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MODERN APPROACH FOR ANTI VIRAL TREATMENT USING CLINICAL APPLICATIONS

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Abstract. – OBJECTIVE: The effects of anti-Hepatitis C virus (HCV) direct-acting antiviral (DAA) medication on survival in patients with advanced hepatocellular carcinoma (HCC) and concurrent HCV infection treated with sorafenib were studied using real-world data.

SUMMARY OF MATERIALS AND METHODS: Patients with advanced HCC and concurrent HCV infection who received first targeted treatment (sorafenib) in 2018-2019 were identified using the Indian National Health Insurance Research Database and the Registration System for Patients Treated with Oral Hepatitis C Antivirals. The Clinical survival analysis was used to compare the overall survival (OS) of the DAA and non-DAA groups. To eliminate confusion between the DAA and non-DAA groups, propensity score matching was done at a ratio of 1:4.

RESULTS: The research comprised 1,684 patients with HCC and concurrent HCV infection who took sorafenib for the first time in 2018-2019 (122 DAA users and 1,562 non-DAA users). In a Clinical survival study, advanced HCC patients who utilized DAAs had a longer OS than those who did not. DAA patients had a median survival duration of 20.7 months, whereas non-DAA patients had a median survival time of 12.5 months. Following propensity matching, the results revealed a substantial difference in OS between the DAA and non-DAA groups.

CONCLUSIONS: A study using large data from Indian's National Health Insurance Research Database found that advanced HCC patients on sorafenib benefitted from DAAs as an HCV infection therapy. Patients who had their HCV infection cured had a better prognosis.

Introduction

Hepatitis C virus (HCV) infection affects 2% to 4% of the world's population. In Indian, between 400,000 and 700,000 persons are infected with HCV, with 3 percent to 4% of the population carrying the virus1. HCV infection is the leading cause of chronic hepatitis-induced cirrhosis and hepatocellular carcinoma (HCC), with 70-80% of acute HCV-infected individuals acquiring chronic HCV infection. The absence of pharmacological therapy will result in the slow development of liver fibrosis, which will result in cirrhosis in 20% of HCV-infected individuals within 20 years2. Every year, people with cirrhosis have a 1 percent to 4% chance of generating HCC cells and a 4% to 5% chance of having hepatic decompensation3. Direct-acting antiviral medications (DAAs), also known as new all-oral anti-HCV medicines, herald a new era in HCV treatment4. In the past, only around 10% of patients who received traditional interferon (IFN)-based therapy achieved sustained virologic response (SVR), which indicated that the infection had been

