Risk of Hepatocellular Carcinoma Recurrence After the Use of Direct-Acting Antivirals in the Treatment of Hepatitis C: Systematic Review and Metanalysis

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Risco de Recorrência do Carcinoma Hepatocelular após o Uso de Antivirais de Ação Direta no Tratamento de Hepatite C: Revisão Sistemática e Metanálise

Riesgo de Recurrencia del Carcinoma Hepatocelular tras el Uso de Antivirales de Acción Directa en el Tratamiento de la Hepatitis C: Revisión Sistemática y Metanálisis

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ABSTRACT

Introduction: Hepatitis C is associated with the development of hepatocellular carcinoma (HCC). The interferon-based therapeutic regimen has been replaced by direct-acting antivirals (DAA) to treat HCV virus infection. However, recent studies have shown an unexpected increase in HCC recurrence in patients treated with DAA to resolve hepatitis C. **Objective**: To assess the risk of hepatocarcinoma recurrence after using DAA in patients with HCV infection. **Method**: A survey was carried out in PubMed, MEDLINE, and LILACS databases according to the descriptors DeCS/MeSH ((hepatocellular carcinoma) AND recurrence) AND Direct-acting antiviral. The review followed the PRISMA protocol and is registered on the PROSPERO platform. The data statistical analysis was performed through RStudio software. **Results**: Seven articles were selected resulting in 847 patients. Among those treated with DAA, the recurrence rate varied between 11.1% to 42.1% and, in the control group, it occurred in 5% to 65.6% of the patients. The relative risk (RR) of recurrence of HCC in the group of patients who received DAA was less than the risk evidenced in the control group, although there is no statistical significance (RR 0.71 95% CI [0.55; 0.93] I^2=38%, p=0.14). The mean time until the diagnosis of recurrence was 9.35 months in the group exposed to therapy and 13.42 months in the control group. **Conclusion**: It is suggested that therapy with DAA does not increase the risk of HCC recurrence compared to control groups. In patients who developed recurrence, it occurred more frequently within the first year after the introduction of DAA.

Key words: Carcinoma, Hepatocellular/etiology; Recurrence; Antiviral Agents; Hepatitis C/complications.

RESUMO

Introdução: A hepatite C está associada ao desenvolvimento do carcinoma hepatocelular (CHC). O regime terapêutico baseado em interferon vem sendo substituído pelos antivirais de ação direta (AAD) para tratamento da infecção pelo vírus da hepatite C (HCV). Contudo, estudos recentes evidenciaram um aumento inesperado da recorrência do CHC em pacientes tratados com AAD para resolução da hepatite C. **Objetivo**: Avaliar o risco de recorrência de hepatocarcinoma após uso de AAD em pacientes com infecção por HCV. **Método**: Realizou-se um levantamento nas bases de dados PubMed, MEDLINE e LILACS de acordo com os descritores DeCS/MeSH ((*hepatocellular carcinoma*) *AND recurrence*) *AND Direct-acting antiviral.* A revisão obedeceu ao protocolo PRISMA e está cadastrada na plataforma PROSPERO. A análise estatística dos dados foi realizada no *software* RStudio. **Resultados**: Sete artigos foram selecionados resultando em 847 pacientes. Entre os tratados com AAD, a taxa de recorrência variou entre 11,1% e 42,1% e, no grupo controle, ocorreu em 5% a 65,6% dos pacientes. O risco relativo (RR) de recorrência do CHC no grupo de pacientes que recebeu AAD foi menor do que o risco evidenciado no grupo controle, apesar de não haver significância estatística (RR 0,71 95% IC [0,55;0,93] I^2=38%, p=0,14). O tempo até o diagnóstico da recorrência teve uma média de 9,35 meses no grupo exposto à terapia e 13,42 meses no grupo controle. **Conclusão:** Sugere-se que a terapia com AAD não aumenta o risco de recorrência do CHC em comparação com grupos controle. Nos pacientes que desenvolveram recorrência, ocorreu com maior frequência dentro do primeiro ano após introdução dos AAD.

Palavras-chave: Carcinoma Hepatocelular/etiologia; Recidiva; Antivirais; Hepatite C/complicações.

