Provider Attitudes and Practice Patterns for Direct-Acting Antiviral Therapy for Patients With Hepatocellular Carcinoma

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Abbreviations used in this paper: **APP, advanced practice provider; DAA, direct-acting antiviral; F3, stage 3 fibrosis; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; SVR, sustained virologic response.**

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BACKGROUND & AIMS: **Direct-acting antivirals (DAAs) are effective against hepatitis C virus and sustained virologic response is associated with reduced incidence of hepatocellular carcinoma (HCC). However, there is controversy over the use of DAAs in patients with active or treated HCC and uncertainty about optimal management of these patients. We aimed to characterize attitudes and practice patterns of hepatology practitioners in the United States regarding the use of DAAs in patients with HCC.**

METHODS: **We conducted a survey of hepatology providers at 47 tertiary care centers in 25 states. Surveys were sent to 476 providers and we received 279 responses (58.6%).**

RESULTS: **Provider beliefs about risk of HCC recurrence after DAA therapy varied: 48% responded that DAAs reduce risk, 36% responded that DAAs do not change risk, and 16% responded that DAAs increase risk of HCC recurrence. However, most providers believed DAAs to be beneficial to and reduce mortality of patients with complete response to HCC treatment. Accordingly, nearly all providers (94.9%) reported recommending DAA therapy to patients with early-stage HCC who received curative treatment. However, fewer providers recommended DAA therapy for patients with intermediate (72.9%) or advanced (57.5%) HCC undergoing palliative therapies. Timing of DAA initiation varied among providers based on HCC treatment modality: 49.1% of providers reported they would initiate DAA therapy within 3 months of surgical resection whereas 45.9% and 5.0% would delay DAA initiation for 3–12 months and >1 year post-surgery, respectively. For patients undergoing transarterial chemoembolization (TACE), 42.0% of providers would provide DAAs within 3 months of the procedure, 46.7% would delay DAAs until 3–12 months afterward, and 11.3% would delay DAAs more than 1 year after TACE.**

CONCLUSIONS: **Based on a survey sent to hepatology providers, there is variation in provider attitudes and practice patterns regarding use and timing of DAAs for patients with HCC. Further studies are needed to characterize the risks and benefits of DAA therapy in this patient population.**

Keywords: Liver Cancer; HCV; TACE; Drug.

Hepatocellular carcinoma (HCC) is the fastest rising cause of cancer-related death in the United States, with most cases attributed to chronic hepatitis C virus (HCV) infection.[1–3] Highly effective direct-acting antivirals (DAAs) have revolutionized HCV treatment, resulting in high rates of sustained virologic response (SVR). HCV eradication in patients with cirrhosis with DAAs is cost-effective[4] and has several benefits including reduced risk of hepatic decompensation,[5] improvement in all-cause mortality,[6,7] and decreased incident HCC.[7–9]

However, the effect of DAAs on risk of tumor recurrence in patients with a history of treated HCC remains controversial after an observational study from Spain found a higher-than-expected proportion of patients with HCC recurrence after DAA treatment.[10] Subsequent studies have produced conflicting data, including a large multicenter study showing no significant difference in early HCC recurrence, overall recurrence, or tumor aggressiveness between DAA-treated and untreated patients.[11] Furthermore, there are unknown benefits of DAA treatment in patients with active HCC, particularly in light of reports showing reduced rates of SVR.[12,13]

While awaiting prospective data, there remains uncertainty about the optimal management of patients with HCV and HCC, which may lead to confusion among providers. To our knowledge, provider attitudes and practice patterns in this patient population have not been assessed. Therefore, we conducted a nationwide survey study to evaluate attitudes and practice patterns of US hepatology practitioners regarding the use and timing of DAA treatment in patients with HCC.

Methods

Participants

We conducted a survey among hepatology providers at 47 tertiary care centers, safety-net hospitals, and Veterans Affairs hospitals from 25 states in the United States. Participating sites were a convenience sample of academic centers, representing each US region. A single

provider at each site, whose email was obtained from their institutional Web site, was asked to distribute the survey to all hepatology providers at his or her institution. Eligible providers included physicians (MD/DO) and advanced practice providers (APPs) involved in clinical care of patients with HCV. We excluded providers who primarily treat patients <18 years of age, nonhepatology providers, and those with incomplete surveys. The study was approved by the institutional review board at the University of Texas Southwestern Medical Center.

Survey Information

We distributed an anonymous web-based survey to eligible hepatology providers between February 1, 2019 and February 28, 2019. We sent a single email reminder to those who had not completed the survey after 1–2 weeks. The survey had 38 questions and took an average of 10 minutes to complete.

