

ANSWERING REVIEWERS



January 25, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 5844-Review.).

Title: Corticosteroid-free immunosuppression in liver transplantation: An evidence-based review

Author: George Sgourakis, Georgia Dedemadi

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 5844

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 reviewer

(1) 02456611

We thank the reviewer for the kind comments.

(2) 00051373

We thank the reviewer for the kind comments.

(3) 00054993

We thank the reviewer.

(4) 00058365

- **This is an evidence based review of steroid avoidance immunosuppression in OLT. Individual articles and meta-analysis are critiqued but no methodology or search method is evident.**

This is an important comment and according to the reviewer's comment, we have added our search methodology.

- **The references appear comprehensive.**

References have been formulated using "Endnote" software according to the Journal's Style.

(5) 00058255

- **The authors failed to mention two important points: First, were there any differences between the tacrolimus blood levels (both initially planned and eventually applied) of the steroid and steroid-free groups in any of the studies?**
- This is an important comment. The following quote was added in the results: "Only 7 studies give detailed information about the percentage of patients in each treatment arm which had received the allocated regimen".

- The following quote *“The corticosteroid-free immunosuppression group was superior with impact as to the number of patients receiving the allocated intervention (O.R =1.55 [1.17, 2.05], p=0.003)”* was already included on the paragraph *“Graft and Patient survival”* of the manuscript.
- **Second, what was the typical steroid dose given to the patients after the first two weeks?**
- This is a difficult question to answer. Steroid dosage was calculated by different formulas at different time points in each study.
- **Were mild rejection episodes (laboratory abnormalities that cannot be explained otherwise in asymptomatic patients) treated with dose modification for tacrolimus only or for both tacrolimus and steroid?**
- Every single study’s rejection protocol treatment is provided on column 7-Table 3.
- **How were the data of the ‘steroid-free’ patients who received pulse steroids and a taper included in the comparison between steroid and ‘steroid-free’ arms?**
- This is an important comment. Both Steroid and Steroid-free arms received the same *“pulse steroid regimen”* for rejection treatment as depicted on column 7-Table 3. Data analysis in each RCT and the 2 meta-analyses was done on an intention to treat basis.
- **The coherence of the data presentation is compromised by the use of expressions ‘steroid replacement’ (i.e. given no steroids after two weeks?) and ‘steroids were replaced’ (i.e. given another immunosuppressive agent, usually after two weeks?) in the same manuscript because the reader feels compelled to stop and consider what has been done.**
- This kind of information already exists on column 4-Table 3. Regimens administered in each individual study have been given in detail.

(6) 00054001

- **Issues dealt with in this manuscript were very important. Content is excellent.**

We thank the reviewer for the kind comments.

- **However, many redundant descriptions spoiled the clearness of the content.**

This comment comes to imbalance with those of Reviewer 00058255 who requests two more descriptions. Nevertheless, for clarity reasons, in this revised version of the manuscript we have analyzed the results of the two meta-analyses together. The following paragraph has been deleted in the Graft and patient Survival section, since this information adds nothing to the already mentioned evidence: *“Monotherapy in both groups was used in the study of Cholangitis et al. Actuarial survival according to Kaplan–Meier curves at five years was 72% for TACRO and 70% for CyA. Graft survival at five years was 59% for TACRO and 57% CyA. Neither patient survival nor graft survival differed statistically between groups. Only 2 patients in the TACRO group required a second LT, compared to 5 (14%) in the CyA group (p = 0.007). (Level of Evidence: 2b, Degree of Recommendation: B)”*

We believe that we have found a good balance between providing the reader all key information and avoiding redundancy.

- **The authors should make an effort for gaining readability.**

We agree with the Reviewer's recommendations. As shown in the answer to **Reviewer 00053888** the manuscript has been revised grammatically and linguistically by an English native speaker. Recommendations and levels of evidence have been summarized on a new table (Table 4). A title has been added on top of each issue analysis in order to make results flow smoothly.

(7) 00053888

- **The authors have decided to carry out a review and meta-analysis of steroid free immunosuppression following liver transplantation. This is timely as we move towards a more targeted immunosuppression in liver transplantation.**

We thank the reviewer for the kind comments.

- **The manuscript suffers from being disjointed with some aspects of poor grammar. For example the paper could be structured differently such that the recommendations and levels of evidence were presented elsewhere (e.g. conclusions, summary, or even tabulated) and the results could be more discursive and less disjointed.**

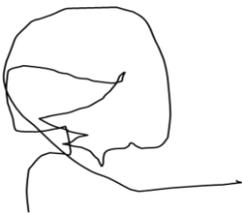
We have changed the structure of the manuscript according to the Reviewer's instructions. The manuscript has been revised grammatically and linguistically by an English native speaker. Recommendations and levels of evidence have been summarized on a new table (Table 4). A title has been added on top of each issue analysis in order to make results flow smoothly.

- **Similar applies to the conclusion which suffers from being a series of bullet points.** Conclusions have been revised according to the Reviewer's instructions.

3 References and typesetting were corrected.

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

Sincerely yours,

A simple line drawing of a handwritten signature, appearing to read 'G. Sgourakis', written in a cursive style.

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