RESUMEN

Introducción: La hepatitis C está asociada con el desarrollo de carcinoma hepatocelular (CHC). El régimen terapéutico basado en interferón ha sido reemplazado por antivirales de acción directa (AAD) para tratar la infección por VHC. Sin embargo, estudios recientes han mostrado un incremento inesperado en la recurrencia del CHC en pacientes tratados con AAD para resolución de la hepatitis C. **Objetivo**: Evaluar el riesgo de recurrencia del hepatocarcinoma después de usar AAD en pacientes con infección por VHC. **Método**: Se realizó una pesquisa en las bases de datos PubMed, MEDLINE y LILACS según los descriptores DeCS/MeSH ((carcinoma hepatocelular) AND recurrencia) AND antiviral de acción directa. La revisión siguió el protocolo PRISMA y está registrada en la plataforma PROSPERO. El análisis estadístico de los datos se realizó mediante el software RStudio. **Resultados**: Fueron seleccionados 7 artículos resultando en 847 pacientes. Entre los tratados con AAD, la tasa de recurrencia varió entre el 11,1% y el 42,1% y, en el grupo de control, ocurrió entre el 5% y el 65,6% de los pacientes. El riesgo relativo (RR) de recurrencia del CHC en el grupo de pacientes que recibieron AAD fue inferior que el riesgo evidenciado en el grupo control, aunque no hay significación estadística (RR 0,71; IC del 95% [0,55; 0,93] I^2=38%, p=0,14). El tiempo hasta el diagnóstico de recidiva fue de 9,35 meses en el grupo expuesto a terapia y de 13,42 meses en el grupo control. **Conclusión**: Se sugiere que la terapia con AAD no aumenta el riesgo de recurrencia del CHC en comparación con los grupos control. En los pacientes que desarrollaron recurrencia, esta ocurrió con mayor frecuencia durante el primer año después de la introducción de los AAD.

Palabras clave: Carcinoma Hepatocelular/etiología; Recurrencia; Antivirales; Hepatitis C/complicaciones.

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INTRODUCTION

The hepatitis C virus (HCV) infection is the second viral hepatitis most common in Brazil. From 1999 to 2018, 228,695 cases of hepatitis C were notified in the country, corresponding to 36.1% of the total cases of viral hepatitis. It is an important cause of morbidity and mortality, the main cause of the chronic liver disease, and associated with several complications[2,3]. The HCV-related mortality accounts for 76% of the cases of death by viral hepatitis in Brazil[1].

Hepatitis C is strongly associated with the development of hepatocellular carcinoma (HCC), increasing in approximately 15 to 20-fold the risk of development of this neoplasm[3,4]. When the cirrhosis process is installed, the rate of development of HCC is nearly 1% to 4% annually[3]. In 2020, the estimated number of new cases of liver neoplasms in Brazil was 12,674[5], the sixth cause of mortality by cancer in men and the eighth in women in the country[6]. Further to HCC, hepatitis C is related to hepatic insufficiency and cirrhosis decompensation, in addition to several extrahepatic manifestations and may include liver transplantation[2].

The HCV infection treatment has the objective of eliminating the infection, reduce the transmissibility rates and the risk of developing hepatocellular carcinoma[3]. Until recently, anti-HCV therapy was based in IFN regimen which ensured the cure or sustained virologic response (SVR)/HCV-RNA indetectable from 12 weeks after the end of the treatment)[7] in approximately 50% of the patients. For the patients who reached SVR, HCC incidence reduced and recurrence after curative therapy reduced as well. The mechanism of this phenomenon is unclear – whether related to sustained viral response (SVR) or IFN[8,9]-related immune-mediated antitumor effect.

IFN-α is a cytokine with antiviral, immunomodulatory and antiproliferative activity through the inhibition of the transcription, translation, processing, post-translation, maturation and viral liberation[8]. It has a better response when combined with ribavirin (analogous of guanosine) and a process of pegylation (attachment of one molecule of polyethylenoglycol to the molecule of IFN to extend its half-life, allowing the administration of the drug weekly)[8,10].

In despite of this, the IFN-based regimens have high toxicity, mostly hematologic, autoimmune, neurologic and psychiatric, in addition to symptoms as fever, chills, headache, myalgia, arthralgia, nausea, vomits, and diarrhea occurring after their intravenous administration. Furthermore, the prolonged duration of the treatment, the high cost and the resulting lower adherence led to the discontinuation of this treatment[8,11]. Consequently, it was attempted to pursue new therapies able to replace the IFN-based regimens[4].