The content of the survey was based on a conceptual model, adapted from a previously proposed model of physician behavior (Figure 1).[14] Survey questions were organized into 5 sections:

1. Provider experience (4 questions): assessed provider experience with HCV and HCC treatment.
2. Provider practice patterns (7 questions): assessed provider practice patterns with regard to HCV treatment, HCC treatment, and HCC surveillance.
3. Clinical vignettes (10 questions): included 4 clinical vignettes to assess provider practices for patients with different stages of HCC undergoing curative and palliative HCC treatments.
4. Provider attitudes and beliefs (9 questions): assessed provider attitudes and beliefs about potential benefits and risks of DAA therapy in patients with HCC.
5. Provider demographics (8 questions): recorded provider demographics including age, sex, race/ethnicity, number of years in clinical practice, provider type (physician vs APP), presence of an institutional multidisciplinary tumor board, and number of patients treated annually with HCV and HCC.

Questions were adapted from validated surveys when available.[15] The survey was pretested among 5 MD providers, at which time saturation of feedback was believed to have been achieved. Each provider participated in a cognitive interview after survey completion, and the survey was iteratively revised based on feedback before distribution to study participants. The complete survey can be found in the Supplementary Material.

What You Need to Know

Background

The use and timing of direct acting antivirals (DAAs) for patients with a history of treated hepatocellular carcinoma (HCC) is controversial due to concerns about risk of HCC recurrence.

Findings

In a survey of 279 hepatology practitioners, we found variation in perceived risk of HCC recurrence after DAA therapy. Most providers believe DAAs reduce mortality in patients with a history of complete response to HCC therapy. Recommendations for DAA therapy in HCC patients varied by tumor stage, with fewer providers recommending DAAs for patients with a history of intermediate or advanced HCC than early HCC. Timing of DAA therapy also varied among providers, with some starting DAA around time of HCC treatment and others delaying DAA for months to confirm complete response to HCC treatment.

Implications for patient care

Future studies characterizing the risks and benefits of DAAs for patients with a history of HCC might help standardize clinical practice for these patients.

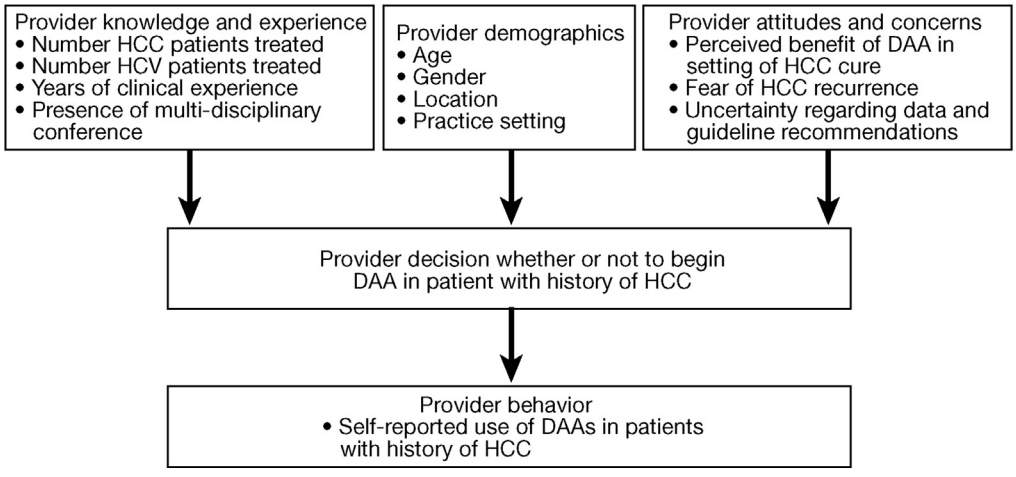

Figure 1. Conceptual model for provider decision-making.

Statistical Analysis

Survey responses were summarized using descriptive statistics. The primary outcome of interest was provider-reported practice patterns for DAA recommendations in patients with HCC, based on provider responses to 4 clinical vignettes. Secondary outcomes included provider attitudes regarding the use of DAAs in patients with HCC. Fisher exact and chi-square tests were performed for categorical variables to identify factors associated with DAA recommendation patterns. Independent variables included provider demographics and perceived DAA benefit in patients with HCC. Tests were 2-sided and performed at the 5% significance level. Statistical analysis was performed using Stata version 14.0 (College Station, TX).

Results

Provider and Institutional Characteristics

Of 331 surveys returned, 52 were excluded because of being incomplete, leaving a total of 279 responses. This represented a 58.6% (279 of 476) provider-level and 92.2% (47 of 51) institution-level response rate. Characteristics of respondents are summarized in Table 1. Most respondents were MD or DO providers, over 50% were female, and the sample was racially and ethnically diverse. Most providers identified their primary practice location as a tertiary referral center with a transplant program, approximately three-fourths had been in practice for >5 years, and nearly two-thirds spent >75% of time on clinical care. More than 75% of providers had treated more than 50 total patients with HCV with DAAs, and 90% reported being directly involved in HCC management.