successfully cured4. Since 2000, the use of long-acting interferons (pegylated IFNs) in combination with the oral antiviral ribavirin has significantly boosted the cure rate to >50%. (4) In 2013, the introduction of all-oral IFN-free regimens resulted in a cure rate of >90% in patients with varying degrees of liver fibrosis4. SVR is linked to lower hepatic decompensation, transplant, and liver-related mortality, as well as overall mortality5. DAAs are also highly safe, which is beneficial to many HCV-infected patients, particularly those who are at high risk of progressive hepatic insufficiency or HCC5. Antiviral drugs are still not considered a standard of care in the treatment of HCV-related HCC. In patients with HCV-related HCC6, SVR after surgery and local therapy improves recurrence-free survival and overall survival (OS). Individuals with HCV infection and concomitant HCC had a lower post-DAA treatment SVR than HCV-infected patients without HCC (regardless of cirrhosis severity), but those who underwent curative HCC management had a better response to DAA treatment7, with patients with active HCC having a worse response than those with inactive HCC8. DAA treatment may potentially cause immunological alterations, such as a reduction in the cytotoxicity of natural killer (NK) cells and mucosal-associated invariant T (MAIT) cells against cancer cells. Furthermore, even after HCV eradication, the increased frequency of regulatory T cells (Tregs) persists, suppressing the immune response and preventing cancer cell eradication9,10. Some prior studies9,10 have shown the quick development of new-onset HCC or early recurrence of HCC following DAA therapy, whereas others have found that effective DAA treatment of HCV infection does not raise the risk of new-onset HCC5. The consequences of effective DAA therapy of HCV infection on the return of early HCC in individuals who had curative HCC treatment, on the other hand, are still being debated. There are currently no limits on the use of DAA medication to prevent hepatic disease progression in HCV-induced cirrhotic patients who have received surgical resection or ablation therapy for HCC5. HCV-induced cirrhotic individuals who have been cured of HCV infection should have their livers imaged and their alpha-fetoprotein (AFP) levels tested twice a year to check for HCC5 recurrence. Relevant data suggests that, for individuals with mid-stage and advanced HCC (BCLC stage B or C), treating cancer-related symptoms and hepatic decompensation should take precedence over improving hepatic function by DAA therapy11. Whether patients are diagnosed with BCLC-B/C owing to liver dysfunction caused exclusively by HCV infection, they should be evaluated individually to see if DAA therapy should be prioritized; they should also be fully educated about the advantages and dangers of DAA treatment11. Existing data do not support the regular use of DAAs for patients whose BCLC stage is assessed based on cancer-related symptoms or tumor load and stays unaltered owing to the administration of DAAs, since there is a lack of evidence proving the therapeutic benefits of DAAs in this patient population11. According to a recent study12, HCV-infected cancer patients should get antiviral medication unless they have one of the following contraindications: ch member states of the World Health Organization pledged to eliminate viral hepatitis by 2030 due to uncontrollable cancer, comorbidities, and a life expectancy of ch member states of the World Health Organization pledged to eliminate viral hepatitis by 2030 due to uncontrollable cancer, comorbidities, and a life expectancy of ch member states of the World The Indian Hepatitis C Policy Guideline 2018–202517 was created by Indian. The purpose of this guideline is to treat 250,000 HCV-infected individuals with innovative oral medicines between 2018 and 2025, with the goal of eliminating HCV altogether by 202517. Following the approval of the first DAA on September 16, 2015, additional DAAs have acquired marketing permission in Indian, and from January 24, 2017, innovative DAAs have been listed as reimbursement items of Indian's National Health Insurance (NHI) program. The National Health Insurance Administration (NHIA) has also launched the NHI Payment Implementation Plan for Novel All-Oral Hepatitis C Drugs and established the Registration System for Patients Treated with Oral Hepatitis C Antivirals to effectively manage and track patients' treatment status17 in order to optimize the allocation of limited resources and achieve maximum benefits. However, there are few trials and real-world evidence on DAAs' therapeutic efficacy in HCV-infected patients with advanced HCC. In this research, we looked at real-world data to see how anti-HCV DAA medication affected survival in patients with advanced HCC and concurrent HCV infection who were taking sorafenib.

Materials and Methods

Retrospective observational research was carried out. We identified patients with advanced HCC and concurrent HCV infection who received first targeted treatment (sorafenib) between 2018 and 2019 using the Indian National Health

