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Oral Direct-acting antivirals and the incidence or recurrence of hepatocellular carcinoma: a systematic review and meta-analysis.

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Background

Background The influence of Direct Acting Antiviral (DAA) therapy for chronic hepatitis c virus (HCV) on the risk of hepatocellular carcinoma (HCC) is conflicting. Our objective was to determine the incidence or recurrence of HCC associated with oral DAA therapy.

Methods We conducted a systematic review and meta-analysis of observational studies. We searched PubMed, Scopus, Embase from inception to August 2017 to identify studies reporting on HCC among patients with chronic hepatitis c virus treated with DAAs. Two independent reviewers extracted data and assessed the risk of bias. Data were pooled by random-effects model. The primary outcome was the proportion of participants with incidence or recurrence of HCC. This study is registered with PROSPERO number CRD42017057040

Results. After reviewing 2080 citations we included 8 controlled studies and 36 uncontrolled studies. We limited the primary analysis to studies with a minimum follow up duration of 24 weeks. The pooled proportion for incident HCC was 1.5 % [95% CI, 01.1% to 2.1%; I^2=90.1%; n= 543/38177) from 18 uncontrolled studies, and 3.3% (95 % CI 1.2% to 9%; I^2 =96%; n=109 /6909) from 5 controlled studies, respectively. The pooled proportion for recurrent HCC was 16.7% (95 % CI, 10.2% to 26%; I^2=84.8 %; n=136/867) from 12 uncontrolled studies, and 20.1% (95 % CI 5.5% to 52.1%; I^2 =87.5%; n=36 /225) from 3 controlled studies, respectively. There was no statistically significant effect on the risk of recurrent HCC (OR 0.50, 95% CI 0.16 to 1.59; I^2 =73.4%) in a meta-analysis of three studies. The quality of the evidence was low for each of the outcomes. The duration of follow-up may have been limited to detect the long-term risk of HCC. **Conclusions.** Our findings show low proportion of incident HCC, but high proportion of recurrent HCC on treatment with DAAs. Continued active surveillance for HCC after treatment with DAAs remains prudent.

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What is known on the topic

There is conflicting evidence on the association between oral direct acting antivirals for chronic hepatitis C and the development of hepatocellular carcinoma

What this study adds

Our findings show low proportion of incident HCC, but high proportion of recurrent HCC on treatment with DAAs. Continued active surveillance for HCC after treatment with DAAs remains prudent. Continued active surveillance for HCC after treatment with DAAs remains prudent.

Abbreviations

CI, Confidence Interval

DAA, Direct Acting Antivirals

GRADE, Grading of Recommendations Assessment, Development and Evaluation

GT, Genotype

HCC, Hepatocellular carcinoma

NOS, Newcastle-Ottawa Scale

OR=Odds Ratio

Person-Years= Person-Years

RR= Relative Risk

Background:

Approximately 2.7-3.9 million patients suffer from chronic hepatitis C in the US, a contributing cause for 19,659 deaths in 2014.[1] The National Academy has set a goal of eradication of chronic hepatitis C by 2030 as a high priority because it is the leading cause of infectious disease mortality.

The direct acting antivirals (DAAs) are considered a novel and innovative treatment for chronic active hepatitis C, which affects millions of people world-wide. Several randomized controlled trials (RCTs) have established their efficacy on sustained virologic response (SVR) 12 weeks or 24 weeks after treatment. These agents have excellent tolerability for patients and have the unique ability to achieve viral clearance and maintain SVR remission. While they have the potential to reduce long term complications of end-stage liver disease a recent Cochrane review of 157 trials identified the lack of evidence on long term clinical outcomes.[2] Randomized controlled trials have been of limited duration and are inadequately powered to assess long term outcomes and complications of chronic active hepatitis such as hepatocellular carcinoma.

The influence of sustained virologic response induced by oral direct acting antivirals on the risk of hepatocellular carcinoma (HCC) among patients with chronic hepatitis c is conflicting and is mainly derived from small case series and observational studies and few systematic reviews have rigorously and systematically evaluated this association. [3]

Objective: Our objective was to determine the incidence or recurrence of HCC associated with oral DAA therapy among patients with chronic active hepatitis C in real world settings.\

Methods

Systematic review registration. We carried out a systematic review and meta-analysis according to a prespecified protocol. The protocol was registered at PROSPERO 2017 CRD42017057040. We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses checklist for reporting the results.