Table 1. Provider and Institution Characteristics (n = 279)

Characteristics	N (%)
Provider	
Sex (% male)	133 (48.4)
Race/ethnicity	
Non-Hispanic white	146 (53.3)
Black	4 (1.5)
Hispanic	11 (4.0)
Asian/Pacific Islander	81 (29.6)
Other	32 (11.7)
Type of practitioner	
Physician (MD/DO)	195 (70.1)
APP	83 (29.9)
Years in practice	
<5	71 (25.5)
5–9	84 (30.2)
10–20	75 (27.0)
>20	48 (17.3)
Time spent on clinical care, %	
<50	46 (16.6)
50–75	57 (20.5)
>75	175 (62.9)
Approximate total number patients with HCV treated with DAAs	
<50	57 (20.5)
50–100	57 (20.5)
>100	164 (59.0)
Personally involved in HCC management (% yes)	253 (91.3)
Institution	
Region	
Northeast	48 (17.2)
Midwest	72 (25.8)
South	76 (27.2)
West	83 (29.8)
Institution type	
Tertiary referral center with transplant program	245 (88.4)
Tertiary referral center without transplant program	8 (2.9)
Veterans Affairs hospital	9 (3.3)
Community-based hospital	7 (2.5)
Safety-net hospital	8 (2.9)
Approximate number of patients with HCC treated at institution annually	
0–50	19 (6.9)
51–100	57 (20.8)
101–150	58 (21.2)
>150	140 (51.1)
Presence of multidisciplinary HCC clinic and/or conference (% yes)	274 (98.6)

APP, advanced practice provider; DAA, direct-acting antiviral; DO, Doctor of Osteopathic Medicine; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; MD, Medical Doctor.

Provider Attitudes Regarding Use of Direct-Acting Antivirals in Patients With Hepatocellular Carcinoma

Provider-reported attitudes regarding the use of DAAs in the setting of HCC are reported in Table 2. Nearly 80% of providers believed DAAs reduce risk of incident de novo HCC in patients with cirrhosis. However, there was wider variation in perceived risk of HCC recurrence after DAA therapy in patients with complete response to HCC treatment, with 48% believing DAAs reduce risk of recurrence, 36% believing DAAs do not change HCC recurrence risk, and 16% believing DAAs increase recurrence risk. Despite this, most still believed DAAs reduce mortality, are cost-effective, and have overall benefit in patients with complete response to HCC treatment. In fact, nearly all providers were likely to recommend DAAs in patients with a history of HCC, although 50% delayed initiation of DAA therapy by 4–6 months following HCC complete response. Only 5% of providers believed HCC recurrence after DAA therapy could pose legal liability, compared with more than one-third believing this was possible in untreated patients who experience hepatic decompensation. However, 60% of providers reported counseling their patients regarding the risk of HCC recurrence before DAA therapy. Overall, 85% of providers believed this is an area of continued controversy in need of more data and guidance.

Table 2. Provider Attitudes Regarding Use of DAAs in Patients With HCC (n = 279)

