Occurrence and Recurrence of Hepatocellular Carcinoma After Successful Direct-Acting Antiviral Therapy for Patients With Chronic Hepatitis C Virus Infection

Sirisha Grandhe, MD, and Catherine T. Frenette, MD

Dr Grandhe is a resident in the Department of Medicine at Scripps Green Hospital in La Jolla, California. Dr Frenette is the medical director of liver transplantation and director of the hepatocellular carcinoma program at the Scripps Center for Organ Transplant at Scripps Green Hospital.

Address correspondence to:
Dr Catherine T. Frenette
10666 N. Torrey Pines Rd N200
La Jolla, CA 92037
Tel: 858-554-4310
Fax: 858-554-3009
E-mail: Frenette.catherine@scrippshealth.org

Abstract: Chronic hepatitis C virus (HCV) infection has generally been associated with a slightly increased risk of developing hepatocellular carcinoma (HCC). For the past several decades, most patients with chronic HCV cirrhosis have been treated with pegylated interferon and ribavirin therapies, which were known to achieve sustained virologic response (SVR) but also carried their own side effects and toxicities. The recent implementation of direct-acting antiviral (DAA) treatments revealed an increased efficacy in difficult-to-treat populations and higher adherence rates given the all-oral nature of the regimens. However, while these regimens are excellent in terms of improving the side-effect profile and achieving SVR at a higher rate and in a shorter time frame than interferon and ribavirin, some researchers are now discovering an increased rate of de novo and recurrent HCC in patients with HCV cirrhosis compared to interferon treatment protocols. Although other studies were not able to reproduce similar findings, the question as to the role of DAA therapy in HCC occurrence after achieving SVR in patients with HCV cirrhosis continues to persist. Possible theories as to the mechanisms behind tumor relapse after DAA therapy include alterations of immunosurveillance and gene expression, a protective and antineoplastic effect from inflammation secondary to chronic HCV infection that is then abolished with DAA therapy, and delay in radiographic identification of previously undetectable tumors. This article reviews the current literature regarding concern for the possible increase of HCC after DAA therapy.

Keywords
Hepatitis C virus, direct-acting antiviral agents, hepatocellular carcinoma, sustained virologic response, cirrhosis

The association between chronic hepatitis C virus (HCV) infection and the development of hepatocellular carcinoma (HCC) is well known. Currently, the risk of the development of HCC in patients with HCV infection is highest in those with cirrhosis, estimated to be 2% to 8% per year in this population.[1] The risk is noted to be lower in patients with chronic HCV

infection without cirrhosis and in those who have achieved sustained virologic response (SVR).[1] Although the rate of new HCV cases has declined, the prevalence of HCV infection in patients with HCC is rising.[2] In fact, the risk of developing HCC continues to persist in those patients with HCV cirrhosis even after they have achieved SVR.[2]

In the era of interferon-based treatment, patients with HCV cirrhosis who achieved SVR were shown to be less likely to develop HCC.[3] Additionally, those patients with HCV-induced chronic liver disease showed improvement in fibrosis and even cirrhosis with this treatment.[4] Unfortunately, patients with decompensated cirrhosis, who also carried the highest rate of HCC per year, were difficult to treat with interferon and ribavirin due to the toxicity of these medications and the low likelihood of response.[5,6]

The advent of direct-acting antiviral (DAA) treatments has transformed management of HCV infection. Given their efficacy in achieving SVR in HCV patients and improving liver function in a short period of time, DAA treatments have reduced the need for liver transplantation for decompensated HCV infection, thereby allowing these organs to be used for other purposes.[7,8] However, it has been suggested that HCC may occur or recur in patients with chronic HCV infection who achieved SVR with DAA therapy. Because this phenomenon was not seen in patients treated with interferon or ribavirin, some experts speculate that these novel DAA agents may in fact play a significant role in tumor development. The presumed immunostimulatory as well as direct antineoplastic effects of interferon may inherently lower the risk of HCC development in patients who achieved SVR with interferon treatment protocols, compared to interferon nonresponders. This article examines the controversy regarding the role of DAA therapy in terms of HCC occurrence after achieving SVR and the possible mechanisms that could be contributing to tumor formation and recurrence.

