Title

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Journal

Gastroenterology, 156(6)

ISSN

0016-5085

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Publication Date

2019-05-01

DOI

10.1053/j.gastro.2019.01.027

Peer reviewed

Published in final edited form as:

Gastroenterology. 2019 May ; 156(6): 1683–1692.e1. doi:10.1053/j.gastro.2019.01.027.

Direct-Acting Antiviral Therapy not Associated with Recurrence of Hepatocellular Carcinoma in a Multicenter North American Cohort Study

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Author contributions: Dr. Singal had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design (Singal and Parikh); Acquisition, analysis and interpretation of the data (all authors); Drafting of the manuscript (Singal); Critical revision of the manuscript for important intellectual content (all authors); Obtained funding (Singal, Parikh); Administrative, technical, and material support (Singal and Parikh); Study supervision (Singal)

Conflicts of Interest:

Amit Singal was on speakers bureau for Gilead, Bayer, and Bristol Meyers Squibb. He has served on advisory boards for Gilead, Abbvie, Bayer, Eisai, Wako Diagnostics, Roche, and Exact Sciences. He serves as a consultant to Bayer, Eisai, Roche, and Glycotest. He has received research funding from Gilead and Abbvie.

Neil Mehta has received research funding from Wako Diagnostics.

Anjana Pillai serves as a consultant and is on speakers bureau for Eisai and BTG.

Jordan Feld has received research support from Gilead, Abbvie, Merck, and Janssen.

Binu John has served on advisory boards for Eisai.

Catherine Frenette is on speakers bureaus for Bayer, Bristol Meyers Squibb, Gilead, Merck, Abbvie, and Eisai. She served on advisory boards for Gilead, Eisai, and Wako. She served as a consultant for Bayer and Gilead. She received research funding from Bayer.

Parvez Mantry is on speakers bureaus and served on advisory boards for Gilead, Abbvie, Bayer, BMS, Eisai, Merck, and BTG. He has received research funding from Gilead and Sirtex.

Michael Leise has received research funding from Abbvie.

Kalyan Ram Bhamidimarri serves as scientific advisory board member for Gilead, Merck, and Abbvie. He has received research funding from Gilead.

Laura Kulik is on speakers bureau for Eisai, Gilead, and Dova. She serves as an advisory board member for BMS, Eisai, Bayer, Exelixis

Reena Salgia is on speakers bureau for Bayer. She has served on advisory boards for Bayer, Eisai, and Exelixis.

Sanjaya Satapathy has received research support from Gilead and Bayer.He has served on advisory boards or as a consultant for Abbvie and Gilead.

Robert Wong is on the speakers bureau, served as consultant and on advisory boards, and has received research funding from Gilead. He has also received research funding from Abbvie. He was on the speakers bureau for Bayer.

Neehar Parikh serves as a consultant to Exelexis and Bristol-Myers Squibb. He has served on advisory boards for Eisai and Bayer. None of the other authors have any relevant conflicts of interest.

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Abstract

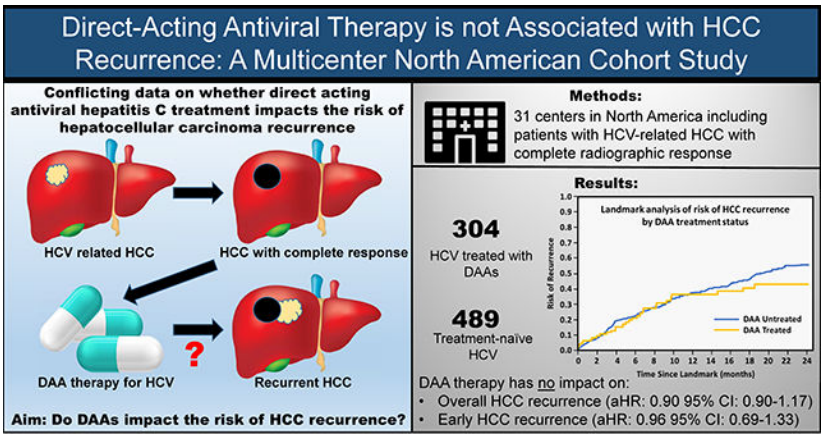
Background & Aims—There is controversy over the effects of direct-acting antiviral (DAA) therapies for hepatitis C (HCV) infection on hepatocellular carcinoma (HCC) recurrence and tumor aggressiveness. We compared HCC recurrence patterns between DAA-treated and untreated HCV-infected patients who had achieved a complete response to HCC treatment in a North American cohort.

Methods—We conducted a retrospective cohort study of patients with HCV-related HCC with a complete response to resection, local ablation, trans-arterial chemo- or radioembolization, or radiation therapy, from January 2013 through December 2017 at 31 health systems throughout the United States and Canada. Cox regression was used to examine the association between DAA therapy and time to recurrence after a complete response, with DAA therapy analyzed as a time-varying exposure. We also estimated the association between DAA therapy and risk of early HCC recurrence (defined as 365 days after complete response).

