Clinical Observations in Hepatology

Challenges in Treatment of Hepatitis C among Patients with Hepatocellular Carcinoma

Behnam Saberi[1], Alia S. Dadabhai[1], Christine M. Durand[2], Benjamin Philosophe[3], Andrew M. Cameron[3], Mark S. Sulkowski[2], Ahmet Gurakar[1]

[1]The Johns Hopkins University School of Medicine, Division of Gastroenterology and Hepatology, Baltimore, MD, United States
[2]The Johns Hopkins University School of Medicine, Division of Infectious Disease, Baltimore, MD, United States
[3]The Johns Hopkins University, Department of Transplant Surgery, Baltimore, MD, United States

Conflict of interest:

Behnam Saberi: None

Christine M. Durand: Received research grants and served on advisory boards for Gilead, Merck and BMS.

Alia S. Dadabhai: None

Benjamin Philosophe: None

Andrew M. Cameron: None

Mark S. Sulkowski: Research grants and personal fees from AbbVie, personal fees from Cocrystal, research grants and personal fees from Gilead, research grants and personal fees from Janssen, research grants and personal fees from Merck, and personal fees from Trek.

Ahmet Gurakar: Served on advisory Board for Gilead and BMS**.**

Funding used for this work: None

Corresponding author:

Behnam Saberi, MD

Section of Gastroenterology/Hepatology

1830 E Monument St., Room 423, Baltimore, Maryland, 21205, USA

Phone: 410-550-0790, **Fax:** 410-550-2962, **E-mail:** saberi.behnam@jhmi.edu

Keywords: Hepatitis C virus (HCV); Direct-Acting Antiviral (DAA); Sustained Virologic Response; Liver Transplantation.

Patients with hepatitis C virus (HCV) and hepatocellular carcinoma (HCC) present the unique challenge of when to treat their hepatitis C. In a group of 21 patients with HCV/HCC, we investigated the response to Direct-Acting Antiviral (DAA) drugs prior to receiving a deceased donor liver transplant (LT). Subjects whose HCC was diagnosed on imaging either before or during HCV treatment were included. Seven of the 21 patients (33.3%) relapsed following treatment with various DAA regimens (Table 1A, Table 1S). Of these seven patients, four were infected with HCV genotype 1A, one genotype 2, and two with genotype 3. In the relapsers, the DAA regimens used were: two with Ledipasvir/Sofosbuvir, one with Simeprevir and Sofosbuvir, and four with Sofosbuvir and Ribavirin (Table 1A). Subsequently, all of the seven relapsers were transplanted and their explant pathology was carefully reviewed. Six of the seven patients had received loco-regional therapy prior to LT and one had no evidence of viable tumor on the explant. One of the seven had microvascular invasion on explant (Table 2A, Table 2S). Liver transplants were performed between 2-12 months after the end of treatment with DAAs (Figure 1).

Discussion:

After the development of DAAs, the treatment of HCV has been revolutionized.(1) The first-generation NS3/4A protease inhibitors were approved by the FDA in 2011 which required the use of Ribavirin and Interferon. Subsequently, second-generation NS3/4A, NS5A, and NS5B inhibitors were approved which allowed Interferon and Ribavirin sparing regimens.(1) Multiple clinical trials have demonstrated the efficacy of different DAA regimens in the treatment of patients with HCV with SVR rates higher than 90%.(2) Although the existence of cirrhosis and prior treatment experience is integrated into the guidelines, the presence of HCC does not require a change in the duration or type of treatment at the present time.(2)

A controversial aspect of managing patients with HCV/HCC in the era of DAAs is the timing of HCV treatment: before or after LT. Although pre-LT DAA treatment of HCV/HCC patients, is an attractive option, there is a potentially negative impact on patient outcomes specifically in procurement regions with a high volume of HCV positive donors. In other words, treatment of HCV prior to transplant may lead to an increase in wait time on the transplant list(3) and longer wait times can result in progression of the existing tumors and/or development of new

tumors with an increase in dropout rates and death. Therefore, prioritizing the management of HCC rather than the hepatitis C in this particular setting should be considered.

One major finding in our series, was the 33% SVR rates which was significantly lower than expected pre-transplant SVR.(4) Our proposed explanation for the lower cure rates in HCC patients may be related to poor penetration of Sofosbuvir drug metabolites into the tumor, as HCC blood supply is from the branches of hepatic artery rather than the portal venous system.

