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Hepatitis C Virus - Related Hepatocellular Carcinoma in the Era of Direct - Acting Antiviral Agents

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Abstract

Context: The emergence of direct - acting antiviral agents (DAAs) with high sustained virological responses (SVR) is an epoch - making revolution. However, the value of antiviral agents in the field of hepatitis C - related hepatocellular carcinoma (HCC) is not clear. Further, the risk of tumor occurrence or recurrence following an antiviral regimen is not yet reached a consensus.

Evidence Acquisition: All scientific evidence was collected through a systematic review of studies discussing DAA regimen and hepatitis C-related HCC, in PubMed, EMBASE, and Web of Science. The relevant articles were obtained and reviewed carefully before working on the paper.

Results: The current review study aimed at discussing recent studies on hepatitis C - related HCC in the era of DAAs, including application of DAAs in the field of treatment of hepatitis C virus (HCV), efficacy of DAAs on HCV-associated HCC, and the effect of DAAs on occurrence and recurrence of HCC.

Conclusions: It was shown that DAAs had a relatively poor therapeutic effect on HCV patients with HCC, based on the current studies. After analyzing the existing data, the conclusion cannot yet be reached that DAA treatment influences the risk of HCC in patients with HCV infection.

Keywords: Direct - Acting Antiviral Agents, Hepatocellular Carcinoma, Hepatitis C Virus, Review

1. Context

According to the latest World Health Organization (WHO) statistics, 71 million people worldwide have chronic hepatitis C (CHC) (1), and approximately 60% - 80% of the patients with hepatitis C are in a state of continuous viral infection (2). Due to the biological characteristics of HCV, host immune - function differences, and other factors, HCV has a higher risk of cirrhosis (3) and hepatocellular carcinoma HCC (4). Studies showed that HCV infection causes a 15- to 20 - fold increase in the risk of developing HCC. The incidence of HCC is 3% - 5% per year in the HCV population with cirrhosis (5). Among HCV - infected individuals, Asian patients (primarily Southeast Asian) are older, have lower body mass index (BMI) values, and are more likely to be in advanced liver diseases with a greater chance of progression to HCC in the event of cirrhosis (6, 7). In the United States, approximately 50% - 60% of the patients with HCC have chronic infection of HCV (8, 9), whereas in China, HCC is mainly caused by infection of hepatitis B virus (HBV). Authors' previous study showed that seroprevalence of anti - HCV antibodies was approximately 16% (10). The mortality of HCC in the United States increased by 72% from 2003 to 2012 (11), and the main cause of carcinoma was long-term HCV infection (12-14). At present, the number of patients with viral hepatitis - related HCC in China is large; however, with the popularization of HBV vaccine and the success of mother - infant blockage, the composition of the etiology of HCC changes. The field of HCV - related HCC is of increasing concern, and antiviral treatments are the key to HCV - related liver diseases.

Since 2011, oral direct - acting antiviral regimens gradually replaced the traditional interferon (IFN) and had a cure rate as high as 90% or more (15). Prior to this, due to the poor efficacy and contraindications of IFN, anti - HCV treatment in patients with HCC was relatively rare. Recently, with the wide - spread use of direct - acting antiviral agents (DAAs), more and more patients with HCC infected with HCV are trying to continue antiviral therapy with DAAs after receiving standard anti - tumor therapy. However, the efficacy needs to be fully evaluated. In addi-

tion, there are different opinions about the effect of DAAs on the incidence of HCC in patients with CHC, especially on the recurrence rate of HCC in patients successfully cured. A considerable number of scholars believe that DAAs may increase the occurrence or recurrence of HCV - related HCC, which is a potentially significant clinical problem. Therefore, the current review study aimed at focusing on the following two research hotspots: the antiviral efficacy of DAAs in CHC patients with HCC and the effect of DAAs on the incidence or recurrence of HCV-related HCC.

