

Reviewer 1

(1) The aim of this manuscript resumed as “an evaluation of the efficacy of tolvaptan treatment in ascites pathology in patients with advanced carcinoma” is very interesting in the conceptual idea. This consideration is further confirmed by scarce literature data regarding analogues treatment in patients with ascites pathology aggravated by advanced carcinoma although, a paper by Suzuki et al. (*Hepatology Research* 2015; 45: E161–E162), recently published report analogous study objective in only 9 patients. This lack in bibliography is evident in this part of bibliography where more other references have to be reported. This premise is important to clarify that the introduction must be rewrite completely by adding also references and by explaining in a clearly way the purpose of this manuscript.

We added the next sentence in the part of introduction with a reference.

“Furthermore, scarce investigators payed attention to the influence of HCC on the effect of TLV. Suzuki et al. recently reported the efficacy and safety of TVT for the patients with advanced HCC, but the number of the enrolled patients was only 9 [15].”

15 **Suzuki E**, Chiba T, Ogasawara S, Saito T, Kanogawa N, Motoyama T, Ooka Y, Tawada A, Maruyama H, Ogawa M, Yokosuka O. Tolvaptan treatment for patients with decompensated cirrhosis and advanced hepatocellular carcinoma. *Hepatol Res* 2015; 45: E161-2 [PMID: 26510648 DOI: 10.1111/hepr.12465]

(2) Moreover, some sentences in the paragraph are not completely true. ES. The text reports “The renin–angiotensin–aldosterone (RAA) system, another hormonal regulator of hepatic ascites, is thought to be one of the main causes of hepatic ascites” must be inserted in a more wide concept. In fact, a paper (Hernandez-Guerra M, Garcia-Pagan JC, Bosch J. Increased hepatic resistance: a new target in the pharmacologic therapy of portal hypertension. *J Clin Gastroenterol* 2005) cited in another very interesting paper (A. KASHANI, C.

LANDAVERDE, V. MEDICI and L. ROSSARO, Fluid retention in cirrhosis: pathophysiology and management, *Q J Med* 2008; 101:71–85) reported a specific concept on ascites pathophysiology by using this interesting sentence “consequence of distortion of hepatic architecture and increased hepatic vascular tone”.

We added the next paragraph at the top of introduction with 2 references.

“Fluid retention such as ascites, edema or pleural effusion is a major complication of advanced liver cirrhosis, which results from distortion of hepatic architecture and increased hepatic vascular tone, and a subsequent derangement in the extracellular fluid volume regulatory mechanisms [1, 2].”

1 **Kashani A**, Landaverde C, Medici V, Rossaro L. Fluid retention in cirrhosis: pathophysiology and management. *QJM*. 2008;101:71-85. [PMID: 18184668 DOI: 10.1093/qjmed/hcm121]

2 **Hernández-Guerra M**, García-Pagán JC, Bosch J. Increased hepatic resistance: a new target in the pharmacologic therapy of portal hypertension. *J Clin Gastroenterol*. 2005; 39:S131-7. [PMID: 15758648]

(3) A question regarding the dose of 15 mg TLV (probably too high dose). In numerous studies (7 or 15 days treatment) the maximal dose used is 7 mg.

In 2010, Okita et al. reported that TLV dose-dependently decreased body weight and abdominal circumference and improved ascites and edema beginning from 15 mg/day in comparing with 30mg/day in a multicenter, open-label, dose-ranging study. They later performed a dose-finding trial of TLV in cirrhotic patients, and reported that TLV at 7.5 mg/day was considered the optimal dose in liver cirrhosis patients in 2014. We started the treatment with TLV in 2011, considering the Okita’s earlier report. That’s the reason we administered TLV in 3.75 to 15mg/day.

(4) In addition, regarding the results, the used figures should be modified a

little. Es. Figure 1 could be improved by adding the significative effect of daily treatment with Tolvaptan by using Friedman test with multiple comparison.

The number of the patients treated in 7.5mg/day TLV was quite larger than those in 3.75 or 15mg/day (The number of the patients treated with 3.75/ 7.5/ 15mg/day was 3/ 24/ 5 in HCC(+) group, and 2/ 22/ 5 in HCC(-) group. A comparison figure among the groups with such a different number could mislead readers. We confirmed that the dose of TLV did not influence on the decreased BW% in univariate and multivariate regression analysis.

(4) Furthermore, Figure 2 could be transformed or added in a table with results more significative.

As described in the part of results, the difference of the average of the decreased BW% in every pair of the groups was not significant both in the patients with and without HCC. However, it was obvious that the influence of proceeding furosemide dosage on the decreased BW% was contrary between the patients with and without HCC. Especially, we considered that a relative strong resistance to TLV in the patients with HCC who had been treated with high dose furosemide was important. To emphasize this point, a box-plot figure seemed to be appropriate.