Provider attitude	N (%)
Impact of DAA on incident HCC risk in patients with cirrhosis	
Significant reduction in risk	167 (60.1)
Small reduction in risk	53 (19.1)
No change in risk	41 (14.7)
Small increase in risk	15 (5.4)
Significant increase in risk	2 (0.7)
Impact of DAA on risk of HCC recurrence in patients with CR to HCC treatment	
Significant reduction in risk	46 (16.7)
Small reduction in risk	85 (30.8)
No change in risk	99 (36.0)
No change in risk but shortens time-to-recurrence	15 (5.4)
Small increase in risk	30 (10.9)
Significant increase in risk	0 (0.0)
Impact of DAA on mortality in patients with CR to HCC treatment	
Significant reduction in mortality	104 (37.8)
Small reduction in mortality	110 (40.0)
No change in mortality	56 (20.4)
Small increase in mortality	4 (1.4)
Significant increase in mortality	1 (0.4)
Impact of active HCC on likelihood of achieving SVR with DAA treatment	
Significant reduction in SVR rates	57 (20.4)
Small reduction in SVR rates	114 (40.9)
No change in SVR rates	104 (37.3)
Small increase in SVR rates	4 (1.4)
Significant increase in SVR rates	0 (0.0)
DAAs are cost-effective in patients with CR to HCC treatment	
Strongly agree	114 (40.9)
Agree	151 (54.1)
Disagree	13 (4.7)
Strongly disagree	1 (0.4)
Overall, DAAs are beneficial in patients with CR to HCC treatment	
Strongly agree	133 (47.7)
Agree	139 (49.8)
Disagree	6 (2.1)
Strongly disagree	1 (0.4)
Treating patients with HCC with DAAs may pose legal liability if patients have HCC recurrence	
Strongly agree	2 (0.7)
Agree	15 (5.4)
Disagree	161 (57.7)
Strongly disagree	101 (36.2)
Not treating patients with HCC with DAAs may pose legal liability if patients develop hepatic decompensation	
Strongly agree	27 (9.7)
Agree	80 (28.8)
Disagree	134 (48.2)
Strongly disagree	37 (13.3)
More data and guidance are needed on risk of HCC recurrence after DAAs	
Strongly agree	117 (41.9)
Agree	122 (43.7)
Disagree	35 (12.5)
Strongly disagree	5 (1.8)
How have recent studies on DAA and HCC risk changed your clinical practice?	
No longer use DAAs in patients with HCC	0 (0.0)
Less likely to use DAAs in patients with HCC	12 (4.4)
Equally likely to use DAAs but I delay therapy 4–6 mo after CR	138 (50.6)
Equally likely to use DAAs with no change in my practice	123 (45.0)
Does HCC treatment modality that led to CR impact your decision regarding timing of DAA?	
Yes	64 (23.5)
No	192 (70.6)
Not applicable, I use DAA in patients with active HCC	8 (2.9)
Other	8 (2.9)
How often do you counsel patients with HCC on risk of recurrence after DAA?	
Always	119 (43.4)
Sometimes	50 (18.2)
Rarely	49 (17.9)
Never	56 (20.4)
Timing of DAA therapy in transplant candidate with HCC	
Routinely treat pretransplant on waitlist	15 (5.3)
Case-by-case basis	119 (41.9)
Routinely treat with DAA within 3 mo post-transplant	122 (43.0)
Routinely defer DAA >6 mo post-transplant	298 (9.9)

CR, complete response; DAA, direct-acting antiviral; HCC, hepatocellular carcinoma; SVR, sustained virologic response.

MD and DO providers were significantly more likely than APPs to believe that DAAs reduce risk of incident HCC (84.5% vs 66.3%; $P = .002$); however, attitudes about HCC incidence or recurrence did not otherwise differ by provider sex, race/ethnicity, years in practice, provider experience with HCV or HCC treatment, type of institution, or region of the United States in which they practiced.

Provider Attitudes Regarding Hepatocellular Carcinoma Surveillance After Sustained Virologic Response

Surveillance practices in patients without a history of HCC are shown in Table 3. More than 90% of providers continue to follow post-SVR patients with cirrhosis in their clinics and perform HCC surveillance with imaging $\pm$ α-fetoprotein every 6 months indefinitely. Nearly 95% reported performing HCC surveillance in some patients with stage 3 fibrosis (F3), with 61% performing surveillance in all F3 patients.

Provider Practices Regarding Use of Direct-Acting Antivirals in Patients With Hepatocellular Carcinoma

Provider practice patterns for DAA use and DAA timing among patients undergoing HCC therapy are

Table 3. HCC Surveillance Practice Patterns in Post-SVR Patients (n = 279)

Provider practice	N (%)
Length of time patients with cirrhosis with SVR post-DAAs are followed in hepatology clinic	
Indefinitely	255 (91.7)
Approx. 1 y then discharge to PCP	9 (3.2)
Approx. 3–5 y then discharge to PCP	6 (2.2)
Not routinely followed; seen as needed	9 (2.9)
Method of HCC surveillance in patients with cirrhosis after SVR	
Imaging (US, CT, or MR) ± AFP every 6 mo indefinitely	264 (95.0)
Imaging (US, CT, or MR) ± AFP every 12 mo indefinitely	8 (2.9)
Imaging (US, CT, or MR) ± AFP every 6 mo, stop after few years	2 (0.7)
Other	4 (1.4)
Do you perform HCC surveillance in patients with F3 after SVR?	
Yes	169 (61.0)
Sometimes	91 (32.9)
No	17 (6.1)

AFP, α-fetoprotein; CT, computed tomography; DAA, direct-acting antivirals; F3, stage 3 fibrosis; HCC, hepatocellular carcinoma; MR, magnetic resonance imaging; PCP, primary care physician; SVR, sustained virologic response; US, ultrasound.