2. Evidence Acquisition

To gather data and information for the current review, authors systematically searched for relevant articles that described the relationship between DAAs and HCV - related HCC, in PubMed, EMBASE, Web of Science with date limitation (within 10 years). Free text words and MeSH terms were used along with Boolean operators such as the following keywords in the search: hepatitis C, viral hepatitis, viral liver disease, hepatocellular carcinoma, HCV - associated HCC, hepatitis C - related HCC, direct - acting antiviral agents, DAA, etc. A review of the title and abstract of studies identified in the search was performed to exclude studies that did not answer the research question of interest. Full texts of the rest of the articles were then examined to determine whether they contained the sought data. After browsing the full texts, clinical studies were included in the current review study except for the ones with the following conditions: 1) non - English articles; 2) studies on liver diseases other than hepatitis C; 3) HCC that occurred not based on HCV; 4) studies on antiviral treatments other than DAAs.

3. Results

3.1. Application of DAAs in the Field of HCV Treatment

The pharmacological mechanism of traditional IFN is that IFN binds its receptors to the cell membrane, turning on a signaling pathway that activates transcription factors called IFN regulatory factors, which induce the host to produce IFN - stimulated gene (ISG) products and inhibit the virus. Proteases, helicases, and RNA polymerases are non - structural proteins that are targets for DAAs. However, due to the rapid development of resistance mutations in HCV to a single drug, monotherapy cannot be used to treat HCV.

Effective antiviral therapy allows patients to achieve sustained virological responses (SVR), which can reduce the incidence of HCV - related complications, liver transplantation, and even death (16, 17). The partial response (PR) regimen of peginterferon - α (PegIFN - α) combined with ribavirin (RBV) used to be the standard of care for HCV (18). The SVR rate of patients in China with HCV treated by the PR regimen ranged 44% to 83% (19). However, the standard course of this regimen was relatively long, had significant side effects, and was better to treat non - genotype 1 HCV; whereas, genotype 1b infection was predominant in Chinese patients (20). In addition, antiviral therapy with IFN had a high recurrence rate (approximately 30%) (21). When non - responders with genotype 1 were re - administered a high-dose PR regimen, the SVR rate was less than 18% (22).

DAAs are small - molecule compounds for therapies targeting viral proteins in the life cycle of HCV. The first NS3/4A serine protease inhibitor was approved by the United States Food and Drug Administration (FDA) in 2011, and a total of 10 drugs were approved from 2011 to 2016. Daclatasvir (DCV) combined with asunaprevir (ASV) was the first DAA regimen approved by China in 2017 to treat genotype 1b CHC (non - cirrhosis or compensated cirrhosis) among adults. The emergence of DAAs is a revolutionary breakthrough that effectively eradicates HCV in a short period of time, typically 12 weeks, with a high SVR rate (7, 23-25). Further, DCV in combination with sofosbuvir (SOF) improved the efficacy of monotherapy; it was also highly recommended by the European Association for the Study of The Liver (EASL) in 2015 to treat all genotypes of HCV infection.

3.2. Efficacy of DAAs on HCV - associated HCC

It is demonstrated that treatment with IFN in CHC patients with HCC brought about survival benefit (26-28), presumably because IFN inhibited the pro - inflammatory and carcinogenic effects of HCV through anti - inflammatory, anti - angiogenic, and antiviral functions. However, a lower SVR rate and certain side effects limited the use of IFN, and patients with decompensated cirrhosis could not use IFN for antiviral therapy (21). Nowadays, the approval of oral DAAs regimens extends the clinical treatment of HCV to HCV - related cirrhosis with HCC. However, until now, the data on the efficacy of DAAs in patients with HCV - related HCC are limited. Over the past two years, related studies appeared in China and other countries.

In the area of DAA therapy for HCV - associated HCC with or without cirrhosis, Chang et al., published a cohort of Asian - American patients (N = 110) in 2017 showing that an overall SVR12, defined as having no detectable HCV RNA upon polymerase chain reaction (PCR) 12 weeks following the end of treatment, was as high as 93% after an IFN - free SOF - based regimen compared with only 82% in 17 patients with HCC (29). Coincidentally, in the study by Prenner et al., a total of 421 CHC patients with cirrhosis were identified, of whom 33% had active HCC or a history of HCC. The

team found that after DAA therapy, CHC patients without HCC had an SVR of 88% compared with 79% in the ones with HCC; the differences were statistically significant. Of the patients with HCC who did not achieve SVR, 93% had an active tumor. DAA therapy achieved a significant SVR rate in the presence of an inactive tumor or after removal of tumor, similar to the patients without HCC. After multivariate analysis, the primary predictor of failure for DAAs was the initial presence of active HCC (30).

