MINIREVIEWS

Impact of direct acting antivirals on occurrence and recurrence of hepatocellular carcinoma: Biologically plausible or an epiphenomenon?

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Abstract

Hepatocellular carcinoma (HCC) is a major cause of morbidity and mortality worldwide. Chronic hepatitis C virus infection (HCV) is the most common cause of HCC in many European countries, Japan and Pakistan. Introduction of the new direct acting antivirals (DAAs) has revolutionized the management of HCV worldwide, with high rates of sustained virologic response in patients who could not have tolerated the previous interferon based treatments. However, recently there have been reports raising caution about the long term effects of DAAs, particularly a possible increased risk of HCC. Therefore this review explores the current molecular studies as well as clinical data that investigate the impact of DAAs on occurrence and recurrence of HCC.

Key words: Hepatocellular carcinoma; Direct acting antivirals; Hepatitis C

Core tip: Our aim is to consolidate the existing literature as well as to identify whether there is a particular subset of the population in which this phenomenon was witnessed. The ground-breaking discovery of the new group of direct acting antiviral agents (DAAs) had led to a paradigm shift in the management of chronic hepatitis C (CHC). Wide variations have been observed in the studies assessing the long-term role of DAA based therapy on occurrence and recurrence of HCC. There is a need to differentiate weather the reported higher occurrence and recurrence rates are due to DAA or host and disease related factors and to identify subset of individuals particularly at risk. Also, future investigations should be directed towards

assessing the long-term effects of DAAs on group of patients that have not been studied thus far. Some important Centers in Europe and United States have been delaying antiviral treatment for 6 mo or more after the recent treatment for HCC. Hence, until more robust data is available, clinical practices should continue as per current guidelines in those patient groups who can benefit from DAA therapy with close surveillance of patients with advance fibrosis.

INTRODUCTION

The ground breaking discovery of the new group of direct acting antiviral agents (DAAs) had led to a paradigm shift in the management of chronic hepatitis C (CHC) which is the most common cause of hepatocellular carcinoma (HCC) in Japan, Pakistan, United States and many European countries[1,2]. With annual incidence of HCC ranging from 1% to 7% in patients with HCV related cirrhosis, (HCC) is a leading cause of morbidity and the second most common cause of cancer related deaths worldwide[3,4]. Besides contribution of several host and viral factors in the pathogenesis of disease progression, achieving sustained virologic response (SVR) has been found as the single most important factor in reducing HCV associated HCC incidence[5].

The novel DAAs not only provided a potent, oral alternative to injectable interferons, but also had a shorter duration of treatment, better efficacy with over 90% achievement of SVR and a more favorable side effect profile[6]. However, since 2016, concerns were raised regarding the effect of DAAs on progression to HCC[7]. In addition, their long-term benefits including impact on HCC have been questioned in the context of specific populations and subgroups which were not included in the landmark trials investigating DAA based therapy[3].

Therefore, this review aims to explore existing molecular studies as well as clinical observations in order to determine whether there is an association between the use of DAAs and the occurrence or recurrence of HCC among patients with HCV related liver disease. We also aim to evaluate whether there is a subset of the population in which this phenomenon has been observed.

DAA AND CARCINOGENESIS: BIOLOGICALLY PLAUSIBLE OR NOT?

The carcinogenesis of HCC is a chronic process with several steps that may serve as potential targets for drug therapy. Unlike the hepatitis B virus, HCV is an RNA virus which is unable to integrate into the host genome and thus it is unlikely to have direct carcinogenic activity[8]. While the mechanism of carcinogenesis due to HCV is not completely understood, observations from transgenic mice models suggest that liver cancer occurs because of rapid hepatocyte turnover, dysregulation of apoptosis and generation of reactive oxygen species, arising in the setting of a chronic inflammatory state induced by HCV[9,10]. This indirect mechanism of cirrhosis driven carcinogenesis is supported by clinical data which shows a greater risk of HCC with chronic HCV infection and worsening liver fibrosis[8].