Among the innovations conquered in this area, one of them was the discovery of the direct-acting antivirals (DAA) which improved the profile of tolerability of the patients who reached cure rates of HCV for more than 90% of them[4]. DAA are drugs acting in defined mollecular targets. There are three main classes of DAA: protease inhibitors NS3 (boceprevir, telaprevir, simeprevir, asunaprevir, paritaprevir and grazoprevir); NS5A inhibitors (daclatasvir, ledipasvir, ombitasvir, elbasvir and velpatasvir), and polymerase inhibitors NS5B (sofosbuvir and dasabuvir). These drugs block the processing, replication and viral assembly[10,12].

However, for being a recent therapy, medium and long-term effects are little known. Some studies suggest that DAA are beneficial for HCV treatment as the ability to reduce the hepatic venous pressure gradient in cirrhotic patients with portal hypertension because of modifications in the liver consistency[4], and improvement of the liver function, decreasing the risk of HCC incidence. Other benefits include the dispensation of the coadministration of ribavirin in most of the cases (except in patients with decompensated cirrhosis) and reduced duration of the treatment to eight to 12 weeks only, much lower when compared with the duration of IFN therapy[9,13-15].

Furthermore, DAA are administered orally, with few significant adverse events and are well tolerated by most patients[14]. The most common are headache, fatigue, nausea and diarrhea and occur in ≥ 1/10 patients; the levels of the enzyme glutamate-pyruvate transaminase (GPT) and bilirubin that can rise during the treatment with DAA must be monitored[16].

However, other studies brought evidence of a possible favoring of HCC recurrence in patients previously cured and treated with DAA. This hypothesis, nevertheless, is not a consensus in the scientific mean since some studies do not demonstrate this relation[4].

Therefore, the present study aims to evaluate HCC recurrence risk after the use of DAA in HCV-infected patients. The following research question was elaborated: does the risk of HCC recurrence increase after the use of DAA in HCV-infected patients?

METHOD

The current study is a systematic review with meta-analysis guided by the research question elaborated through PICO criteria (P: population/patients; I: intervention; C: comparison/control; O: outcome). In addition, the Preferred Reporting Items for Systematic Review and Meta-analysis Statement (PRISMA)

was followed for the methodological construction[17]. The present systematic review is registered in the International Prospective Register of Systematic Reviews (PROSPERO) to avoid duplications of scientific articles (ID: CRD42020182702).

The eligibility criteria were publications in the last five years (January 2015 to April 2020), controlled randomized clinical trials, case-control studies, prospective (or competing) cohort studies, trials involving already HCC-affected patients in remission, HCV-infected patients and patients submitted to DAA therapy for at least three months with any dosage or regimen. The exclusion criteria were articles which correlated the role of DAA only with the first neoplastic event and studies with participants younger than 18 years old.

The studies were identified in the databases MEDLINE, LILACS and PubMed utilizing the descriptors DeCS/MeSH: *((*hepatocellular carcinoma*)* AND recurrence*)* AND Direct-acting antiviral. The articles were selected pursuant to the method: search in the databases, exclusion of duplicate articles, review of titles and abstracts and matching to eligibility criteria.

After the selection, the studies were tabulated according to author, title, year of publication, geographic location and journal of publication. Later, they were analyzed and tabulated matched to the research, methods, objective and results obtained.

The Cochrane Risk of Bias In Non-randomized Studies of Interventions (ROBINS-I) tool was utilized to evaluate the risk of bias that the authors conducted and analyzed the studies selected independently. The ROBINS-I tool evaluates the overall risk of bias of non-randomized intervention studies through some domains: 2 pre-intervention (bias of domains of confusion and selection), 1 during the intervention (bias of classification of interventions) and 4 post-intervention (bias of deviation of interventions, missing data, outcome and selection of results reported). These domains are evaluated through signalling questions in the tool to help judge the risk of bias. The responses to these questions (yes/probably yes/probably no/no/without information) are responsible for providing the base for the judgment of the bias level of each domain which can be low, moderate, severe, critical or without information. The risk of overall bias occurs by the combined evaluation of the risks of bias of the domains. A low overall risk occurs when all the domains have low risk. The moderate risk of bias assumes that all the domains have low or moderate risk. If at least one of the domains presented severe risk and no domain presented a critical risk, then the overall risk is considered critical. When there is not enough information to evaluate the risk of bias of the domains or the overall risk, it is concluded that the evaluation has no information. Further details about the definition of the risks in each domain and of the process of evaluation can be found in the tool ROBINS-I and its user guide[18].