Recent studies showed that the effect of DAA therapy on HCV - related HCC can be corrected by liver transplantation (LT). The report by Beste et al., published in the Journal of Hepatology supported this point of view. Of 17,487 HCV - treatment recipients, 624 had prior HCC, including 142 who underwent LT (HCC/LT) and 482 with no LT (HCC/NLT). The results showed that overall SVR was up to 91.9% in CHC patients without HCC and 93.4% in HCC/LT, but only 74.5% in HCC/NLT after DAA therapy. For different genotypes of HCV, efficacy of DAAs is different. In patients with HCC, the highest SVR (HCC/NLT 79.0% vs. HCC/LT 96.0%) was obtained for genotype 1 and the lowest for genotype 3 (HCC/NLT 47.0% vs. HCC/LT 88.9 %) (31, 32).

It is not yet clear why HCV - related HCC had lower SVR rates compared with CHC without HCC when the selected studies were analyzed. Presumably, the presence of a tumor induces the long - term inflammatory response, which leads to the disruption of normal liver structure and alters the microenvironment of cytokines and chemokines (33, 34); thus, affecting the process of the intrahepatic immune response. In addition, patients with HCC are mostly at the cirrhosis stage, and the burden of advanced liver disease increases the difficulty of antiviral therapy. By contrast, LT corrects disorders of liver function and removes potential tumor cells, thus achieving high SVR in patients with HCC after transplantation. Patients with LT generally have a strong desire for survival and good compliance; therefore, they may better comply with antiviral therapy (35, 36). Based on the current study results, it was demonstrated that DAAs had a relatively poor therapeutic effect on HCV - associated HCC.

3.3. Effect of DAAs on Occurrence and Recurrence of HCV - associated HCC

The availability of highly effective, oral antiviral regimens, which gradually replaced IFN - based antiviral therapies, changed the treatment options for patients with CHC. Most of these patients are fortunate enough to achieve virus clearance; however, clearance does not represent a cure for CHC - associated liver disease. In addition, studies showed that HCV RNA persists in the liver and peripheral blood mononuclear cells in some sustained viral responders (37). Patients with cirrhosis after HCV clearance still require comprehensive treatment to delay the progression and complications of cirrhosis. As a matter of fact, it can be observed that the benefits of virus removal increases patients' survival rate and avoids complications. For the clinical application of new DAAs, more time is needed to observe their safety and their correlation with the occurrence or recurrence of HCC. Initially, some scholars believed that the DAA therapy for patients with HCV infection can reduce the risk of HCC, but there were also many studies emphasizing the use of DAAs in patients with decompensated cirrhosis after viral clearance in which the occurrence or recurrence of liver cancer may increase, resulting in queries on such treatments (38). Previously, due to the immunostimulatory and anti - tumor effects of IFN, this phenomenon was never observed in IFN - based HCV treatment.

3.3.1. "De novo HCC" in DAA - treated Patients

Several studies discussed DAAs and de novo HCC, the individual study details are outlined in Table 1. An uncontrolled study from the United States followed the outcomes of 66 patients with cirrhosis who achieved an SVR using DAA therapy. Ravi et al., observed an occurrence of de novo HCC in about 9% of the patients during or within six months of DAA therapy (39). DAA therapy seemed to increase the de novo occurrence of HCC among patients with HCV - related cirrhosis (40). However, other studies showed opposite conclusion (41-43). For example, Li DK et al., performed a retrospective population - based cohort of 17,836 individuals; the results showed that DAA therapy was not associated with a higher risk of HCC in cirrhotics with CHC in the short - term (44). Ioannou et al., reported, after analyzing the association between SVR and HCC risk and between the type of antiviral regimen and HCC risk by the Cox proportional hazards, that DAA - induced SVR was associated with a 71% reduction in HCC risk, and treatment with DAAs was not associated with increased HCC risk compared with the treatment with IFN (45). Cheung et al., from Queen Mary University of London, found that nearly one - third of the newly detected liver cancers developed in patients occurred early, within three months of commencing DAA treatment, suggesting it as an event of cancers that were radiologically undetectable at treatment baseline rather than de novo development, in other words, rather than induced by drugs (46).

