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Hepatocellular Carcinoma after Treatment of Cirrhotic Hepatitis C Virus Patients with Direct Acting Antiviral Treatment

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Abstract: Earlier treatment plans based on the use of interferon (IFN) were characterized by a sustained virological response (SVR) of 40–50%.However, Since direct acting anti-viral therapy (DAAs) was introduced to treat chronic hepatitis (C) patients, there was a high rate of sustained virologic response (SVR) by 95% with a good safety profile and reduction in death rate as well as hepatocellular carcinoma (HCC). Despite this high rate of SVR, the risk of (HCC) was not eliminated. The data published in 2016 after DAAs therapy , were a source of worry regarding the appearance of HCC in the post treatment period whether as de novo or recurrence , in addition tumor characteristic after DAAs is more aggressive compared to post INF therapy , previous studies discovered that following DAAs tumors displayed aggressive behavior, had a larger number of nodules, and had extra hepatic metastases, demonstrating that cancer growth is faster than expected in these patients, this is because the use of powerful DAAs treatments may result in rapid viral clearance and reduce inflammatory cytokine responses .

Keywords: Hepatitis C virus, Sustained virologic response, Direct-acting antiviral therapy, Hepatocellular carcinoma, Liver cirrhosis.

1. HCV infection

Hepatitis C virus (HCV) is closely related to flaviviruses and pestiviruses. Its genetic organization and protein products classify it in the Flaviviridae family, although its diversity is great enough for it to be classified as a separate genus **[1]**. HCV is classified into eleven genotypes (designated as 1-11) differing in their nucleotide sequence by 30%-50%, six of them are the major ones (genotypes 1 to 6) **[2]**.

Infection with HCV accounts for approximately 15%-20% cases of acute hepatitis. After acute infection, around 50% to 80% of HCV patients will develop chronic infection. Approximately, HCV infects 170 million individuals worldwide **[3]**.

HCV occurs in all world health organization (WHO) regions. The highest burden of disease is in the Eastern Mediterranean Region and European Region, with 12 million people chronically infected in each region. In the South-East Asia Region and the Western Pacific Region, an estimated 10 million people in each region are chronically infected. Nine million people are chronically infected in the African Region and 5 million the Region of the Americas**[4]**.

Hepatitis C virus constitutes an epidemic in Egypt having the highest prevalence in the world of 13.9% among healthy populations and 78.5% among HCC cases, with 70,000 up to 140,000 newly reported cases annually. The Demographic National survey in Egypt in 2015 reported that people who aged (1-59 Y) had prevalence of anti-HCV antibody was 6.3% but the positive PCR HCV RNA was 4.4% **[5]**. With the introduction of effective direct-acting antiviral agents in 2014 to treat HCV infection, the National Committee for Control of Viral Hepatitis (NCCVH) set a national strategy to make treatment paid for by the Egyptian government available for all

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and to scale up treatment to millions, as described previously [6]. More than 2 million patients were treated by 2018 (representing 40% of the total HCV-infected population), with cure rates above 90%. However, most infected persons remained unidentified. By late 2017, the number of persons with new cases who presented for treatment decreased to less than 5000 a month, whereas the model to eliminate the disease by 2030 required diagnosing and treating 360,000 cases a year [7].

The economic burden of HCV infection in Egypt has been calculated previously, and it was estimated that the lifetime direct medical cost and indirect cost of disability and early death for a patient with HCV infection was in excess of $100,000 (in U.S. dollars) [8]. The cost of identifying and curing a patient in the current campaign was $131, which clearly shows the magnitude of cost saving by population screening [9].

The current screening program has shown that, although Egypt had treated more than 2 million patients since 2014, HCV infection was still a major problem by the start of this program in 2018, with 4.6% of the previously untreated adult population seropositive [9].

1.2 Development of hepatocellular carcinoma (HCC):

Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer in adults, and is the most common cause of death in people with cirrhosis. Hepatocellular carcinoma (HCC) is the fifth most common cancer and the second leading cause of cancer-related deaths [10].

Primary liver cancer is the seventh-most frequently occurring cancer in the world and the second-most common cause of cancer mortality [11]. The highest incidence rates in the world are found in Asia and Africa [12]. Globally, hepatocellular carcinoma (HCC) is the dominant type of liver cancer, accounting for ~75% of all liver cancers [12]. Incidence rates of HCC have been decreasing in some high-rate areas, but increasing in many low-rate areas [13].