Insurance Research Database and the Registration System for Patients Treated with Oral Hepatitis C Antivirals. The usage of DAAs among these patients was looked into, and the patients were followed up on until December 31, 2020, to see how they fared. Patients who had taken DAAs before starting sorafenib treatment were not included in the study. Since August 2012, the NHIA has covered the expenses of sorafenib therapy in adult patients who have failed or are unsuitable for local treatment for metastatic or unresectable advanced HCC (Child–Pugh class A) who have failed or are unsuitable for local treatment18. As a result, the usage of sorafenib treatment is considered a key criterion in identifying individuals with advanced HCC. The usage of DAAs was determined by whether any of the following drugs had been used: daclatasvir plus asunaprevir, glecaprevir/pibrentasvir, ombitasvir/paritaprevir/ritonavir plus dasabuvir, elbasvir/grazoprevir, ledipasvir/sofosbuvir, sofosbuvir, sofosbuvir/velpatasvirthe outcome variable was OS, with the index date being the date of sorafenib treatment beginning and the end date being the date of death or observation endpoint (December 31, 2020). The patient's sex, age, comorbidities in the year before to starting sorafenib (hepatitis B virus [HBV] infection, cirrhosis, or metastatic malignancy), and treatment received were all considered control factors (radiofrequency tumor ablation, liver tumor resection, chemotherapy, or liver trans-arterial chemo-embolization [TACE]). The current research looked at SVR to see whether there were any variations in the survival of individuals who had their HCV infection cured after using DAAs. At 12 weeks after finishing anti-HCV medication, SVR was defined as the absence of detectable HCV RNA in the blood or a fall in serum HCV RNA levels to undetectable levels (i.e., below the lower limit of detection of certain testing techniques). SAS software was used to process and analyze the data. The t-test and the 2 test were used to assess differences in continuous and categorical variables independently. The Kaplan–Meier survival analysis was used to compare the OS of the DAA and non-DAA groups. The log-rank test was used to examine the differences between the two groups after survival curves were drawn. Propensity score matching was utilized at a ratio of 1:4 to produce generally comparable distributions of control variables in the DAA and non-DAA groups, reducing study bias caused by confounders and simulating randomization. Patients' sex, age, comorbidities, and treatment status in the previous year; the number of months between the time of initial diagnosis of HCV infection and the time of initial diagnosis of HCC; and the number of months between the time of initial diagnosis of HCC and the time of initiation of sorafenib treatment were among the variables used in the matching. Logistic regression was used to compute the likelihood for each patient in the DAA group, and four patients in the nonDAA group were matched based on comparable probability values. Finally, the matching findings were subjected to a survival analysis. TMU's Joint Institutional Review Board approved the procedure. Given the retroactive nature of this investigation, informed consent was not necessary.

Results

This analysis comprised 1,684 patients with HCC and concurrent HCV infection who started sorafenib for the first time between 2018 and 2019; 122 (7.2%) were DAA users, whereas 1,562 (92.8%) were non-DAA users. The average age of the research participants was 68.5 years (standard deviation [SD]=10.0). There were 1,172 males (69.6%) and 511 women among the total number of patients (30.3 percent). A total of 407 individuals (24.2%) had previously been infected with HBV, 1,051 (62.4%) had cirrhosis, and 905 (53.7%) had been diagnosed with metastatic cancer (i.e., stage 4 cancer). Radio frequency tumor ablation was utilized in 290 patients (17.2%), liver tumor resection was used in 161 patients (9.6%), chemotherapy was used in 326 patients (19.4%), and liver TACE was used in 326 patients (19.4%). (931 patients, 55.3 percent). The mean time between HCV diagnosis and HCC diagnosis was 12.5 months (SD=29.0, median=0 months, first quartile [Q1]=0.5 months, and third quartile [Q3]=33.15 months). The average time between first HCC diagnosis and sorafenib therapy commencement was 24.6 months (SD=26.6, median=12.2 months, Q1=1.6 months, and Q3=45.7 months). Furthermore, 1,378 individuals (81.8%) died at the conclusion of the study period. Before matching, the DAA and non-DAA groups had substantially different distributions of HBV infection history, liver tumor resection, chemotherapy, and the time between HCC diagnosis and sorafenib usage. After matching, there were no significant differences in any of the control variables. The baseline characteristics of the research participants are shown in Table I. The Kaplan–Meier survival study revealed that advanced HCC patients who took DAAs had a longer overall survival than those who did not. The DAA and non-DAA groups had median survival durations of 20.7

months (SD=1.1 months, median=20.8 months) and 12.5 months (SD=0.3 months, median=8.3 months). The DAA group had survival rates of 86.9%, 70.5 percent, and 37.9% at six months, twelve months, and twenty-four months, respectively, whereas the non-DAA group had survival rates of 59.1%, 38.2%, and 18.9%, respectively. The difference in survival rates between the two groups was significant, according to the results of the comparison using the log-rank test.