Results—Of 793 patients with HCV-associated HCC, 304 (38.3%) received DAA therapy and 489 (61.7%) were untreated. HCC recurred in 128 DAA-treated patients (42.1%; early recurrence in 52 patients) and 288 untreated patients (58.9%; early recurrence in 227 patients). DAA therapy was not associated with HCC recurrence (hazard ratio, 0.90; 95% CI, 0.70–1.16) or early HCC recurrence (hazard ratio, 0.96; 95% CI, 0.70–1.34), after we adjusted for study site, age, sex, Child Pugh score, alpha-fetoprotein level, tumor burden, and HCC treatment modality. In DAA-treated and untreated patients, most recurrences were within the Milan criteria (74.2% vs 78.8%; P=.23). A larger proportion of DAA-treated than untreated patients received potentially curative HCC therapy for recurrent HCC (32.0% vs 24.6%) and achieved a complete or partial response (45.3% vs 41.0%) but neither achieved statistical significance.

Conclusion—In a large cohort of North American patients with complete response to HCC treatment, DAA therapy was not associated with increased overall or early HCC recurrence. HCC recurrence patterns, including treatment response, were similar in DAA-treated and untreated patients.

Graphical Abstract



Keywords

Hepatitis C; liver cancer; recurrence; direct acting antiviral

BACKGROUND

Chronic hepatitis C virus (HCV) infection affects over 3.2 million persons in the United States, where it is the most common cause of hepatocellular carcinoma (HCC).(1) Highly effective direct acting antiviral (DAA) therapies against HCV infection have the potential to decrease HCV-related HCC incidence;(2, 3) however, suboptimal rates of HCV screening and treatment make this unlikely in the near future. It is estimated that 50% of HCV patients are currently unaware of their infection and over one-fourth of HCC patients have unrecognized HCV at time of tumor diagnosis.(4) Therefore, HCV-related HCC incidence may continue to increase over the next decade, if not longer.

Patients diagnosed with HCC at an early stage are eligible for curative treatments including surgical resection or local ablative therapies; however, unlike liver transplantation, these therapies are limited by high recurrence.(5, 6) Historically, sustained viral response (SVR) using interferon (IFN)-based therapy for HCV was associated with significant reductions in HCC recurrence after curative treatment.(7) However, IFN-based therapy was only able to yield SVR in approximately 40–50% of treated patients and could not be tolerated by many patients with cirrhosis.

It is unclear if DAAs have similar chemopreventive benefits for reducing HCC recurrence in patients who achieved complete response (CR) to prior HCC-directed treatment. In fact, some observational data suggest potential increased risk of HCC recurrence after DAA therapy.(8, 9) One study reported high early tumor recurrence risk in HCC patients who received DAA therapy.(9) Among 58 patients with a CR, HCC recurred in 27% at a median follow up of 5.7 months. However, the small cohort size, lack of an untreated control arm, and short median duration of follow-up limited any definitive conclusions about harms related to HCV therapy, including which patients were at highest risk for early recurrence. (10) Larger multicenter efforts, particularly those with comparator groups, are crucial to better understand the potential benefits and harms of HCV therapy with DAAs among

patients with HCC. The aim of our multi-center study was to compare overall and early HCC recurrence between DAA-treated and untreated patients in a large cohort of patients with CR to prior HCC-directed therapy.

METHODS

Study Design and Patient Population

We conducted a multi-center retrospective cohort study of adult patients with HCV-related HCC who achieved HCC complete response between January 2013 and December 2017. Patients were recruited from 31 health systems throughout the United States and Canada. HCC diagnosis was based on AASLD criteria, i.e. histological confirmation or lesions > 1 cm with characteristic appearance on imaging (arterial enhancement and delayed washout).(11) Patients were required to have liver-localized tumor burden at time of presentation, and patients with extrahepatic disease (lymph node involvement or metastatic spread) were excluded. We included patients who achieved complete HCC response by surgical resection, local ablative therapies, transarterial chemoembolization (TACE) or bland embolization, transarterial radioembolization (TARE) or stereotactic body radiation therapy (SBRT); however, patients with complete response after liver transplantation or systemic therapy were excluded. Complete response to HCC treatment was defined by mRECIST criteria, i.e. disappearance of arterial enhancement from all HCC lesions on contrast-enhanced cross sectional imaging. We excluded patients with unknown HCC response, e.g. lack of contrast-enhanced imaging after HCC treatment, and patients with HCC recurrence within 30 days of CR.

Patients were categorized into two groups: a) DAA-treatment and b) untreated. The DAA-treatment group included patients who received DAA therapy, independent of SVR12, after HCC CR; the untreated group included those who did not receive DAA therapy. We excluded patients who received IFN-based therapy during the study period, completed DAA therapy prior to HCC complete response, or completed DAA therapy after suspected HCC recurrence. The study was approved by Institutional review boards at each study site.

