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Interaction Between Hepatocellular Carcinoma and Hepatitis C Eradication With Direct-acting Antiviral Therapy

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Abstract

Purpose of review The approval of direct-acting antiviral (DAA) therapy has revolutionized hepatitis C virus (HCV) treatment. However, the publication of a study from Barcelona in 2016 raised concern for an increased risk of recurrence of hepatocellular carcinoma (HCC) after potentially curative therapy in patients receiving DAAs. This article reviews the current literature on the interaction between HCC and hepatitis C eradication with DAAs. *Recent findings* Following publication of the initial observation in 2016, a number of studies have looked at the impact of active HCC on the success of antiviral therapy, as well as that of treatment with DAAs on both the occurrence and recurrence of HCC. The presence of active HCC decreases sustained virologic response (SVR) rates with DAAs. However, SVR rates improve in patients who have achieved complete radiological response or are treated post transplantation. With respect to occurrence of HCC after DAAs, many small single-center studies without a control group have documented high incidence. The rates are also higher when compared to those of historical controls treated with interferon, but these patients are not comparable because DAA-treated population is more likely to have advanced fibrosis or decompensation. In large studies that have included a control group (patients treated concurrently who did not achieve SVR), a decrease in the occurrence of HCC has been demonstrated. With regard to recurrence of HCC, while smaller single-center studies have

shown an increase, larger studies with control group have not replicated those findings. However, methodological limitations in the published studies limit our ability to make a firm conclusion on both the occurrence and recurrence of HCC after DAA therapy.
Summary The presence of active HCC decreases treatment success rates with DAAs. Therefore, it is recommended that treatment of HCV in patients with HCC be deferred till there is complete radiological response. Though there are major limitations with the currently published studies, the data does not support an increase in the occurrence or recurrence of HCC after DAA therapy.

Introduction

Hepatocellular carcinoma (HCC) is the fifth most common cancer in men and seventh most common cancer in women, and it is estimated that approximately 20,000 new cases are identified every year in the USA [1, 2]. In the USA, HCC is predominantly attributed to infection with chronic hepatitis C virus (HCV) [3]. The risk of developing HCC increases with the advancement of liver fibrosis and cirrhosis, and the annual incidence rate ranges between 3 and 5% per year [4]. The risk is lower in patients who achieved sustained virologic response (SVR) [5] with interferon-based therapy.

The introduction of interferon-free direct-acting antiviral (DAA) treatments with the initial approval of sofosbuvir in December 2013 in the USA has changed the landscape of HCV therapy dramatically with reported SVR rates of more than 95% [6, 7]. Based on the experience of SVR following interferon therapy, it was initially presumed that SVR after DAAs would be associated with a reduction in incidence of new or recurrent HCC. However, a report by Reig et al. [8•] suggesting that DAAs may increase the risk of HCC recurrence created uncertainty in the field. This was followed by publication of number of studies in various populations looking at both new and recurrent HCC. In this review, we will discuss the impact of HCC on the efficacy of HCV treatment with DAAs as well as the potential effect of DAA therapy on both the occurrence and recurrence of HCC.

Impact of active HCC on SVR with DAAs

Recent studies have shown that presence of active HCC decreases the SVR rates when treated with DAAs. Prenner et al. [9•] compared SVR rates between 137 cirrhotics with HCC to 284 controls with HCV alone. The majority (86%) of the population were genotype 1 with a median Model for End-Stage Liver Disease (MELD) of 10. Eighty-one percent of the HCC patients were child A compared to 71% of the controls. The most commonly used regimen was 12 weeks of sofosbuvir and simeprevir (46%). Despite having a higher proportion of well-compensated cirrhotics, 21% in HCC group failed to achieve SVR compared to 12% among controls. Within the HCC group, the failure rate of the patients with active HCC at the time of DAAs was 43%, compared to only 3% among patients with history of HCC that was resected or transplanted before antiviral therapy.

The limitation of this study is a relatively high proportion of patients who were treated with an inadequate regimen (sofosbuvir and simeprevir without ribavirin for 12 weeks) in approximately half of the patients. Therefore, based on this study alone, it is unclear if the high

failure rate is because of the antiviral regimen used or the presence of HCC.