Discussion

In this research, we discovered that sorafenib-treated advanced HCC patients who received DAA treatment had a better prognosis than those who did not (median survival after sorafenib initiation: 19.7 months vs. 6.7 months, p0.001). Patients in the DAA group who had their HCV infection effectively treated had a superior survival rate (median survival=23.9 months), according to our findings. Although there are no published survival assessments of HCV-positive advanced HCC patients in Western nations who received sorafenib and DAAs at the same time, our findings are comparable to those of previous studies completed in Japan and Indian. Kawaoka et al16 included 58 patients with advanced HCC (Child–Pugh class A illness) who had received DAAs prior to sorafenib treatment at a single medical institution in Japan, of whom 27 were cured of HCV infection (SVR group) and 31 were not cured (non-SVR group)16. The SVR group had a longer PPS and OS than the non-SVR group16, according to the findings. As a result, the researchers asserted that HCV eradication enhanced hepatic function, resulting in the preservation of hepatic function and the adoption of additional treatment approaches after sorafenib failure16. Another study compared the differences in OS (time from the start of sorafenib treatment to death or loss to follow-up) and PFS between patients with detectable HCV RNA and those with undetectable HCV RNA19 in 168 HCV-positive advanced HCC patients with limited life expectancy who had been treated with sorafenib. The median OS for all patients was 232 days19, according to the findings. The undetectable HCV RNA group (32 of 45 patients were cured after receiving interferon treatment) had a longer OS (median=351 days) and a longer time to progression from an A–B Child–Pugh score, but there was no meaningful difference in PFS19. Five of the 51 patients who had detectable HCV RNA at the time of sorafenib beginning also got DAA treatment. Despite the limited number of instances, all five patients had improved OS and PFS, indicating that DAAs had beneficial benefits19. The findings of this trial show that HCV eradication before or after sorafenib therapy is favorable to preserving liver function and extending survival19. Some studies20-22 that looked at the impact of DAAs on survival in patients with varying stages of HCC found findings that were comparable to those found in advanced HCC patients using stratified analyses of DAA usage. This data implies that advanced HCC patients who have been cleared of HCV infection after DAA therapy have a higher survival rate20-22. In a multinational, multi-center retrospective observational analysis including 1,389 HCC patients with concurrent HCV infection fromnine clinical institutions in four countries, researchers found that Individuals cured of HCV infection before being diagnosed with HCC (post-SVR HCC: 301 patients) had improved clinical and tumor features, as well as a longer OS18 across four countries (the United States, Japan, Korea, and Indian). Patients who tested positive for HCV after HCC diagnosis (viremic HCC: 1,088 patients) exhibited superior survival rates than those who were cured of HCV infection (239 patients), which were higher than the post-SVR HCC group18.

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Table I. Baseline characteristics of the study participants.

		Before matching			After matching		
	Total	DAA group	Non-DAA group		DAA group	Non-DAA group	
	n (%)	n (%)	n (%)	p	n (%)	n (%)	p
No. of patients	1684	122	1562		98	362	
Follow-up status				<.001			<.001
Survived	306 (18.2)	37 (30.3)	269 (17.2)		27 (27.6)	45 (12.4)	
Died	1378 (81.8)	85 (69.7)	1293(82.8)		71 (72.4)	317 (87.6)	
Age (M, SD)	68.5 (10.0)	67.0 (9.1)	68.6 (10.1)	0.090	68.1 (9.2)	66.9 (10.2)	0.301
Sex				0.539			0.810
Male	1172 (69.6)	88 (72.1)	1084(69.4)		70 (71.4)	263 (72.7)	
Female	511 (30.3)	34 (27.9)	477 (30.5)		28 (28.6)	99 (27.3)	
Comorbidities*							
HBV infection	407 (24.2)	14 (11.5)	393 (25.2)	<.001	13 (13.3)	65 (18.0)	0.272
Cirrhosis	1051 (62.4)	74 (60.7)	977 (62.5)	0.699	58 (59.2)	219 (60.5)	0.814
Metastatic cancer	905 (53.7)	74 (60.7)	831 (53.2)	0.104	58 (59.2)	218 (60.2)	0.853
HCC treatment*							
Radiofrequency tumor ablation	290 (17.2)	14 (11.5)	276 (17.7)	0.077	10 (10.2)	53 (14.6)	0.257
Liver tumor resection	161 (9.6)	18 (14.8)	143 (9.2)	0.045	13 (13.3)	45 (12.4)	0.835
Chemotherapy	326 (19.4)	33 (27)	293 (18.8)	0.026	21 (21.4)	95 (26.2)	0.330
Liver TACE	931 (55.3)	71 (58.2)	860 (55.1)	0.523	54 (55.1)	212 (58.6)	0.538
Interval between HCV infection and HCC (months) (M, SD)	12.5 (29.0)	12.6 (24.0)	12.4 (29.3)	0.929	13.7 (25.4)	12.6 (27.0)	0.714
Interval between HCC and sorafenib use (months) (M, SD)	24.6 (26.6)	14.9 (21.1)	25.4 (26.8)	<.001	15.2 (21.1)	15.4 (21.3)	0.931
SVR				<.001			<.001
Uncured	1568 (93.1)	7 (5.7)	1561(99.9)		7 (7.1)	361 (99.7)	
Cured	86 (5.1)	86 (70.5)	0 (0)		66 (67.3)	0 (0)	
Could not be determined	30 (1.8)	29 (23.8)	1 (0.1)		25 (25.5)	1 (0.3)	