The software RStudio version 1.3.959 through the Mantel-Haenszel method was used to perform statistical analysis of the data collected. For each study, the proportion of patients who developed HCC recurrence with confidence interval of 95% was calculated. The relative risk (RR) was calculated according to the model of random effects of DerSimonian and Laird. The heterogeneity among the studies was evaluated by the index of inconsistency (I^2), with values >50% being consistent with the possibility of substantial heterogeneity. P was considered significant when <0.05.

The results were summarized and presented as a description containing the characteristics of the studies and synthesis of the results.

RESULTS

The pathway to select the studies commenced with the search in the databases with the descriptors mentioned, reaching 147 articles found in PubMed, two articles in LILACS and 34 articles in MEDLINE. After excluding the duplicate articles from the bases (n=31), 152 articles remained which were analyzed through reading of titles and abstracts and 138 articles were excluded.

Of the 138 articles excluded after reading the titles and abstracts, 54 articles did not respond to the research question and 84 failed to meet the eligibility criteria, 78 because of the study method (letter to editor, case report and series, meta-analyzes and retrospective cohort studies) and six for not having a control group.

The 14 articles selected in total were fully revaluated according to the eligibility criteria and matched to the research question, resulting in seven articles (Figure 1).

Therefore, the studies were organized in tables and specified per authors, year, title, place, objective and methodology (Chart 1).

The variables described in each study and the results were detailed and assigned comparatively (Table 1).

847 patients were addressed in the seven articles selected. Of these, 452 were exposed to DAA and 395 enrolled as control group. The HCC recurrence rate in patients exposed to antivirals ranged between 11.1% and 42.1%, mean of 26.7% (standard deviation [SD] ± 12.18), in contrast with the control group, whose variation was from 5% to 65.6%, with mean recurrence rate of 36.6% (SD±23.2).

The time to the diagnosis of the recurrence of the group exposed to the therapy was on average 9.35 months

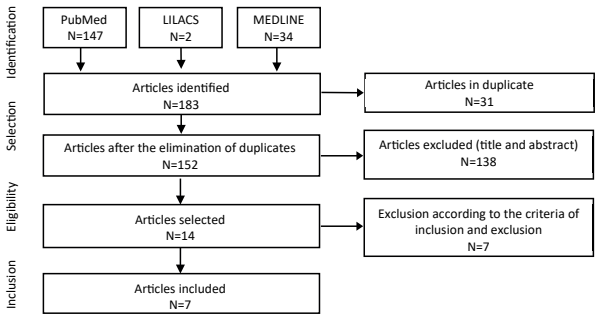


Figure 1. Selection Flowchart – PRISMA

(minimum 7 months and maximum 12 months) with SD±1.79). As for the control group, the mean was 13.42 months (minimum of ten and maximum of 17.7 months).

The follow up of patients evaluated in each study is summarized in this review with the following variables: time of observation, clinical, laboratory and imaging tests. It ranged between ten and 60.85 months with mean of 23.2 months, with quarterly, four-monthly or biannual physical exam, imaging (computed tomography and/or ultrasound of abdomen and/or magnetic resonance) and quarterly or biannual alpha fetoprotein dosage.

