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Answering reviewers

Reviewer's code: 01439175

COMMENTS TO AUTHORS

The work of Shi and co-workers investigates the impact of sinusoidal endotheliitis for qualification of liver graft rejection. This parameter is an additional parameter to the qualification categories of the RAI Score currently used in clinical routine to express the degree of rejection activity after liver transplantation. Since quantification of sinusoidal endotheliitis reached a sensitivity of 81% and a specificity of 85% it may reflect a more sensitive parameter than the currently used categories (lymphocyte infiltration around portal veins, centrilobular veins and bile ducts). Alternatively, this new category might reflect an additional parameter, which would improve the accurateness of the RAI score. The manuscript is well written and would be of great value for the readers, when published in the WJG. I would therefore recommend the acceptance of the manuscript as submitted.

Answer:

We greatly appreciate this reviewer's comments. Thank you very much!

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Reviewer's code: 00503243

COMMENTS TO AUTHORS

The authors clearly document that sinusoidal endotheliitis is a good marker of acute cellular rejection after liver transplantation with high sensitivity and specificity. In the study group there are a very high number of patients with cirrhosis due to hepatitis C. My two questions are: a)Why in the ACR group the number of hepatitis C patients is higher with respect to ACR negaive group? b) Why in the ACR positive group, patients with recurrent hepatitis C are excluded, while they are not excluded in the ACR negative group?

Answer:

We greatly appreciate this reviewer's questions. They have made us reflect and discuss further in regards to our study design. Since the two questions are related, we will answer them together but in a reverse order.

Hepatitis C virus (HCV)-caused cirrhosis is the most common indication for liver transplantation (LT) in Canada.[1] Despite advances in antiviral therapy, reinfection of HCV in liver allografts is almost universal.[2] [3] The recurrence of HCV as defined by elevation of HCV RNA in serum, and histologic evidence of HCV can be demonstrated in 70-90% of recipients after 1 year and in 90-95% after 5 years.[4] [5] Most post-transplant liver biopsies in our institute were cases with or without serum HCV RNA to rule out acute cellular rejection (ACR). Since recurrent HCV shares some histology features with ACR, cases of ACR with high HCV RNA were excluded from ACR group to simplify the comparison. In ACR negative group, cases with high HCV RNA were included because there weren't enough cases of HCV RNA negative patients in this group (response to question b). Post-liver transplant patients with neither ACR nor HCV RNA were rarely indicated for biopsy. Exceptions are the cases with other etiology liver diseases, such as non-alcoholic steatohepatitis (NASH), or cholestatic disease. Therefore, there were more non-HCV cases in ACR negative group than those in ACR group. Or in other words, ACR group had more HCV patients than ACR negative group (response to question a). We have integrated the responses into limitations of the study in discussion section (page 12, paragraph 3, line 4).

References:

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2 Wright TL, Donegan E, Hsu HH, Ferrell L, Lake JR, Kim M, Combs C, Fennessy S, Roberts JP, Ascher NL, et al. Recurrent and acquired hepatitis C viral infection in liver transplant recipients. *Gastroenterology* 1992; **103**(1): 317-322 [PMID: 1377143]

3 Garcia-Retortillo M, Forns X, Feliu A, Moitinho E, Costa J, Navasa M, Rimola A, Rodes J. Hepatitis C virus kinetics during and immediately after liver transplantation. *Hepatology* 2002; **35**(3): 680-687 [PMID: 11870384 DOI: 10.1053/jhep.2002.31773]

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5 Gane E. The natural history and outcome of liver transplantation in hepatitis C virus-infected recipients. *Liver Transpl* 2003; **9**(11): S28-34 [PMID: 14586892 DOI: 10.1053/jlts.2003.50248]