Data Collection

We used a standardized data collection template to obtain demographic and clinical variables at time of HCC presentation from electronic medical records at each site for all patients including age, sex, race/ethnicity, body mass index (BMI), presence of hepatitis B (HBV) and HIV co-infection, platelet count, AST, ALT, HCV viral load, HCV genotype, Eastern Cooperative Oncology Group (ECOG) performance status, and alpha fetoprotein (AFP). Degree of liver dysfunction was assessed by Child Pugh and MELD scores. Tumor burden, as determined by interpretation of imaging by local radiologists at each site, was categorized as very early stage (single tumor < 2 cm), early stage (single tumor < 5 cm or 2–3 tumors with each < 3 cm in maximum diameter), or intermediate stage (beyond early stage but without extra-hepatic spread). We recorded the number of HCC-directed treatments needed to achieve CR and type of treatment leading to HCC CR. For DAA-treated patients, we collected DAA treatment regimen, time from HCC complete response to DAA initiation, HCV viral load at week 4 and 12 of treatment, and DAA treatment outcome (i.e. SVR).

We assessed time from initial HCC complete response to last imaging with confirmed complete response as well as first imaging with HCC recurrence. For patients with HCC recurrence, we collected data regarding degree of liver dysfunction, type of recurrence (local vs. new intrahepatic lesion), tumor burden, AFP and type of HCC-directed treatment.

Statistical Analysis

We compared treatment groups (DAA-treated and untreated) using Chi-square and Student's t test for categorical and continuous variables, respectively. We characterized time to recurrence from time of HCC complete response. Patients in both groups were followed from complete response until recurrence, death, liver transplantation, or last clinic visit. Patients who initiated DAA therapy after HCC recurrence or liver transplantation were considered as untreated.

We estimated crude and adjusted hazard ratios comparing patients treated with DAAs to those who were not treated with DAAs using a Cox-proportional hazards regression model, with DAA therapy as a time-varying exposure. In brief, this method assigns follow-up time for patients before DAA initiation as unexposed time and time after DAA initiation as exposed time. We present crude and confounder-adjusted hazard ratios (adjusted for study site, age, sex, Child Pugh class, HCC tumor stage, AFP level, and type of HCC treatment). Confounders were selected *a priori* given their known association with DAA therapy receipt and HCC recurrence risk. We also estimated risk of early HCC recurrence by truncating follow-up time at 365 days of complete response. In this analysis, patients who initiated DAA >365 days after achieving HCC complete response were included in the untreated group.

To account for the possibility that DAAs have a time-varying treatment effect, we compared the untreated group to patients who initiated DAA ≤6 months after CR and those in whom DAA therapy was delayed >6 months after CR. We also conducted secondary analyses stratified by tumor burden (within vs. beyond Milan criteria), treatment leading to HCC complete response (resection vs. ablation vs. TACE/SBRT), and SVR status.

To assess the robustness of the time-varying exposure approach, we performed a sensitivity analysis using a landmark approach to compare risk of HCC recurrence between DAA-treated and untreated groups. This approach avoids immortal time bias by synchronizing the start of follow-up for the treated and untreated groups.(12, 13) We started follow-up at 90, 120, and 180 days after CR to investigate the impact of landmark choice on the outcome. Patients who had HCC recurrence, died, received liver transplantation, or had a last clinic visit before the landmark point were excluded. Patients who initiated DAA before the landmark were categorized as DAA-treated, and those initiating DAA after the landmark were included in the untreated group.

Finally, to minimize potential for confounding, we computed a propensity score for each patient, predicting the probability of initiating DAA conditional on the patient characteristics (at complete response) using multivariable logistic regression. The propensity score model included factors associated with initiating DAA therapy and/or recurrence, including study site, age, sex, Child Pugh class, baseline tumor burden, AFP level, and treatment leading to

complete response. We estimated crude and adjusted (via inverse probability of treatment weights) hazards ratios, comparing patients treated with DAAs and those who were untreated using a Cox proportional hazards regression model.

All tests were two-sided and performed at the 5% significance level. Statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC USA).

RESULTS

Patient Characteristics

Selection of the study population is illustrated in Figure 1. We initially identified 1075 HCV-infected HCC patients who achieved complete response to HCC-directed therapy between January 2013 and December 2017. After excluding 225 patients who initiated DAA therapy before complete response to HCC therapy, there were 850 patients remaining. We excluded an additional 45 patients with DAA initiation and 12 patients with HCC recurrence within 30 days of HCC complete response. A total of 793 patients were included in the final analysis, of whom 304 had been treated with DAA therapy and 489 were untreated.