Table II. Results of the survival analysis of the unmatched and propensity scored-matched patients.

Group	Unmatched		Matched (1:4)	
	DAA group	Non-DAA group	DAA group	Non-DAA group
No. of patients	122	1562	98	362
Survival time (months)				
Mean (SD)	20.7 (1.1)	12.5 (0.3)	20.2 (1.2)	11.1 (0.6)
75th percentile (Q3)	34.9	18.9	34.9	15.3
Median (Q2)	20.8	8.3	**19.7**	**6.7**
25th percentile (Q1)	10.2	3.4	9.9	3.1
Survival rate				
6 months	86.9%	59.1%	86.7%	53.6%
12 months	70.5%	38.2%	68.4%	33.2%
24 months	37.9%	18.9%	35.6%	15.5%
Log-rank *p*	<.0001		<.0001	

Direct-acting antiviral agent (DAA).

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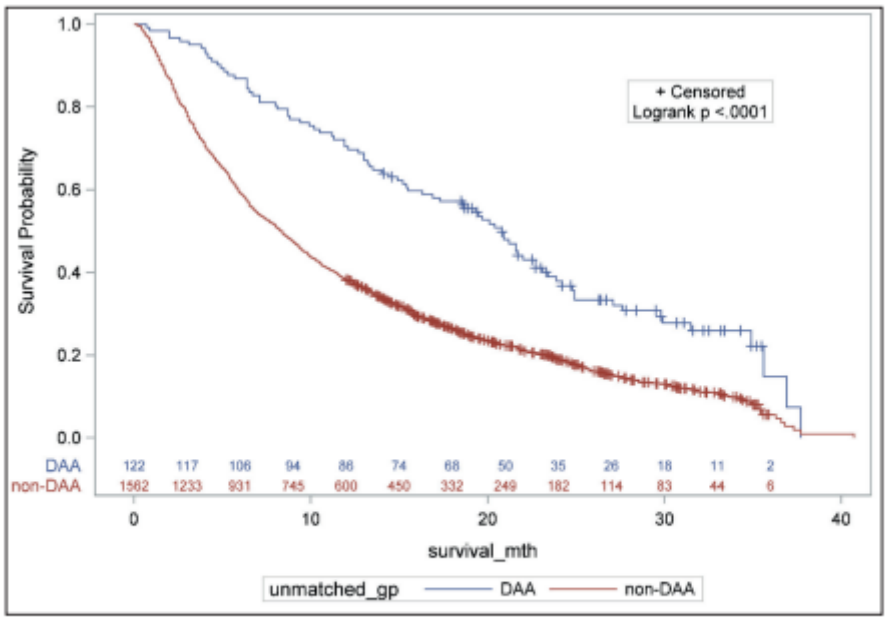

Figure 1. Kaplan-Meier survival analysis between the DAA and non-DAA groups in 2018-2019 (unmatched, total N=1684). DAA, direct-acting antiviral.

