Editorial
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Is direct-acting antiviral treatment beneficial or harmful for patients with hepatitis C virus-related hepatocellular carcinoma?

Hye Won Lee[1,2,3]

[1]Department of Internal Medicine, Yonsei University College of Medicine, [2]Institute of Gastroenterology, Yonsei University College of Medicine, [3]Yonsei Liver Center, Severance Hospital, Seoul, Korea

Whether direct-acting antiviral (DAA) treatment can prevent hepatocellular carcinoma (HCC) recurrence is a subject of debate. In a prior study, Ahn et al.[1] investigated cases of hepatitis C virus (HCV)-related HCC in patients who received curative treatment using a nationwide database; specifically, the authors investigated whether DAA therapy following curative HCC treatment decreased the likelihood of HCC recurrence compared to interferon (IFN)-based therapies or no treatment.[1] Notably, several studies have shown an unexpectedly high rate of early HCC recurrence in patients with HCV-related HCC following DAA treatment.[2] Additionally, in a landmark analysis, DAA treatment significantly reduced all-cause mortality compared to no treatment at 6 and 12 months after the first HCC treatment.

Several questions remain unanswered in the DAA era: the first concerns the optimal time to start DAA treatment after curative treatment of HCC.[3] The American Gastroenterological Association (AGA) clinical practice guidelines recommends that patients with HCC eligible for curative treatment should defer DAA therapy until after the completion of HCC treatment.[4] However, the parameters used to determine when to complete HCC treatment are still ambiguous. Numerous studies have suggested that early HCC recurrence may not be associated with DAA use; instead, any observed effect is more likely to be due to the timing of DAA treatment initiation; a short interval between curative treatment and DAA may lead to a high rate of early HCC recurrence. The AGA also recommends DAA treatment 4-6 months after surgery, while the German Alliance for Liver Cancer recommends DAA therapy initiation at 6-12 months after curative treatment of HCC.[5] Considering the two guidelines, it would be safe to wait approximately 6 months after surgery. Further research regarding the optimal time for initiating DAA treatment is needed.

DAA is a newer drug than IFN. Thus, the second question is whether it is appropriate to compare the risks of HCC recurrence between DAA- and IFN-based treatments. Similar to the debate regarding the relative risk of HCC development between tenofovir disoproxil fumarate and entecavir in patients with chronic hepatitis B, it is necessary to consider whether this comparison is vulnerable to immortal time bias. Given that IFN is an older drug than DAA, patients with severe chronic liver disease may tend to be the first to receive IFN, as it was approved earlier than DAA. In fact, this time bias was not considered in Brar's study,[6] and propensity score matching to adjust for differences between the two groups was not performed. Additionally, most clinical trials have not enrolled patients with HCC. Data on the sustained virological response rate and risk of HCC recurrence following DAA treatment is predominantly retrospective. Some retrospective studies using big data were complicated by missing data, and were limited in that they do not accurately

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Corresponding author: **Hye Won Lee**

Department of Internal Medicine, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemun-gu, Seoul 03722, Korea
Tel. +82-2-2228-2288, Fax. +82-2-2227-7860
E-mail: lorry-lee@yuhs.ac

reflect the actual clinical environment. Therefore, a prospective and well-designed clinical trial is required to answer questions regarding the benefits of DAA for HCC recurrence; however, this will not be easy to perform in practice.

Ahn et al.[1] attempted to address the controversial topic of HCC recurrence risk in Korean patients, and may prompt clinicians to reconsider the optimal timing of DAA use following curative treatment. Cirrhosis is another risk factor for HCC, and a recent retrospective study showed that patients with HCV-related HCC and sustained virological response were less likely to experience hepatic decompensation than viremic patients.[7] Thus, a different, more careful approach to DAA treatment should be considered in patients with HCV-related HCC, especially in those with cirrhosis.

In conclusion, DAA treatment is expected to reduce the likelihood of recurrence of HCV-related HCC. However, it is important to carefully consider various factors, such as the patient's age, surgical pathology, tumor markers, timing of treatment, and degree of cirrhosis to prevent HCC recurrence.

Conflicts of Interest

Hye Won Lee currently serves on the Editorial Board of J Liver Cancer. She was not involved in the review process of this article. Otherwise, the author has no conflicts of interest to disclose.

Ethics Statement

This editorial is fully based on the articles which were already published and did not involve additional patient participants. Therefore, IRB approval is not necessary.

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Data Availability

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ORCID

Hye Won Lee https://orcid.org/0000-0002-3552-3560

Author Contribution

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