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No difference between direct-acting antivirals for hepatitis C in hepatocellular carcinoma risk.

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Abstract

BACKGROUND & AIMS: It is unclear if there are differences between direct-acting antivirals (DAAs) for hepatitis C virus (HCV) in risk of hepatocellular carcinoma (HCC) after antiviral therapy. We aimed to compare different DAA regimens with respect to risk of *de novo* HCC following antiviral therapy.

METHODS: We identified 33,137 patients who initiated HCV antiviral treatment in the Veterans Affairs (VA) healthcare system between 12/06/2013 and 12/31/2015 with one of four DAA-only regimens ($\pm$ ribavirin): Paritaprevir/Ritonavir/Ombitasvir/Dasabuvir (ProD) (n=6,289), Sofosbuvir (n=4,356), Sofosbuvir+Simeprevir (n=3,210), and Ledipasvir/Sofosbuvir (n=19,282). We retrospectively followed patients until 6/15/2017 to identify incident (*de novo*) cases of HCC. We used propensity score-adjusted Cox proportional hazards regression to compare different DAA regimens with respect to HCC risk.

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Author Contributions

All authors approved the final version of the manuscript.

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Pamela Green: Acquisition of data, creation of analytic variables

Kristin Berry: Study design, analysis of data, interpretation of data, critical revision of manuscript.

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RESULTS: During a mean follow-up of 1.52 years, 741 new cases of HCC were diagnosed after antiviral treatment (annual incidence = 1.47%). Patients treated with Sofosbuvir+Simeprevir had the highest annual HCC incidence (2.47%), followed by Sofosbuvir (1.91%), Ledipasvir/Sofosbuvir (1.26%), and PrOD (0.95%). However, there were great differences between DAA-treated patients in prevalence of cirrhosis, markers of advanced fibrosis, thrombocytopenia, and other HCC risk factors. After adjustment for baseline characteristics associated with HCC, there were no significant differences in HCC risk between the four DAA regimens.

CONCLUSIONS: There are no significant differences between DAA regimens in HCC risk after antiviral treatment. This suggests that DAAs do not have direct carcinogenic effects as it would be unlikely that different DAAs would have identical carcinogenic effects.

Keywords

liver cancer; carcinogenic; immune modulation

INTRODUCTION

Direct-acting antivirals (DAAs) for hepatitis C virus (HCV) achieve sustained virologic response (SVR) in more than 90-95% of treated patients. Despite these promising results, some studies have paradoxically reported higher rates of HCC occurrence^{1, 2} and recurrence^{1, 3, 4} in patients treated with DAAs compared to patients treated with interferon-based regimens (IFNs). However, some of these studies are limited by their small sample size²⁻⁴, short length of follow up^{1, 2}, and lack of adjustment for potential confounders³. Additionally, subsequent studies have shown no difference in HCC occurrence⁵⁻⁷ or recurrence⁸ between DAAs and IFNs, including a recent systematic review and meta-analysis of 41 studies showing no difference in HCC occurrence or recurrence in over 13,000 patients treated with DAAs or IFNs⁹.

It has been postulated that rapid suppression of viral replication leading to impairment of immune tumor surveillance may be the mechanism by which DAAs increase HCC risk¹⁰, assuming that DAAs do indeed increase HCC risk. A rapid suppression of viral replication would be induced by *all* DAA regimens. However, another possible mechanism is a direct carcinogenic effect of one or more DAA classes. DAAs belong to four different classes (nonstructural proteins 3/4A [NS3/4A] protease inhibitors, NS5B nucleoside polymerase inhibitors, NS5B non-nucleoside polymerase inhibitors, and NS5A inhibitors), each with a unique structure and mechanism of action¹¹. Therefore, if certain DAAs have a direct carcinogenic effect, this effect will likely be different between different DAAs. We would then expect to find that some DAAs are associated with higher HCC risk than others. Conversely, if there are no differences between DAA regimens in HCC risk, this would strongly argue against DAAs having a direct carcinogenic effect. We aimed to compare DAA regimens with respect to incident (*de novo*) HCC developing after antiviral treatment.