From this small series of HCV/HCC patients who relapsed after 12-24 weeks of therapy with various DAAs while awaiting LT, we propose that "waiting to treat" in high HCV donor regions may be advantageous. Our study is limited by small size and heterogeneous patient population. Lower SVR rates can be partly explained by including patients with decompensated cirrhosis, genotype 3, and/or using inadequate regimens: Sofosbuvir/Ribavirin.(1, 2)

CONCLUSION: The actual pre-LT SVR rates in patients with HCV and HCC should be investigated in larger, multicenter trials to further characterize the appropriate type and duration of treatment needed to achieve SVR. HCC patients may require longer duration of HCV treatment, if treatment is given prior to liver transplantation. The timing of treatment, before or after LT, in patients with HCV/HCC should be further explored. It is critical to determine if pre-LT HCV treatment affects the LT wait time or patient outcomes, particularly in areas with high percentages of HCV positive donors.

References:

1. Saxena V, Terrault N. Current Management of Hepatitis C Virus: Regimens for Peri-Liver Transplant Patients. Clin Liver Dis 2015;19:669-688, vi.
2. Alqahtani S, Sulkowski M. Current and Evolving Treatments of Genotype 1 Hepatitis C Virus. Gastroenterol Clin North Am 2015;44:825-843.
3. Ofosu A, Durand CM, Saberi B, Alqahtani S, Ucbilek E, Belden M, Cameron AM, et al. Implications of Treating Hepatitis C Virus Infection Among Patients Awaiting Cadaveric Liver Transplant: A Single-Center Experience. Exp Clin Transplant 2015;13 Suppl 3:7-10.
4. Kowdley KV, Gordon SC, Reddy KR, Rossaro L, Bernstein DE, Lawitz E, Shiffman ML, et al. Ledipasvir and sofosbuvir for 8 or 12 weeks for chronic HCV without cirrhosis. N Engl J Med 2014;370:1879-1888.

HEP-16-2287

Table 1A.

	Age/Sex	Genotype	Child-Turcotte-Pugh class	Biological MELD score	Treatment experienced	Baseline HCV RNA (IU/L)	DAA regimen	Ribavirin	Duration of therapy (In weeks)	4 week RNA (IU/L)	8 week RNA (IU/L)	EOT RNA (IU/L)	Time relapse diagnosed after EOT (In weeks)	HCV RNA at relapse (IU/L)	Time to LT after relapse (In days)
	54/F	1A	A	7	No	1,900,000	Ledipasvir/ Sofosbuvir	No	12	30	UD	UD	4	720,010	310
	58/F	1A	A	6	No	2,290,000	Ledipasvir/ Sofosbuvir	No	12	UD	UD	UD	8	24,000	Relapse diagnosed the day following LT*
	68/M	2	A	8	No	124,000	Sofosbuvir	Yes	12	18	UD	UD	12	163,530	121
	69/M	3	B	11	Yes	219,390	Sofosbuvir	Yes	24	UD	UD	UD	8	127,000	260
	50/M	1A	C	15	Yes	11,430,000	Simeprevir/ Sofosbuvir	No	16	310	UD	UD	8	1,946,844	410
	62/M	1A	A	7	Yes	4,061,230	Sofosbuvir	Yes	24	D	UD	UD	4	3,737,680	62
	47/M	3	C	24	No	79,800	Sofosbuvir	Yes	24	UD	UD	UD	8	306,000	49