Eligibility criteria. *Inclusions*: We included any observational study including cohort and case control studies reporting on the association between direct acting antiviral use and incidence and recurrence of hepatocellular carcinoma. The RCTs have been of limited duration and were not designed to measure HCC and will not be the focus of this review. A recent Cochrane review did not find sufficient data in the trials to inform on this outcome.[2] *Exclusions*: We excluded case reports, cross sectional studies, narrative reviews and animal or pharmacokinetic or pharmacodynamic studies. We also excluded non-English articles, letters and those for which full text articles cannot be retrieved. For the analysis of incident hepatocellular carcinoma, we limited the sample size of uncontrolled studies to studies with sample size > 100 as smaller cohorts are unlikely to provide reliable estimates of the incidence of HCC, which is a rare outcome. We did not impose such sample size restrictions on the outcome of recurrent hepatocellular carcinoma.

Participants. We included adult participants with chronic hepatitis C of any genotype treated with any of the direct acting antiviral agents alone or in combination. We did not impose any restrictions based on Child-Pugh Curtis class and cirrhosis

Interventions:

We examined the following direct acting antivirals and their combinations shown in our protocol.

Comparators. These comprised of the group of participants not receiving DAAs. We also included studies in which interferon-based regimens were administered in both groups if the difference between the groups was the DAA or DAA combination alone.

Outcomes. The co-primary outcomes were the incidence and recurrence of HCC as defined in the primary studies. We required a minimum of 12 weeks of treatment duration. We did not impose any lag period after exposure as the exact timing of occurrence of HCC after oral DAA exposure is unknown.

Systematic Searches. We searched multiple databases including Pubmed, Embase and Scopus using the search strategy outlined in Supporting information through August 24, 2017. An outline of the search strategy for PubMed is shown in the protocol. It was modified and adapted for various databases. Details of the search strategy for each database are shown in the Supporting Information, which also identifies the oral DAAs that were included. Additional searches were carried out by manually looking at the reference lists of included studies.

Data extraction. Studies were selected for inclusion based on the review of titles and abstracts that were exported into a web-based data management repository (www.rayyan.qcri.org). [4] Two reviewers were independently involved in all stages of study selection, data extraction and quality assessment. All discrepancies were resolved with agreement after rechecking the source papers and further discussion among the reviewers with full consensus prior to inclusion. Data to be extracted included study design, location of the study, drug exposure, mean age of

participants, duration of drug use and duration of follow-up and method of outcome ascertainment.

Risk of bias assessment. We used an adapted version of the Newcastle-Ottawa Scale for evaluating the quality of included studies. [5] We also used the Eggers test and funnel plot to evaluate for publication bias.

Data synthesis. All data were extracted into a pre-specified Excel data sheet. The unit of the analysis was the individual participant. We conducted both qualitative and quantitative synthesis. We considered reporting the results of meta-analysis when 2 or more studies could be pooled in the absence of both clinical and statistical heterogeneity. Examination for clinical heterogeneity included examination for differences in population, intervention, follow-up duration and other characteristics. Statistical heterogeneity was estimated using the I^2statistic. We considered both random and fixed effects meta-analysis. We conducted a meta-analysis of proportion to determine incidence and recurrence rates which were reported as pooled proportions. The primary analysis was focused on studies of more than 24 weeks follow up. In secondary analyses we pooled studies irrespective of duration of follow up. For studies with comparators we conduct meta-analysis using Risk ratios or odds ratio when appropriate. All analyses were conducted in Comprehensive Meta-Analysis, Englewood, NJ) and StatsDirect statistical software (England, StatsDirect Ltd, 2013

Strength of Evidence Rating. We also rated the strength of evidence on each of the primary outcomes using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach using the major domains of risk of bias, imprecision, inconsistency, strength of association and publication bias.[6]

Ethical approval and Funding. We did not obtain ethical approval since the study was a systematic review of summary data. There were no sources of funding for this study.