One of the mechanisms proposed regarding the risk of DAAs towards development of HCC is that DAAs downregulate interferon genes, disrupting the innate immunosurveillance of the body[8]. In the chronic phase of HCV, an estimated 10^{12} virions are produced per day by infected hepatocytes[11]. These trigger an immune response mediated primarily by natural killer (NK) cells which release cytokines such as interferon (IFN)-γ. IFNs upregulate interferon stimulated genes which have an anti-proliferative response by prolonging all phases of the cell cycle and decreasing viral replication. When HCV infection becomes persistent, NK cells become dysfunctional due to continuous antigenic stimulation by the high load of virions, resulting in impaired production of IFNs[12]. In mice models, it was observed that decreased levels of IFN-γ independently control tumorigenesis[13]. Thus the downregulation of these genes in IFN free therapy could contribute to development of HCC.

Analysis of the peripheral blood mononuclear cells (PBMCs) of CHC patients treated with DAAs has shown that in comparison to healthy controls, these patients have attenuated activity of both NK cells and monocytes, reflected by a decreased level of inflammatory cytokines in patients who had achieved rapid virological response (RVR), *i.e.*, undetectable HCV RNA at the end of 4 wk of DAA treatment[14]. Natural Killer cell group 2D (NKG2D) is an activating receptor of immune responses which has been studied in the context of HCV associated HCC. It has been found that in HCV patients treated with IFN free DAA therapy, an on treatment decrease in the expression of NKG2D correlated to the early occurrence and recurrence of clinically evident HCC within the 6-mo surveillance period following treatment[15].

With DAA based therapy, HCV RNA becomes undetectable in days to weeks, a much more rapid response than that observed with IFN based regimens. It is hypothesized that rapid eradication of HCV and subsequent abrupt resolution of the chronic inflammatory state disrupts the natural immune response of the body, possibly favoring the proliferation of neoplastic cells[16]. Since clinical studies have shown no difference among different DAA regimens and development of HCC, it is hypothesized that if this effect does exist then it would have to be a class effect of the DAAs[17,18].

Table 1 Possible factors contributing to hepatocellular carcinoma after hepatitis C virus eradication by direct acting antivirals

Down regulation of *IFN* genes
Presence of fibrosis
Sudden disruption of chronic inflammatory state
Impaired immune response by NK cells
T cell dysfunction
Decreased microRNA-122

IFN: Interferon; NK: Natural killer.

An experimental study analyzing the soluble inflammatory milieu from plasma cells of cirrhotic HCV patients found that HCV specific CD8+ T cells failed to recover from the baseline after DAA therapy. These cells play a role in HCC surveillance; therefore, their reduced activity in IFN free therapy could potentially affect development of HCC[19]. Furthermore, serum levels of microRNA (miRNA) 122 were found to be reduced in DAA treated HCV patients after achieving SVR[20]. Previous evidence shows that miRNA-122, which is the most abundant miRNA in the liver, functions as a tumor suppressor against HCC[21]. Thus it is hypothesized that decreased miRNA-122 in DAA treated patients could contribute to an increased risk of HCC recurrence[22]. Table 1 summarizes the possible factors that could lead to HCC in DAA treated HCV patients.

DAA AND CARCINOGENESIS: REVIEW OF EXISTING EVIDENCE/DATA

Studies that observed increased incidence of HCC

While DAAs represented a major breakthrough in the treatment of CHC, one of the first reports questioning their long-term role in development of HCC came from Reig *et al*[8] in 2016. The authors retrospectively assessed a cohort of 58 patients who had a history of HCC secondary to HCV and had received different regimens of DAA based therapy. After a median follow up of 5.7 mo (range 0.4-14.6 mo), 16 out of their 58 patients (27.6%) showed radiographic evidence of HCC. This study alerted the scientific community regarding the potential risks associated with use of DAAs and the authors called for a large-scale assessment to confirm their findings[8]. However, their method of statistical analysis was questioned by Camma and colleagues who felt that reporting the crude rate of recurrence was a weakness of the study because of the variation in time elapsed from treatment of HCC and starting DAAs (median 11.2 mo, range 1.2-87.7 mo)[23]. Cammà *et al*[23] used the data presented by Reig *et al*[24] to calculate the actuarial probability of HCC recurrence by plotting a Kaplan Meier curve. For their analysis, Cammà *et al*[23] used the time of HCC treatment as the initiation point, not the time of initiating DAA treatment as used by the original authors. With this method they found a much lower recurrence rate than that reported in the original study (7% and 13% at 6 and 12 mo

respectively).