When these previously published studies were consulted, issues were as follows: smaller sample size, shorter follow - up period, and lack of controllability in retrospective cohort studies, which may bias the outcome. Recently, Ji et al., from the Beijing 302 Hospital of China presented a new prospective study at the 52nd EASL (the European Association for the Study of the Liver). A total of 1498 pa-

Table 1. Summary of Studies on HCC Occurrence after HCV Treatment with DAAs

Study	Country	Study Type	Patients[a], N	Age	Male (%)	Liver Cirrhosis (%)	DAA Regimen	SVR (%) for DAAs	Median Follow - up (Years)	HCC (%)	Risk of HCC
Ravi, 2017 (39)	America	Retrospective	66	60	62	100.0	SOF/LDV	92.0	0.5	9.1	High
Conti, 2016 (47)	Italy	Retrospective, Prospective	285	63	60	100.0	SOF/SMV/DCV /LDV/3D ± RBV	100.0	0.7	3.2	Unrelated
Rinaldi, 2016 (48)	Italy	Prospective	280	68	53	100.0	SOF/SIM/DCV /LDV/3D ± RBV	97.1	0.3	3.2	Unrelated
Li, 2017 (44)	America	Retrospective	5834	62	97	19.9	SOF/SMV/DCV /LDV/3D ± RBV	96.2	1.1	0.9	Unrelated
Cheung, 2016 (46)	UK	Prospective	406	54	—	100.0	SOF/DCV/LDV ± RBV	78.1	1.3	5.4	Unrelated
Zeng, 2016 (41)	China	Prospective	21	54	19	100.0	SOF/DCV ± RBV	95.2	1.3	0.0	Low
Nagaoki, 2017 (49)	Japan	Prospective	154	73	38	54.5[b]	DCV/ASV	—	1.9	4.5	Unrelated
Cardoso, 2016 (40)	Portugal	Retrospective	54	59	70	100.0	SOF/LDV	100.0	1.0	7.4	High
Kobayashi, 2017 (42)	Japan	Retrospective	77	63	44	29.9[b]	DCV/ASV/3D/ telaprevir	100.0	4.0	2.6	Low
Kanwal, 2017 (43)	America	Retrospective	22,500	62	97	39.0	SOF/SIM/DCV /LDV/3D	86.7	1.0	1.2	Unrelated
Ioannou, 2017 (45)	America	Retrospective	21948	61	97	23.8	SOF/SIM/DCV /LDV/3D	90.7	6.1	2	Unrelated

Abbreviations: 3D, 3 - drug combination paritaprevir/ritonavir/ombitasvir plus dasabuvir; ASV, asunaprevir; DCV, daclatasvir; LDV, ledipasvir; RBV, ribavirin; SIM, simprevir; SMV, simeprevir; SOF, sofosbuvir.
[a] DAA Treated.
[b] Percentage for severe fibrosis.

tients were enrolled in the study. After screening for exclusion criteria, 397 patients treated with IFN and 324 patients treated with DAAs were enrolled. The patients were followed for an average of 12 - 36 months. The incidence of HCC did not significantly increase in either group. The study, with the prominent features of a longer follow - up period and more patients aroused heated discussions. Other successively published prospective studies that included tumor occurrence also supported Dr. Ji's point of view. Nagaoki et al., after a relatively long observation period, showed that carcinoma development after HCV eradication was similar between the patients treated with the PR regimen and DAA therapy (49).