(5) In addition, table 2 should be reported first of all other data.

As the reviewer described, the background of the enrolled patients is generally shown in the beginning. We exchanged the numbering of Table 1 and 2, and referred to Table 1 in the part of Patients and Methods.

(6) Also the conclusion should be modified and rewritten by adding more literature on the field. Here, some papers reported the relation between cirrhosis and hyponatremia as well as predictive treatment effect of tolvaptan. 1. Gaglio P1, Marfo K, Chiodo J 3rd. Hyponatremia in cirrhosis and end-stage liver disease: treatment with the vasopressin V₂-receptor antagonist tolvaptan.

Dig Dis Sci. 2012 Nov;57(11):2774-85. doi: 10.1007/s10620-012-2276-3. Epub 2012 Jun 26. 2. Yoshitaka Takuma, Hirokazu Miyatake, Shota Iwadou, Shuji Uematsu, Ryouichi Okamoto, Yasuyuki Araki. Predictive factors for the effectiveness of tolvaptan in liver cirrhosis patients with refractory ascites. *Kanzo* Vol. 57 (2016) No. 12 p. 684-687. 3. Ji-Dong Jia , Wen Xie , Hui-Guo Ding , Hua Mao , Yonggang Li , Xiaojin Wang , Jie-Fei Wang , Wei Lu , Cheng-Zhong Li , Yimin Mao , Gui-Qiang Wang , Yue-Qiu Gao , Bangmao Wang , Qin Zhang , Yan Ge , Vincent Wai-Sun Wong. Utility and Safety of Tolvaptan in Cirrhotic Patients With Hyponatremia: A Prospective Cohort Study. *Ann Hepatol* 16 (1), 123-132. 1 2017 2017 Jan-Feb 2017. The manuscript could be accepted only after a major revision.

Referring to the suggested papers, we inserted the next sentences in the part of discussion, and added a reference.

“Nakagawa et al. reported the analysis of 40 cirrhotic patients treated with TLV including 12 with HCC. They showed that the progression of portal hypertension attenuated the effect of TLV, but the mechanism was unclear. A multivariate analysis including the dose of concomitant natriuretic diuretics and serum sodium concentration might have been helpful to clarify the process.”

22 **Nakagawa A**, Atsukawa M, Tsubota A, Kondo C, Okubo T, Arai T, Itokawa N, Narahara Y, Iwakiri K. Usefulness of portal vein pressure for predicting the effects of tolvaptan in cirrhotic patients. *World J Gastroenterol*. 2016; 22:5104-13. [PMID: 27275103 DOI: 10.3748/wjg.v22.i21.5104]

Reviewer 2

(1) Authors concluded that tolvaptan was unable to decrease body weight in liver cirrhosis patients with HCC due to portal vein hypertension. Please show us any data or papers about portal vein hypertension in patients with HCC. In clinical situation, I cannot agree that advanced HCC increases portal pressure so much.

We also had not expected that advanced HCC would increase portal pressure. As we described in discussion, however, Chen et al. showed that micro- and macrovascular invasion of HCC were independent factors relating to the development of ascites (*Tumour Biol.* 2015;36:6255-63), and Pawlik et al. reported that HCC tumors were frequently accompanied with minor vascular invasion (*Liver Transpl.* 2005;11:1086-92). Taken together, their findings indicate that HCC tumors could cause segmental increase of sinusoidal pressure.

(2) Table 1 shows that stepwise multiple regression analysis to predict the decreased BW%. I would like to know the predictive factors for effect of tolvaptan. Could you show us the univariate analysis including patients and HCC characters? Are the portal vein thrombus and HCC staging the predictive factors?

The results of univariate analysis were as follows;

Variables		Coefficient	95%CI	t	p-value
Tumor thrombus(+)		-1.8141	[-3.6553, 0.0271]	-1.97	0.0534
BCLC staging	B-A	-1.1986	[-8.5002, 9.4449]	-0.34	0.7389
	C-B	1.2971	[-5.7727, 8.3668]	0.38	0.7095
	D-C	-4.7585	[-9.5062, -0.0107]	-2.06	0.0495

In the patients with tumor thrombus or advanced BCLC staging, the effect of TLV seems to be decreased.

(3) Table 2 shows that HCC patients decreased BW smaller than non-HCC patients. The authors need to show the information about baseline data including body weight and approximate volume of ascites. Percentage of body weight decrease does not mean the effect of tolvaptan itself.

We added a variable of BW(kg) in table 2.