Reig *et al*[24] later went on to present a follow up of their original cohort. In 2017, they reported that not only did they observe a higher recurrence rate of HCC among the DAA treated patients in their study; they also found a more aggressive pattern of recurrence in terms of tumor staging and subsequent treatment options. Renzulli *et al*[25] have also reported a rapid development of HCC following DAA treatment with a more aggressive pattern of microvascular invasion. The median duration between completion of DAA treatment and diagnosis of HCC in their patients was 82 d (range 0-318).

A retrospective study from Italy by Conti *et al*[18] reported HCC occurrence and recurrence rates of 3.16% (95%CI: 1.45-5.90) and 28.81% (95%CI: 17.76-42.07) respectively in a cohort of 344 CHC patients treated with different DAA regimens over a follow up of 24 wk. Approximately 69% of this patient population had HCV genotype 1 and 91% had achieved SVR. However, the lack of a control group makes the interpretation of these findings difficult. The authors attempted to account for this limitation by comparing their findings to those of a historic cohort of untreated cirrhotic patients at their center. They found an HCC occurrence rate of 3.2%, which was similar to their current study. Conti *et al*[18] have interpreted their results with caution. The authors claim that while DAA treatment of HCV does not seem to reduce the occurrence or recurrence of HCC, anitviral treatment should be started as early as possible to prevent the development of cirrhosis and recommend active surveillance of all cirrhotic patients, during and after DAA therapy.

In Portugal, Cardoso *et al*[26] found HCC incidence to be 7.4% within a one year follow up of cirrhotic patients that had achieved SVR after being treated with sofosbuvir and ledipasvir. These *de novo* HCC patients had been asymptomatic, and were detected on radiological screening. This emphasizes the recommendation of Conti *et al*[18] that there should be close monitoring of CHC patients for development of HCC, despite achieving SVR[25]. In a larger study from Belgium, it was found that there was no difference in the early occurrence of HCC among patients treated with DAAs with or without Peg-IFN. However, this study reported HCC recurrence of 15% in patients treated with DAAs alone as compared to 0% in those who received a combination of Peg-IFN and DAAs. This study had a predominantly HCV Genotype 1 population. In these patients the authors also noted that those who developed HCC had a higher baseline risk of HCC which is a potential confounder[27].

The most recent study on this research question is by Ida *et al*[28], published in October 2017. The study population comprised 100 patients from Japan with HCV genotype 1, treated with Daclastavir and Asunaprevir, who were followed for 15 mo. In this group, there were 5 new cases and 12 recurrences of HCC. The authors

have hypothesized that the high rate of HCC seen in this study could be related to a history of HCC, as these patients already had advanced fibrosis which is known to be implicated in the process of hepatocarcinogenesis. Table 2 summarizes the studies that report an increased incidence of HCC in DAA treated HCV patients.

Studies that did not note any significant effect

In 2016 and 2017 there have been several other similar reports, fueling the debate regarding the role of DAAs in HCC. Two large retrospective cohort studies have been conducted in the United States to investigate this matter; one by Ioannou *et al*[33] with a sample size of 62354 and the other by Kanwal *et al*[34] with 22500 study participants. Both studies concluded that DAAs are not associated with a significant risk of HCC as compared to IFN based treatment. Ioannou *et al*[33] found that DAA induced SVR reduced the risk of HCC by 71%. This effect was similar in groups who had received DAAs alone, DAAs in combination with IFN or IFN alone regimens, thus suggesting that achieving SVR could be the crucial factor for risk reduction of HCC, regardless of the therapeutic agents used[33]. Kanwal *et al*[34] found that while there was a relative risk reduction in HCC, the absolute risk of HCC still persisted in those patients who had DAA induced SVR. In both studies the risk of HCC was greater in cirrhotic patients. Additionally, Kanwal *et al*[34] found that diabetes mellitus, alcohol use and a higher Fib-4 Index for assessment of fibrosis were risk factors for occurrence of HCC in patients who had achieved SVR. However, both study populations were restricted to United States veterans and were mostly patients with HCV genotype 1. The specific population included in these studies might limit the generalization of their findings.