Chart 1. General characteristics of the studies included

Author/year	Title	Journal	Country	Objetive	Methodology
Ikeda et al., 2017[19]	*Direct-Acting Antivirals Decreased Tumor Recurrence After Initial Treatment of Hepatitis C Virus-Related Hepatocellular Carcinoma*	Digestive Diseases and Sciences	Tokio, Japan	Analyze the impact of IFN-free DAA in the recurrence rates of HCV-related HCC in patients with history of curative treatment of HCC	Retrospective cohort study. 89 patients with history of HCC submitted to DAA therapy. Time of administration was from 12 to 24 weeks. As control group, 89 patients did not receive any therapy
Warzyszyńska et al., 2017[20]	*Accelerated hepatocellular carcinoma recurrence rate after postoperative direct-acting antivirals treatment - Preliminary report*	Clinical and Experimental Hepatology	Warsaw, Poland	Observe the influence of DAA therapy on the timing and frequency of recurrence after surgical treatment of HCC	Case control study. 51 HCV infected patients were observed. Of these, 19 received DAA therapy and 32 did not receive antiviral regimen
Zanetto et al., 2017[21]	*Dropout rate from the liver transplant waiting list because of hepatocellular carcinoma progression in hepatitis C virus-infected patients treated with direct-acting antivirals*	Liver Transplantation	Padua, Italy	Investigate whether HCV patients treated with DAA have increased rate of tumor progression and wait-list dropout for transplantation at Padua Liver Transplant Center	Case-control retrospective study. 46 patients were selected; of these, 23 were submitted to antiviral treatment and 23 did not receive the therapy. Antiviral regimen adopted was 12 weeks
Adhoute et al., 2018[22]	*Hepatocellular carcinoma recurrence in hepatitis C virus-related cirrhosis treated with direct-acting antivirals: A case-control study*	European Journal of Gastroenterology and Hepatology	Barcelona, Spain	Investigate the impact of DAA in HCC recurrence after curative intent therapy	Case-control retrospective study. 71 patients were selected, of which, 22 received antiviral therapy and 49 did not. DAA regimen from 12 to 24 weeks
Cabibbo et al., 2019[23]	*Direct-acting antivirals after successful treatment of early hepatocellular carcinoma improve survival in HCV--cirrhotic patients*	Journal of Hepatology	Palermo, Italy	Assess whether DAA prolong the global survival of patients with compensated related to HCV and HCC treated previously	Case-control retrospective study. 204 patients were assessed, 102 received antiviral therapy and 102 did not. 12 weeks was the minimum therapy time
Jain et al., 2019[24]	*Is there increased risk of hepatocellular carcinoma recurrence in liver transplant patients with direct-acting antiviral therapy?*	Hepatology International	Hershey, USA	Compare the rate of HCC recurrence in LTx recipients who did or did not receive DAA therapy and analyze the factors that may have impacted the HCC recurrence	Case-control retrospective study. 47 HCV-positive patients were selected and subdivided in two groups. Group A consisted of 27 individuals who received antiviral therapy and group B, 20 patients who did not
Kuo et al., 2020[25]	*The influence of direct-acting antivirals in hepatitis C virus related hepatocellular carcinoma after curative treatment*	Investigational New Drugs	Taoyuan City, Taiwan	Elucidate the influence of direct-acting antiviral (DAA) agents on the recurrence of hepatocellular carcinoma (HCC) in patients with HCC related to HCV after curative therapies	Case-control retrospective study. The patients were divided in 3 groups: treated with DAA (82) patients, treated with IFN (80 patients) and untreated (160). Treatment duration was 12 weeks at least

Captions: DAA: direct-acting antiviral; HCV: hepatitis C virus; HCC: hepatocellular carcinoma; IFN: interferon.

Table 1. Clinical outcomes of the studies included

Study	Patients (n)		Recurrence rate (%)		Time until the diagnosis of recurrence (mean of months)		Time of follow up of patients (mean of months)	Methods of periodic evaluation
Author/year	Group treated with DAA	Control Group	Group treated with DAA	Control Group	Group treated with DAA	Control Group		
Ikeda et al., 2017[19]	177	89	25	46.5	NI	NI	20.7	CT and/or MR of abdomen every 3 to 4 months
Warzyszyńska et al., 2017[20]	19	32	42.1	65.6	8.8	17.7	NI	CT and/or MR of abdomen and AFP serum level dosage quarterly to semiannually
Zanetto et al., 2017[21]	23	23	12.5	8.3	7	12	10	CT and/or MR of abdomen quarterly in the first year and semiannual henceforth, dosage of AFP serum levels
Adhoute et al., 2018[22]	22	49	41	35	12	14	50	CT and MR of abdomen during the first 2 years of follow-up quarterly and semiannually henceforth, AFP serum dosage in the first 2 years of follow up quarterly and semiannually henceforth
Cabibbo et al., 2019[23]	102	102	27.5	37.3	NI	NI	19.47	Physical exam, lab tests, US abdomen, quarterly, CT or dynamic MR semiannually
Jain et al., 2019[24]	27	20	11.1	5	9.6	10	60.85	CT of chest, abdomen and pelvis with contrast or MR quarterly
Kuo et al., 2020[25]	82	160	27.5	58.8	NI	NI	NI	US of abdomen and AFP dosage quarterly

Captions: DAA: direct-acting antiviral; NI: no information; US: ultrasound; CT: computed tomography; MR: magnetic resonance; AFP: alpha fetoprotein

In Graph 1, the HCC recurrence risk among the DAA and control groups included in this review was evaluated through meta-analysis. The HCC recurrence RR in the group of patients receiving DAA was lower than the risk of the control group (RR 0.71 95% CI [0.55; 0.93] I^2=38%, p=0.14).

