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Decreased risk of hepatocellular carcinoma recurrence with direct-acting antivirals compared with no treatment for hepatitis C: a meta-analysis

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Abstract

Background Studies investigating the association between direct-acting antivirals (DAAs) and the recurrence of hepatocellular carcinoma (HCC) related to hepatitis C (HCV) have yielded conflicting results. The objective of this meta-analysis was to define the short- and long-term recurrence rates of HCC after DAA treatment.

Methods A search of multiple databases was performed, including Scopus, Cochrane, MEDLINE/PubMed and abstracts from gastroenterology meetings. Only studies reporting the recurrence of HCC in patients receiving DAA treatment, compared to HCV controls without DAA treatment, were evaluated. A meta-analysis was completed using the Mantel-Haenszel model.

Results A comprehensive literature search resulted in 32 abstracts and papers. Six papers met our inclusion criteria and were included in the analysis. Follow up ranged from 1.25-4 years. Analysis of these 6 studies found a >60% lower risk of HCC recurrence in patients exposed to DAA compared to controls (odds ratio [OR] 0.36, 95% confidence interval [CI] 0.27-0.47; P<0.001; I^2=88%). A sensitivity analysis, which excluded studies showing the lowest recurrence rate to reduce heterogeneity, showed that patients receiving DAA still had a 60% lower risk of developing HCC (OR 0.4, 95%CI 0.26-0.61; P<0.0001; I^2=39%) and a 66% lower risk of developing HCC beyond 1 year (OR 0.34, 95%CI 0.22-0.54; P<0.00001; I^2=0%) compared to controls.

Conclusions The use of DAA is associated with a significantly lower risk of HCC development compared to DAA-untreated patients, both overall and beyond 1 year of treatment. Further studies are needed to assess the impact of DAAs on early recurrence.

Keywords Hepatocellular carcinoma, hepatitis C, direct-acting antivirals

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Introduction

Chronic hepatitis C virus (HCV) is one of the leading causes of end-stage liver disease, hepatocellular carcinoma (HCC), and liver-related death in the Western world [1-3]. HCV is believed to be a major cause of HCC, by creating an inflammatory, fibrogenic, and carcinogenic tissue microenvironment [4,5].

The introduction of direct acting antiviral (DAA) agents has had many positive impacts, including improvement in fibrosis and decreasing rates of HCV-related decompensation. However, some studies have shown that DAA agents have also been associated with an increase in the recurrence of HCC in patients previously cured by liver transplantation, surgical resection or local ablative therapy [6-9]. Other studies show conflicting results, indicating a lower risk of developing HCC compared to those who did not receive DAA [10,11]. The mechanism remains largely unknown, but it has been hypothesized that it may be secondary to interferon (IFN)-mediated suppression of tumor cells via alterations in the microenvironment of the hepatocyte, specifically involving interferon gene expression and natural killer cell function, both of which have antiproliferative properties [5,12]. The current

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concern for most practitioners revolves around the safety and timeliness of DAA administration post-HCC treatment [13]. The purpose of this study was to evaluate HCC recurrence rates in those patients treated with DAAs compared to a control group without DAA treatment.

Materials and methods

A systematic and comprehensive literature search of Scopus, MEDLINE/PubMed, CINAHL, Cochrane databases and recent abstracts (between January 2016 and December 2017) from major American meetings (Digestive Disease Week, American College of Gastroenterology, American Association of Liver Diseases) was carried out in December 2017. In addition, the reference lists of all articles were searched. Search terms used were "HCC recurrence" or "DAA." Two reviewers (FL and SH) independently reviewed all abstracts returned by the search. A third reviewer (DN) confirmed these results and mutual agreement was necessary in cases of discrepancy or disagreement. Only studies that involved adult patients and compared the HCC recurrence rate with DAA to that of controls not receiving DAA were included in the analysis. Studies without controls were excluded. A meta-analysis was conducted using calculated pooled estimates of recurrence rates at 1 year and beyond 1 year Results were presented as odds ratio (OR) using 2 models, the Mantel-Haenszel, the fixed effect, model in outcomes with no heterogeneity and the DerSimonian and Laird, the random effects, and model in outcomes with significant heterogeneity. The I^2 measure of inconsistency was used to assess heterogeneity ($P<0.05$ or $I^2>50\%$ was considered significant). If statistically significant heterogeneity was observed, a sensitivity analysis was performed and certain studies were removed, leading to heterogeneity. RevMan 5.3 (Review Manager, Version 5.3, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2012) was used for the statistical analysis. Quality assessment of the included studies was performed using the Cochrane Collaboration's tool for assessing risk of bias. A grade was assigned to each outcome based on the quality of evidence: very low, low, moderate, or high quality.

