

Accepted Manuscript

Unexpected high incidence of hepatocellular carcinoma in patients with hepatitis C in the era of DAAs: too alarming?

Qing-Lei Zeng, Zhi-Qin Li, Hong-Xia Liang, Guang-Hua Xu, Chun-Xia Li, Da-Wei Zhang, Wei Li, Chang-Yu Sun, Fu-Sheng Wang, Zu-Jiang Yu

PII: S0168-8278(16)30399-3

DOI: <http://dx.doi.org/10.1016/j.jhep.2016.07.029>

Reference: JHEPAT 6209

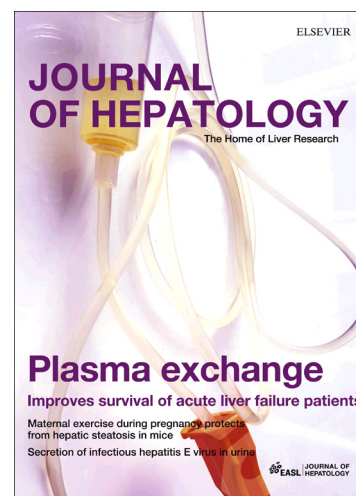
To appear in: *Journal of Hepatology*

Received Date: 12 July 2016

Accepted Date: 19 July 2016

Please cite this article as: Zeng, Q-L., Li, Z-Q., Liang, H-X., Xu, G-H., Li, C-X., Zhang, D-W., Li, W., Sun, C-Y., Wang, F-S., Yu, Z-J., Unexpected high incidence of hepatocellular carcinoma in patients with hepatitis C in the era of DAAs: too alarming?, *Journal of Hepatology* (2016), doi: <http://dx.doi.org/10.1016/j.jhep.2016.07.029>

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.



**Unexpected high incidence of hepatocellular carcinoma in patients with hepatitis C in
the era of DAAs: too alarming?**

Qing-Lei Zeng^{1,¶}, Zhi-Qin Li^{1,¶}, Hong-Xia Liang^{1,¶}, Guang-Hua Xu², Chun-Xia Li², Da-Wei
Zhang³, Wei Li⁴, Chang-Yu Sun¹, Fu-Sheng Wang^{3,*}, Zu-Jiang Yu^{1,*}

¹Department of Infectious Diseases and Hepatology, The First Affiliated Hospital of
Zhengzhou University, Zhengzhou, Henan Province, China, ²Department of Infectious

Diseases, The Affiliated Hospital of Yan'an University, Yan'an, Shaanxi Province, China,

³Research and Treatment Center of Infectious Diseases, Beijing 302 Hospital, Beijing, China,

⁴Department of Infectious Diseases, Henan Provincial People's Hospital, Zhengzhou, Henan
Province, China

[¶]These authors contributed equally to this letter.

*Corresponding author:

Zu-Jiang Yu, MD, PhD, Prof,

Department of Infectious Diseases and Hepatology,

The First Affiliated Hospital of Zhengzhou University,

Zhengzhou, Henan Province, China

1 East Jianshe Road, Zhengzhou, China

Phone & Fax: +86 371 6796 6932

E-mail: johnyuem@zzu.edu.cn

Fu-Sheng Wang, MD, PhD, Prof,

Research and Treatment Center of Infectious Diseases,

Beijing 302 Hospital,

Beijing, China

100 Western 4th Middle Ring Road, Beijing, China

Phone & Fax: +86 10 6693 3332

E-mail: fswang302@163.com

Conflict of Interest

No conflict of interest was declared by the authors.

Authors' contributions

Q.-L.Z., F.-S.W. and Z.-J.Y. conceived the study. Q.-L.Z., Z.-Q.L., and H.-X.L. wrote the manuscript. All authors reviewed the manuscript.

Acknowledgements

This study was supported by The National Natural Science Foundation of China (No. 81302593) and The Key Scientific Research Project of Henan Higher Education Institutions of China (No. 15A320083)

To the Editor,

As a terminator of hepatitis C virus (HCV) infection, sofosbuvir-based direct-acting antiviral agent (DAA) regimens have achieved great success in the eradication of HCV in patients with hepatitis C and related end stage liver diseases[1, 2]. Recently, we read with interest the studies by Reig et al.[3] and Kozbial et al.[4] on the surprisingly high incidence of hepatocellular carcinoma (HCC) recurrence and occurrence in patients with advanced liver diseases during interferon-free therapy and after sustained virologic response (SVR), respectively. Notably, the time interval between the initiation of DAAs (or SVR) and tumour occurrence is very short. These studies promote the current awareness and understanding of the risk for hepatocarcinogenesis in the era of DAAs. However, similar episodes have not frequently been observed in Chinese patients until now.

In our previous open-label study[5], cirrhotic patients who had previously undergone interferon treatment were administered sofosbuvir and daclatasvir, with (group 1, n = 15) or without (group 2, n = 6) ribavirin for 12 weeks, and patients with small hepatocellular carcinoma (HCC) who previously underwent radiofrequency ablation (group 3, n = 10) were treated with triple therapy. In group 3, 8 of the 10 patients met the inclusion and exclusion criteria described by Reig et al.[3], and 2 patients had 'non-characterized nodules' at the initiation of therapy, which indicates that patients in our group may have been more 'advanced'. A magnetic resonance or computed tomography scan was performed every 3 months after the initiation of triple therapy. However, no tumour recurrence or new occurrence were observed in group 3 after a median follow-up time of 15.0 (13.7-16.3) months. Additionally, for a median follow-up time of 15.0 (14.0-16.0) months, no tumour

occurrence was detected in 21 patients from group 1 and group 2, which is different from the results of the study reported by Kozbial et al.[4], although our sample size was smaller.