RESULTS

Systematic search. We screened 2080 citations and identified 8 controlled studies and 36 uncontrolled studies that were eligible for inclusion. The process of study selection is shown in **Figure 1**. The baseline characteristics of the uncontrolled and controlled studies are shown in the **Supporting Information Table 1** and **Supporting Information Table 2**, respectively. The incidence and recurrence of HCC associated with oral DAAs in controlled and uncontrolled studies are shown in the Supporting Information **Supporting Information Table 3** and **Supporting Information Table 4**, respectively. The risk of bias of all included studies is shown in **Supporting Information Table 5**.

Study characteristics.

There were 29 uncontrolled studies that evaluated incident HCC,[7-11 12-36] while 12 studies reported on recurrent HCC. [9-11 14 17 29 37-42] Some studies reported on both incident and recurrent HCC. The uncontrolled studies encompassed a diverse range of patients, with some single-center studies but also many other multicenter or global cohorts. Treatment durations tended to be 12-24 weeks with different antiviral combinations in the cohorts. Follow-up was also highly varied, ranging from 12 weeks to 70 months. Among the 29 uncontrolled studies, 18 studies had a minimum follow up duration of 24 weeks. The mean age of participants in each study ranged from about 50 years to 72 years.

Five controlled studies reported on incident HCC in those receiving DAA as compared to controls.[22 38 43-45] Recurrent HCC was monitored in 3 studies, two of which were part of the ANRS cohort (HEPATHER and CirviR).[46 11 47]The controlled observational studies were conducted in UK, Japan, US, and France. Treatment duration was typically 12-24 weeks, whereas follow-up ranged was up to 416 weeks. The average age of participants in the studies varied from 51 years to 73 years. A wide variety of oral DAAs were evaluated, whereas the control groups tended to be participants who did not have any treatment, historical controls or received combination of interferon and Ribavarin.

Primary analyses

Proportion of incident HCC associated with DAAs in uncontrolled cohorts. A total of 543 cases of HCC were reported in the 38177 participants on Oral DAAs among the 18 uncontrolled studies. The random effects meta-analysis of 29 studies yielded a pooled proportion of 1.5 % [95% CI, 1.1%-2.1%; I^2=90.1%) for incident HCC with evidence of substantial statistical heterogeneity among the included studies as shown in **Figure 2**.

Proportion of incident HCC associated with DAAs in controlled cohorts. Among 5 controlled cohort studies the pooled proportion of patients who had incident HCC while on treatment with oral DAAs was 3.3% (95 % CI 1.2% to 9%; I^2 =96%), with evidence of substantial statistical heterogeneity among the included studies as shown in **Figure 3**.

Proportion of recurrent HCC associated with DAAs in uncontrolled cohorts. There were 136 cases of recurrent HCC among 867 participants in 12 uncontrolled studies. The random effects meta-analysis of 12 studies yielded a pooled proportion of 16.7% (95 % CI 10.2% to

26%; I^2=84.8) with evidence of substantial statistical heterogeneity among the included studies as shown in **Figure 4**. Estimates of individual studies ranged from as low as 0% (in a study that included only 8 participants with preexisting HCC[41] to as high as 42.6%.[39]

Proportion of recurrent HCC associated with DAAs in controlled cohorts. There were 36 cases of recurrent HCC among 225 participants on oral DAAs in the controlled cohort studies, which yielded a pooled proportion of 20.1% (95 % CI 5.5% to 52.1%; I^2 =87.5 %) with evidence of substantial statistical heterogeneity among the included studies as shown in **Figure 5**.

Relative Risk of incident or recurrent HCC associated with oral DAA in controlled cohorts. We did not conduct a meta-analysis of risk ratios or odds ratios comparing the oral DAA and control arms on incident HCC because of varying levels of clinical heterogeneity, follow-up and the choice of comparators. [22 38 43-45] Among the 5 controlled cohort studies that reported on incident HCC, there were 36 HCC recurrences in 225 patients having DAA, as compared to 253 cases of HCC among 4828 control patients (5.2%). Kobayashi et al. reported no significant differences in newly diagnosed HCC between the DAA and IFN/RBV group at 3-year and 5-year follow-up. [44]Similarly, Li et al. reported a hazard ratio of 1.07 (95% CI 0.55 to 2.08) for HCC in the DAA group as compared to IFN group.[22]

Among the 3 studies that reported on recurrent HCC, [46 11 47] there were 36 HCC recurrences (16%) in 225 patients having DAA, as compared to 80 recurrences (42.3%) in 189 control patients. The relative risk meta-analysis [46 11 47] of these showed RR 0.50 (95% CI, 0.16 to 1.59; I^2 =73.4%) for recurrent HCC which was not statistically significant as shown in **Figure 6**.