Results

Study selection

The initial literature search (PubMed, Cochrane, Google Scholar, CINAHL) identified a total of 32 articles, excluding duplicates. A total of 26 studies were excluded as they did not address the primary clinical question or were reviews, non-English articles, letters to the Editor, or did not have a control group included in the analysis. Therefore, 6 studies were included in the final meta-analysis.

Study details

Details of the 6 studies included are summarized in Table 1 and in the Discussion. Five of these 6 were retrospective cohort studies, while that of Cheung *et al* [10] was a prospective cohort study. These studies included a total of 1105 patients treated with DAA and 1912 controls, including 1594 patients who received no antiviral therapy and 318 patients treated with pegylated IFN-based regimens.

The majority of studies assessed HCC recurrence following exposure to DAA in patients who had previously undergone curative therapies. Studies varied in terms of inclusion criteria on the basis of initial treatment of HCC. While all studies included patients treated with surgical resection or radiofrequency ablation, the ANRS cohort [14] excluded those who had undergone chemoembolization, as it has been associated with high rates of early recurrence due to independently higher risk of recurrence. The disease severity also varied amongst studies. The ANRS cohort only included patients with Child-Pugh Class A disease, while the study by Cheung *et al* [10] enrolled patients with prior or current decompensated cirrhosis. Regarding the control groups, several studies compared the risk of HCC recurrence following DAA therapy to a population of untreated patients, while others also assessed the risk in relation to those treated with IFN-based regimens. Prior reports have suggested IFN may have anti-cancer properties independent of its antiviral effects. Specific DAA regimens varied amongst studies (Table 1). The ANRS study pooled data from 3 separate groups, including the following: the

Table 1 Summary of studies included

Study	Study type	Location	*N*	Duration of follow up	Methods of HCC treatment
ANRS Collaborative Study Group [16]	Retrospective cohort	France	660	30 mo.	Radiofrequency ablation, liver resection, liver transplant
Cheung, *et al* [12]	Prospective cohort	England	667	15 mo.	
Ikeda, *et al* [17]	Retrospective cohort	Japan	688	2 years	Radiofrequency ablation, liver resection, radiation therapy, TACE
Minami, *et al* [18]	Retrospective cohort	Japan	926	3 years	Radiofrequency ablation
Virlogeux, *et al* [19]	Retrospective cohort	Italy	68	4 years	Radiofrequency ablation, liver resection, radiation therapy, TACE
Vukotic, *et al* [20]	Retrospective cohort	France	68	3 years	Radiofrequency ablation, liver resection

HCC, hepatocellular carcinoma; TACE, transarterial chemoembolization

HEPATHER cohort, comprised hepatitis B and HCV patients followed to assess the efficacy of new antiviral treatments; the CirVir cohort, comprised HCV patients followed to assess the incidence of complications of cirrhosis; and the CUPILT cohort, comprised HCV patients with prior liver transplant treated with DAA. Among this large group of clinically diverse patients, authors reported no increase in HCC recurrence in the HEPATHER (hazard ratio [HR] 1.21) and CirVir (HR 0.41) cohorts, and an actual 2.2% lower observed recurrence rate compared to that expected among transplant patients. Similarly, Ikeda *et al* demonstrated that DAA therapy was associated with a significant decrease in HCC recurrence [15]. Minami *et al* also reported that the use of DAA was not significantly associated with recurrence within 3 years compared to both untreated controls and the IFN-treated group (DAA group vs. control: HR 0.57, P=0.12; DAA group vs. IFN group: HR 0.65, P=0.28) [16,17]. Interestingly, Vukotic *et al* [18] also compared recurrence in patients treated with DAA to those with IFN, and reported that the time to recurrence was longer with IFN-based therapies. Virlogeux *et al* [17] also noted lower rates of recurrence, as well as longer intervals between HCC remission and recurrence, compared to untreated controls.