illustrated in Figure 2*A* and Figure 2*B*, respectively. Based on the clinical vignettes, the proportion of providers recommending DAA therapy and timing of such therapy varied by HCC stage and treatment type. Providers were significantly less likely to recommend DAAs in patients with intermediate- or advanced-stage HCC undergoing palliative treatments than early stage patients with HCC undergoing curative therapy. Although nearly 95% would recommend DAAs in a patient with early stage HCC undergoing surgical resection, this was reported by only 73% and 57% of providers for intermediate-stage patients with HCC undergoing transarterial chemoembolization and advanced-stage patients with HCC undergoing systemic therapy, respectively. However, providers seemed willing to treat patients with more advanced HCC if they had a response to HCC-directed therapies, with nearly 40% willing to treat advanced-stage patients with HCC if they had an objective response to treatment. Nearly 70% of providers reported the modality leading to an HCC complete response would not impact their likelihood to recommend DAA therapy. Provider responses varied with regard to timing of DAA initiation based on HCC stage and treatment modality as demonstrated in Table 4. Overall, 15%–20% of providers reported they would initiate DAA therapy before HCC treatment; however, more than 50% delayed DAA initiation at least 3 months and 5%–10% delayed initiation more than 1 year. In patients with HCC listed for liver transplantation, only 5% of providers reported routinely treating patients with DAAs while on the waiting list, with most (53%) treating HCV post-transplant or on a case-by-case basis (42%).

Physicians (MDs and DOs) seemed less likely than APPs to treat patients with HCC undergoing palliative therapies; the difference did not reach statistical significance for patients undergoing transarterial chemoembolization (55.7% vs 62.2%; $P = .32$) but was significantly lower in patients undergoing systemic therapy (68.4% vs 83.1%; $P = .01$). Providers were also more likely to recommend DAAs in patients receiving systemic therapy if they reported fearing potential legal liability for untreated patients who experience hepatic decompensation (65.4% vs 52.1%; $P = .03$). There was no significant variation in use or timing of DAAs in any clinical vignettes based on institution type (transplant center vs other), region, or provider experience (number of patients treated with HCV or HCC).

Discussion

To the best of our knowledge, this study represents the first nationally representative survey assessing hepatology provider attitudes and practice patterns regarding DAA use in patients with HCC. Although there was variation in provider beliefs regarding HCC recurrence risk after DAA therapy, we found that most still believed DAAs are beneficial and likely reduce mortality in patients with complete response to HCC treatment. Accordingly, nearly all providers reported recommending DAA therapy in patients with early HCC undergoing curative treatment; however, fewer providers recommended DAA therapy in those with intermediate- or advanced-stage HCC undergoing palliative therapies.

In contrast to the strong data showing reduced risk of incident de novo HCC after DAA therapy,[7–9] there are conflicting data about HCC recurrence risk after DAA therapy in patients with a history of HCC. Although data from a multicenter cohort in North America suggested no difference in recurrence risk between DAA-treated and untreated patients,[11] most studies share similar notable limitations: retrospective study design, heterogeneity of tumor burden and treatment leading to complete response, potential for misclassification of complete response, and ascertainment bias for recurrence given lack of a surveillance protocol. Therefore, there is a lack of consensus among professional society guidance statements regarding timing of DAA therapy in patients with a history of HCC. The American Association for the Study of Liver Diseases practice guidance recommends DAA therapy after 3–6 months if no evidence of recurrence,[16] whereas an American Gastroenterological Association clinical practice update highlights a lack of sufficient data to determine if there is increased or decreased recurrence risk,[17] and the European Association for the Study of the Liver guidelines state that it remains unclear if DAA therapy increases recurrence but advises caution in this population.[18] This is reflected in the variation in perceived risk of HCC recurrence after DAA therapy among providers in our survey. However,