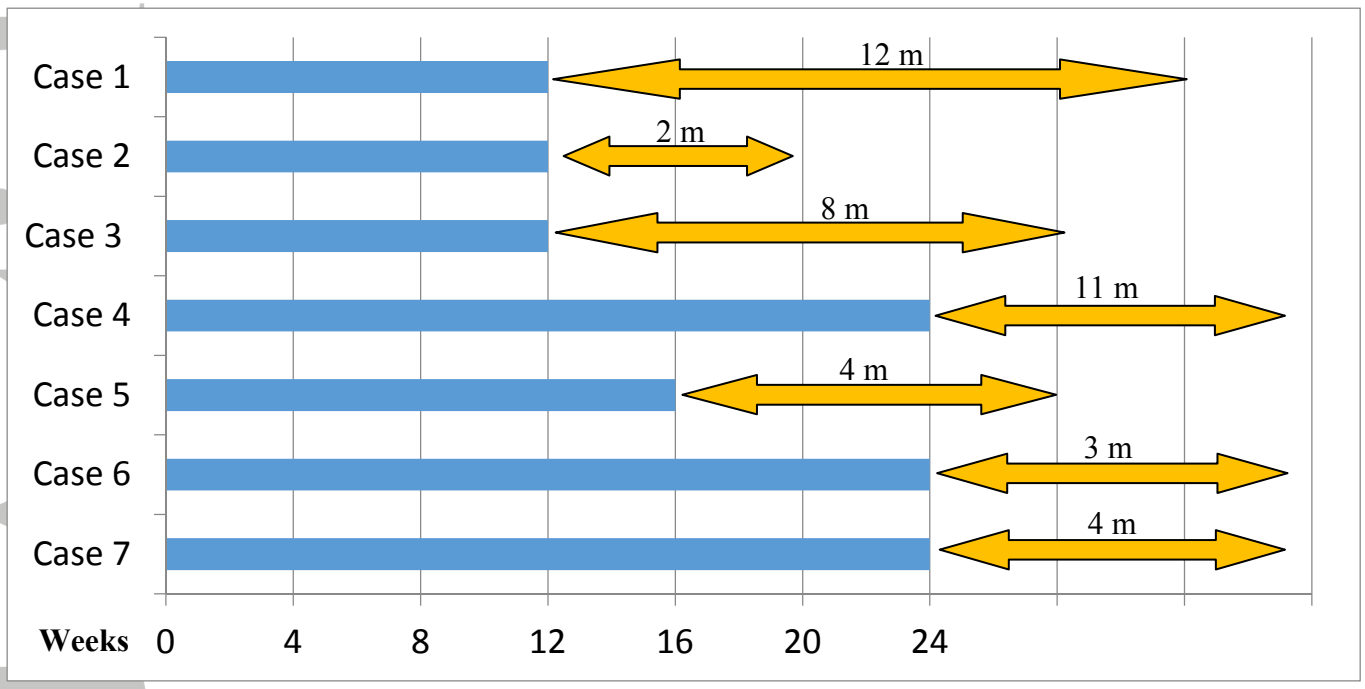
HEP-16-2287
Saberi et al.

Table 1B.

	Number of HCC lesions	TACE	Viable tumor	MVI	Tumor Differentiation
1	1	Yes	Yes	No	Moderate
2	5	Yes	Yes	Yes	Moderate
3	2	Yes	Yes	No	Well
4	3	Yes	Yes	No	Moderate
5	1	Yes	Yes	No	Moderate
6	2	Yes	No	No	-
7	2	No	Yes	No	Poor

HEP-16-2287
Saberi et al.

Figure 1.



HEP-16-2287
Saberi et al.

Figure legends

Table 1A. Characteristics of 7 DAA-treated patients with HCV/HCC who relapsed. All patients underwent deceased donor liver transplantation. M = Male; F = Female; HCV = Hepatitis C virus; HCC = Hepatocellular carcinoma; DAA = Direct-acting antiviral; LT= Liver transplant; EOT = End of treatment; UD = Undetectable; D = Detectable with low level viremia; MELD = Model for End- stage Liver Disease.

*Patient 2, underwent liver transplant 8 weeks after starting treatment with DAA. One day following transplant, patient was diagnosed with HCV relapse.

Table 1B. Explant characteristics of HCC in 7 DAA-treated patients with HCV/HCC who relapsed. HCV = Hepatitis C virus; HCC = Hepatocellular carcinoma; DAA = Direct-acting antiviral; TACE = Transarterial chemoembolization; MVI= Microvascular invasion.

Figure 1. Timing of HCV treatment and liver transplant. Duration of treatment with DAAs in 7 HCV/HCC patients is shown in blue bars. The timing of liver transplant relative to the end of treatment, is shown in yellow arrows. Point 0 illustrates the time when DAA was started. m = month; HCV = Hepatitis C virus; HCC = Hepatocellular carcinoma; DAA = Direct-acting antiviral.

HEP-16-2287
Saberi et al.

Table 1 Supplementary.