A second study using a large VA database was published by Beste et al. [10•] and helped to clarify this question better. They examined SVR rates among veterans with and without HCC. The overall treatment failure rate was 20.9% in HCC group compared to 8.9% in patients with HCV without HCC and 3.6% in post-transplant patients with history of HCC. Unlike the prior study, the majority of patients received a recommended regimen, with sofosbuvir and ledipasvir (with or without ribavirin) being the most common. Only a small group of patients received regimens that are associated with low SVR (primarily sofosbuvir and ribavirin in genotype 2/3). However, this study too had several limitations. Firstly, the HCC group had twice as many patients with advanced fibrosis (Fib 4 score > 3.25) compared to controls. Also, the HCC group had higher number of patients with genotype 3. Therefore, some of the decrease in the treatment rates may be attributable to the above factors. Moreover, since this data was abstracted from corporate data warehouse, and the diagnosis of HCC was obtained using ICD codes, the relative number of patients with active versus resected or ablated HCC and the SVR rates in these populations could not be evaluated from this paper. Another limitation of the study was the non-availability of SVR outcome and missing HCC treatment data in a substantial proportion of the cohort. Regardless, patients with history of HCC were less likely to achieve SVR than non-HCC patients (AOR 0.38) after adjusting for genotype, cirrhosis, and other characteristics.

The exact mechanism for this phenomenon is unclear. One of the hypotheses that has been raised is that HCC might be acting as a reservoir for the HCV virions which may shield the virus from the medications. The other hypothesis is that many of the patients in the first study received radioembolization, and it has been suggested that this may result in local hepatic fibrosis and decreased bioavailability of antiviral medications. However, there is no data shown that patients who received radioembolization had a lower SVR rate than patients receiving other treatments. Other reasons suggested include variability in the tumor blood flow resulting in differences in accessibility of the treatment drugs and alterations in tumor chemokine environment.

Occurrence of HCC following DAA therapy

The studies that described the incidence of new HCC after DAA therapy are summarized in Table 1.

The first study that investigated the occurrence of HCC after DAA therapy was done by Conti et al. [11]. In this retrospective study, the authors analyzed 285 patients with HCV cirrhosis treated with DAAs and no prior history of HCC (mean age of 63 years, 60.2% males, 68.9% genotype 1; mean Model for End-Stage Liver Disease score of 8.6). During the median follow-up of 6 months, 9 (3.16%) patients developed a new diagnosis of HCC. The incidence of new HCC in this cirrhotic population after achieving SVR with DAAs was similar to that of viremic cirrhotics from the pre-DAA era, raising the possibility that the decrease in the incidence of HCC might not occur this early after SVR with DAAs. The limitations of this study include very short follow-up as well as the possibility of patients having underlying HCC at time of DAAs that were missed during surveillance. Other limitations include the fact that the study had no

Table 1. Incidence of new HCC after DAA therapy

Author/year (reference no.)	Study design	Cohort	*N* (no HCC, DAA treated)	*N* (controls)	Cirrhosis % (cases/ controls)	Median follow-up	Incidence of HCC DAA treated (% or PY)	Incidence of HCC controls (% or PY)
Conti, 2016 [11]	Cross-sectional	Single-center, retrospective, Italy	285	NR	NR	5.5 months after treatment completion	9/285 (3.16%)	NR
Ravi, 2017 [12]	Cross-sectional	Single-center, retrospective, USA	66	NR	NR	6 months	6/66 (9.1%)	NR
Cardoso, 2016 [13]	Cross-sectional	Single-center, retrospective, Portugal	54	NR	63%/none	12 months post viral suppression	4 (7.4%)	NR
Kanwal, 2017 [14•]	Cross-sectional	Multicenter, retrospective, USA	22,500	2982—DAA treated with no SVR	38.4/42.6%	20,415 PY	183/19518 (0.9%) or 0.90 per 100 PY	3.45 per 100 PY
Kozbial, 2016 [15]	Cross-sectional	Multicenter, prospective, Austria	195	94—treated with interferon	NR	11 months (5.5 months after treatment completion)	13 (6.6%)	10 (1% PY)
Ogata,2017 [16]	Cross-sectional	Single-center, retrospective, Japan	1170	105—DAA treated with no SVR	NR	15 months after treatment completion	15 (1.4%) at 1 year and 19 (1.8%) at 2 years	NR
Cheung, 2016 [17]	Cross-sectional	Multicenter, prospective, UK	377	78/377—DAA treated with no SVR	62.5/92%	15 months (12 months after treatment completion)	15 (4.7%)	8/78 (10%)
Ionnaou, 2017 [18]	Cross-sectional	Multicenter, retrospective, USA	21,948	2039—DAA treated with no SVR	22.6/36%	18 months	0.92 per 100 PY	5.19 per 100 PY