Patient demographics are described in Table 1. Median age was 61.6 years. The majority of patients were male and non-Hispanic white. At time of HCC diagnosis, nearly three-fourths of patients had a unifocal HCC and over 80% were within Milan Criteria. Over 50% of patients achieved HCC complete response from locoregional therapy such as TACE, while one-third achieved complete response from local ablation and 14% from surgical resection. Median time from HCC diagnosis to treatment was 2.7 (IQR 1.4 – 5.6) months and median time from treatment to HCC complete response confirmation was 1.6 (IQR 1.1 – 3.2) months. DAA-treated patients were older, had more preserved liver function (higher proportion of compensated cirrhosis and less portal hypertension), and were more likely to have achieved HCC complete response by resection than untreated patients; however, the two groups had similar tumor burden at presentation, with no significant difference in the proportion presenting within Milan Criteria. A higher proportion of DAA-untreated patients were listed and underwent liver transplantation than DAA-treated patients (29.4% vs. 18.8%, p=0.001).

Median time from HCC CR to DAA initiation was 5.8 (IQR 3.0 – 11.5) months, with 25.0% treated within 3 months, 26.3% between 3–6 months, 24.7% between 6–12 months, 18.4% between 12–24 months, and 5.6% more than 24 months after HCC CR confirmation. Most patients had genotype 1 HCV infection, and the most common DAA regimens were sofosbuvir/ledipasvir +/− RBV and sofosbuvir with RBV. SVR12 was documented in 81.8% of DAA-treated patients, with no significant differences by HCV genotype (p=0.16), DAA regimen (p=0.11) or time to DAA treatment after HCC complete response (p=0.44).

Time-to-HCC Recurrence

Over a median follow-up of 10.4 (IQR 5.3 – 20.8) months, there were a total of 416 recurrences, including 128 after initiation of DAA treatment and 288 in untreated patients. DAA therapy, when analyzed as a binary exposure, was associated with reduced risk of HCC recurrence (HR 0.32, 95%CI 0.25 – 0.41) after adjusting for study site, age, sex, Child Pugh,

AFP level, initial tumor burden and HCC therapy. The median time to recurrence among DAA-treated patients was 13.2 (IQR 8.4 – 21.8) months, compared to 6.0 (IQR 3.6 – 10.6) months for untreated patients.

However, after accounting for time-varying exposure, DAA therapy was no longer associated with HCC recurrence in crude (HR 0.79, 95%CI 0.63 – 1.00) and adjusted (HR 0.90, 95%CI 0.70 – 1.16) analyses. The propensity score model demonstrated similar results, with DAA therapy not associated with HCC recurrence risk (HR 0.91, 95%CI 0.69 – 1.19). In sensitivity analyses using a landmark approach to minimize immortal time bias, DAA therapy was not significantly associated with increased or decreased risk of HCC recurrence. These results were consistent whether follow-up was started at 90 days (HR 0.92, 95%CI 0.60 – 1.41), 120 days (HR 0.99, 95%CI 0.66 – 1.48), or 180 days (HR 0.98, 95%CI 0.69 – 1.40) from HCC complete response (Figure 2).

Results were consistent across all subgroup analyses, stratified by tumor burden and treatment type leading to complete response (Supplemental Table). Although DAA therapy was associated with lower recurrence risk in the subgroup of patients who achieved complete response after resection, this difference did not reach statistical significance (HR 0.61, 95%CI 0.28 – 1.32). We also found no difference in the association between DAA therapy and HCC recurrence risk by SVR status, although the number of patients who failed to achieve SVR was small, or timing of DAA therapy in relationship to complete response (Supplemental Table). In a sensitivity analysis excluding 27 patients with prior HCC recurrence, DAA therapy continued to not have a significant association with HCC recurrence (HR 0.91, 95%CI 0.70 – 1.18). Compared to untreated patients, DAA therapy was not associated with differential recurrence risk in patients who initiated DAA therapy within 6 months of complete response (HR 0.90, 95%CI 0.67 – 1.21) or those who delayed DAA >6 months after complete response (HR 0.90, 95%CI 0.64 – 1.27). The proportions of patients with HCC recurrence were 44.0% for those initiating DAA within 3 months of HCC complete response, 50.0% for those initiating DAA 4–6 months after HCC complete response, and 36.9% for those initiating DAA after 6 months.

Time-to-Early HCC Recurrence

There were 52 (17.1%) patients in the DAA-treated group and 227 (46.4%) in the untreated group who experienced early recurrence within 365 days of HCC complete response. DAA therapy, when analyzed as a binary exposure, was associated with reduced risk of early HCC recurrence (HR 0.44, 95%CI 0.32–0.61) after adjusting for study site, age, sex, Child Pugh, AFP level, initial tumor burden and HCC therapy. However, accounting for time-varying exposure, there was no significant association between DAA therapy and early HCC recurrence in crude (HR 0.81, 95%CI 0.60 – 1.10) or adjusted (HR 0.96, 95%CI 0.70 – 1.34) analyses. The propensity score model demonstrated similar results, with DAA therapy not associated with increased HCC recurrence (HR 0.96, 95%CI 0.67– 1.38).