Direct-Acting Antiviral Treatments

The novel DAA agents represent the latest frontier in HCV treatment. With cure rates over 90% in almost all groups of patients and in all genotypes, DAA agents achieve SVR at much higher rates compared to interferon-based therapy and can be used in a wider array of patients, including those with advanced cirrhosis, who are at highest risk of HCC.[2,3]

DAA agents are now available as all-oral treatment options for HCV genotypes 1 through 6. These agents comprise 4 classes of drugs: protease inhibitors, nucleoside polymerase inhibitors, nonnucleoside polymerase inhibitors, and nonstructural 5A inhibitors.[9] DAA agents initially took the place of interferon therapy and were studied in combination with ribavirin in patients with advanced liver disease. The SOLAR-1 (Ledipasvir and Sofosbuvir Plus Ribavirin for Treatment of HCV Infection in Patients With Advanced Liver Disease) trial noted high rates of SVR at 12 weeks in patients with HCV genotype 1 and more advanced liver disease who were treated with ledipasvir/sofosbuvir (Harvoni, Gilead) and ribavirin. In addition, this therapy showed improvements in Model for End-Stage Liver Disease (MELD) and Child-Pugh scores, suggesting that SVR may reduce HCV-induced inflammation and injury.[6] Combinations of DAA agents were also studied in liver transplant patients with mild HCV fibrosis as well as those who had received interferon-based regimens previously, and both of these populations achieved SVR at 12 weeks.[5,10] Calleja and colleagues studied patients receiving DAA agents outside of randomized, controlled trials and found similar rates of cure and frequency of side effects.[11] DAA agents have been effective even in difficult-to-treat populations, including patients coinfected with HIV, patients with a liver or kidney transplant, and patients with end-stage renal disease.[2] Interestingly, Ahmed Sakr and colleagues reported SVR at 24 weeks with DAA therapy plus ribavirin in a patient with mixed HCV genotype, which has been reported in patients with hemodialysis, intravenous drug use, and multiple transfusions.[12]

In addition to their efficacy in difficult-to-treat populations, DAA agents have shown much fewer side effects compared to interferon and ribavirin regimens. Unlike ribavirin, DAA agents have low rates of direct toxicity. Patients have high rates of compliance with these treatments, and less than 0.5% of patients have discontinued therapy due to adverse events.[2] However, certain patients should take caution when using these drugs. Nucleoside inhibitors and protease inhibitors are relatively contraindicated in patients with end-stage renal disease and decompensated cirrhosis, respectively.[2] Likewise, patients with a liver or kidney transplant may experience allograft dysfunction or require immunosuppression dose adjustment with close follow-up to avoid experiencing adverse effects.[13]

Discrepancy Regarding the Occurrence of Hepatocellular Carcinoma After Successful Direct-Acting Antiviral Therapy

Although DAA agents initially showed significant promise when first introduced to the market, subsequent studies noted a few limitations to these treatments. Researchers were particularly concerned over the possible increase in occurrence and recurrence of HCC noted in patients infected with HCV after SVR was achieved with DAA

therapy. Of these patients, those with previous HCC were noted to have higher Child-Pugh scores, increased rates of liver stiffness and portal hypertension, and decreased platelet counts than those with no history of HCC.[14,15] Prenner and colleagues performed a retrospective study from 2014 to 2015 and compared patients treated with DAA therapy who either had active HCC on initiation or had previously received curative treatment for HCC with patients who had no history of HCC.[16] Approximately 21% of patients with HCC failed to achieve SVR, which was significantly greater than the rate in those without HCC (12%). After multivariate analysis, the authors concluded that patients with active HCC upon initiation of DAA therapy were almost 6 times more likely to fail treatment, whereas those who had already received curative treatments for HCC showed SVR by 24 weeks after completion of DAA treatment.[16] These findings led to further speculation as to whether the HCV/HCC interaction may have a more significant role than previously recognized.

Reports investigating long-term effects of DAA therapy continued to question the effect of DAA agents on the occurrence of HCC in patients with HCV cirrhosis, especially in those with a history of HCC. This was initially highlighted in a study by Reig and colleagues that primarily focused on HCV patients who had achieved complete radiologic response (no identifiable tumors on imaging) after treatment for HCC with ablation, resection, or chemoembolization and subsequently underwent all-oral DAA therapy.[17] Patients with a history of interferon therapy or with noncharacterized nodules (<10-mm, radiographically detectable lesions) were excluded. In this study, the authors noted HCC recurrence at a median of 5.7 months, with half of these recurrences characterized as multinodular and 20% having infiltrative or extrahepatic lesions.[17] Further studies continued to question the role of HCV therapy on HCC recurrence. A meta-analysis of 11 studies of adjuvant therapy with interferon compared to DAA agents showed accelerated HCC recurrence at 6 months in the latter group (Cabibbo et al, unpublished data, 2017). More specifically, between 0% and 12.5% of untreated patients experienced HCC recurrence at 6 months, which was significantly less than the rate found in patients who received DAA therapy (>28%)[14] (also Cabibbo et al, unpublished data, 2017). Patients with HCC recurrences were also noted to be younger (56 vs 73 years) and more frequently treatment-experienced (88.2% vs 61.9%).[15] Pretransplant patients receiving DAA therapy had higher recurrences of HCC, but such data may be limited because of sample size and selection bias.[7]