Overall risk of HCC recurrence

Pooling the 6 studies included in this meta-analysis, totaling 3017 patients, there was a 64% lower rate of HCC recurrence amongst patients treated with DAA compared to untreated controls (OR 0.36, 95% confidence interval [CI] 0.27-0.47; P<0.00001; I^2=88%) (Fig. 1). Follow-up time ranged from 1.25-4 years. Following sensitivity analysis, which excluded studies with the lowest recurrence rates to reduce heterogeneity, there was still a significant 60% decrease in rate of HCC recurrence (OR 0.4, 95%CI 0.26-0.61; P<0.0001; I^2=39%).

Risk of HCC recurrence at one year

Three of the included studies assessed HCC recurrence at 1 year, totaling 1682 patients, which cumulatively noted a 39% lower rate of HCC recurrence compared to controls (OR 0.61, 95%CI 0.37-1.02; P=0.06; I^2=59%). When one study was excluded to reduce heterogeneity, the rate of HCC recurrence was reduced by 16% (OR 0.84, 95%CI 0.47-1.50; P=0.55; I^2=0%) (Fig. 2). Notably, 38 patients in the control group had received IFN therapy.

Risk of HCC recurrence beyond 1 year

Several studies also assessed more distant HCC recurrence beyond the initial year after DAA therapy. Follow-up time ranged from 2-4 years and 38 patients in the control group received IFN therapy. Amongst the 2432 patients included in these studies, the overall rate of recurrence over this longer time period was nearly 80% lower (OR 0.22, 95%CI 0.16-0.31; P<0.0001; I^2=74%). The ANRS study was subsequently excluded as it had the lowest recurrence rate. Subsequent analysis still noted a 66% lower rate of HCC recurrence following DAA therapy (OR 0.34, 95%CI 0.22-0.54; P<0.0001; I^2=0%) (Fig. 3).

Discussion

DAAs have revolutionized the treatment of chronic hepatitis C. Chronic HCV is known to lead to liver cirrhosis in 10-15% of infected patients and, once established, is associated with 3-5% annual risk of HCC [19]. In these patients, viral eradication has been shown to improve disease severity as well as decrease the