Results of the time-varying exposure analysis were consistent in subgroup analyses, stratified by tumor burden and treatment leading to complete response (Supplemental Table). Similarly, there was no difference in the association between DAA therapy and early HCC recurrence risk by SVR status. Compared to untreated patients, risk of early HCC recurrence

appeared to potentially differ by timing of DAA therapy. DAA initiation within 6 months of HCC complete response was not associated with early HCC recurrence (HR 1.05, 95%CI 0.74–1.48). Although patients who delayed DAA therapy >6 months after HCC complete response had lower risk of early HCC recurrence (HR 0.56, 95%CI 0.22– 1.38), this did not reach statistical significance likely related to small sample size.

Recurrence Patterns and Treatment Response

Recurrence patterns did not significantly differ between DAA-treated and untreated patients (Table 2). HCC recurrence presented as local recurrence, new intrahepatic lesion, and extrahepatic disease in 28.9%, 55.5%, and 7.8% of DAA-treated patients versus 38.2%, 50.3%, and 5.9% of untreated patients, respectively. In both DAA-treated and untreated groups, most recurrences were detected at an early stage (74.2 vs. 78.8% within Milan Criteria, respectively; 70.3% vs. 67.7% at BCLC stage 0/A, respectively). A larger proportion of DAA-treated received potentially curative therapy (transplant, resection or ablation) for HCC recurrence compared to untreated patients (32.0% vs. 24.6%), although this did not reach statistical significance (p=0.15). Similarly, there was no significant difference in the proportion that achieved complete or partial response to treatment of HCC recurrence.

DISCUSSION

To the best of our knowledge, our study represents the largest study to date comparing HCC recurrence risk between DAA-treated patients and a contemporary group of untreated patients. We found DAA therapy was not associated with overall or early HCC recurrence after complete response. Similarly, we did not observe any differences in patterns or aggressiveness of HCC recurrence between DAA-treated and untreated patients.

A prior meta-analysis of relevant literature found no association between DAA therapy and *de novo* or recurrent HCC.(31) Similarly, an updated meta-analysis identified nine studies that compared HCC recurrence in DAA-treated (n = 947) patients to IFN-treated (n = 210) and/or untreated (n = 641) patients.(10) Among studies reporting relative risk of recurrence, DAA-treated patients had a lower pooled recurrence risk than untreated patients (OR: 0.55, 95% CI: 0.25–0.85); however, most prior studies analyzed DAA treatment as a fixed binary exposure, which ignores the time dependency of DAA exposure and potentially leads to inaccurate hazard ratio estimates.(14) Our results highlight the importance of analyzing DAA therapy as a time-varying exposure, as we found significant differences compared to the binary exposure analysis. There is a tendency for patients with early HCC recurrence to be artefactual members of the untreated group simply because early recurrence reduces the time available to start DAAs prior to recurrence. Given cohort studies can also be limited by immortal time bias, in which HCC recurrence could not occur prior to DAA exposure, we also conducted landmark analyses anchored at three different time points. While we found decreased risk of HCC recurrence among DAA-treated patients in binary analyses, this difference was mitigated in time-varying analyses.

Although we found no association between DAA therapy and risk of HCC recurrence, we found the risk of early recurrence may differ by timing of DAA therapy. Prior studies have

reported an association between HCC recurrence and timing of DAA therapy initiation, with later initiation associated with lower HCC recurrence risk;(15–17) however, the mechanism underlying this association remains unclear. It has been hypothesized that early DAA therapy and rapid viral clearance may quickly blunt hepatic inflammation, resulting in an "immune break" that allows unchecked growth of microscopic tumor clones;(18) however, this has yet to be proven. Alternatively, delaying DAA therapy may allow more time for repeat imaging to verify HCC complete response and minimize the chance of misclassification bias. This is important because over 50% of subcentimeter lesions and over 25% of 1–2 cm lesions can be missed by one-time CT or MRI.(19) Therefore, many "early HCC recurrences" may actually be preexisting HCC that were preclinical on imaging prior to DAA initiation. Future studies should evaluate optimal timing of DAA therapy after HCC complete response and if this is associated with differential recurrence rates.

Although prior single arm studies suggested HCC recurrences after DAA therapy may be more aggressive than expected,(9, 20, 21) we found no difference between DAA-treated and untreated patients in several measures of tumor aggressiveness, including similar recurrence patterns, tumor burden, treatment eligibility and treatment response. Our data are consistent with more recent studies, which have found most recurrences are detected at an early stage and can be treated with potentially curative treatments.(22–25) Of note, most studies, including ours, reported intermediate outcomes such as recurrence patterns and treatment response and none have evaluated HCC-related mortality. While it remains important to monitor patients for recurrence during and after DAA therapy, available data suggest HCC surveillance intervals and treatment decisions do not need to differ from DAA-naïve patients.