Other studies have shown the opposite effect on HCC recurrence after DAA therapy, with decreased occurrence or recurrence rates. Affronti and colleagues analyzed outcomes, including HCC, death, and transplantation, in HCV patients with advanced cirrhosis who received DAA therapy.[18] Over the course of 82 weeks and after adjustment for confounders, the authors noted a significantly greater HCC-free survival rate in patients who achieved SVR compared to those who did not.[18] Similarly, Nagaoki and colleagues noted reduced HCC development in patients with HCV genotype 1b after achieving SVR and determined that such an impact was comparable to that of interferon-based therapy.[19] Muir and colleagues arrived at similar conclusions, noting that the incidence of de novo HCC was higher in patients with decompensated cirrhosis and in those who achieved SVR with pegylated interferon/ribavirin therapy, compared to those with compensated cirrhosis or who were treated with DAA therapy.[20]

Not only have DAA agents increased treatment rates for chronic HCV infection, but they have also impacted the need for liver transplantation. In a cohort study for adults wait-listed for liver transplant, the rate of liver transplant wait-listing in the setting of decompensated cirrhosis secondary to HCV infection had decreased by 32% in the period of high DAA use, compared to a 5% reduction in the period of high pegylated interferon use.[21]

Although many studies have highlighted HCC recurrence after DAA therapy, some studies have suggested that there may be insufficient evidence for such a claim. The European studies that postulated an association between HCC recurrence and DAA therapy were noted to be mostly observational and were not randomized, controlled trials, which thereby allowed for possible confounding variables.[2,3,17] Additionally, HCC rates in some of these data sets were higher than expected and could not be reproduced in the US population, suggesting possible selection bias.[2] Further analyses continued to cast doubt on the evidence at hand. A retrospective analysis of the ANRS (France Recherche Nord & Sud Sida-HIV Hépatites) study in France could not confirm an increased risk of HCC recurrence in a cohort study of over 6000 patients, noting that the 6-month recurrence rate (10.6%) in patients treated with DAA agents was lower than that of patients who did not receive DAA therapy (18.7%). This finding suggests that DAA therapy in patients with cirrhosis may decrease the risk of HCC development, similar to what has been reported in patients treated with interferon.[22] Cheung and colleagues performed a prospective study on patients with HCV infection and decompensated cirrhosis and noted a decreased HCC incidence with SVR obtained by DAA agent, compared to patients who did not achieve SVR despite DAA therapy.[4,14] The authors noted that patients treated with DAA agents experienced fewer adverse events,

including decompensation and MELD deterioration, compared to patients not treated with DAA agents, but did not show increased rates of mortality, liver transplantation, or HCC occurrence.[4,14] Lastly, Chokkalingam and colleagues performed a retrospective study using claims data to evaluate the risk of incidence of HCC following sofosbuvir (Sovaldi, Gilead)–based therapy.[23] Initially, the authors noted a higher HCC incidence in patients treated with DAA therapy compared to patients not treated with DAA agents. However, when adjusted for age, cirrhosis, and portal hypertension, the incidence rates of HCC appeared to show no difference between the 2 groups.[23]

Possible Mechanisms of Tumor Relapse

The possible association between DAA therapy and HCC recurrence raises questions regarding mechanisms that may explain such a phenomenon. Generally, tumors that reemerge within 2 years after treatment have been characterized as tumor metastases and those occurring later are classified as second primary tumors.[24] Metastases are associated with cell dedifferentiation, elevated α-fetoprotein levels, microscopic vascular invasion, and nonanatomic resection, whereas later occurrences are a result of increased liver cell inflammation and proliferation usually due to underlying liver disease.[24] Therefore, the appearance of second primary tumors should be thwarted by optimal antiviral therapy.