At last, the evaluation of the risk of bias was weighed according to the protocol ROBINS-I[18]. After all the domains were evaluated, overall risk of bias for each study was defined (Table 2).

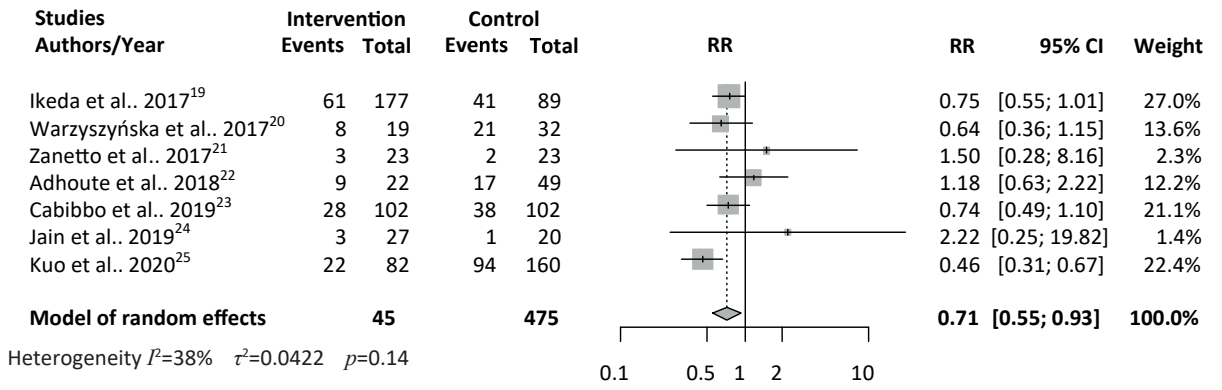
DISCUSSION

Some observational studies suggested a higher incidence of HCC and higher risk and aggressiveness (fast growth and vascular invasion) of HCC recurrence after DAA therapy[9,13]. Villani et al.[26] described possible routes of the unexpected physiopathological mechanism of HCC recurrence after the use of DAA. Among them, it stands out immune dysfunction, alteration of the cytokines network and activation of the neoangiogenesis caused by the action mechanisms of the DAA[26].

With the objective of elucidating what is the influence of DAA in HCC recurrence, the variables recurrence rate and time and follow-up found in the studies included in this review were compared with the data from other systematic reviews and meta-analyzes as described next.

The current study found a mean response rate of HCC recurrence of 26.7% in the group of patients treated with DAA, contrasting with the mean rate of 36.6% in the control group. The RR of HCC recurrence in the group of patients treated with DAA was lower than the risk of the control group (RR 0.71 05% CI [0.55; 0.93] I^2=38%, p=0.14). In spite of this, there was no statistical significance.

In a systematic review with meta-analysis involving 24 studies published between January 2015 and December 2017 (n=1,820 patients) Saraiya et al.[9] found a mean recurrence rate of 24.4% in the group of patients who received DAA therapy[9]. Guarino et al.[13] have also found



Graph 1. Forest plot to evaluate the HCC recurrence risk in the DAA and control groups (patients that did not receive any therapy)

Captions: RR = relative risk; CI= confidence interval.

Table 2. Evaluation of risk of bias – ROBINS-I

Study	Pre-intervention		Intervention	Post-intervention				Overall risk of bias
Author/year	Domains of confusion	Selection	Classification of interventions	Deviations of interventions	Missing data	Outcome	Selection of results reported	
Ikeda et al., 2017[19]	🙂	😐	🙂	🙂	🙂	😐	🙂	😐
Warzyszyńska et al., 2017[20]	🙂	😐	NI	🙂	🙂	🙂	🙂	😐
Zanetto et al., 2017[21]	😐	🙂	☹	🙂	🙂	🙂	🙂	☹
Adhoute et al., 2018[22]	😐	😐	🙂	🙂	🙂	🙂	🙂	😐
Cabibbo et al., 2019[23]	🙂	🙂	🙂	🙂	🙂	🙂	🙂	🙂
Jain et al., 2019[24]	NI	🙂	NI	🙂	🙂	🙂	🙂	😐
Kuo et al., 2020[25]	🙂	😐	😐	🙂	🙂	🙂	🙂	😐

Captions: 🙂 : low risk of bias; 😐 : moderate risk of bias; ☹ : high risk of bias; NI: no information.

a similar variable proportion of patients treated with DAA who developed HCC recurrence – from 0% to 47.9%[13].