control group and subjects were older, had more fibrosis than historical controls treated with interferon, and had a higher BMI (which may all predispose to higher incidence of HCC). Moreover, the higher BMI can negatively impact the detection of HCC on ultrasound surveillance [19].

In another single-center retrospective study, Ravi et al. [12] analyzed 66 HCV cirrhotics with available imaging and no prior history of HCC, out of 123 treated with DAAs (mean age 60 years; 62% males; 71% Caucasian; 71% genotype 1a; mean MELD 10; mean alpha-fetoprotein, 19.9 ng/mL). Six patients (9.1%) developed HCC either during or within 6 months of treatment. This study too did not have a control group, but the incidence of new HCC was higher than what was traditionally reported in cirrhotics after SVR with interferon. Limitations of this study include the small sample size (only six developed HCC), relatively short duration of follow-up, and exclusion of almost half of the DAA-treated patients primarily because of lack of imaging.

Cardoso et al. [13] evaluated 54 patients (mean age 59 years, 70% males; 70 % Caucasian; 78% genotype 1a; mean MELD of 8) treated with DAAs (sofosbuvir/ledipasvir) for a period of 24 weeks. After a median follow-up of 1-year post-viral suppression, the incidence of new HCC was 7.4% and the median time for development of HCC was 7.6 months after first undetectable HCV RNA. This study too lacked a control group, but the occurrence of HCC was higher than prior reports with interferon-based therapy. Also, the duration of follow-up in relation to SVR was short (median follow-up less than 2 months).

Kanwal et al. [14•] looked at patients treated with DAAs in the VA system in the year 2015 and compared the rates of occurrences of HCC in patients who did and did not achieve SVR. They examined 22,500 subjects (mean age 61.6 years; 97.9% males; 49% Caucasian; 86.8% genotype 1) of which 39% carried a diagnosis of cirrhosis. The incidence of new HCC was compared between the 19,518 patients who achieved SVR and the 2098 who did not. Failure to achieve SVR was associated with more advanced fibrosis and a history of alcohol abuse. There was no difference in the prevalence of age, diabetes, or Deyo score between the two groups. One hundred eighty-three of the patients who achieved SVR developed new HCC at an annual incidence of 0.90 per 100 person-years (PY). On the other hand, the incidence of HCC was 3.45 per 100 PY in patients without SVR. The median time to HCC diagnosis was 5.2 months in patients with SVR versus 6.1 months in patients without SVR ($p = 0.06$). Therefore, data from this large retrospective study showed that achievement of SVR with DAAs was associated with a reduced annual incidence of HCC. The major limitation of this study was the unavailability of HCC surveillance rates in the groups with and without SVR. Since the surveillance rates for HCC in the VA population have previously been shown to be low [17], it is possible that the study underestimated HCC rates both in SVR and non-SVR groups. Also, it is possible that the non-SVR group had greater HCC surveillance since they continued to be evaluated for re-treatment by a hepatology provider, thereby potentially introducing a bias. Moreover, the study included HCV patients both with and without cirrhosis with a greater proportion of cirrhosis and alcohol use in the non-SVR population, which may account for an increased incidence of HCC in that group.

Kozbial et al. [15] evaluated a total of 198 cirrhotics from Austria (99% genotype 1), of whom 195 had no prior history of HCC. Over a mean follow-up of 48 weeks, 13 (6.6%) developed new HCC. This was compared with a historical cohort of 94 cirrhotics who achieved SVR treated with interferon/ribavirin, of whom 10 developed HCC over a mean follow-up of 7.8 years (1% per PY). The advantage of the study was the use of a control group. However, limitations include the fact that the two groups were dissimilar and with different durations of follow-up. Also, it is unclear what proportion of patients in either group underwent regular HCC surveillance. Moreover, two of the patients that developed HCC had an elevated AFP at both baseline and end of treatment, indicating that the patients likely had underlying HCC predating DAAs.