METHODS

Data Source

The Veterans Affairs (VA) healthcare system is the largest integrated healthcare provider of HCV antiviral treatment in the United States¹².

The VA uses a single, nationwide, comprehensive electronic healthcare information network (known as the Veterans Information Systems and Technology Architecture or VistA), which consists of nearly 180 applications of clinical, financial, administrative, and infrastructure needs integrated into a single, common database of all Veterans' health information. We derived electronic data on all patients who initiated antiviral treatment in the VA system using the VA Corporate Data Warehouse (CDW), a national, continually updated repository of data from VistA developed specifically to facilitate research¹³. Data extracted included all patient pharmacy prescriptions, demographics, inpatient and outpatient visits, problem lists, procedures, vital signs, diagnostic tests, and laboratory tests.

The study was approved by the Institutional Review Board of the Veterans Affairs Puget Sound Healthcare System.

Study Population

We identified all patients who initiated DAA-only antiviral regimens (n=36,560) in the VA from 12/06/2013 to 12/31/2015 and followed them until 6/15/2017 for the development of incident HCC. We excluded 1,259 patients who had a diagnosis of HCC (ICD-9 code 155.0 or ICD-10 code C22.0) ever recorded prior to their first DAA treatment, 505 who died within 180 days from the start-date of DAA treatment or had fewer than 180 days of available follow-up, and 234 patients who were diagnosed with HCC within 180 days from the start-date of their DAA treatment (including 155 who achieved SVR, 61 who did not, and 18 with missing SVRs) since these cases were unlikely to be incident (new) cases. We excluded 1,425 patients with missing SVR leaving 33,137 patients in the final analysis, including 741 who developed HCC more than 180 days after the treatment start-date.

In a secondary analysis, we moved up the starting time point to the DAA start-date (as opposed to 180 days after DAA start-date) yielding 33,876 patients, including 991 who developed HCC after the treatment start-date, with similar exclusion criteria as mentioned above.

DAA Treatment Regimens

The four DAA-only ($\pm$ ribavirin) treatment regimens included were:

- a. Paritaprevir/Ritonavir/Ombitasvir/Dasabuvir (ProD) (n=6,289)
- b. Sofosbuvir (n=4,356)
- c. Sofosbuvir+Simeprevir (n=3,210)
- d. Ledipasvir/Sofosbuvir (n=19,282)

All VA pharmacy data are included in the CDW; dispensed drugs (rather than just prescribed drugs) were used to define antiviral treatment regimens, as we previously published^{14–21}.

Baseline Patient Characteristics

We collected baseline data including age, sex, body mass index (BMI), HCV genotype, HCV viral load, and receipt of prior antiviral treatment. We extracted relevant laboratory tests prior to treatment and recorded the value of each test closest to the treatment starting date within the preceding 6 months (except serum AFP that was recorded within 1 year). We defined HBV coinfection by positive HBV surface antigen or viral load. We also determined the presence of cirrhosis, manifestations of decompensated cirrhosis (ascites, encephalopathy, gastroesophageal varices, and hepatorenal syndrome), type 2 diabetes mellitus, alcohol use disorders, substance use disorders, HIV infection, and liver transplantation based on appropriate ICD-9 or ICD-10 codes recorded at least twice *prior to* treatment initiation in any inpatient or outpatient encounter (Supplemental Table 1). These ICD-based definitions of cirrhosis and other comorbidities^{22–28} have been widely used and validated in studies using VA medical records.

Sustained Virologic Response (SVR)

We defined SVR as a serum HCV RNA viral load below the lower limit of detection performed at least 12 weeks after the end of HCV treatment²⁹.

Incident Hepatocellular Carcinoma

We identified incident cases of HCC diagnosed for the first time at least 180 days after the initiation of antiviral treatment based on ICD-9 code 155.0 or ICD-10 code C22.0 documented at least twice. The ICD-9 code-based definition of HCC using VA records has been shown to have a positive predictive value of 84–94% compared to chart extraction^{26, 30, 31} and has been widely used by us^{18, 28, 32, 33} and other investigators^{34–36}.