Reinforcing the findings of the present study, the meta-regression of Waziry et al.[27], after adjustment of the studies included for age and follow-up demonstrated that DAA therapy was not associated with higher HCC recurrence (RR 0.62, 95% CI 0.11, 3.45, p=0.56)[27]. Cabibbo et al.[23] have also shown that the HCC recurrence rate in the group of patients receiving DAA was lower when compared with the control group, regardless of the lack of statistical significance (HR 0.70, 95% CI 0.44-1,13; p=0.15)[23]. The study of Ikeda et al.[19] brought statistical significance for the same data through multivariate analysis with a hazard ratio of 0.353 (95% CI 0.191-0.651) and p=0.001[19]. In addition, the cure of the HCV infection using DAA reduces the individual risk of HCC similarly to the IFN therapy. A previous meta-analysis estimated this reduction in 77% and the subgroup analysis of Waziry et al.[27] estimated the risk reduction in 63%.

The apparent higher risk of HCC incidence and recurrence associated with the use of DAA can be explained by the comparison of basal characteristics among the IFN and DAA groups of patients. In this last, the age and cirrhosis stage were more advanced – they are predictor factors of the HCC development[27]. This occurred because of the DAA safety profile which ensured that these drugs could be administered in patients who did not have previous indications for IFN treatment as, for instance, older patients, with advanced hepatic disease (Child-Pugh B and C), HIV-coinfected with decompensated cirrhosis, severe renal chronic disease and liver transplanted[10,19,22,28]. In this group of patients, the administration of IFN caused severe

adverse events and low rate of viral elimination[19]. Several studies point out that there is no difference in the rates of SVR using DAA in older patients according to Pariente et al.[29]. In this French study with chronic hepatitis C patients in use of DAA, a SVR of 91% was reached in population with mean age of 56 years. In the analysis of subgroups, patients with 51-56 years and older than 64 years had the highest SVR rates[29]. Another study of Elbaz et al.[30] with patients with mean age of 65.9 years had a SVR rate of 91.9% with the combined use of sofosbuvir + daclatasvir associated or not with ribavirin[30]. However, one of the limitations of this scenario relies in the fact that most of the phase II and III studies excludes patients older than 70-75 years and severe associated comorbidities. Another important conclusion of the French study was that the age in itself must not be considered as contraindication to the treatment with DAA, but the presence of associated comorbidities should be evaluated because of major odds of negative drug interactions and high development of adverse effects[29,31]. In addition, Keast et al.[31] showed that chronic hepatitis C patients while using concomitant drugs with DAA (HR 3,218, 95% CI 1,584-6,530, p=0.001) had higher therapeutic failure. The main significant interactions indicated were between DAA and proton pump inhibitors, benzodiazepines and inhibitors of calcium channels[31]. Among the combinations of the available DAA agents, a Spanish study pointed out that the combination of sofosbuvir and velpatasvir has lower number of clinically significant interactions[32]. These evidences suggest the necessity of conducting a proper selection of the patients for DAA therapy.

The factors most associated with HCC recurrence, according to Saraiya et al.[9] were the former history of HCC recurrence as Cabibbo et al.[23] and Ikeda et al.[19] reported in this review and short interval between the complete therapeutic response to HCC and the beginning of DAA. Other factors that can be associated with high recurrence rate are the elevated AFP serum levels, multifocal HCC, advanced hepatic disease, microscopic vascular invasion, histologic degree, presence of satellite nodes, patients who received TACE (transarterial chemoembolization) non-curative treatment which has more odds of recurrence or other non-curative therapies and patients who needed more than one curative intervention before the introduction of DAA[9,13,22,23]. Cabibbo et al.[23] have also reinforced in their study that SVR is an important independent predictor of the outcome of patients receiving DAA, both in terms of HCC recurrence or hepatic decompensation and mainly, mortality, being statistically significant (HR 0.02, 95% CI 0-0.19; p<0.001). This finding is more beneficial in a context of waitlist for liver transplantation where the use of DAA can prevent the removal from the list due to tumor progression or death of the patients. The author points out yet that the global survival of the group of patients who received DAA was higher than the control group who did not receive DAA in its study, being statistically significant (HR 0.39, 95% CI 0.17-0.91, p=0.03)[23].