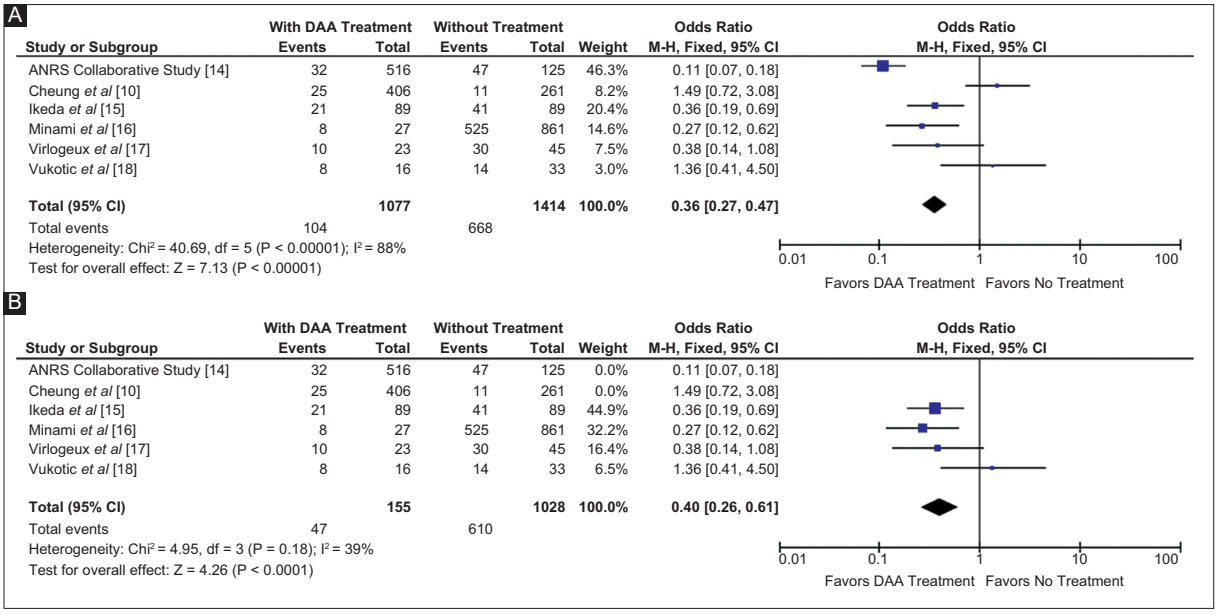

Figure 1 (A) Overall HCC recurrence after DAA treatment. (B) Lowest recurrence rates removed to decrease heterogeneity
CI, confidence interval; HCC, hepatocellular carcinoma; DAA, direct-acting antiviral agents

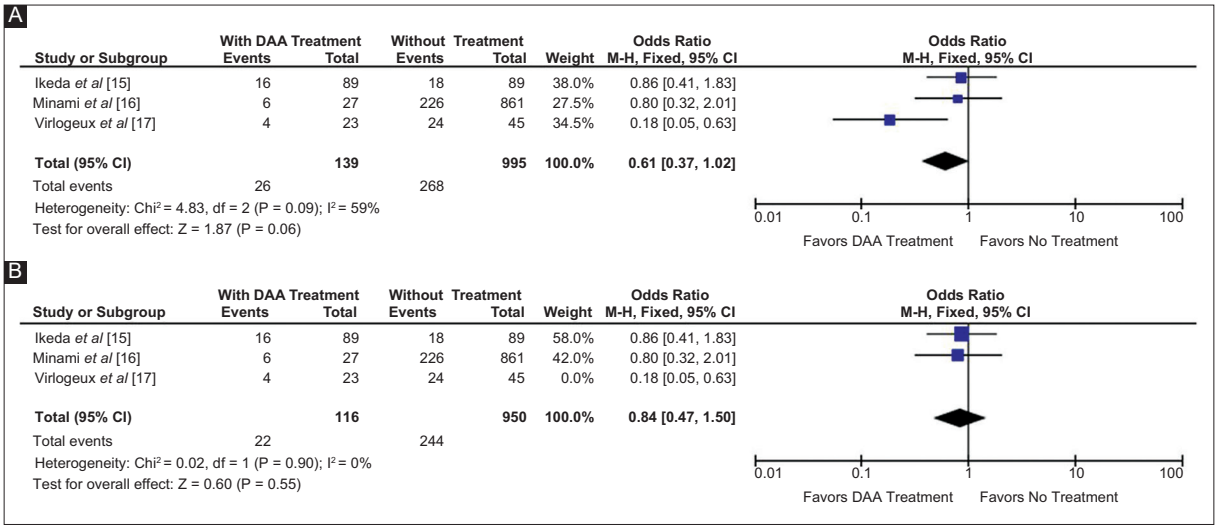

Figure 2 (A) HCC recurrence within 1 year after DAA treatment. (B) Lowest recurrence rates removed to decrease heterogeneity
CI, confidence interval; HCC, hepatocellular carcinoma; DAA, direct-acting antiviral agents