Secondary analysis.

Proportion of incident HCC associated with DAAs in uncontrolled cohorts irrespective of follow up duration

A total of 567 cases of HCC were reported in the 48 327 participants on Oral DAAs among the 29 uncontrolled studies. The random effects meta-analysis of 29 studies yielded a pooled proportion of 1.2 % [95% CI, 0.09%-1.6%; I^2=87.6%) for incident HCC with evidence of substantial statistical heterogeneity among the included studies as shown in **Supplementary Figure 1**. The proportion varied from as low as 0.06% to 4.83% due to clinical heterogeneity and variation in method of and duration of follow-up.

Sensitivity analysis. The results of the fixed effect analysis for the above outcomes are shown in Supplementary **Table 6**.

Risk of bias and GRADE assessment. Most of the studies were considered to have reliable data on the actual use of antiviral therapies. Selection of controls was not always well-defined and there were differences in the baseline variables between the DAA treated participants and the control group. The handling of confounding variables and statistical adjustment was poorly reported. Specific active ascertainment for HCC was performed in 6 controlled cohorts and 10 of the uncontrolled cohorts. The lack of active surveillance may result in an underestimate of the risk. The GRADE of evidence was designated as low for each of these outcomes because of imprecision of summary estimates, substantial heterogeneity, and high risk of bias.

DISCUSSION

Our findings show that the estimates for incident HCC range from ≈ 1. 5 % in uncontrolled cohorts to ≈ 3.8% in controlled cohorts in patients with chronic active hepatitis C. Our meta-

analysis shows that the estimates for recurrent HCC range from ≈ 16.7 % in uncontrolled cohorts to ≈ 21.7 % in controlled cohorts (**Supplementary Figure 1**). Assuming baseline proportions seen in the uncontrolled cohort studies, approximately 1 among 67 participants who use an oral DAAs would develop incident HCC, and approximately 1 among 6 participants oral DAA users would develop recurrent HCC. The meta-analysis of recurrent HCC from controlled studies showed a ≈ 50 % reduction in the risk of HCC which was not statistically significant. The overall quality of the evidence was low for each of the outcomes and comparisons. In the absence of high quality-controlled cohorts with long term follow-up, our findings can neither confirm nor rule out, an increase or decrease in the risk of incident or recurrent HCC after oral DAA therapy.

***Comparison with other studies*.** There are some similarities and differences between and our findings and other meta-analysis. A previous meta-analysis reported a low rate of 2.96/100 Person-Years (95 % CI 1.76-4.96) for HCC occurrence from 9 studies and a rate of 12.16/100 PYs / (95 % CI 5 to 29.8) for recurrent HCC from 10 studies. [3] Our database of included studies for the risk of HCC associated with oral DAAs was substantially larger (n=44), and we included participants irrespective of the stage of liver disease,[48] and also assessed HCC either as an adverse event or as a prespecified outcome irrespective of whether participants achieved SVR. In contrast, the other meta-analysis excluded patients without cirrhosis, or those who had a subset of cirrhosis, or those without clear delineation of HCC outcomes, and was restricted to participants with chronic HCV who had undergone curative treatment. Our findings should be interpreted in the context of the historical rates of HCC reported with untreated chronic hepatitis C or the risk of HCC reported with interferon-based treatments, although these populations are not directly comparable as patients treated with oral DAAs have more advanced liver disease as compared to historical interferon-based controls. Among patient chronic active hepatitis c, the

rate of HCC is around 1-3% per year and higher among those with cirrhosis. In a Japanese cohort study, the presence of HCV antibody was associated with a more than fourfold increased risk of liver cancer (RR 4.09, 95 % CI 1.30 to 12.85) (age range = 40-79 years; % cirrhosis) over a three-year period.[49] The other meta-analysis reported incident rates for HCC occurrence [1.14/100 PYs [95% CI 0.86-1.52)] and recurrence [9.21/100 PYs (95% CI 7.18 - 11.81)] associated with interferon-based treatment[3]. Another meta-analysis of observational studies reported a substantial (≈ 77%) reduction in the risk of HCC with IFN-based treatments in patients with fibrosis and advanced liver disease compared to untreated controls. [50]