The mean time between the introduction of DAA therapy and the diagnosis of recurrence was 9.35 months (SD±1.79). There was homogeneity among those authors who brought these data: of those who developed recurrence, it was earlier in the groups exposed to antivirals than the time of the control group whose incidence was delayed. Adhoute et al.[22] reported that HCC recurrence was significantly higher in patients treated with DAA in less than four months interval after the treatment[22]. Saraiya et al.[9] suggest precaution and wait at least six months after the complete response to HCC to introduce DAA[9].

Saraiya et al.[9], in short, expose heterogeneous results varying according to the follow-up time. However, the mean time was 23.2 months, higher than the mean time reported in the present study[9]. Guarino et al.[13] described concurrent data in the systematic review published in 2018. Among the results, the appearance of the recurrence was higher in the first 36 months, however, the distribution of the incidence during the period was not provided. Finally, these same authors point out that the frequency of the recurrence increases as times passes, growing 20%[13] annually.

Kuo et al.[25] indicate in their study that HCC patients are at risk either of early or late recurrences, the first are more related to the tumor intrinsic factors while the latter, to cirrhosis related factors as active viremia and severity of the hepatic deterioration[25]. Adhoute et al.[22] had also pointed out that early recurrences in an HCC context may have occurred because of indetectable tumors in imaging tests, usually related to cellular dissemination before the treatment or a new HCC occurrence in the cirrhotic liver[22].

Another possibility Reig et al.[33] indicated, related to the short period of time between HCC previous treatment and introduction of DAA is the drugs-induced abrupt interruption of the immune surveillance with the sudden resolution of the chronic inflammatory status leading to tumor progression[33]. In the study of Reig et al.[33], 27.6% of the patients developed radiologic tumoral recurrence after mean follow-up of 5.7 months[33].

The mean follow-up time of the patients in the present review was 23.2 months. Saraiya et al.[9] presented observation of at least three and maximum of 36 months[9]. Likewise, Guarino et al.[13] described a variation between three and 21.6 months. Therefore, the time of observation of the patients of the studies analyzed in the present review is higher than the systematic reviews already mentioned[13].

Saraiya et al.[9] and Guarino et al.[13] concurred about the modality of follow-up: physical, imaging and laboratory exams[9,13].

The data of the studies included in this review are conflicting and their methodologies have limitations. All the studies are case-control or cohort retrospective, possibly biased in relation to the patients enrolled. In addition, the groups evaluated are almost always very heterogeneous and few studies present adjusted-to-data analysis. Also, the studies showed very variable measurements as, for instance, time to recurrence which, in some studies is measured since the last curative treatment for HCC and in other studies, is considered from the beginning of the DAA therapy. Therefore, the quality of the data is questionable and consequently, studies with methodological rigor are necessary to reduce the risk of bias and produce data with better quality and reliability.

CONCLUSION

It is suggested that DAA therapy does not increase the RR of HCC recurrence in HCV-infected patients. When compared with IFN-based therapeutic regimen, the patients benefit with more efficacy (higher rate of RVS), less time of treatment, wider coverage and better profile of tolerability.

The results showed higher incidence in the first-year post-intervention in relation to the time between the introduction of the antiviral and the diagnosis of recurrence. However, the time of follow up of each clinical trial can impact this data. Among the patients who relapsed, there was homogeneity in the studies analyzed: the incidence was earlier in the patients exposed to DAA therapy.

The procedures applied to monitor the patients were common to all the studies analyzed and concurred with the previous literature. However, the time of follow-up of this review was positive when compared to the data already described.

More scientific production evaluating the long-term incidence of HCC recurrence and analyzing the time the patient is observed until the diagnosis is recommended.

CONTRIBUTIONS

All the authors contributed for the study conception, design, collection, analysis and interpretation of the data, wording, critical review and approved the final version to be published.

DECLARATION OF CONFLICT OF INTERESTS

There is no conflict of interests to declare.

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