Statistical Analysis

We compared patients who initiated HCV antiviral treatment with one of four DAA-only regimens with respect to HCC risk using Cox proportional hazards regression with or without adjusting for potential confounders. We calculated time starting from 180 days after initiation of antiviral treatment since cancers diagnosed within 180 days of treatment start-date were likely present but undiagnosed at the time of antiviral treatment initiation and likely not due to the antiviral treatment with DAA itself (i.e. not truly “incident” cancers). However, we also performed a secondary analysis with starting time point moved up to DAA start-date to address the question of whether occult cancers could be accelerated by DAAs. Follow-up for HCC incidence extended until 6/15/2017 so that even patients treated in late 2015 (i.e. the most recent in our cohort) would have substantial follow-up. Patients without incident HCC were censored at time of death or last follow-up in the VA.

To determine whether DAA regimen was independently associated with HCC risk, our multivariable proportional hazards models were adjusted for 22 baseline characteristics potentially associated with HCC risk ascertained at time of treatment initiation, as shown in Table 1. Continuous variables were categorized and modeled as dummy categorical

variables. Survival analyses are stratified by the VA facility at which antiviral treatment was administered.

In addition, we used propensity score (PS) adjustment to account for the nonrandom assignment of patients to different DAA regimens. We used a matching weights method based on estimated PS³⁷. Matching weights have better performance than matching or inverse probability of treatment weights when treatment groups are unequal in size or there is poor covariate balance. Missing information due to censoring required specialized methods to estimate PS³⁸. Conditional independence was assumed by the inclusion of confounders in the model. After the application of matching weights, sufficient overlap was assumed. The censoring process was assumed independent of outcome after adjusting for the confounders in a Weibull model.

RESULTS

Baseline characteristics of study population

The most common DAA regimen used was Ledipasvir/Sofosbuvir (n=19,282), followed by PrOD (n=6,289), Sofosbuvir (n=4,356), and Sofosbuvir+Simeprevir (n=3,210). Patients treated with Sofosbuvir were more likely to be White, compared to patients treated with other DAA regimens. Patients treated with Sofosbuvir+Simeprevir were more likely to have cirrhosis, decompensated cirrhosis, liver transplantation, higher AFP level and AST/ALT ratio, lower platelet count, and prior treatment experience than patients treated with other DAA regimens. Most patients treated with Sofosbuvir had genotype 2, whereas most patients treated with other DAA regimens had genotype 1.

Association between DAA regimen and HCC risk

During a mean follow-up of 1.52 years, 741 new cases of HCC were diagnosed in 33,137 patients (annual incidence = 1.47% or 1.47 per 100 patient years). Annual incidence of HCC was highest in patients with cirrhosis who failed SVR (8.9%), followed by patients without cirrhosis who failed SVR (2.9%), patients with cirrhosis who achieved SVR (2.6%), and patients without cirrhosis who achieved SVR (0.4%). Patients treated with Sofosbuvir+Simeprevir had the highest annual HCC incidence (2.47%), followed by Sofosbuvir (1.91%), Ledipasvir/Sofosbuvir (1.26%), and PrOD (0.95%). Compared to patients treated with PrOD, patients treated with Sofosbuvir (crude hazard ratio 1.95, 95% CI 1.48-2.57), Sofosbuvir+Simeprevir (crude hazard ratio 2.67, 95% CI 2.03-3.51), and Ledipasvir/Sofosbuvir (crude hazard ratio 1.30, 95% CI 1.02-1.65) were more likely to develop HCC in unadjusted analyses. However, after adjustment for baseline characteristics, there was no significant difference between any DAA regimens in HCC risk (Table 2). Additionally, adjusting for SVR (which is not a true confounder but a downstream effect of each regimen) did not substantially change the results (Table 2).

