

PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 33765

Title: A DELAYED AND SHORT COURSE OF RAPAMYCIN PREVENTS ORGAN REJECTION AFTER ALLOGENEIC LIVER TRANSPLANTATION IN RATS

Reviewer's code: 00739827

Reviewer's country: Reviewer_Country

Science editor: Ze-Mao Gong

Date sent for review: 2017-03-03

Date reviewed: 2017-03-03

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input checked="" type="checkbox"/> Grade A: Priority publishing	Google Search:	<input checked="" type="checkbox"/> Accept
<input type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> The same title	<input type="checkbox"/> High priority for publication
<input checked="" type="checkbox"/> Grade C: Good	<input type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> Duplicate publication	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade D: Rejected	<input type="checkbox"/> Plagiarism	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E: Poor		<input checked="" type="checkbox"/> No	<input type="checkbox"/> Major revision
		BPG Search:	
		<input type="checkbox"/> The same title	
		<input type="checkbox"/> Duplicate publication	
		<input type="checkbox"/> Plagiarism	
		<input checked="" type="checkbox"/> No	

COMMENTS TO AUTHORS

- Have you tried to rescue animals rejected under low dose with high dose of rapa ?
- There was an clinical report in the literature regarding rescue of acute rejection in liver transplant with rapa resistant to any other modalities which may help you

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Title: A DELAYED AND SHORT COURSE OF RAPAMYCIN PREVENTS ORGAN REJECTION AFTER ALLOGENEIC LIVER TRANSPLANTATION IN RATS

Reviewer's code: 00051373

Reviewer's country: Taiwan

Science editor: Ze-Mao Gong

Date sent for review: 2017-03-03

Date reviewed: 2017-03-05

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input checked="" type="checkbox"/> Grade A: Priority publishing	Google Search:	<input checked="" type="checkbox"/> Accept
<input checked="" type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> The same title	<input type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C: Good	<input type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> Duplicate publication	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade D: Rejected	<input type="checkbox"/> Plagiarism	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E: Poor		<input checked="" type="checkbox"/> No	<input type="checkbox"/> Major revision
		BPG Search:	
		<input type="checkbox"/> The same title	
		<input type="checkbox"/> Duplicate publication	
		<input type="checkbox"/> Plagiarism	
		<input checked="" type="checkbox"/> No	

COMMENTS TO AUTHORS

An interesting and readable manuscript to explore a delayed and short course of rapamycin initiated on day 4 following allogeneic OLT in rats resulted in the survival of grafted rats for more than 100 days. This study is very clear and well manuscript written. Hopefully, this animal study to be treat in the human being as soon as possible.

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Manuscript NO: 33765

Title: A DELAYED AND SHORT COURSE OF RAPAMYCIN PREVENTS ORGAN REJECTION AFTER ALLOGENEIC LIVER TRANSPLANTATION IN RATS

Reviewer's code: 02530754

Reviewer's country: Spain

Science editor: Ze-Mao Gong

Date sent for review: 2017-03-03

Date reviewed: 2017-03-13

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	Google Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B: Very good	<input checked="" type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> The same title	<input type="checkbox"/> High priority for publication
<input checked="" type="checkbox"/> Grade C: Good	<input type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> Duplicate publication	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade D: Rejected	<input type="checkbox"/> Plagiarism	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E: Poor		<input checked="" type="checkbox"/> No	<input type="checkbox"/> Major revision
		BPG Search:	
		<input type="checkbox"/> The same title	
		<input type="checkbox"/> Duplicate publication	
		<input type="checkbox"/> Plagiarism	
		<input checked="" type="checkbox"/> No	

COMMENTS TO AUTHORS

The study by Hamdani et al. evaluated the efficacy and safety of a delayed and short course of rapamycin after liver transplantation within a rat model. The authors studied the effect on rejection, wound healing complications and induction of tolerance. The manuscript is well written and structured. English language is appropriately used. The main flaws of the study are its limited translational component and the lack of control group receiving calcineurin inhibitors, which are currently considered the standard of care. 1- The potential translational implications of this research are not apparent. Rapamycin (sirolimus) and its analogous everolimus are already part of the therapeutic arsenal in transplantation, and there are several phase III/IV randomized trials available for each of them. The efficacy of these drugs and their safety profile are well known and I am not sure on whether the present study provides any novel information. Besides, a delayed short course of rapamycin as monotherapy is not an option for transplant patients. As I understand it, the most relevant finding in the study pertains to induction

of tolerance, and the manuscript would be improved by emphasizing on this aspect. 2- The rationale of the study is also questionable. The authors said that "In order to circumvent the side effects of rapamycin at time of liver transplantation, we tested a shortened delayed administration protocol". In liver transplantation this strategy was already implemented, for instance, in the registration trial of everolimus (H2304 trial, De Simone et al, Am J transplant 2012) where randomization was performed at day 30 after liver transplantation. 3- The study would be greatly improved by including a control group treated with calcinurin inhibitors (and maybe a third group receiving everolimus, which has shown a safer profile as compared with sirolimus). This would strengthen the conclusions, particularly those regarding efficacy and induction of tolerance. 4- The authors said in the introduction that: "-rapamycin- is not recommended as first-line treatment for liver transplantation due to deleterious side effects such as delayed wound-healing processes...". The reference provided to support this statement is a study performed in heart transplantation. In any case, this is a controversial aspect and it is not difficult to find studies with contradictory results. Most probably, this is a dose-dependent effect, which could be avoided by using lower dosage.