The ANRS Collaborative Study Group assessed HCC recurrence rates among 3 French multicenter prospective cohorts who had received DAA based therapy after HCC curative treatment[35]. Their study included a diverse patient population with cirrhotics, non-cirrhotics and liver transplant recipients. They did not find any evidence that DAAs increases the risk of HCC recurrence. The strength of this study was that analysis of data from 3 distinct patient cohorts yielded fairly consistent results. Secondly, they included patients who had received curative therapy for HCC as opposed to non-curative therapies such as chemoembolization, leading to speculation that some of the earlier studies that had reported a higher recurrence rate might have included patients in whom the initial tumor staging was incorrect or was incompletely treated[35]. Table 3 summarizes the studies that do not show an increased risk of HCC in DAA treated patients.

Geographical variation of incidence of HCC in DAA treated patients

Many of the studies investigating the link between DAAs and HCC have been from Japan or European countries. Racial differences are known to be implicated in the progression to HCC among HCV infected patients[52]. In a large cohort of United States veterans with HCV, it was found that Hispanics were at greater risk of developing cirrhosis and HCC. Black race and Hispanic ethnicity have also been identified as independent predictors of treatment failure[53]. Indeed the first report raising caution about the possible association of DAAs with recurrence of HCC in an aggressive form did come from the Spanish cohort followed by Reig *et al*[8].

A systematic review and meta-analysis by Waziry *et al*[54] found that there was no difference in HCC occurrence and recurrence in CHC patients who received IFN based or DAA based regimens. However, the authors acknowledge that in their analysis they were unable to account for geographical variations. Due to the heterogeneity in the studies included in this meta-analysis, the results should be interpreted with caution. In this meta-analysis most of the IFN based studies were from Japan whereas DAA based studies were from Europe. Hence, due to baseline difference in between two populations it's hard to draw an accurate conclusion regarding occurrence or recurrence of HCC among DAA and IFN based therapy. Furthermore, they had to exclude several studies which had incomplete data regarding BCLC staging of HCC.

In our literature review, the populations that we have found to be under-represented in terms of the current research question include Indians, Arabs and Africans. Additionally, while the 2 studies with the largest sample size are from the United States, these were limited to veterans only[33,34].

Genotype based variation of HCC in DAA treated patients

HCV genotype is an important consideration when considering progression to HCC. HCV genotype 3 is generally more aggressive and is associated with a higher risk of progression to cirrhosis and HCC[55]. To the best of our knowledge, the studies published so far suggesting a greater risk of HCC with DAA treatment have not identified a particular genotype of HCV that is significantly associated with this disease progression. However, as most of these reports are from Japan or European countries such as France and Italy, therefore the major disease burden studied has been of HCV genotype 1[35,37]. Table 4 lists the factors predisposing to development of HCC in DAA treated HCV patients.

WAY FORWARD

There is wide variation in the studies assessing the long-term role of DAA based therapy on occurrence and recurrence of HCC, both in terms of the baseline characteristics of study population and the different DAA regimens used. At present, most of the studies have been reported from regions where HCV genotype 1 is the most prevalent one[34,35]. Data is very limited from Asian populations where HCV Genotype 3 is the most common genotype. This is an important consideration as the different genotypes of HCV have a unique

Table 2 Studies showing an increased incidence of hepatocellular carcinoma in direct acting antivirals treated patients