In a secondary analysis with starting time point moved up to DAA start-date, 991 new cases of HCC were diagnosed in 33,876 patients (annual incidence = 1.48%). The associations between DAA regimen and HCC risk were very similar to our primary analysis. Although in unadjusted analyses patients treated with Sofosbuvir-containing regimens (especially

Sofosbuvir+Simeprevir) had higher HCC risk than PrOD-treated patients, there were no significant differences after appropriate adjustments (Table 3).

When we used propensity score adjustment to account for nonrandom assignment of treatments, there was no significant association between DAA regimen and HCC risk (Tables 2 and 3).

DISCUSSION

In a national cohort of HCV-infected patients treated with DAAs, annual HCC incidence was highest in patients treated with Sofosbuvir+Simeprevir (2.47%), followed by Sofosbuvir (1.90%), Ledipasvir/Sofosbuvir (1.26%), and PrOD (0.95%). However, after adjustment for potential confounders associated with HCC risk, there was no significant association between DAA regimen and HCC risk. Differences in HCC incidence between DAA regimens were explained by differences in baseline characteristics, especially cirrhosis, decompensated cirrhosis, AST/ALT ratio, and platelet count.

We found no association between DAA regimen and HCC risk. This suggests that there is no direct carcinogenic effect related to particular DAA regimens as it would be extremely unlikely for a carcinogenic effect to be identical in magnitude between different regimens. A direct carcinogenic effect refers to a cancer-causing effect directly attributable to the drug itself, which is distinguished from an indirect carcinogenic effect that is the result of a downstream effect of the drug. No studies have implicated any direct drug-induced carcinogenic mechanisms associated with DAAs. Our study's finding further supports this.

Our finding does not exclude the possibility that different DAAs increase HCC risk *equally*. However, this hypothesis is not consistent with previous studies by us⁷ and others⁵ showing no difference in HCC risk between DAA and interferon-treated patients. It has been postulated that DAAs might increase HCC risk equally by rapid viral suppression causing an immune-modulating effect. However, this theory is speculative, largely being derived from reports of hepatitis B virus and herpes virus reactivating in the face of DAAs¹⁰. A recent study argues against immune modulation as a mediating mechanism triggering HCC³⁹. Serum levels of numerous immune mediators (consisting of cytokines, growth factors, and apoptotic markers) were evaluated in a cohort of 13 patients with HCC (10 with *de novo* HCC and 3 with recurrent HCC) and 10 matched controls before, during, and after HCV antiviral treatment with DAAs. Significantly higher levels of 12 immune mediators were found pretreatment with DAAs in patients who went on to develop *de novo* HCC compared with controls. This suggested that immune modulation mediated by DAAs likely did not trigger HCC formation, and rather pointed towards a modification of the immune milieu even prior to DAA treatment initiation.

The higher HCC incidence observed in Sofosbuvir-containing regimens (especially Sofosbuvir+Simeprevir) is explained by the higher proportion of patients with cirrhosis, decompensated cirrhosis, and other adverse characteristics associated with HCC treated with these regimens than with PrOD. This is likely due to the fact that PrOD has been associated with reports of fulminant hepatitis and hepatic decompensation occurring within weeks of

receiving treatment in cirrhotic patients⁴⁰, and was thus largely avoided in patients with advanced cirrhosis. Furthermore, the Sofosbuvir+Simeprevir regimen became available at a time when patients with cirrhosis were actively prioritized for treatment, which explains the particularly high proportion of patients with cirrhosis among patients treated with this regimen.

A secondary analysis with starting time point moved up to the DAA start-date showed no significant difference in HCC risk between different DAA regimens. HCCs diagnosed within six months of treatment are unlikely to be truly incident cancers and rather likely represent cancers present but undiagnosed (occult) at the time treatment was initiated. Therefore, our results additionally suggest that DAAs are not associated with the acceleration of occult HCCs. This further argues against the carcinogenic nature of DAAs.