In interferon era, the incidence of HCC in SVR-achieving or even in antiviral-treated hepatitis C patients is very low[6]. Our previous study[7] reported that the overall rate of HCC after SVR was 1.2% (26/2,130) during a median post-SVR time of 17.5 months at The First Affiliated Hospital of Zhengzhou University and Beijing 302 Hospital, which are the largest tertiary general hospital (containing 11,000 clinical beds) and the largest liver disease hospital (containing 1,200 clinical beds) in China, respectively. However, the unexpectedly high incidence of HCC in the DAA era is in sharp contrast to that in the former interferon era. We would like to present some ideas and viewpoints regarding this topic.

First, the indications of anti-HCV therapy have largely expanded during the era of DAAs[2, 8]. As in prior reports[6, 7], older age and the presence of cirrhosis at SVR or initiation of treatment were two important factors related to the development of HCC after SVR. We have sound reasons to believe that relatively older and more advanced cirrhotic patients are currently receiving and will receive DAA therapy in the future. The higher percentage of this type of more advanced population will undoubtedly contribute to the higher incidence of HCC after SVR in the future. Second, apart from the essential difference of drug components, the different treatment courses of DAAs would also be the main contributing factor to the diverse incidence of HCC after SVR in the future. As mentioned in previous studies, interferon is an immune modulator with antiproliferative roles, which could then suppress hepatocarcinogenesis by various mechanisms[3], and DAAs may contribute to hepatocarcinogenesis by causing host immune changes after SVR[9, 10]. It is well known that

many adverse events are dependent on exposure duration to some extent; however, future treatment duration will be shorter than the current 12/24-week regimen. The altered host immune status after SVR may vary for different treatment durations, and whether a shorter duration will lead to a decreasing rate of hepatocarcinogenesis is largely unclear. Lastly, the 'high incidence of HCC issue' will be questioned in the period ahead because 'head to head' confirmation studies are difficult to perform. Apart from the existence of essential differences in agents and treatment courses, fewer patients will undergo interferon plus ribavirin therapy in the future. Therefore, future studies to examine this issue at the molecular level are equally urgent.

Indeed, caution should be used when considering the HCC incidence with interferon-free therapy because many additional factors are associated with tumour occurrence. Furthermore, our observation demonstrated a different result, indicating a slight decrease in the incidence rate. Therefore, individuals should consider the 'higher incidence of HCC issue' more rationally to avoid panic. More importantly, this issue should be confirmed because millions of hepatitis C patients were/are/will be using DAAs in the past, present, and future.

References

- [1] Zeng QL, Zhang JY, Zhang Z, Wang LF, Wang FS. Sofosbuvir and ABT-450: terminator of hepatitis C virus? *World J Gastroenterol* 2013;19:3199-3206.
- [2] European Association for the Study of the Liver. EASL Recommendations on Treatment of Hepatitis C 2015. *J Hepatol* 2015;63:199-236.
- [3] Reig M, Marino Z, Perello C, et al. Unexpected early tumor recurrence in patients with hepatitis C virus -related hepatocellular carcinoma undergoing interferon-free therapy: a note of caution. *J Hepatol* 2016; In press.
- [4] Kozbial K, Moser S, Schwarzer R, et al. Unexpected high incidence of hepatocellular carcinoma in cirrhotic patients with SVR following IFN-free DAA treatment. *J Hepatol* 2016; In press.
- [5] Zeng QL, Li CX, Zhang DW, et al. Letter: safety and efficacy of sofosbuvir plus daclatasvir with ribavirin for 12 weeks in Chinese treatment-experienced cirrhotic genotype 1b patients with HCV. *Aliment Pharmacol Ther* 2016;43:842-843.
- [6] El-Serag HB, Kanwal F, Richardson P, Kramer J. Risk of hepatocellular carcinoma after sustained virological response in Veterans with hepatitis C virus infection. *Hepatology* 2016;64:130-137.
- [7] Zeng QL, Li B, Zhang XX, et al. Clinical Model for Predicting Hepatocellular Carcinomas in Patients with Post-Sustained Virologic Responses of Chronic Hepatitis C: A Case Control Study. *Gut Liver* 2016; In press.
- [8] European Association for the Study of the Liver. European Association for Study of Liver. EASL Clinical Practice Guidelines: management of hepatitis C virus infection. *J Hepatol* 2011;55:245-264.
- [9] Meissner EG, Wu D, Osinusi A, et al. Endogenous intrahepatic IFNs and association with IFN-free HCV treatment outcome. *J Clin Invest* 2014;124:3352-3363.
- [10] Serti E, Chepa-Lotrea X, Kim YJ, et al. Successful Interferon-Free Therapy of Chronic Hepatitis C Virus Infection Normalizes Natural Killer Cell Function. *Gastroenterology* 2015;149:190-200 e192.