Ref.	Treatment groups	Country/sample size	Male gender n (%)	Age (yr)	Genotype n (%)	Duration of follow up	Cirrhosis n (%)	History of HCC n (%)	HCC occurrence	HCC recurrence
Reig et al[8]	All DAA treated	Spain n = 58	40 (69)	Median 66.3 (45-83)	G1a = 8 (13.8%), G1b = 45 (77.6%), G3 = 2 (3.4%), G4 = 3 (5.2%)	median 5.7 mo	55 (94.8)	58 (100)	Not applicable	16 (27.6%)
Conti et al[18]	All DAA treated	Italy n = 344	207 (60.2)	Median = 63 (29-85)	G1 = 237 (69), G2= 40 (11.6), G3= 38 (11), G4= 29 (8.4)	24 wk	All cirrhotic	59 (17)	9 of 285 patients (3.16%, 95%CI: 1.45-5.90)	17 of 59 patients (28.81%, 95%CI: 17.76-42.07)
Cardoso et al[26]	All DAA treated	Portugal n = 54	>70%	No HCC: 59 yr (41-81). Patients with HCC: 58 yr (55-72)	No HCC: G1 = 78%, G3 = 18%. Patients who developed HCC: G1 = 75%, G3 = 25%	Median = 12.0 mo (9.4-12.5 mo)	All cirrhotic	0 (0)	4 (7.4%)	Not applicable
Ida et al[28]	All DAA treated	Japan n = 100	46 (46)	Median 72.5 (26-87)	G1 = 100 (100), G1a = 3 (15.8), G1b = 13 (68.4), G3a = 2 (10.5), G4 = 1 (5.2)	15 mo		26 (26)	5 (5)	12 (12)
Kozbial et al[29]	All DAA treated	Austria	-	56-74 yr				3 (15.8)	6.60%	3 patients
Issachar et al[30]	All DAA treated	Israel n = 273	-	Median 55 (49-60) yr	-	15 mo	-	-		3 (1.05)
Kwong et al[31]	patients divided into 3 eras: IFN era (2003-2010), protease inhibitor era (2011-2013), and DAA era (2014-2015)	United States n = 48158	29858 (62)			Median 493 d	All cirrhotic		6 (2.1) Incidence Rate of HCC was 49% higher in the DAA era (IR 6.6/100 person-years [py], 95%CI: 5.6-7.9) vs the IFN era (4.5/100 py, 95%CI: 4.2-4.7; IRR 1.49, 95%CI: 1.24-1.79, P < 0.001).	Not applicable
Strazulla et al[32]	daclatasvir and simeprevir for 24 weeks to reach SVR	Italy n = 1 case report	1 male	53	G1	24 wk	Decompe-nsated cirrhosis	Treated	Not applicable	1 recurrence
Bielen et al[27]	PEG-IFN+ DAA =77 (13.5), DAAs only = 490 (86.4)	Belgium n = 567	PEG IFN + DAA group: 55 (71.4) DAA only group: 307 (62.7)	PEG IFN + DAA group age : 52 ± 9, DAA only group: 59 ± 12	PEG IFN + DAA group: all genotype 1. DAA only: G1 = 69%, G4 = 14.7%	6 mo	Metavir fibrosis score F3/F4 included only	PEG IFN + DAA = 1/77 (1.3%),DAA alone: 41/490 (8.4%)	Early occurrence rate of HCC = 1.7% and 1.1% in patients treated with DAA with and without PEG-IFN, respectively	Early recurrence rate was 0% in patients treated with PEG-IFN+DAA and 15.0% in patients treated with DAA without PEG-IFN

DAAs: Direct acting antivirals; IFN: Interferon; HCC: Hepatocellular carcinoma.

Table 3 Studies that do not report an increased risk of hepatocellular carcinoma with direct acting antivirals