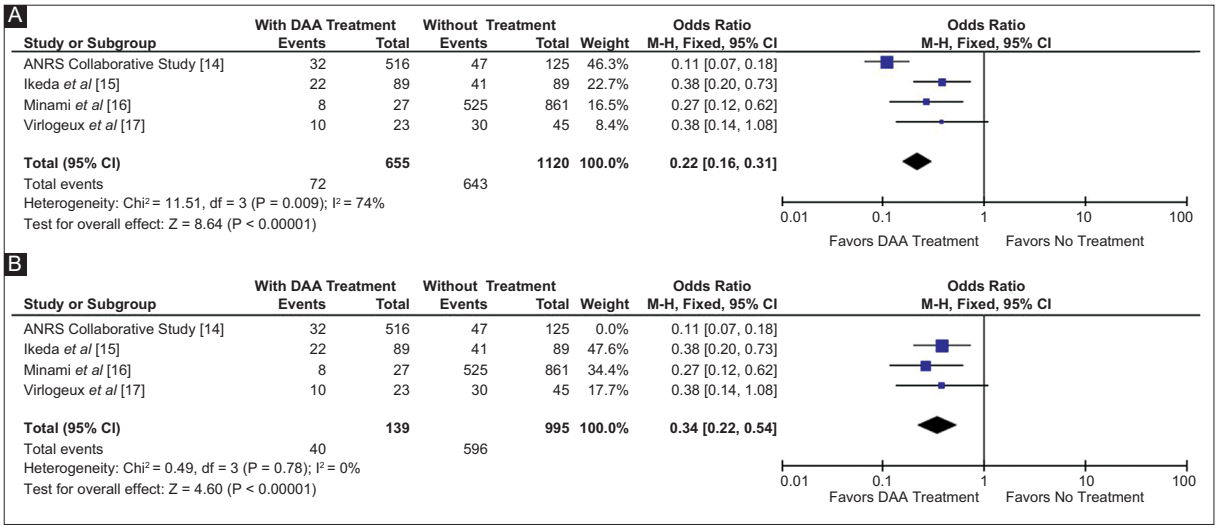

Figure 3 (A) HCC recurrence beyond 1 year after DAA treatment. (B) Lowest recurrence rates removed to decrease heterogeneity
CI, confidence interval; HCC, hepatocellular carcinoma; DAA, direct-acting antiviral agents

risk of liver complications, including the development of HCC [20,21]. Prior to the introduction of DAA, pegylated IFN-based regimens used to treat chronic HCV yielded lower rates of sustained virological response (SVR), while being associated with more significant adverse effects. Additionally, patients with more advanced disease were ineligible for treatment, limiting the number of patients for whom such treatments were available [20]. By contrast, DAAs are associated with SVR rates of 95-97% in patients with compensated disease and up to 85-90% in patients with more advanced disease. Additionally, these regimens require a shorter course of therapy and are generally better tolerated [22].

Chronic HCV is among the most common causes of HCC in the United States. This occurs through a complex set of both direct and indirect mechanisms, including activation of liver fibrogenic pathways and dysregulation of host immune and metabolic systems, as well as other host genetic factors that induce liver injury and initiate oncogenesis [23]. In the past, treatment of HCV with achievement of SVR was associated with a decrease in the rate of primary and recurrent HCC [23]. While IFN is known to have anti-cancer properties independent of its effect on HCV, it is thought that a quiescence of chronic inflammation associated with viral eradication also probably contributes to this [21,22].

Given this, it was thought that DAA regimens would similarly decrease the rates of HCC recurrence. However, several recent studies reported a paradoxical increase in the rates of HCC recurrence following eradication therapy. First reported by Reig *et al*, researchers found a nearly 30% recurrence rate among patients treated with DAA, with many cases occurring soon after the initial remission [24]. Similar results were also reported by Conti *et al*, who also noted similar rates of HCC