Results from our study must be interpreted in light of other limitations. First, we used imaging interpretation through routine clinical care instead of centralized imaging review. This limitation could have affected classification of HCC complete response as well as HCC recurrence. However, all included health systems were academic centers with GI-trained radiologists, and most centers use multidisciplinary tumor boards.(26, 27) Our results were consistent across all types of HCC treatment, including surgical resection which would be less prone to misclassification of complete response, suggesting this was not a major issue. Second, there is a possibility of ascertainment bias given the retrospective nature of the study and lack of strict surveillance protocol across sites. This may have led to misclassification of early vs. late recurrences as well as missed cases of recurrence. However, standard practice at each site is to perform surveillance with cross sectional imaging every 3–6 months in all patients after HCC complete response and adherence with surveillance for cancer recurrence is typically higher than screening for incident tumors.(28, 29) Third, although we performed several analyses including propensity score analyses, there is potential for residual confounding. For example, DAA-treated patients were more likely to be non-Hispanic white and had less portal hypertension than untreated patients, which could impact results if these factors also influence risk of HCC recurrence. Fourth and perhaps most importantly, our study's primary outcome was HCC recurrence; however this is only one aspect of prognosis after HCC treatment. DAA therapy is known to result in improvements in portal hypertension and liver dysfunction, which has been shown to be a major driver of prognosis in patients with a history of HCC.(30) Ongoing multi-center

prospective cohort studies with longer follow-up will hopefully address some of these limitations; however these are years away from reporting and our data can provide important insights in the interim.

These limitations were felt to be outweighed by the study's notable strengths including its multi-center design with a large cohort of patients, rigorous statistical analysis plan, and inclusion of a contemporary untreated control group. Most prior studies evaluating HCC recurrence risk and patterns after DAA treatment have been single arm studies, with significant heterogeneity in recurrence estimates between studies. Further, comparisons to historical controls may not be ideal given differences between cohorts including aging of HCV-infected cohorts and increasing prevalence of other HCC risk factors such as the metabolic syndrome.

In summary, risk of HCC recurrence did not significantly differ between DAA-treated and untreated patients. Similarly, HCC recurrence patterns and response to treatment do not significantly differ between the two groups. Overall, our results suggest use of DAA therapies is safe and potentially beneficial in HCV-infected patients with a history of HCC.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Financial Source: This study was conducted with support National Cancer Institute (NCI) RO1 CA222900 and grant support from Abbvie. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health or Abbvie. The funding agencies had no role in design and conduct of the study; collection, management, analysis, and interpretation of the data; or preparation of the manuscript.

Abbreviations

AASLD	American Association for the Study of Liver Diseases
AFP	alpha fetoprotein
BCLC	Barcelona Clinic Liver Cancer
CR	complete response
DAA	direct acting antiviral
ECOG	Eastern Cooperative Oncology Group
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
IFN	interferon
NASH	nonalcoholic steatohepatitis

SBRT	stereotactic body radiation therapy
TACE	transarterial chemoembolization
TARE	transarterial radioembolization

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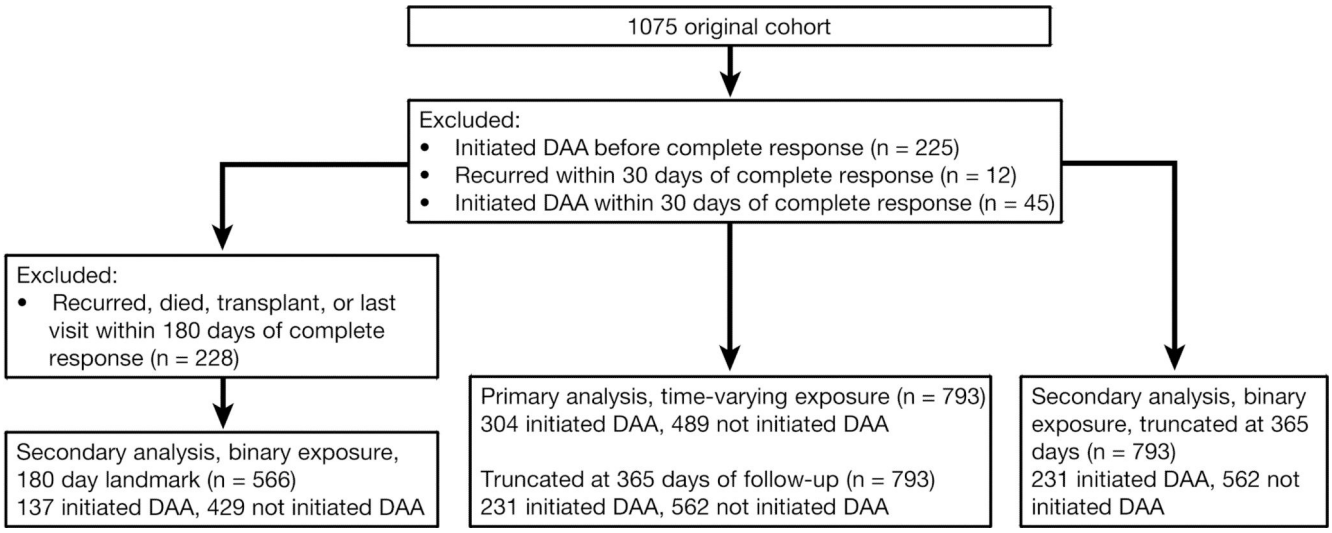

