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10/12/15

Dear Sir/ Madam,

Thank you very much for your comments pertaining to our paper submitted for the World Journal of Pharmacology titled “Non selective beta-blockers in cirrhosis: current concepts and controversies” written by myself and Dr Tripathi.

Since the original commissioning of article earlier in the year there have been a number of trials and new data in the field we hope would be relevant to readers of the journal.

Thank you for the opportunity to discuss and address the reviewer’s comments as follows:

Reviewer 00181421 – “agree to publish” – thank you.

Reviewer 00074337 – the reviewer notes the data from Leithead et al 2014 was from our own centre which we have indeed now acknowledged and cited as our own group when 1<sup>st</sup> referenced. The reviewer mentions further mathematical modelling comments and meta-analysis, especially pertaining to SBP and HRS. In this new draft of the manuscript we have not only included a recent meta-analysis abstract from AASLD 2015, but also including a pertinent abstract of patient groups with HRS from the multicentre American NASCLED group. We have included detailed comments and strategies regarding sub-group analysis of patients as they advance through the window hypothesis including potential strategies for further trial designs. We have also included the post-hoc analysis paper from Bossen et al, published since when we 1<sup>st</sup> submitted this paper – based on cirrhotic patients from 3 trials (originally looking at Vaptans in patients with ascites). This is an interesting paper exploring the safety of NSBBs in such patients – and their effects on in-patient mortality and although the paper has criticisms, does suggest safety of NSBB in patients with cirrhosis and indeed refractory ascites.

Reviewer 00504596 – the reviewer states there is “no new information in our article”. This is slightly polarized from the other 2 reviewers. We would have to respectfully challenge this reviewer on this comments.

Our article not only summarises the pre-existing data relating to NSBBs in cirrhosis, but also succinctly and comprehensively outlines the current debate regarding their benefit v detrimental effects in late stage cirrhosis and also the question about the safety of NSBBs . Furthermore, since the 1<sup>st</sup> review we have added new data not only from the recent AASLD 2015 meeting last month, but the data re: NSBB and ACLF by Mokerjee et al 2015, and also a new paper from Bossen et al 2015 - a post-hoc analysis of 3 RCTs looking at the use of NSBBs in patients with cirrhosis and ascites. Both of these papers suggest NBSSs are indeed safe in patients with advanced cirrhosis. We have also discussed a new paper from Serste et al looking at the role of NSBBs in patients with Alcoholic Hepatitis.

There was indeed a massive change in practice following the paper from Serste et al a few years ago, and with the ever new increasing data, we feel this article is not only scientifically relevant but also relevant to the bedside clinical management of patients throughout the world especially with new data showing that NSBBs may indeed be safe and beneficial in advanced cirrhosis.

We hope these additions and responses answer the comments of the reviewers. All the changes made including the references added have been highlighted as requested.

Thank you

Dr N Rajoriya

Dr D Tripathi