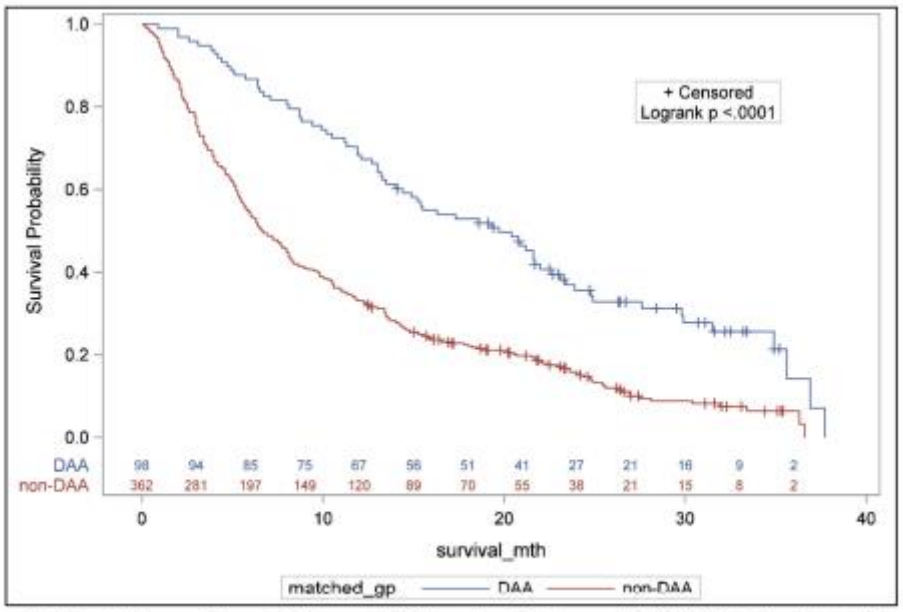

Figure 2. Kaplan-Meier survival analysis between the DAA and non-DAA groups in 2018-2019 (matched 1:4, total N=460). DAA, direct-acting antiviral.

The 849 individuals who were still infected with HCV had the lowest survival rates18. Patients with BCLC stage B and BCLC stage C/D illness who had been cured of HCV infection during HCC diagnosis (SVR) had substantially superior OS than non-cured patients and those diagnosed with HCC after HCV eradication18, according to a stratified analysis based on HCC stage. Rinaldi et al23 performed an updated literature analysis to better understand the influence of DAA SVR on HCC risk, as well as risk variables and epigenetics23. SVR had no effect on HCC incidence in the short to medium term, but lowered the risk of HCC in the medium to long term, according to the researchers. DAAs have not been shown to have a direct function in the development of HCC23. The hypothesised decrease in immune surveillance in response to fast HCV clearance and alterations in the cytokine pattern impacting early carcinogenesis has yet to be confirmed23. Rinaldi et al24 looked at early HCC incidence and risk variables in HCV-infected people who were taking DAAs. Their findings revealed that early HCC incidence is more commonly linked to Sofosbuvir-based

treatment without Ribavirin, which does seem to protect against HCC onset24. As a result, careful monitoring is necessary, particularly in regimens that include Sofosbuvir without Ribavirin24. Patients with BCLC stages B and C disease had SVR rates of 97.1 percent (68/70) and 77.8 percent (7/9), respectively, in a previous study20 looking at the effects of SVR after DAA treatment on outcomes in 199 patients with various stages of HCC and concomitant HCV infection from two medical institutions in Indian (Taipei Veterans General Hospital and Chiayi Christian Hospital). The findings also revealed that a high SVR was the most important predictor of relapse-free survival and overall survival, and that DAA usage did not enhance the risk of HCC recurrence or progression20. Another study22 was undertaken in Indian at a single medical institution.

Table III. Results of the stratified analysis of the DAA group based on HCV infection cure status.