Figure 1.
Study cohort inclusion and exclusion diagram

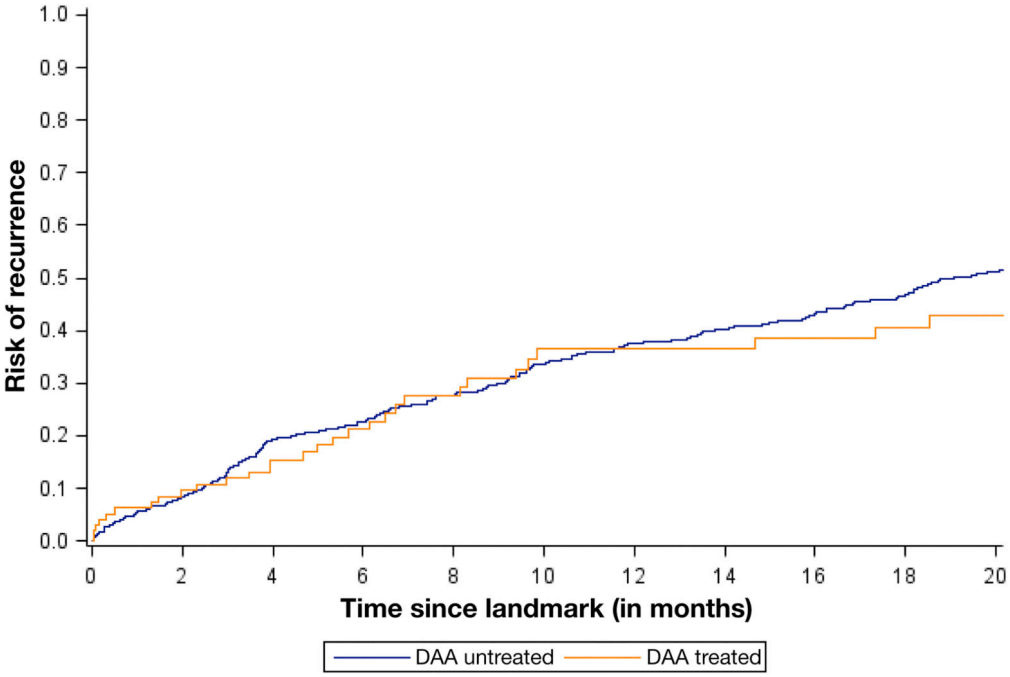

Figure 2.

Time to HCC recurrence, stratified by receipt of direct acting antiviral hepatitis C therapy, landmark analysis of 90 days after HCC complete response

Table 1.

Patient characteristics

Variable*	DAA-treated (n=304)	DAA-untreated (n=489)	p-value
Age at time of complete response (years)	62.4 (59.0 – 66.5)	61.3 (57.4 – 65.2)	0.03
Gender (% male)	214 (70.4)	373 (76.3)	0.07
Race/ethnicity			0.005
Non-Hispanic White	156 (51.3)	191 (39.1)	
Hispanic White	44 (14.5)	82 (16.8)	
Black	59 (19.4)	103 (21.1)	
Other	13 (4.3)	24 (4.9)	
Missing	32 (10.5)	89 (18.2)	
Number of HCC nodules at diagnosis			0.17
One	231 (76.0)	343 (70.1)	
Two	56 (18.4)	99 (20.2)	
Three	12 (4.0)	32 (6.5)	
Four	5 (1.6)	15 (3.1)	
Maximum HCC diameter (cm) at diagnosis	2.4 (1.7 – 3.5)	2.5 (2.0 – 3.6)	0.85
HCC within Milan Criteria at diagnosis	246 (81.7)	400 (82.3)	0.84
AFP at time of HCC diagnosis (ng/mL)	18.5 (7.6 – 64.7)	18.4 (7.7 – 67.3)	0.66
Treatment leading to complete response			< 0.001
Resection	64 (21.1)	47 (9.6)	
Local ablation	107 (35.2)	157 (32.1)	
TACE	107 (35.2)	253 (51.7)	
TARE/SBRT/other	26 (8.5)	30 (6.1)	
Missing	0 (0)	2 (0.4)	
Number of HCC therapies required to achieve complete response			0.04
One	189 (62.1)	243 (49.7)	
Two	68 (22.4)	125 (25.6)	
Three or more	37 (12.2)	86 (17.6)	
Missing	10 (3.3)	35 (7.1)	
Child Pugh class at complete response			< 0.001
Child Pugh A	191 (62.8)	244 (49.9)	
Child Pugh B	96 (31.6)	188 (38.4)	
Child Pugh C	17 (5.6)	57 (11.7)	
Presence of ascites	75 (24.7)	177 (36.2)	0.001
Presence of hepatic encephalopathy	42 (13.8)	106 (21.6)	0.006