Ogata et al. [16] described the occurrence of HCC among 1170 Japanese patients with chronic HCV (with and without cirrhosis, median Fib4 2.93) and treated with DAAs. The population characteristics included median age of 67 years, 42.1% males, and 100% genotype 1, none of whom had a prior diagnosis of HCC. There was no control group. These patients had a median follow-up of 1.3 years from the end of antiviral treatment. The majority of patients in the study were treated with daclatasvir and asunaprevir, a regimen which is unavailable in the USA. In patients who achieved SVR, the cumulative rates of occurrence of HCC were 1.4 and 1.8% at 1 and 2 years respectively (annual incidence of 0.9% per PY). The limitations are inclusion of Asians only (limiting generalizability) and the difficulty in interpreting rates of HCC in a population comprising cirrhotics and non-cirrhotics. However, the incidence of HCC described in this study is lower than traditionally reported, and the median follow-up is longer than many of the other studies.

A prospective study done by Cheung et al. [17] looked at the incidence of HCC after treatment with DAAs in decompensated cirrhotics. They analyzed 406 patients with a median age of 54 years, 48.8% genotype 1, 42.1% genotype 3, and mean MELD of 12. Three hundred seventy-seven patients had no prior diagnosis of HCC. Two hundred ninety-nine out of these (79.3%) achieved SVR. The group that did not achieve SVR was more likely to be child C and has genotype 3 infection. The incidence of new HCC was 5% in the SVR group compared to 10% in the non-SVR controls. This study was different from the prior ones in that it included only decompensated patients and therefore had a higher rate of hepatitis C treatment failure. While the group that achieved SVR had lower HCC rates, the groups were not evenly matched, with a higher number of child C cirrhotics in the non-SVR group.

Ionnaou et al. [18] looked at the rates of occurrence of HCC in patients who did and did not achieve SVR among 62,354 veterans treated between 1999 and 2015. Of this cohort, 21,948 subjects were treated with DAA-only regimens. The overall cohort had a mean age of 55.8 years, 96.6% males, 55.6% Caucasian, and 77.4% genotype 1. The incidence of HCC per 100 PY was 0.92 in the SVR group compared to 5.19 in the non-SVR group. The population that was treated with DAA regimens had a mean follow-up of 1.53 years. The absolute reduction in HCC risk was greater in patients with cirrhosis (3.25 to 1.97 per 100 PY) than that in non-cirrhotics (0.73 to 0.18 per 100 PY). These results suggest that the DAA-induced SVR was associated with 71% reduction in HCC risk. Limitations of this study include differences in the baseline characteristics between the SVR

and non-SVR groups, and the low overall HCC surveillance rates in the VA population.

Limitations of studies on incidence of New HCC

There are major limitations in the above studies that looked at the occurrence of HCC after DAA therapy. The majority of the studies are retrospective, and many did not include a control group. In the studies that included a control group (typically non-SVR patients after DAA therapy or historical controls treated with interferon), the treatment and control groups were not matched. Many of the studies were single center, with small number of patients who developed HCC during follow-up. They had relatively short follow-ups and some of them likely included patients that had HCC at baseline. The proportion of patients who were excluded because of lack of surveillance imaging was variable. The two larger studies using data from VA corporate data warehouse lacked information on the proportion of patients who received HCC surveillance. Also, in studies that showed association of SVR with lower incidence of HCC, it is possible that it was the underlying HCC that led to failure of antiviral therapy and not vice versa.

The ideal study to investigate the development of occurrence of HCC after DAA therapy is a large, prospective, multicenter study where the majority of patients in both SVR and non-SVR groups undergo surveillance with sufficiently long follow-up and where HCC that are diagnosed in the first 6 months are excluded. Based on the studies done thus far, a firm conclusion cannot be made on the impact of DAAs on the occurrence of HCC. One would anticipate that there would need to be an improvement in fibrosis to cause a reduction in the incidence of HCC, and this would likely take several months. Therefore, one would anticipate that there would be no change in the incidence of new HCC in the first several months after DAAs with a gradual drop in HCC rates over time.

Recurrence of HCC following DAAs

The incidence of recurrent HCC after DAA therapy is summarized in Table 2.