The precise biological mechanisms by which oral DAA may influence the risk of HCC is unknown. Alterations in immunosurveillance that remove the protective effective of the hepatitis c virus may potentiate the risk of HCC by accelerating the process of regeneration. Studies have shown an increase in the levels of vascular endothelial growth factor (VEGF) after 4 weeks of therapy with oral DAA therapy and alteration balance between inflammatory and anti-inflammatory processes. [51] Additionally, it is possible that the immunostimulatory effects of interferon may have offered some protection in earlier studies. Several studies in our meta-analysis included participants who had undergone non-curative treatment of HCC, where HCC may reflect reactivation of residual foci of untreated HCC. The high proportion of recurrent HCC among patients treated with oral DAAs may reflect the underlying severity of the disease being treated, as participants with advanced liver disease are eligible for treatment with DAAs, where such participants may have been ineligible for treatment with interferon-based regimens. Finally, ascertainment biases where some tumors which were previously undetectable were

radiographically identified after treatment with oral DAAs may be another potential explanation of our findings.

Limitations. Our meta-analysis has some limitations which primarily reflect the quality of reported data. The duration of follow-up may have been limited to detect the long-term risk of hepatocellular carcinoma as most of the included studies were of short duration. In the absence of patient-level data, we did not evaluate time to event, and determine the influence of geographic location, presence of genotype 1, alcohol use, concomitant hepatitis B, serum alpha-fetoprotein levels and stage of cirrhosis on the rate of development of HCC, as meta-regression based on summary data may be prone to ecological biases. [52] We cannot rule out the presence of length time bias because the data did not allow us to distinguish between the development of fast vs slow growing tumors, and distinguish between early recurrent HCC which may reflect tumor metastases (< 2 years) vs late development of second primary tumors (> 2 years). [53] The estimates for incident HCC may also reflect recurrent HCC as some studies did not clarify that they reliably excluded HCC at baseline. We excluded studies with < 100 participants for incident HCC, as these studies may be susceptible to small study effects. We did not evaluate the differences in rates between individual members of the class of DAAs although there are no biological reasons to suspect any such differences on the risk of hepatocellular carcinoma. We did not include non-English studies which may have biased our estimates.

Implications. Our findings have implications for clinical practice and research. Our findings demonstrate that recurrent HCC is common in patients who are taking oral DAAs, and clinicians should therefore remain vigilant and implement regular monitoring even after achieving a

sustained virologic response. Future studies should be designed with adequate follow up and latency as HCC occurring immediately after treatment may reflect preexisting HCC. [53]

Such studies should use standardized definitions of HCC, conduct periodic surveillance using established radiographic protocols, and evaluate the influence of DAAs on clinical outcomes beyond sustained virologic response. [2] Studies should also evaluate the influence of other variables such as presence of GT1, alcohol use, concomitant hepatitis B, serum alpha-fetoprotein levels and stage of cirrhosis. Study designs that incorporate the evaluate the potential therapeutic benefits of oral DAAs earlier during the course of chronic hepatitis C, before the development of advanced cirrhosis vs strategies that involve treatment with oral DAAs after the onset of more advanced liver disease may offer additional insight. Finally, the influence of SVR induced by these agents on other important patient centered outcomes such as hepatic encephalopathy, liver failure, gastrointestinal bleeding, portal hypertension, hepatic encephalopathy, hepatorenal syndrome and mortality should also be evaluated in such studies.

Conclusions. Our findings show low proportion of incident HCC, but high proportion of recurrent HCC on treatment with oral DAAs in patients with chronic active hepatitis C. Regardless of the whether high proportion of recurrence of HCC reflect the influence of the drug or the severity of the disease continued active surveillance for HCC after treatment remains prudent.

Contributors

SS, AN, YKL contributed to the manuscript by planning the study and reviewing the literature. All the authors collected the data. SS did the meta-analysis. All authors contributed to the assessment and interpretation of data. All authors read, revised and approved the final version of the manuscript.

Competing interest

: None declared

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