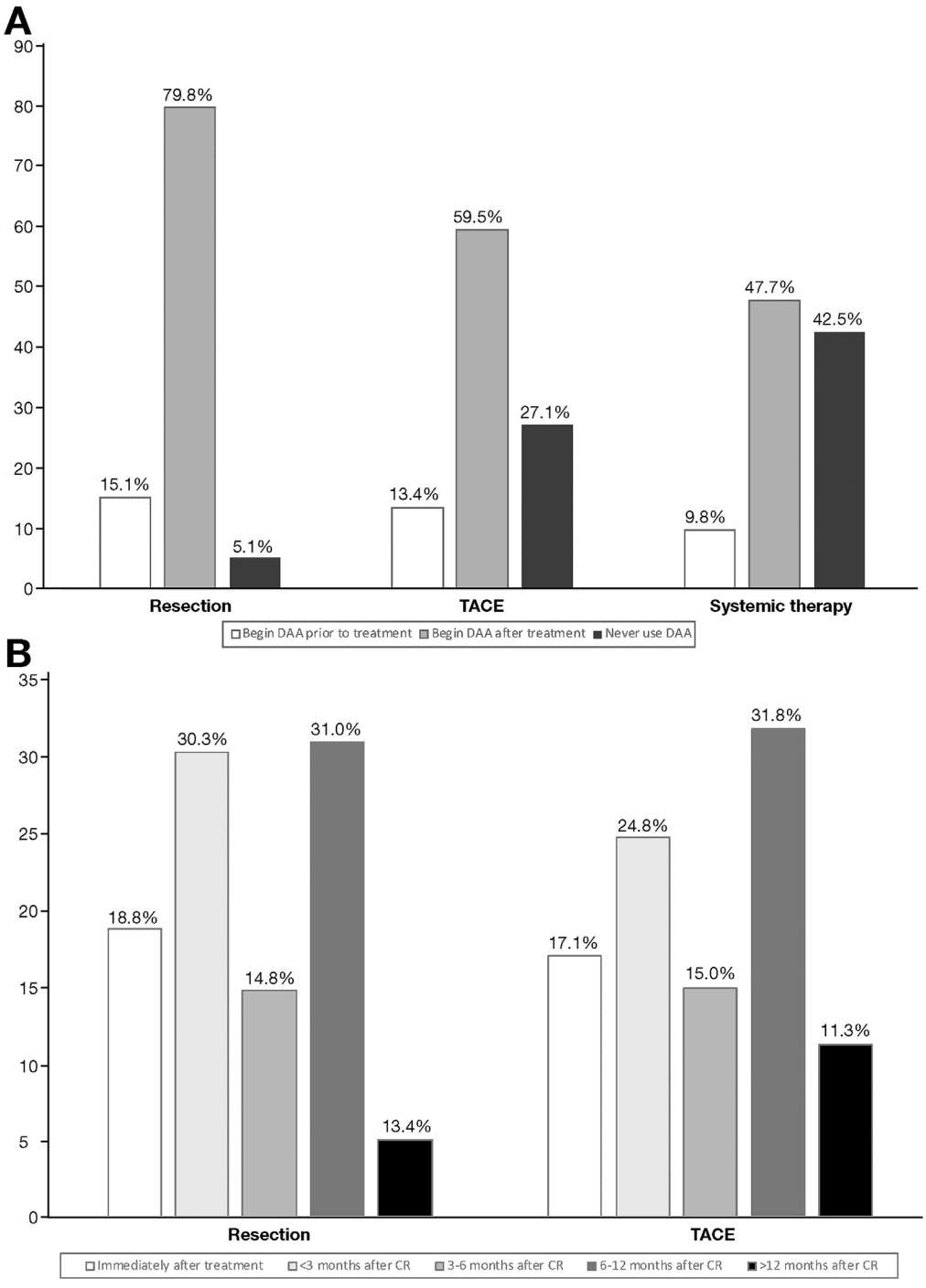

Figure 2. (*A*) Provider practice patterns for DAA treatment in patients with HCC, according to HCC treatment. (*B*) Provider practice patterns for timing of DAA treatment in patients with HCC, according to HCC treatment. CR, complete response; TACE, transarterial chemoembolization.

most providers still believed that DAA therapy would be of overall benefit in patients with HCC. This may be caused, in part, by beliefs that DAAs have a favorable side effect profile or by strong patient preference for viral eradication. Independent of recurrence risk, DAA therapy may improve liver dysfunction and thereby reduce mortality. In fact, hepatic decompensation, not HCC recurrence, is the major driver of mortality in patients with a history of HCC who achieved complete response.[19] Recent data suggest DAAs may reduce hepatic decompensation and improve overall survival among patients with early stage HCC who achieved complete response from resection or ablation.[20] These evolving data suggest that patients with confirmed HCC complete response likely benefit from DAA therapy, although further data with larger sample sizes and more heterogeneous tumor burden are needed to confirm the potential benefit of DAA therapy against the competing risk of liver-related mortality on overall survival.

Provider recommendations for DAA therapy differed by HCC stage and treatment type, with providers being less likely to recommend DAAs in advanced patients with HCC undergoing palliative treatments than in early stage patients undergoing curative therapy. This variation is

Table 4. Timing of DAA Therapy Initiation in Patients With HCC, Stratified by HCC Treatment (n = 279)

Provider practice	N (%)
Timing of DAA initiation in patient with BCLC stage A HCC undergoing surgical resection	
Shortly after resection (before imaging showing CR)	52 (18.8)
<3 mo after CR	84 (30.3)
3–6 mo after CR	41 (14.8)
6–12 mo after CR	86 (31.1)
>12 mo after CR	14 (5.0)
Timing of DAA in patient with BCLC stage B HCC undergoing TACE	
Shortly after TACE (before imaging showing CR)	47 (17.2)
<3 mo after CR	68 (24.8)
3–6 mo after CR	41 (15.0)
6–12 mo after CR	87 (31.7)
>12 mo after CR	31 (11.3)
Timing of DAA in patient with BCLC stage C HCC undergoing systemic therapy	
Begin DAA at time of initiating systemic therapy	27 (9.8)
Start DAA if partial response	34 (12.4)
Start DAA if complete response	78 (28.4)
Would start DAA if develops liver dysfunction, even if active HCC	19 (6.9)
Would never start DAA	117 (42.5)
Timing of DAA therapy in liver transplant candidate with HCC	
Routinely treat pretransplant on waitlist	15 (5.5)
Case-by-case basis	115 (42.0)
Routinely treat with DAA within 3 mo post-transplant	118 (43.0)
Routinely defer DAA >6 mo post-transplant	26 (9.5)