The first study that raised the possibility of an increase in recurrence of HCC after DAAs was described by Reig et al. [8•] who evaluated 58 patients with HCC who achieved complete response with surgery or locoregional therapy and subsequently received DAAs. The most common treatment for HCC that led to complete response was percutaneous or laparoscopic ablation (55.2%) followed by surgical resection (34.5%) and trans-arterial chemoembolization (10.3%). The cohort had a median age of 66.3 years, and 69% were males, 91% genotype 1; 94.8% were cirrhotic (91% child A). 27.6% (16 patients) developed recurrence of HCC with the median time from start of antiviral treatment to recurrence of 3.5 months and median time from HCC treatment to recurrence of 11.2 months. Of the 16 patients who recurred, 7 had resection with two patients described as high risk of recurrence based on pathology. All nine of the other patients who recurred had ablation as the definitive treatment for HCC. The recurrence was primarily intra-hepatic within Milan, with three patients developing infiltrative HCC and/or extra-hepatic disease. Though there was no control group in the study, the rate of recurrence was higher than

Table 2. Incidence of recurrence of HCC after DAA therapy

Author/year (reference no.)	Study design	Cohort	*N* (H/o of HCC, DAA treated)	*N* (controls)	Cirrhosis % (cases/controls)	Median follow-up after treatment completion	Recurrence of HCC in DAA (% or PY)	Recurrence of HCC in controls (% or PY)
Reig, 2016 [8•]	Cross-sectional	Retrospective, multicenter, Spain	58	NR	NR	5.7 months	27.6%	NR
EL Kassas, 2018 [20]	Cross-sectional	Prospective, single-center, Egypt	53	63—untreated	100/100%	16 months	37.7%	25.4%
Zavagila, 2017 [21]	Cross-sectional	Retrospective, multicenter, Italy	31	0—DAA treated with no SVR	81%/NR	5 months	3.2%	NR
Conti, 2016 [11]	Cross-sectional	Retrospective, single-center, Italy	59	6—DAA treated with no SVR	NR	5.5 months	28.8%	NR
ANRS cohort (CO22), 2016 [22]	Cross-sectional	Prospective, multicenter, France	189	78—untreated	80/72%	17.4 months	12.7% or 8.8 per 100 PY	8 per 100 PY
Singal, 2017 [23•]	Cross-sectional	Retrospective, multicenter, USA	191	34—DAA treated with no SVR	NR	12 months (median time to recurrence)	46.8%	53.3%

traditionally described and the time to recurrence was short, indicating a potentially aggressive course of HCC after HCV eradication. Limitations of this study include an absence of control group, as well as unavailability of pathology in the vast majority of patients. Several patients had elevated AFP at the time of initiation of treatment (as high as 369 ng/mL), and it is possible that HCC was missed on imaging in at least some of these subjects. Nevertheless, the incidence of recurrent HCC in 27.5% of the cohort over a median follow-up of 5.7 months was high compared to an expected annual recurrence rate of less than 20% in historical cirrhotic controls who were not treated for HCV.

In a study from Egypt by El Kassas et al. [20], 116 HCV patients who achieved complete response with locoregional therapies for HCC were included. Fifty-three were treated with DAAs and compared to 63 untreated controls. The DAA cohort had a mean age of 56.7 years, and 66% were males, with child A cirrhosis in 98%. 1.9% of subjects in the DAA group were child B compared to 17.5% among controls. 96.2% of the DAA group underwent either percutaneous ablation or ethanol injection while 3.8% underwent surgical resection. There was a HCC recurrence rate of 37.7% in the DAA group (16 month median follow-up) compared to 25.4% in the untreated group (median follow-up of 23 months). Unlike the paper by Reig et al. [8•], this study included a control group. However, the control group had more decompensated cirrhotics and a longer follow-up. Moreover, the paper did not describe rates of HCC recurrence in the DAA-treated patients who did not achieve SVR.