Variable*	DAA-treated (n=304)	DAA-untreated (n=489)	p-value
Platelet count at complete response	112 (76 – 163)	89 (60 – 135)	< 0.001
Bilirubin at complete response (mg/dL)	1.0 (0.6 – 1.7)	1.2 (0.7 – 2.0)	0.32
HCV genotype			< 0.001
Genotype 1	240 (78.9)	331 (67.7)	
Genotype 2	26 (8.6)	17 (3.5)	
Genotype 3	31 (10.2)	70 (14.3)	
Genotype 4 – 6	5 (1.6)	17 (3.5)	
Missing	2 (0.7)	54 (11.0)	
Viral co-infection			0.10
Hepatitis B	8 (2.6)	5 (1.0)	
HIV	7 (2.3)	8 (1.6)	
DAA regimen**			
Sofosbuvir/ledipasvir	188 (61.8)		
Sofosbuvir	49 (16.2)		
Simeprevir/sofosbuvir	27 (8.9)		
Sofosbuvir/velpatasvir	15 (4.9)	N/A	
Daclatasvir/sofosbuvir	10 (3.3)		
Ombitasvir/partiprevir/ritonavir/dasabuvir	6 (2.0)		
Elbasavir/grazoprevir	3 (1.0)		
Other	6 (1.9)		
DAA regimen duration			
Less than 12 weeks	10 (3.3)		
12 weeks	169 (55.6)		
>12 weeks but < 24 weeks	18 (5.9)	N/A	
24 weeks	97 (31.9)		
Greater than 24 weeks	6 (2.0)		
Missing	4 (1.3)		
Time from HCC complete response to DAA			
Less than 3 months	76 (25.0)		
>3 – 6 months	80 (26.3)	N/A	
>6 – 12 months	56 (18.4)		
Greater than 24 months	17 (5.6)		

* Continuous data presented as median (IQR)

** All DAA regimens are with or without ribavirin

AFP – alpha fetoprotein; DAA – direct acting antiviral; HCC – hepatocellular carcinoma; HCV – hepatitis C virus; SBRT – stereotactic body radiation therapy; TACE – transarterial chemoembolization; TARE – transarterial radioembolization

Table 2.

Hepatocellular carcinoma recurrence patterns and treatment

Variable*	DAA-treated (n=128)	DAA-untreated (n=288)	p-value
Type of recurrence			0.33
Local recurrence	37 (28.9)	110 (38.2)	
Distant recurrence	81 (63.3)	162 (55.3)	
Missing	10 (7.8)	16 (5.5)	
Number of HCC nodules			0.87
One	77 (60.1)	173 (60.1)	
Two	30 (23.4)	61 (21.2)	
Three	8 (6.3)	20 (6.9)	
Four or more	8 (6.3)	15 (5.2)	
Infiltrative	4 (3.1)	15 (5.2)	
Missing	1 (0.8)	5 (1.4)	
Maximum tumor diameter (cm)	1.8 (1.2 – 2.7)	1.6 (1.2 – 2.5)	0.29
Vascular invasion	7 (5.4)	10 (3.5)	0.34
Distant metastases	11 (8.6)	17 (5.9)	0.28
HCC within Milan Criteria	95 (74.2)	227 (78.8)	0.23
BCLC Tumor Stage			0.16
Stage 0/A	90 (70.3)	195 (67.7)	
Stage B	11 (8.6)	17 (5.9)	
Stage C	16 (12.5)	28 (9.7)	
Stage D	11 (8.6)	46 (16.0)	
Missing	0 (0)	2 (0.7)	
Treatment of HCC recurrence			0.15
Liver Transplantation	10 (7.8)	18 (6.2)	
Surgical resection	2 (1.6)	11 (3.8)	
Local ablation	29 (22.6)	42 (14.6)	
TACE/TARE/SBRT	55 (43.0)	153 (53.1)	
Systemic therapy	8 (6.3)	11 (3.9)	
Best supportive care	21 (16.4	47 (16.3)	
Missing	3 (2.3)	6 (2.1)	
Response to HCC treatment			0.31
Complete response	43 (33.6)	91 (31.6)	
Partial response	15 (11.7)	27 (9.4)	
Stable disease	15 (11.7)	40 (13.9)	
Progressive disease	17 (13.3)	57 (19.8)	
Unknown/Missing	38 (29.7)	73 (25.3)	

*Continuous data presented as median (IQR)

BCLC – Barcelona Clinic Liver Cancer; DAA – direct acting antiviral; HCC – hepatocellular carcinoma; SBRT – stereotactic body radiation therapy; TACE – transarterial chemoembolization; TARE – transarterial radioembolization