BCLC, Barcelona Clinic Liver Cancer; CR, complete response; DAA, direct-acting antiviral; HCC, hepatocellular carcinoma; TACE, transarterial chemoembolization.

presumably driven by the perceived likelihood of achieving a complete response to HCC therapy and the competing risk of HCC-related mortality in patients with more advanced HCC. However, it is possible that DAA therapy in patients with intermediate- or advanced-stage HCC may still be beneficial as expected survival for these patients continues to improve. For example, the median survival for Child Pugh A patients with intermediate stage HCC is approaching 3 years,[21,22] whereas median survival for advanced-stage patients with HCC is also improving with new systemic options in first- and second-line settings.[23,24] Prior small studies have suggested patients with HCC who have achieved SVR have improved prognosis compared with those with active viremia.[25] The reported variation in practice observed may also have been driven by prior reports of lower SVR rates in patients with active HCC.[12,13] In fact, nearly two-thirds of providers raised this concern in patients with active HCC. The American Association for the Study of Liver Diseases practice guidance for HCV therapy recommends consideration of DAA therapy in patients with expected survival exceeding 1 year, raising the question if this should be considered in patients with intermediate and advanced HCC.[26] As we aim for HCV elimination in all populations, this remains 1 of the few subgroups in whom the benefit of DAA treatment remains unclear.

We observed variation in timing of DAA initiation for all HCC treatment modalities, with some providers treating HCV shortly after HCC complete response and others deferring for several months. We did not find any factor associated with timing of DAA therapy, including a lack of association with provider type, years in practice, or geographic region; this variation may reflect provider knowledge and attitudes that were not included in our survey. There are conflicting data about the importance of DAA timing when considering HCC recurrence risk. Some studies have reported increased recurrence risk with early DAA treatment after HCC complete response when compared with deferred DAA treatment; however, this finding has not been replicated in subsequent studies.[10,11] An American Gastroenterological Association clinical practice update recommends deferring DAA therapy for 4–6 months following HCC treatment based on the importance of confirming complete response rather than a concern about increasing HCC recurrence risk.[17] Given the imperfect sensitivity of imaging to detect small HCC lesions and the nonurgent nature of HCV therapy, this seems like a reasonable approach for timing of DAA therapy after HCC complete response.

The important consideration of DAA timing in the context of liver transplantation may have influenced provider responses to the survey. More than half of the providers reported their practice is to routinely delay HCV treatment until the post-transplant period in patients with HCC (who may be undergoing locoregional therapy). This strategy allows for expansion of the donor pool by increasing use of organs from HCV-positive donors, in light of data showing excellent graft and overall survival.[27] This may have produced variation in practice patterns for the patient undergoing locoregional therapy in the second clinical vignette. Although our intent was to present a patient beyond Milan Criteria, some respondents may have deferred HCV therapy with downstaging and transplantation in mind.

Lastly, our study addressed patterns of HCC surveillance after DAA treatment and subsequent SVR. Although risk of incident HCC is reduced following HCV cure, it is not zero and a proportion of patients will still develop HCC.[28] Thus, continued surveillance is recommended in all patients with HCV cirrhosis even after SVR. Almost all providers in our study reported continuing surveillance with imaging $\pm$ α-fetoprotein every 6 months in patients with cirrhosis. Interestingly, 95% also reported performing surveillance in at least some patients with F3 fibrosis after SVR, with more than 60% performing surveillance in all F3 patients. Kanwal et al[9] demonstrated the risk of HCC is very low ($\sim$0.1%) in patients without cirrhosis except for those with Fib-4 >3.25 (indicating advanced fibrosis), where the annual risk approaches 1%, calling into question the benefit and cost-effectiveness of surveillance in patients with F3 fibrosis after SVR.[29] Notably, some patients labeled as having F3 fibrosis may be misclassified and truly have cirrhosis, suggesting surveillance may be needed in selected

patients. Predictive models may be useful to identify patients with F3 fibrosis at highest risk of HCC after SVR who could benefit from HCC surveillance.[30]