Zavagila et al. [21] reported the outcomes of 31 HCV cirrhotics who achieved complete response of HCC after locoregional treatment or resection and received DAAs at two referral centers in Italy. All patients had a history of HCC that was treated with either surgical resection (42%), ablation alone (19%), or trans-arterial chemoembolization alone (13%) or combinations. The cohort had a mean age of 65 years, 66% were males, 88% were genotype 1, and 81% were child A. The median time between the last HCC treatment and start of DAA was 19.3 months. There was only one (3.2%) HCC recurrence after a median follow-up of 8 months after the start of DAAs. There was no control group. This study was different from the study by Reig et al. in many ways. These subjects had a longer duration of time between last HCC treatment and initiation of DAAs but also a relatively short period of follow-up. The study showed that in patients where antiviral therapy was introduced after a longer period of radiological response, the recurrence of HCC was low.

Conti et al. [11] evaluated 59 patients (17% cirrhotics) with history of prior HCC who achieved complete response with locoregional treatment and received DAAs after. All patients had a history of HCC that was treated with either surgical resection (38.9%) and percutaneous or laparoscopic ablation (47.4%) or trans-arterial chemoembolization (8.4%). The cohort had a median age of 64.5 years, and 67.7% were males with 72.8% genotype 1. 28.8% developed recurrent HCC over a median follow-up of 6 months; however, none had extrahepatic disease or macrovascular invasion. The median interval between HCC treatment and initiation of DAAs was 376 days. This study too did not have a control group, but the rate of HCC recurrence after DAAs was higher than expected for the population.

The ANRS collaborative study on HCC [22] analyzed the incidence of recurrent HCC after DAA therapies in three different cohorts. The ANRS CO22 HEPATHER cohort included 267 patients with history of treated HCC of whom

189 received subsequent treatment with DAAs. The mean age of the cohort was 62 years; 78% were males; 65% were genotype 1; and 80% had cirrhosis. After a median follow-up of 20.2 months, 12.7% recurrence of HCC was noted at a rate of 8.8 per 100 PY which was comparable to the incidence (8 per 100 PY) in the non-DAA-treated patients. The ANRS CO23 CUPILT cohort of liver transplant recipients for HCC also did not show any increase in the post-transplant recurrence of HCC after DAA therapy.

Singal et al. [23•] did a multicenter US-based retrospective cohort study of 191 patients with HCV-related HCC who achieved complete response to HCC-directed therapy between 2013 and 2016. The median age of the cohort was 62 years; 76.2% were males; 83.4% had genotype 1; and 91.6% had cirrhosis (61.2% child A). Initial treatments leading to complete response included 31.9% resection, 34.5% local ablative therapy, and 27.2% TACE. Recurrence was observed in 46.8% (87) patients, with no significant difference between DAA-treated and DAA-naïve patients (42.5 vs. 53.3%, $p = 0.15$). Median time to recurrence was 364 days, with significantly shorter time to recurrence in DAA-treated patients (median 554 vs. 223 days, $p = 0.006$). This study is still ongoing and updated data with larger cohort size is anticipated.

Conclusion

In conclusion, there have been a number of studies evaluating the occurrence of HCC after DAA therapy. The majority of the studies are retrospective; many were single center with small number of incident HCC and lack control groups. The larger studies that used controls were not propensity matched to cases and patients had inconsistent surveillance. Nevertheless, the overall data does not suggest an increase in the occurrence of HCC after DAA therapy.

The studies on recurrence of HCC after DAA therapy are better designed and have failed to corroborate the findings of an increased incidence after DAAs. However, DAA therapy may potentially be associated with decrease in time to recurrence. We anticipate the publication of a multicenter US consortium study will provide a more definitive answer to this question.

The data published thus far does support the fact that the presence of active HCC is associated with decrease in SVR rates with DAAs. Therefore, it is recommended that DAA therapy is deferred till the documentation of complete radiological response of HCC. However, antiviral therapy should not be withheld in patients with HCV based on the risk of occurrence of HCC. Also, currently, there is also no data to support withholding DAAs in patients with history of HCC who have achieved complete response, but we anticipate more clarity with upcoming studies.

Compliance with Ethical Standards

Conflict of Interest

Venkata Rajesh Konjeti declares that he has no conflict of interest.

Binu John declares that he has no conflict of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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This is preliminary results from a multicenter US consortium that looked at patients with HCC who underwent complete radiological response and recurrence rates in SVR and non-SVR patients. The study showed no difference in incidence of recurrent HCC but a shorter time to recurrence in patients who received DAAs.