minor considerations:

1- In the aggressively treated group it is expected that 2 or more drugs have been used together. They should be clearly described and it will a confounding factor for clear conclusion.

Response: Thanks for your comment. In the aggressively treated group, we arranged DFPP and one of the followings: rituximab, IVIG, ATG, bortezomib, or MP pulse therapy every year. Patients were usually treated annually with DFPP plus one of the 5 drugs, but different in each year in order to accomplish a wide blockade of the alloimmunity. The patients didn’t receive 2 or more drugs together. We are very sorry for the misleading.

2- In the table 2, 9th row: "mm &gt; 1" is mistake.

Response: Thanks for your comment. We had make a correction “mm score ≥ 1”

3- Only the barely name of immunosuppressive drugs in each group insufficient. The through levels of CNI are more important in each group.

Response: Thanks for your valuable advice. We had add a column for trough level of CNI in our table. The trough levels between each group were not significantly different.

4- Based on table 1, 3 patients in the conservative group received anti-CD25 therapy as induction therapy, why?

Response: The choices of induction therapy were based on the judgment of each transplant physician. Points to be considered included patient’s immune risk profile and financial status, because anti-CD25 was not reimbursed by insurance company in Taiwan.
Response to comment from Reviewer 2

The manuscript »Treatment of Chronic Active Antibody-mediated Rejection in Renal transplant recipients” is a retrospective single centre clinical study comparing two regimens of treating active antibody-mediated rejection (standard and aggressive treatment) in 82 cases of biopsy proven active rejection.

The major study finding is that graft survival was better in the group of patients with aggressive treatment, however, there were more side effects, mainly infections. The authors conclude that intensive prevention and control of infection should be provided for the group with aggressive treatment.

The limitations of the study are discussed. The major weakness of the study are patients' selection - allocation to the treatment in a retrospective study design. In addition to relatively low number of patients the results may not support the conclusion.

Addressing important issues are necessary, so I recommend it for major revision.

Specific comments

Major

1. Patients selection to standard and aggressive treatment group - please clarify.

Have reimbursement policy in Taiwan influenced patient allocation to standard and aggressive treatment?

Response: Thanks for your insightful comment. The treatment strategies were selected for CAMR treatment according to the patient’s clinical condition and decision of the individual practitioners. We arranged DFPP and one of the followings: rituximab, IVIG, ATG, bortezomib, or MP pulse therapy every year. Rituximab, IVIG, and bortezomib are not reimbursed by national insurance in Taiwan and should be self-paid. Actually, this may have influence on the selection of medication, but not on the allocation to standard or aggressive treatment. A patient who cannot afford self-paid Rituximab/IVIG/bortezomib can still choose ATG or MP pulse therapy for his/her aggressive treatment strategy.
2. In the abstract it is stated 82 graft biopsies were analyzed. Does that mean 82 patients? Please clarify in the abstract and in the text.

Response: Thanks for your valuable comment. We had revised the manuscript: “82 patients with biopsy-proven chronic antibody mediated rejection” in our abstract and main text.

3. DFPP annually - please describe a protocol?

Response: DFPP was performed using a Evaflux 4A as the plasma fractionator. The exchange volume was set at 1~1.5 times of plasma volume. Estimated plasma volume = 0.07 x weight(kg) x (1-hematocrit [Hct]). 300–500 mL saline solution was infused as the replacement fluid. Renal function, biochemistry (especially calcium level), and coagulation profiles were checked regularly.

4. How was graft loss defined?

Response: Returned to dialysis, retransplant or patient death. The definition of graft loss had been added to our “Materials and Methods” section.

5. IVIg may not be considered as aggressive treatment as they may protect from infection (contrary to other aggressive immunosuppressive therapy). Please comment on that.

Response: Although IVIG may protect from getting infection, we still consider it as “aggressive therapy” because IVIG has theoretical therapeutic benefits as opposed to just “wait and see”
Minor

Table 1.

1. Please reduce the number of decimals.
Response: Thanks for your advise. We had reduced the number of decimals in the table.

2. Please explain abbreviations in the table (Banff score)
Response: Thanks for your comment. We had added the abbreviations in the table (Banff score)

3. Please provide units for creatinine, e GFR etc
Response: Thanks for your advise. We added units for creatinine and eGFR in the table.

Again, we appreciate all your insightful comments. We worked hard to responsive to them. We hope that these revisions improve the manuscript such that you and reviewers now deem it worthy of publication in BMC nephrology.