

## ANSWERING REVIEWERS



March 20, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 9355 edited.doc).

**Title:** The “minimizing tacrolimus” strategy and long-term survival after liver transplantation

**Authors:** Jun-Jun Jia, Bin-Yi Lin, Jiang-Juan He, Lei Geng, Dhruba Kadel, Li Wang, Dong-Dong Yu, Tian Shen, Zhe Yang, Yu-Fu Ye, Lin Zhou, Shu-Sen Zheng

**Name of Journal:** *World Journal of Gastroenterology*

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 reviewers

**Reviewer 1 (2861333):** This study introduced a novel method to evaluate the low level of TC by the mean and SD of TC. The manuscript need be revised. 1. Redundant manuscript. Thoroughly rewrite the manuscript. For example, “In cox regression, the patient” should be “the patients”? 2. Some opinions still need debate. For example, “The currently recommended target range for tacrolimus concentration in blood after LT is 10 -15 ng/ml during the first 4-6 weeks”. In fact, the current recommendation is 6 -10 ng/ml or 8 -12 ng/ml. 3. Some sentences are easily misunderstood. For example, what is meaning “Renal insufficiency was determined by serum creatinine  $\geq 130$   $\mu\text{mol/L}$  for 1 year or more after LT, lasting at least 1 month.”? 4. It is not reasonable for that the patients with TC SD  $< 2$  had the worse survival.

### Answers

- (1) We have the paper polished in language by native English speakers (editorial certificate was provided).
- (2) It is true that the recommended early tacrolimus exposure is still controversial. As you mentioned, 6-10 or 8-12 ng/ml was also recommended in some centers, the 10-15 ng/ml was mainly based on the experience of our center and the previous study (cited in the manuscript, especially the one published on J Hepatol). We used mean TC 5-10 ng/ml and SD 2-4 in the initial four weeks following OLT as the optimal range for long-term survival. This “minimizing tacrolimus” strategy protected against the unwanted effects, particularly the rejection. Even the currently recommended early tacrolimus exposure is 6-10 or 8-12 ng/ml, we think our conclusion is still meaningful, because we introduced the parameter of SD, which is also very important for long-term outcome.
- (3) We have corrected the sentence as “Renal insufficiency was defined as serum creatinine  $\geq 130$   $\mu\text{mol/L}$ , lasting at least 1 month after LT.”
- (4) We thought SD $<2$  should indicate better outcome, but the data and statistics showed opposite

result. We searched this in Pubmed and other database but few available was found: high SD in serial TC was related to elevated likelihood of late rejection and graft loss in pediatric organ transplant recipients (Pollock-Barziv, S.M., et al. Variability in tacrolimus blood levels increases the risk of late rejection and graft loss after solid organ transplantation in older children. *Pediatr Transplant* 14(8): 968-75) . They showed the  $SD < 2$  indicated better outcome compared to  $SD > 2$ . The cut point in our study by ROC was 4, according to ROC and above articles, we divided it into three groups  $SD < 2$ ,  $SD 2-4$  and  $SD > 4$ . The data and statistics showed that  $SD 2-4$  indicated better outcome compared to  $SD < 2$ . It was opposite with the results of above articles. The possible reasons may be as follows: 1. the objects of the above articles were children while ours were adults; 2. the number of  $SD < 2$  group was only 21, which may affect the result; and 3. this part of patients were insensitive to TAC. In the future we will enlarge our sample size for further research.

**Reviewer 2** (502871): The authors report on the outcomes of a prospective study of tacrolimus levels and the standard deviation of these values in patients undergoing liver transplantation. The reporting of complication rates at different tacrolimus levels is useful, as is the identification of an optimal level of tacrolimus for maintenance. The manuscript requires careful and extensive rewording for clarity and readability.

#### Answers

According to your suggestion, this manuscript has been improved in language by native English speakers. The careful and extensive rewording was done for better clarity and readability.

3 References and typesetting were corrected

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

Sincerely yours,

*Jun-Iun Jia*

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