The prevailing mechanism behind the phenomenon of tumor relapse after DAA therapy involves alterations of the microenvironment with respect to interferon gene expression and natural killer cell function.[14] Interferons are noted to have antiproliferative as well as immunomodulatory properties by prolonging all phases of the cell cycle.[14,17] Patients treated with interferon had lower rates of recurrent and de novo HCC.[2] With DAA therapy, the interferon genes are likely downregulated, allowing for increased cell proliferation without appropriate checkpoints, therefore promoting tumor development.[17] The protective effect of inflammation from chronic HCV infection is lost with DAA therapy, allowing for liver regeneration and carcinogenesis.[2] Villani and colleagues further noted an early increase in serum vascular endothelial growth factor along with a change in the inflammatory pattern at 4 weeks after DAA initiation, suggesting increased liver cancer angiogenesis and tumor growth during this time.[25]

Other possibilities that could explain HCC recurrence after successful DAA therapy underscore the low level of immunosurveillance in patients with advanced fibrosis. HCC recurrence was noted more in younger patients and in those with advanced liver fibrosis, suggesting poor immunomodulatory properties, which are then further reduced after DAA therapy, hence accelerating HCC growth.[3] Some researchers have also considered that tumors that were previously radiologically undetectable were simply detectable after initiation of DAA therapy, as most of the newly detected liver cancers were noted in the first 3 months of therapy, thereby favoring cancer growth over de novo development.[4] Although most of these theories remain speculative, further preclinical studies are required before any definitive statements can be made regarding the association between DAA therapy and HCC recurrence.

Conclusion

The current available evidence continues to question the association between DAA therapy and HCC recurrence in patients with chronic HCV infection, with no clear answer as of yet. Until further information is available, the recommendations for evaluation and management of patients with HCV infection remain unchanged. All HCV patients with cirrhosis should continue to have at least standard HCV surveillance biannually, and those who are deemed at high risk may benefit with closer follow-up.[2] Because many of the studies suggest possible increased HCC recurrence after DAA treatment, the utmost efforts should be made to ensure adequate tumor clearance in HCC patients prior to initiating HCV therapy.[2] SVR after HCV therapy should not preclude physicians from considering ongoing liver disease from other processes such as concomitant nonalcoholic fatty liver disease, which could also increase the risk of HCC development or progression of liver disease. Overall, patients currently or with a history of HCV-related cirrhosis should continue to be closely monitored for HCC during and after treatment, as there is a potential risk of HCC development despite viral clearance.

Dr Frenette serves on the speakers boards for Gilead, Bristol-Myers Squibb, AbbVie, and Merck, and has served on an advisory board for Gilead. Dr Grandhe has no relevant conflicts of interest to disclose.

References

1. Bruix J, Sherman M; American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma: an update. *Hepatology*. 2011;53(3):1020-1022.
2. Brown RS Jr. The possible association between DAA treatment for HCV infection and HCC recurrence. *Gastroenterol Hepatol (N Y)*. 2016;12(12):776-779.
3. Conti F, Buonfiglioli F, Scuteri A, et al. Early occurrence and recurrence of hepatocellular carcinoma in HCV-related cirrhosis treated with direct-acting antivirals. *J Hepatol*. 2016;65(4):727-733.
4. Cheung MC, Walker AJ, Hudson BE, et al; HCV Research UK. Outcomes after successful direct-acting antiviral therapy for patients with chronic hepatitis C and decompensated cirrhosis. *J Hepatol*. 2016;65(4):741-747.
5. Lawitz E, Makara M, Akarca US, et al. Efficacy and safety of ombitasvir,