Case	Age/Sex	Genotype	Child-Turcotte-Pugh class	Biological MELD score	Treatment experienced	Baseline HCV RNA (IU/L)	DAA regimen	Ribavirin	Duration of therapy (In weeks)	4 week RNA (IU/L)	EOT RNA (IU/L)	Time to LT after EOT (In days)
	60/M	1A	A	7	Yes	3,090,000	Ledipasvir/ Sofosbuvir	No	24	78	UD	397
	55/M	1A	A	8	No	2,828,800	Ledipasvir/ Sofosbuvir	No	12	UD	UD	295
	64/M	1A	B	14	Yes	10,700	Ledipasvir/ Sofosbuvir	No	24	UD	UD	153
	47/M	1	B	10	No	3,157,860	Ledipasvir/ Sofosbuvir	No	12	UD	UD	279
	61/M	1A	B	16	Yes	836,000	Ledipasvir/ Sofosbuvir	No	24	UD	UD	147
	68/M	1A	C	19	No	565,000	Ledipasvir/ Sofosbuvir	No	12	UD	UD	220
	65/M	1A	A	9	No	570,000	Ledipasvir/ Sofosbuvir	No	12	UD	UD	86
	58/M	1B	A	8	Yes	1,692,590	Simeprevir/ Sofosbuvir	No	24	UD	UD	166
	66/M	1A	B	9	No	205,000	Simeprevir/ Sofosbuvir	No	24	UD	UD	14
	69/M	3A	A	10	No	4,260,000	Sofosbuvir	Yes	32	UD	UD	3
	63/M	2	A	8	No	116,480	Sofosbuvir	Yes	12	UD	UD	103
	62/M	1A	A	7	Yes	2,350,000	Simeprevir/ Sofosbuvir	No	16	UD	UD	31
	54/M	1A	B	17	Yes	3,710,000	Sofosbuvir*	Yes	24	UD	UD	Completed the treatment 1 week post LT*
	69/F	4	B	11	No	1,390,000	Simeprevir/ Sofosbuvir**	Yes	12	UD	UD	Completed the treatment 4 weeks post LT**

Table 1S. Characteristics of 14 DAA-treated patients with HCV/HCC who achieved SVR. All patients underwent deceased donor liver transplantation. M = Male; F = Female; DAA = Direct-acting antiviral; LT= Liver transplant; EOT = End of treatment; UD = Undetectable; SVR = Sustained virologic response; MELD = Model for End- stage Liver Disease.

*Patient 13 was initially started on Simeprevir, plus Sofosbuvir, and Ribavirin. Due to the rise in bilirubin, Simeprevir was stopped after 4 weeks. Patient completed the rest of the 24 weeks of treatment, with Sofosbuvir and Ribavirin, ending one week following liver transplant and achieved SVR. The HCV RNA was negative for 107 days prior to LT.

HEP-16-2287
Saberi et al.

**Patient 14 was initially started on Sofosbuvir and Ribavirin. After four weeks, due to severe anemia, the Ribavirin was stopped and Simeprevir was initiated. Four weeks later, patient underwent LT. Simeprevir and Sofosbuvir was continued until four weeks following LT, and patient subsequently achieved SVR. The HCV RNA was negative for 28 days prior to LT.

Table 2 Supplementary.

	Number of HCC lesions	TACE	Viable tumor	MVI	Tumor Differentiation
1	1	Yes	No	No	-
2	1	Yes	Yes	No	Moderate
3	1	Yes	Yes	No	Moderate
4	2	Yes	Yes	No	Well
5	1	Yes	Yes	No	Well
6	2	Yes	Yes	No	Moderate
7	2	Yes	Yes	No	Moderate
8	2	Yes	Yes	Yes	Moderate
9	3	Yes	Yes	Yes	Poor
10	1	Yes	Yes	Yes	Poor
11	3	Yes	Yes	No	Poor
12	2	Yes	Yes	No	Moderate
13	2	Yes	Yes	Indeterminate	Moderate
14	1	Yes	Yes	No	Moderate

Table 2S. Explant characteristics of HCC in 14 DAA-treated patients with HCV/HCC who achieved SVR. HCC = Hepatocellular carcinoma; HCV = Hepatitis C virus; SVR = Sustained virologic response; DAA = Direct-acting antiviral; TACE = Transarterial chemoembolization; MVI= Microvascular invasion.