Ref.	Treatment N /sample size	Country	Male gender n (%)	Age (yr)	Genotype n (%)	Duration of follow up	Cirrhosis n (%)	History of HCC n (%)	HCC occurrence	HCC recurrence
Ioannou et al[33]	IFN only = 35871 (58%), DAA + IFN = 4535 (7.2%), DAA only = 21948 (35%) n = 62354	United States	96.60%	Mean 55.8 ± 7.6	G1 = 77.4 %, G2 = 13.5%, G3 = 8.3%, G4 = 0	Mean follow-up DAA only group = 1.53 years, DAA+IFN group= 3.6 yr, IFN only group = 9.1 yr	Cirrhosis: 16.8%, decompe-nsated cirrhosis: 4.7%	None	Total 3271 incident cases. IFN group = 0.81/100 person years, DAA + IFN = 1.06 /100 py, DAA only = 1.32/100 py	Not applicable
Kanwal et al[34]	All DAA treated n = 22500	United States	21761 (96.7%)	Mean 61.6 ± 6.1	G1 = 19531 (86.8%), G2 = 1422 (6.3%), G3 = 940 (4.2%), G 4-6 = 217 (1%)	22963 person years of follow-up	8766 (39.0%)	None	271 (1.2)	Not applicable
ANRS CO22 HEPATH-ER et al[35]	DAA group = 189, no DAA n =267	France	DAA group = 147 (78%)	DAA group = 62 ± 9 yr, no DAAs = 66 ± 10 yr	65 % genotype 1	Median: 20.2 mo after DAA initiation and 26.1 mo for untreated patients	Cirrhosis: DAA group = 152 (80%), no DAAs = 55 (72 %)	All treated	Not Applicable	DAA group = 24 (12.7%), no DAAs = 16 (20.5%)
ANRS CO12 CIRVIR et al[35]	DAA group = 13, no DAA = 79	France	DAA group = 11 (85%), no DAA = 39 (59%)	DAA group = 61 ± 10 yr, no DAA = 65 ± 9 yr	Genotype 1: DAA group = 11 (85%), no DAA group = 53/63 (84 %)		All cirrhotic	All treated	Not Applicable	DAA group = 1 (7.7%), no DAAs = 31 (47%)
ANRS CO23 CUPILT et al[35]	All DAA treated n = 314	France	257 (82%)	61 ± 8 yr	212 (67.5%) genotype 1		49 (15.6%)	Treated	Not Applicable	7 (2.2%)
Cabibbo et al[36]	All DAA treated n = 143	Italy	80 (60.1)	Mean 70.4 ± 8.9	G1a: 9 (6.3), 1b: 114 (79.7), G2: 9 (6.3), G3: 7 (4.9), G4: 4 (2.8)	6, 12 and 18 mo	All cirrhotic	All treated	Not applicable	6-, 12- and 18-mo HCC recurrence rates were 12%, 26.6% and 29.1%, respectively
Nagata et al[37]	IFN-based: 1145. IFN-free DAA group: 752 n = 1897	Tokyo	IFN group: 621 (54), IFN free: 340 (45)	Median: IFN group: 59 (19-79); IFN free: 69 (24-87)	IFN group: G1a = 8 (7), G1b = 833 (73), G2a = 182 (16), G2b = 105 (9), G3 = 1 (0)	Median for IFN group: 6.8 (0.2-22.0); IFN free: 1.8 (0.1-7.7)		5% of IFN group, 11% of IFN free group	IFN group: 18 (2.5%). IFN-free group: 7 (1.1%)	IFN group: 18 (53%). IFN-free group: 22 (29%)
Ikeda et al[38]	All DAA treated n = 177	Japan	M:F = 52: 37 in each group	DAA group: 71 (39-85)		Median 20.7 mo		All treated	Not applicable	HCC recurrence rates at 1st and 2nd year were 18.1 and 25.0% in pts with DAA therapy and 21.8 and 46.5% in those without DAAs, (P = 0.003)
Zanetto et al[39]	DAA treated = 23, control = 23 n = 46	Italy		DAA group = 59 (49-69), controls= 58 (46 -70)	DAA group: G1a = 5 (22), Gb = 9 (39), G2 = 1 (4), G3 = 5 (22), G4 = 3 (13)	Median= DAA group = 10 mo, Control group = 7 mo	All cirrhotic	All treated	Not applicable	12.5% of DAA-treated patients and 8.3% of control group had HCC recurrence (P = 0.60)