Strengths of this study include its large sample size and high response rate; however, we acknowledge that our study has limitations. First, the survey was distributed using a convenience sample of tertiary academic centers, with >98% having multidisciplinary tumor boards, which may limit generalizability to other practice settings, including community practices, safety-net health systems, and Veterans Affairs hospitals. However, we attempted to mitigate this concern by sampling sites from various US regions and including different provider types (MD/DOs and APPs). Second, the survey was performed and reflects practice patterns in the United States, which may differ from approaches in Europe and Asia. Third, nonhepatology providers involved in HCV treatment, including infectious disease and internal medicine providers, were not included in our sampling frame. Fourth, our results may be limited by response bias, in which providers report how they should practice rather than their actual practice; and nonresponse bias, in which providers who feel more comfortable managing HCV and HCC may be more likely to respond. Fifth, decisions and timing of HCV and HCC treatment are often considered in the context of transplant candidacy, which was not explicitly addressed in some cases and may have influenced provider responses. Similarly, other details that were not explicitly addressed may have impacted providers' interpretation of the clinical vignettes, and thereby explain some observed variation in provider responses. Sixth, we did not address patient preferences (regarding HCV treatment, HCC treatment, and/or transplantation), which play an important role in shared decision-making. Finally, the previously discussed limitations highlight the complexity of decisions about timing of HCV treatment in patients with HCC, thus all potential management options may not have been available for some questions.

In conclusion, in this nationwide survey study of hepatology providers, we found variation in attitudes and practice patterns regarding the use of DAAs in patients with HCC. Our findings highlight a need for high-quality data characterizing the risks and benefits of DAA therapy in patients with a history of HCC after complete response and those with active HCC. These data can inform guideline recommendations to help improve and standardize clinical practice for patients with HCV and HCC.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2019.07.042.

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Conflicts of interest
These authors disclose the following: Ponni Perumalswami has received grant support for research from Gilead. Naim Alkhouri is on speaker's bureau for Gilead, Exelixisi, Eisai, AbbVie, Salix, Intercept, Dova, Shionogi, and Alexion; served on advisory boards for Pfizer, Gilead, Intercept, Eisai, Exelixis, Dova, Shionogi, and Centurion; and received research funding from Gilead, Allergan, Intercept, Genfit, Cirius, Madrigal, Enyo, Inventiva, Hanmi, Novartis, BMS, and Enanta. Neehar Parikh serves as a consultant to Exelixis and Bristol-Myers Squibb; has served on advisory boards for Eisai, Exelixis, Wako, and Bayer; and received research funding from Bayer and Target Pharmasolutions. Neil Mehta has received research funding from Wako Diagnostics. Reena Salgia is on speaker's bureau for Bayer; and has served on advisory boards for Bayer, Eisai, and Exelixis. Laura Kulik is on speaker's bureau for Eisai, Gilead, and Dova; and serves as an advisory board member for BMS, Eisai, Bayer, and Exelixis. James Hanje is on speaker's bureau for Salix and Intercept; and served on advisory boards for Gilead. Anjana Pillai serves as a consultant and is on speaker's bureau for Eisai and BTG. Robert Wong is on the speaker's bureau, served as consultant and on advisory boards, and has received research funding from Gilead; has received research funding from Abbvie; and was on the speaker's bureau for Bayer. Shaun Chandna has served on an advisory board for Dova Pharmaceuticals; has received sponsored travel for research support from Genfit and Covance; and is on the speaker's bureau for Focus Medical Communications, LLC. Catherine Frenette is on speaker's bureaus for Bayer, Bristol Meyers Squibb, Gilead, Merck, Abbvie, and Eisai; served on advisory boards for Gilead, Eisai, and Wako; served as a consultant for Bayer and Gilead; and received research funding from Bayer. Sanjaya Satapathy has received research support from Gilead and Bayer; and has served on advisory boards or as a consultant for Abbvie and Gilead. Parvez Mantry is on speaker's bureaus and served on advisory boards for Gilead, Abbvie, Bayer, BMS, Eisai, Merck, and BTG; and has received research funding from Gilead and Sirtex. Binu John receives research support from Eisai, Bristol Meyers Squibb, Bayer, Exact Sciences, and Varian; and has served on advisory boards for Gilead and Eisai. Michael Leise has received research funding from Abbvie. Nayan Patel has served on advisory boards for Gilead. Z. Gordon Jiang has served as a consultant to Boehringer Ingelheim. Amit Singal was on speaker's bureau for Gilead, Bayer, and Bristol Meyers Squibb; has served on advisory boards for Gilead, Abbvie, Bayer, Eisai, Bristol Meyers Squibb, Wako Diagnostics, and Exact Sciences; serves as a consultant to Bayer, Eisai, Exelixis, Roche, Exact Sciences, and Glycotest; and has received research funding from Gilead and Abbvie. The remaining authors disclose no conflicts.

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