paritaprevir, and ritonavir in an open-label study of patients with genotype 1b chronic hepatitis C virus infection with and without cirrhosis. *Gastroenterology*. 2015;149(4):971-980.e1.
6. Charlton M, Everson GT, Flamm SL, et al; SOLAR-1 Investigators. Ledipasvir and sofosbuvir plus ribavirin for treatment of HCV infection in patients with advanced liver disease. *Gastroenterology*. 2015;149(3):649-659.
7. Yang JD, Aqel BA, Pungpapong S, Gores GJ, Roberts LR, Leise MD. Direct acting antiviral therapy and tumor recurrence after liver transplantation for hepatitis C-associated hepatocellular carcinoma. *J Hepatol*. 2016;65(4):859-860.
8. Foster GR, Irving WL, Cheung MC, et al; HCV Research, UK. Impact of direct acting antiviral therapy in patients with chronic hepatitis C and decompensated cirrhosis. *J Hepatol*. 2016;64(6):1224-1231.
9. Schaefer EA, Chung RT. Anti-hepatitis C virus drugs in development. *Gastroenterology*. 2012;142(6):1340-1350.e1.
10. Kwo PY, Mantry PS, Coakley E, et al. An interferon-free antiviral regimen for HCV after liver transplantation. *N Engl J Med*. 2014;371(25):2375-2382.
11. Calleja JL, Crespo J, Rincón D, et al; Spanish Group for the Study of the Use of Direct-Acting Drugs Hepatitis C Collaborating Group. Effectiveness, safety and clinical outcomes of direct-acting antiviral therapy in HCV genotype 1 infection: results from a Spanish real-world cohort. *J Hepatol*. 2017;66(6):1138-1148.
12. Ahmed Sakr A, Hanifi JM, Valerie Lin M. Successful treatment of mixed hepatitis C genotypes in a cirrhotic patient with an all-oral, interferon-free regimen. *ACG Case Rep J*. 2017;4:e16.
13. Fernández I, Muñoz-Gómez R, Pascasio JM, et al. Efficacy and tolerability of interferon-free antiviral therapy in kidney transplant recipients with chronic hepatitis C. *J Hepatol*. 2017;66(4):718-723.
14. Nault JC, Colombo M. Hepatocellular carcinoma and direct acting antiviral treatments: controversy after the revolution. *J Hepatol*. 2016;65(4):663-665.
15. Buonfigioli F, Conti F, Andreone P, et al. Development of hepatocellular carcinoma in HCV cirrhotic patients treated with direct acting antivirals. Presented at the European Association for the Study of the Liver meeting; April 13-17, 2016; Barcelona, Spain. Abstract LBP506.
16. Prenner SB, VanWagner LB, Flamm SL, Salem R, Lewandowski RJ, Kulik L. Hepatocellular carcinoma decreases the chance of successful hepatitis C virus therapy with direct-acting antivirals. *J Hepatol*. 2017;66(6):1173-1181.
17. Reig M, Mariño Z, Perelló C, et al. Unexpected high rate of early tumor recurrence in patients with HCV-related HCC undergoing interferon-free therapy. *J Hepatol*. 2016;65(4):719-726.
18. Affronti A, Ju M, Catt J, Rosenberg WM, Macdonald D. Successful hepatitis C treatment in advanced cirrhosis with DAA reduces HCC incidence. Presented at the American Association for the Study of Liver Diseases meeting; November 11-15, 2016; Boston, Massachusetts. Abstract 944.
19. Nagaoki Y, Aikata H, Kobayashi T, et al. Hepatocellular carcinoma development in hepatitis C virus patients who achieved sustained viral response by interferon therapy and direct anti-viral agents therapy. Presented at the American Association for the Study of Liver Diseases meeting; November 11-15, 2016; Boston, Massachusetts. Abstract 860.
20. Muir A, Buti M, Nahass R, et al. Long-term follow-up of patients with chronic HCV infection and compensated or decompensated cirrhosis following treatment with sofosbuvir-based regimens. Presented at the American Association for the Study of Liver Diseases meeting; November 11-15, 2016; Boston, Massachusetts. Abstract 880.
21. Flemming J, Kim WR, Brosgart CL, Terrault NA. Reduction in liver transplant wait-listing in the era of direct acting anti-viral therapy. Presented at the American Association for the Study of Liver Diseases meeting; November 11-15, 2016; Boston, Massachusetts. Abstract LB-23.
22. ANRS Collaborative Study Group on Hepatocellular Carcinoma. Lack of evidence of an effect of direct-acting antivirals on the recurrence of hepatocellular carcinoma: data from three ANRS cohorts. *J Hepatol*. 2016;65(4):734-740.
23. Chokkalingam AP, Singer AW, Osinusi AO, Brainard DM, Telep L. Risk of incident liver cancer following HCV treatment with sofosbuvir-containing regimens. Presented at the American Association for the Study of Liver Diseases meeting; November 11-15, 2016; Boston, Massachusetts. Abstract 739.
24. Zucman-Rossi J, Villanueva A, Nault JC, Llovet JM. Genetic landscape and biomarkers of hepatocellular carcinoma. *Gastroenterology*. 2015;149(5):1226-1239.e4.
25. Villani R, Facciorusso A, Bellanti F, et al. DAAs rapidly reduce inflammation but increase serum VEGF level: a rationale for tumor risk during anti-HCV treatment. *PLoS One*. 2016;11(12):e0167934.