Limitations and Strengths. Some of the DAA-only regimens that we included are now rarely used, given the rapid introduction of new antivirals in recent years. However, the DAAs we studied are the ones used in the studies that raised concerns about increased risk of HCC occurrence or recurrence with DAAs. Furthermore, our overarching finding is that HCC risk does not depend on DAA regimen; this finding likely applies to new agents, which all belong to the same DAA classes. We only measured the incidence of *de novo* HCC, and thus, we are unable to comment on the association between DAA regimens and HCC recurrence. We did not have information on the stage of HCC at diagnosis. As with all studies conducted in the VA health care system, our study is based on a national cohort of US Veterans, most of whom are male. Strengths include the study's originality, large sample size, large number of incident HCCs, and the inclusion of four different DAA regimens with representations of all four DAA classes. Additionally, these regimens were used more or less contemporaneously, as opposed to comparison studies of DAAs to antiviral regimens of different eras (i.e. IFNs).

In conclusion, there are no significant differences between DAA regimens in HCC risk after antiviral treatment. This suggests DAAs do not have direct carcinogenic effects as it would be unlikely for different DAAs to have identical carcinogenic effects.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Abbreviations

ALD	Alcoholic Liver Disease
DAA	Direct-Acting Antiviral treatment for HCV

HCC	Hepatocellular Carcinoma
HCV	Hepatitis C Virus
IFN	Interferon
NAFLD	Nonalcoholic Fatty Liver Disease
PEG	Pegylated Interferon
VA	Veterans Affairs

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Table 1.

Baseline characteristics of HCV-infected patients treated with a DAA-only regimen in 2013-2015

Characteristic	PrOD N=6,289	Sofosbuvir N=4,356	Sofosbuvir + Simeprevir N=3,210	Ledipasvir/Sofosbuvir N=19,282
Age, yrs (mean [SD])	61.6 [6.1]	60.4 [7.3]	60.9 [5.6]	61.1 [6.5]
BMI, Kg/m ² (mean [SD])	27.9 [5.2]	28.4 [5.6]	28.5 [5.3]	28.1 [5.4]
Male (%)	97.5	97.3	96.5	96.5
Race/Ethnicity (%)				
White, non-Hispanic	46.5	73.8	52.7	49.9
Black, non-Hispanic	38.1	9.3	31.6	35.9
Hispanic	5.3	6.8	7.2	4.9
Other	1.6	2.2	1.8	1.5
Declined to answer/missing	8.4	7.8	6.8	7.7
Treatment experienced	18.4	21.7	36.9	23.3
Genotype (%)				
Genotype 1	98.9	5.5	98.2	94.2
Genotype 2	0	67	1.2	0.2
Genotype 3	0	21.7	0.3	3.7
Genotype 4	1	0.4	0.3	0.9
Missing	0	5.3	0	1.1
HCV RNA >6 million IU/mL (%)	21.9	22.5	16.4	16.5
Sustained virologic response (%)	91.5	81	85.2	92.1
HIV co-infection	1.7	2.6	3.1	5.8
HBV co-infection	1.5	1	0.9	1.2
Cirrhosis (%)	20.4	27.1	54.2	25.4
Decompensated Cirrhosis (%)	2.8	9.4	18	7.3
Liver Transplantation (%)	0.1	1.5	4.3	1.9
Diabetes (%)	27.6	25.8	35.9	30.4
Alcohol Use Disorder (%)	41.2	45.7	42.9	45.2
Substance Use Disorder (%)	34.5	36.2	34.1	39.6
Laboratory Results (mean [SD])				
Alpha Fetoprotein, ng/mL	6.2 [4.2]	4.9 [3.7]	7.5 [4.8]	6.3 [4.3]
Hemoglobin, g/dL	14.8 [1.4]	14.6 [1.5]	14.1 [1.7]	14.5 [1.6]
Platelet Count, k/ μ L	184.9 [64.9]	169.3 [70.9]	144.9 [70.3]	181.4 [71.5]
Creatinine, mg/dL	1.1 [0.8]	1.0 [0.3]	1.0 [0.5]	1.0 [0.4]
Bilirubin, g/dL	0.7 [0.4]	0.7 [0.6]	0.9 [0.6]	0.7 [0.5]
Albumin g/dL	3.9 [0.4]	3.9 [0.5]	3.7 [0.5]	3.9 [0.5]
INR	1.2 [1.1]	1.2 [0.8]	1.2 [0.8]	1.2 [1.0]
AST/ ALT	7.3 [2.9]	7.6 [3.4]	8.8 [3.8]	7.5 [3.2]

Table 2.