recurrence amongst cirrhotic patients [20]. While the exact mechanism underlying these findings is not well understood, it was postulated that DAAs cause a very rapid inhibition of HCV production, leading to abrupt resolution of the chronic inflammatory state. This may cause a disturbance of homeostatic immunosurveillance mechanisms that normally act to halt tumor progression, specifically mediated by a reduction in the number of natural killer cells, which are known to play an active role in cancer immunosurveillance and decrease rapidly following the initiation of DAA therapy. These alterations ultimately lead to a proliferation of residual tumor clones that are subsequently recognized as recurrence [20]. Since these results were first reported, several additional studies assessing HCC recurrence following DAA treatment have been published. These studies, however, actually reported either no difference in the rates of HCC recurrence, or, as previously predicted, a protective effect of DAA therapy. The studies cumulatively assessed a wide range of patients, including those with compensated versus decompensated disease and a range of modalities for initial HCC therapy. Additionally, unlike the studies by Reig and Conti, which compared their population to a historical cohort of untreated cirrhotic patients, all of these follow-up studies compared treated patients to untreated or IFN-treated controls to minimize the heterogeneity between the populations [21,25,26].

The results of our meta-analysis (Fig. 2) further corroborate the findings reported in these follow-up studies. Assessing the overall risk of HCC recurrence, we found that the risk of recurrence among those treated with DAA therapy was more than 60% lower than that in untreated controls. Similarly lower rates were also noted for the risk of recurrence within 1 year, though the results did not approach significance, as well as beyond 1 year. Lower rates of recurrence following DAA were still seen after the exclusion of several studies for a sensitivity analysis. The discordance between these results and the higher recurrence rates reportedly earlier is not entirely clear. In many of the recurrence cases reported by Reig and Conti there was a very short interval to recurrence, suggesting that many of these cases were not in fact true recurrence, but rather residual, radiologically undetectable tumors previously missed. Additionally, earlier studies included patients who had had multiple recurrences and treatment of HCC prior to DAA therapy. As reported by several studies, multiple prior recurrences were associated with a higher likelihood of recurrence compared to patients who had only one recurrence [23]. Furthermore, as previously noted, these earlier studies did not compare their results against an equivalent control group, which may have further complicated their findings. Consistent with the findings of Li *et al* [26], our study demonstrated lower rates of early recurrence within less than 1 year, but the protective effects may last beyond 1 year. The mechanism underlying our findings of lower rates of early HCC recurrence is probably related to the rapid cessation of chronic inflammation following viral eradication. Chronic inflammation has been implicated in a wide range of cancers. As in other malignancies, inflammation leads to dysregulation of immune pathways and genomic instability, while it also increases systemic oxidative stress, ultimately leading to dysplasia and the development of cancer. Cessation of inflammation ultimately leads to a restoration of homeostasis; however, this homeostasis may be disturbed beyond 1 year [27].

Our study had several key strengths. In combining several existing studies, our analysis included a wide, diverse range of patients who varied in terms of disease severity, specific DAA regimens and interval between initial remission of HCC and initiation of DAA therapy. Our study included studies with controls, which allowed for direct comparisons of recurrence rate rather than extrapolation. Despite this heterogeneous population, however, our results supported findings from individual studies on the protective effect of DAA therapy on early HCC recurrence. Our study also had several limitations. The majority of the studies included in our meta-analysis were retrospective cohort studies, and therefore subject to bias and confounding. Additionally, in the one prospective study included in our analysis only a small percentage of the patients with a prior history of HCC could be assessed.

In conclusion, DAA therapy may have a protective effect on the risk of HCC recurrence amongst patients with HCV, particularly beyond 1 year from treatment. Further prospective studies are needed to assess the short-term effects of DAA therapy, as well as effects on overall mortality from HCC.

Summary Box

What is already known:

- There have been conflicting studies regarding the recurrence of hepatocellular carcinoma (HCC) related to hepatitis C virus (HCV) after direct-acting antiviral (DAA) therapy, as some studies have associated DAA therapy with higher rates of HCC recurrence while others found lower rates
- DAA therapy is effective in reducing HCV-related decompensation

What the new findings are:

- DAA therapy was associated with a significantly lower overall risk for development of HCC compared to DAA-untreated patients, including the risk of development beyond 1 year
- DAA therapy may be associated with a significantly lower risk for development of HCC within 1 year of treatment, but further studies are needed to establish this relationship

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