Ref	Study population	Country	Male n (%)	Age	Genotype	Cirrhosis	Follow-up	Previous treatment	HCC occurrence	HCC recurrence
Zavaglia et al[40]	All DAA treated n = 31	Italy	20 (64.5)	Mean 65 ± 8	G1a = 4 (13), G1b = 23(74), G2 = 2 (6.5), G4 = 2 (6.5)	All cirrhotic	Median 8 mo	All treated	Not applicable	1 (3.2)
Ogata et al[41]	All DAA treated n = 1170	Japan	493 (42)	Median = 67 (21-88)	All genotype 1		Time from the end of DAA therapy until last visit: 1.3 yr	None	22 cases (1.8%)	Not applicable
Minami et al[42]	DAA group = 27, IFN group = 38, Controls = 861 n = 926	Japan	DAA group: 18 (67), IFN group: 27 (71), Controls: 489 (57)	Median age: DAA group = 71 (48-82) IFN group = 66 (49-79), Control = 71 (44-91)	Genotype 1: DAA = 21 (78), IFN = 29 (76), Controls = 633 (74). Genotype 2: DAA= 6 (22), IFN= 9 (24), Control= 147 (17)		1 and 2 yr	All treated	Not applicable	Cumulative recurrence rates at 1 and 2 yr were 21.1% and 29.8%, respectively, in the DAA group, 26.3% and 52.9%, respectively, in the IFN group, and 30.5% and 61.0%, respectively, in the control group
Deterding et al[43]	n = 974	Germany			G1 = 743 (76.2)	All had advanced cirrhosis			12 (1.2)	
Degasperi et al[44]	n = 565	Italy	60%	Median age = 65 (30-87) yr	G1a = 15%, G1b = 49%, G2 = 13%, G3 = 11%, G4 = 12%, G5 = 1%	All cirrhotic	Median 42 wk for occurrence, 39 wk for recurrence	48 (8%)	20 (4%) estimated annual incidence of 1.6%	9 (19%), annual incidence of 7.7%
Bourliere et al[45]	DAA + RBV ± PEG IFN = 21%. IFN free DAA therapy = 79% n = 1393			47 (19-79) yr			2.5 (0.6-4.3) yr		0 (0)	0 (0)
Nagaoki et al[46]	PEG-IFN/ RBV = 244, DCV/ASV = 154 n = 398	Japan			All genotype 1		Median for PEG-IFN/RBV = 96 (10-196) and DCV/ASV group = 23 (4-78) mo		PEG-IFN/RBV = 13 (5.3%), DCV/ASV group = 7 (4.5%)	
Cheung et al[47]	All DAA	United Kingdom		198 (48.8) 171 (42.1)		All decompensated cirrhosis	15 mo	29 (71.4%)	17 (5%)	
Mettke et al[48]	158 DAA treated, 184 controls	Germany				All cirrhotic	Median = 440 (91-908) and 592 (90-1000) d		6 and 14 patients during follow-up, resulting in an HCC incidence of 2.9 (AVT) and 4.48 (Con) per 100 py, respectively	2
Ji et al[49]		China	51%	Mean age 51	82.2% genotype 1b	48% cirrhotic	Median 14 (3-35) mo	None	44 (5.1%)	Not applicable
Innes et al[50]		Scotland					1.8 yr	None	Not applicable	Not applicable
Torres et al[51]	All DAA treated	United States	7 (87.5%)	Median 64 (57-87) years	G1 = 6 (75%), mixed genotype = 2 (25%)	7 (87.5%)	12 mo	All treated	Not applicable	0 (0)

DAAs: Direct acting antivirals; IFN: Interferon; HCC: Hepatocellular carcinoma.

Table 4 Factors predisposing to hepatocellular carcinoma in hepatitis C virus patients treated with direct acting antivirals after sustained virologic response

Past history of hepatocellular carcinoma[18,28,36]
Male gender[28]
Cirrhosis[34]
Hypoalbuminemia[41]
Thrombocytopenia[41]
Raised AFP levels[41]

response to DAA based therapy and are associated with a unique burden of HCC[56]. Beside male patients, group of individuals with prior history of HCC, cirrhosis and elevated AFP at baseline were found with greater risk of HCC if treated with DAAs. Currently, the phenomenon appears to be a class effect rather than an individual drug effect. Hence, focusing on these HCV patients and measuring the impact of DAAs on progression or development of HCC will help to estimate the more accurate risk. In certain studies higher rates of HCC recurrence was found. There is a need to differentiate whether the reported higher recurrence rate and more aggressive pattern of recurrence are due to DAA or host or disease related factors including presence of fibrosis, gaps in initial tumor staging and receiving non-curative therapies such as chemoembolization. Also, future investigations should be directed towards assessing the long-term effects of DAAs on these populations that have not been studied thus far[3]. In the meantime, a consensus recommendation seen in most of the studies at present is that even after achieving SVR, there should be close surveillance of patients with CHC especially with advance fibrosis and those who received a recent treatment for HCC in order to detect HCC at an early stage[18,19,26,32]. Some important Centers in Europe and United States have been delaying antiviral treatment for 6 mo or more after recent treatment for HCC in these patients. Moreover, until more robust data is available to investigate the role of DAAs in HCV related HCC cases, clinical practice should continue as per current guidelines in those patient groups who can benefit from DAA therapy[51].

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