Association between DAA regimen and HCC risk

Regimen	Number of Patients N=33,137	Number (proportion) who developed HCC N=741	Annual HCC Incidence %	Crude Hazard Ratio (95% CI)	Adjusted* Hazard Ratio (95% CI)	Adjusted (+SVR)* Hazard Ratio (95% CI)	Matching Weights Propensity Score Adjusted* Hazard Ratio (95% CI)
Paritaprevir/Ritonavir/Ombitasvir/Dasabuvir (ProD)	6,289	82(1.3)	0.95	1	1	1	1
Sofosbuvir	4,356	143(3.3)	1.91	1.95 (1.48-2.57)	0.98 (0.63-1.51)	0.76 (0.50-1.16)	0.93 (0.57-1.51)
Sofosbuvir + Simeprevir	3,210	168(5.2)	2.47	2.67 (2.03-3.51)	1.22 (0.90-1.65)	1.10 (0.81-1.50)	1.31 (0.95-1.80)
Ledipasvir/Sofosbuvir	19,282	348(1.8)	1.26	1.30 (1.02-1.65)	1.05 (0.80-1.38)	1.12 (0.85-1.47)	1.03 (0.77-1.38)

* Adjusted for cirrhosis, decompensated cirrhosis, age, sex, race/ethnicity, treatment experienced, BMI, HCV genotype, HCV viral load, HIV co-infection, HBV co-infection, type 2 diabetes mellitus, alcohol use disorders, substance use disorder, platelet count, serum bilirubin, creatinine, albumin, and AST/ALT ratio, blood INR and hemoglobin levels (+ adjust for SVR). Laboratory tests were categorized into quartiles and modeled as dummy categorical variables.

Table 3. Association between DAA regimen and HCC risk (with starting time point moved up to DAA-start date)

Regimen	Number of Patients N=33,876	Number (Proportion) who developed HCC N=991	Annual HCC Incidence %	Crude Hazard Ratio (95% CI)	Adjusted* Hazard Ratio (95% CI)	Adjusted (+SVR)* Hazard Ratio (95% CI)	Matching Weights Propensity Score Adjusted* Hazard Ratio (95% CI)
Paritaprevir/Ritonavir/Ombitasvir/Dasabuvir (ProD)	6,396	117(1.8)	1.0	1	1	1	1
Sofosbuvir	4,470	178(4.0)	1.84	1.86 (1.46-2.36)	0.99 (0.68-1.44)	0.81 (0.56-1.17)	1.02 (0.64-1.64)
Sofosbuvir + Simeprevir	3,294	205(6.2)	2.44	2.57 (2.03-3.25)	1.15 (0.89-1.49)	1.06 (0.82-1.39)	1.17 (0.89-1.54)
Ledipasvir/Sofosbuvir	19,716	491(2.5)	1.32	1.35 (1.10-1.66)	1.04 (0.83-1.31)	1.10 (0.87-1.38)	1.04 (0.82-1.33)

* Adjusted for cirrhosis, decompensated cirrhosis, age, sex, race/ethnicity, treatment experienced, BMI, HCV genotype, HCV viral load, HIV co-infection, HBV co-infection, type 2 diabetes mellitus, alcohol use disorders, substance use disorder, platelet count, serum bilirubin, creatinine, albumin, and AST/ALT ratio, blood INR and hemoglobin levels (+ adjust for SVR). Laboratory tests were categorized into quartiles and modeled as dummy categorical variables.