Since approved in 2011, it is believed that DAAs are still generally used for a short time; however, the occurrence of HCC is a long - term and potentially ongoing process. Changes at cellular or molecular levels may occur 1 - 2 years prior to an imaging diagnosis of cancer. After summarizing the main work throughout these researches, it should be clarified that DAA - treated groups were usually confined to the ones with failure of IFN treatment or contraindications for IFN administration such as decompensated liver cirrhosis. While initial liver diseases were more serious and risks of developing cirrhosis were higher in such population, they had a higher risk of HCC occurrence, possibly leading to bias of results that could interfere with discussions of the effects of DAAs on HCC. Therefore, as proven by previous studies, there is ample body of evidence now that the risk for de novo HCC development in successfully treated cirrhotic patients is not increased, when data are properly adjusted to the stage of disease.

3.3.2. "HCC Recurrence" in DAA - treated Patients

Although the risk of HCC after a DAA regimen is of great concern, some scholars considered that this risk is primar-

ily aimed at patients with a previous HCC (50). In other words, DAA may have an influence on tumor recurrence. Relevant studies are summarized in Table 2. Reig et al., published a retrospective cohort with small sample size (N = 58) (51); 58 patients with prior carcinoma meeting the inclusion criteria received DAAs. After a median follow - up of 5.7 months, three patients died and 16 developed radiologic tumor recurrence (27.6%). The data showed an unexpectedly high rate and pattern of tumor recurrence coinciding with HCV clearance. Other studies (52, 53), with similar results, held the shared view that patients receiving DAAs had a greater risk for the recurrence of HCC. Conti et al., also found that after DAA therapy, 17 of 59 (28.8%) patients had HCC recurrence, whereas only nine of 285 (3.16%) patients were diagnosed with HCC for the first time (47). Scholars emphasized on the issue that DAA therapy may increase the recurrence of tumors and speculated that in the process of eliminating HCV, DAAs may induce the tumor by changing the immune status of the host. It is well - known that CHC activates an intrahepatic immune response, leading to increased expression of ISGs and activation of natural killer cells, the most prevalent innate immune cell in the liver. After the DAA therapy, with the clearance of HCV followed by the retreat of immune surveillance, C - X - C motif chemokine (CXCL) 10, CXCL11 decreased, and vascular endothelial growth factor increased significantly, which supported tumor development (54), contributing to the proliferation of isolated tumor cells (55). Therefore, it is suggested that rapid changes to the immune surveillance system and/or anti - tumor response following DAA therapy could be a reason for the apparent increase in HCC recurrence.

Contrarily, the French National Agency for Research on AIDS (ANRS) collaborative study group analyzed individual data from three French prospective multicenter ANRS cohorts and concluded that there was currently no evidence to suggest that DAAs may increase the risk of HCC recurrence (57). A prospective multicenter study by Cabibbo et al., (58) and a retrospective cohort by Huang et al., (56) also showed the risk of HCC recurrence was not higher than that of observed in DAA - unexposed patients. Ikeda et al., even suggested that DAA therapy significantly decreased recurrence rate after adjustment with covariates of tumor multiplicity, alpha - fetoprotein (AFP) value, and prothrombin time on the basis of a multivariate analysis (59). Further, there was a significant decrease in AFP in patients with cirrhosis achieving a SVR with DAAs. Maybe AFP should be further studied as a screening modality for HCC in patients with HCV - related cirrhosis achieving SVR (63). To solve the inconsistency in the findings and increase the statistical power, a statistical analysis of a large collection of research results from individual studies could be more useful. A systematic review published in 2017 provided this summary. A total of 41 studies were included. In a meta - regression adjusting for study follow-up and age, DAA therapy was not associated with higher HCC incidence, and there was no evidence to show differences between DAA and IFN therapy on HCC occurrence or recurrence (64).

Combined with the current researches (48, 60-62), the conclusion that DAAs may increase the risk for early HCC recurrence still needs more large - scale data and prospective studies to confirm. Therefore, the relevant research in the future should consider the following: a large enough sample size, a long follow - up, a prospective study design, and the same baseline. Among them, the most important one is the consistency of disease background in all groups. Since the patients treated with DAAs may be different from the ones using IFN, controlled studies with sufficient sample size are necessary to shed light on this controversial issue. It is noteworthy that due to the current decreasing use of IFN, observational studies using IFN as a control group are no longer easy to conduct. Only the available data can be used as a control. Choosing HCV patients as a study population and ruling out the status of advanced liver disease may prevent the disease itself from affecting the results. Additionally, since withholding DAA therapy in patients with advanced liver disease and HCC may have negative consequences, including a higher risk of decompensation and death, studies on DAA regimen should consider the competing risks of death due to HCC recurrence and decompensated cirrhosis (56). The effects of DAAs on hepatocarcinogenesis, tumor progression, and metastasis should be further studied to fully explain these unexpected clinical observations.