Subgroup	Uncured, i.e., residual virus detected	Cured	Premature treatment termination	Untested after treatment completion
No. of patients	7	86	13	16
Follow-up status				
Died	4	52	13	16
Reached endpoint (survived)	3	34	0	0
Survival time (months)				
Mean (SD)	20.3 (2.7)	25.4 (1.1)	5.5 (1.1)	6.5 (0.8)
75th percentile (Q3)	.	35.6	7.1	7.9
Median (Q2)	24.9	23.9	5.7	5
25th percentile (Q1)	13	18.6	2	4.15
Survival rate				
6 months	100.0%	100.0%	46.2%	43.8%
12 months	85.7%	89.5%	7.7%	12.5%
24 months	57.1%	49.5%	0.0%	0.0%
Log-rank *p*	<.0001			
Degree of fibrosis (N, %)				
F0	0 (0)	1 (1.2)	0 (0)	0 (0)
F1	0 (0)	1 (1.2)	1 (7.7)	1 (6.3)
F2	0 (0)	6 (6.98)	1 (7.69)	0 (0)
F3	1 (14.29)	27 (31.4)	5 (38.46)	5 (31.25)
F4	6 (85.71)	51 (59.3)	6 (46.15)	10 (62.5)
Cirrhosis (N, %)				
No	2 (28.6)	33 (38.4)	4 (30.8)	9 (56.3)
Yes	5 (71.4)	53 (61.6)	9 (69.2)	7 (43.8)
Interval between sorafenib use and DAA use (months) (M, SD)	3.6 (4.3)	4.8 (4.5)	3.5 (3.6)	2.0 (2.8)
Interval between DAA use and follow-up endpoint (months) (M, SD)	16.8 (8)	17.5(7.5)	2.0 (1.4)	4.5 (1.2)

Direct-acting antiviral agent (DAA); Hepatitis C virus (HCV).

Individuals cured of HCV infection before being diagnosed with HCC (post-SVR HCC: 301 patients) had improved clinical and tumor features, as well as a longer OS18 across four countries (the United States, Japan, Korea, and Indian). Patients who tested positive for HCV after HCC diagnosis (viremic HCC: 1,088 patients) exhibited superior survival rates than those who were cured of HCV infection (239 patients), which were higher than the post-SVR HCC group18. The 849 individuals who were still infected with HCV had the lowest survival rates18. Patients with BCLC stage B and BCLC stage C/D illness who had been cured of HCV infection during HCC diagnosis (SVR) had substantially superior OS than non-cured patients and those diagnosed with HCC after HCV eradication18, according to a stratified analysis based on HCC stage. Rinaldi et al23 performed an updated literature analysis to better understand the influence of DAA SVR on HCC risk, as well as risk variables and epigenetics23. SVR had no effect on HCC incidence in the short to medium term, but lowered the risk of HCC in the medium to long term, according to the researchers. DAAs have not been shown to have a direct function in the development of HCC23. The hypothesised decrease in immune surveillance in response to fast HCV clearance and alterations in the cytokine pattern impacting early carcinogenesis has yet to be confirmed23. Rinaldi et al24 looked at early HCC incidence and risk variables in HCV-infected people who were taking DAAs. Their findings revealed that early HCC incidence is more commonly linked to Sofosbuvir-based treatment without Ribavirin, which does seem to protect against HCC onset24. As a result, careful monitoring is necessary, particularly in regimens that include Sofosbuvir without Ribavirin24. Patients with BCLC stages B and C disease had SVR rates of 97.1 percent (68/70) and 77.8 percent (7/9), respectively, in a previous

study20 looking at the effects of SVR after DAA treatment on outcomes in 199 patients with various stages of HCC and concomitant HCV infection from two medical institutions in Indian (Taipei Veterans General Hospital and Chiayi Christian Hospital). The findings also revealed that a high SVR was the most important predictor of relapse-free survival and overall survival, and that DAA usage did not enhance the risk of HCC recurrence or progression20. Another study22 was undertaken in Indian at a single medical institution.

Conclusion

By analysing large data from Indian's NHI database, the effects of DAA therapy on the survival of patients with advanced HCC and concurrent HCV infection were studied. The findings showed that advanced HCC patients who got sorafenib benefited from the use of DAAs to treat HCV infection, with patients who had their HCV infection treated having a greater overall survival.

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