4. Conclusions

With the advent of DAAs, viruses can be efficiently removed and SVR can be achieved in most patients. However, compared with acute HCV infection, DAAs are less effective when treating CHC patients with HCC. In addition, whether DAA could induce the occurrence or recurrence of HCC in the treatment of HCV is a controversy in China and other countries. After analyzing the existing studies, it cannot yet be concluded that DAA therapy influences the risk of HCV - related HCC, although some prospective studies with larger - scale data indicated that the incidence of HCC did not increase significantly after DAA therapy. Therefore, more prospective studies with homogeneous baseline are still needed to determine the impact of DAA on the occurrence or recurrence of HCC.

Table 2. Summary of Studies on HCC Recurrence after HCV Treatment with DAAs

Study	Country	Study Type	Patients[a], N	Age	Male (%)	DAA Regimen	SVR for DAAs (%)	Median Follow - up (Years)	HCC (%)	Risk of HCC
El Kassas, 2017 (53)	Egypt	Prospective	53	57	35	SOF/SIM/DCV /LDV ± RBV	77·4	1.3	37.7	High
Huang, 2018 (56)	America	Retrospective	62	63	46	-	98.4	2.6	47.0	Unrelated
Reig, 2016 (51)	Spain	Prospective	58	66	69	SOF/SMV/DCV/ LDV/3D ± RBV	91.4	0.5	27.6	High
Yang, 2016 (52)	America	Prospective	18	-	-	SOF/telaprevir, ± RBV ± IFN	-	-	27.8	High
Conti, 2016 (47)	Italy	Retrospective Prospective	59	65	68	SOF/SMV/DCV /LDV/3D ± RBV	89.8	0.7	24.6	High
Pol, 2016 (57)	France	Prospective	189	62	78	SOF/SMV/DCV /LDV/3D ± RBV±IFN	78.3	2.0	12.7	Unrelated
Pol, 2016 (57)	France	Prospective	314	61	82	SOF/SMV/DCV /LDV/3D± RBV ± IFN	80.0	1.0	2.2	low
Pol, 2016 (57)	France	Prospective	13	64	63	SOF/SMV/DCV /LDV/3D ± RBV±IFN	100.0	1.8	7.7	Unrelated
Cabibbo, 2017 (58)	Italy	Prospective	143	70	86	SOF/SIM/DCV /LDV/3D ± RBV	96.0	0.8	16.8	Unrelated
Ikeda, 2017 (59)	Japan	Retrospective	177	71	60	SOF /DCV /LDV /ASV/3D ± RBV	89.6	1.7	34.5	low
Minami, 2016 (60)	Japan	Retrospective	26	71	67	SOF /DCV /LDV /ASV ± RBV	84.6	1.3	30.8	Unrelated
Torres, 2016 (61)	America	Prospective	8	64	88	SOF/SIM/LDV /3D ± RBV	100.0	1.6	0	Unrelated
Zavaglia, 2016 (62)	Italy	Prospective	31	65	65	SOF/SIM/DCV /LDV/3D ± RBV	100.0	2.3	3.2	Unrelated
Rinaldi, 2016 (48)	Italy	Prospective	15	68	53	SOF/SIM/DCV/ LDV/3D ± RBV	100.0	0.3	6.7	Unrelated

Abbreviations: 3D, 3 - drug combination paritaprevir/ritonavir/ombitasvir plus dasabuvir; ASV, asunaprevir; DCV, daclatasvir; LDV, ledipasvir; RBV, ribavirin; SIM, simeprevir; SMV, simeprevir; SOF, sofosbuvir.
[a] DAA Treated.

Footnote

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