Liver cancer accounts for 11.75 % of all digestive organ cancers and for 1.68 % of all cancers in Egypt. In the Egyptian population, HCC represent 70.48 percent of all hepatic tumours. HCC is the most common cirrhosis consequence, and its frequency is increasing in Egypt [14]. Hepatocellular carcinoma (HCC) mostly occurs in people with cirrhosis of the liver, and so risk factors generally include factors which cause chronic liver disease that may lead to cirrhosis include hepatitis B viral (HBV) infection , chronic hepatitis C viral (HCV) infection, hereditary hemochromatosis and alcohol [15].

A strong association between chronic HCV infection and HCC has been observed, but the mechanisms involved in carcinogenesis remain unclear [16]. The suggested association is caused by indirect pathway by causing chronic inflammation, cell death, proliferation, and cirrhosis. HCV genomes can be detected in the tumor and surrounding liver tissues for an association with the genotype of HCV and HCC, the incidence of genotype 1b is markedly high among the patients where it is associated with a more rapid deterioration of the liver histology in chronic hepatitis [17].

By interacting to retinoblastoma protein, which controls cell division and promotes its breakdown, NS5B leads to cell cycle disruption and therefore HCC formation. By altering RAF/mitogen-activated protein kinase/extracellular signal-regulated kinase-regulated pathways, the additional products E2, NS3, and NS5A promote aggressive HCC growth. NS2, NS3, and NS5A are examples of products that block p53, resulting in an aberrant cell cycle and death [18].

DAAs therapy targeting viral proteins such as NS3/4A protease, NS5B polymerase, as well as the NS5A replication complex accomplishing SVR in more than 95 percent of patients also keeping a consistent safety profile as well as excellent tolerability. [19-21]. Despite evidence that SVR protects against HCC development, a number of studies published between 2016 and 2021 revealed a surprising rise in occurrence, recurrence, and severity of HCC in cirrhotic HCV patients after DAAs treatment [22-26]. Other studies have not consistently verified comparable results. The controversy concerning the danger of developing HCC following HCV clearance by DAAs as well as DAAs' possible role in hepatic carcinogenesis has aroused intense discussion [27, 28]. Table 1 shows denovo occurrence of hepatocellular carcinoma in patient treated with DAAs

2. Drugs used in treatment of HCV:

Prior to 2014, Peg-interferon and ribavirin were used in conjunction to treat HCV, with one injection per week and Ribavirin doses ranging from 1,000 to 1,200 mg per day for forty-eight weeks. Despite its potent antiviral activity, interferon has low specificity against HCV and a low sustained virologic response [29]. Interferon (IFN)-based therapy tends to decrease hepatocellular carcinoma (HCC) in chronic HCV infection patients who achieve SVR even though IFN-based therapy is restricted by its multiple negative effects, non-oral administration, and unsatisfying SVR rate [30].

Table 1. Studies show de novo hepatocellular carcinoma occurrence.

REFERENCES	**Study type**	**Patient characteristic**	**Follow up period**	**incidence of Newley developed HCC**
Singer et al (2018) [48]	Retrospective	DAAs treated	12 months	1.18%
Nahoon et al (2018) [47]	Retrospective	Compensate cirrhotic patient take DAAS	21.2 months	2.6%
Waizary et al (2017) [50]	Meta analysis	Patient treated with DAAs	12 months	2.96%
Ravi et al (2017) [24]	Retrospective	Cirrhotic patient treated with DAAs n= 66	6 months	9%
Cardoso et al. (2016)[54]	Prospective	Cirrhotic HCV patient treated with DAAs	12 months	7.4%
Conti et al (2016) [45]	Retrospective	Cirrhotic HCV patient treated with DAAs	5.6 months	3.16 %
Calvarsu et al. (2018)[56]	Prospective	Cirrhotic HCV patient treated with DAAs	16 months	3.5%
Kanwal et al. (2017) [52]	Retrospective	Cirrhotic HCV patient treated with DAAs	12 months	1.82 %
Shiha et al (2020) [53]	Prospective	Cirrhotic HCV patient treated with DAAs	12months	2.3%
Pinaro et al. (2019) [33]	Prospective	Cirrhotic and non cirrhotic HCV patient treated with DAAs .	16 months	3%

When compared with patients lacking SVR or with untreated patients, IFN-based therapy offered a therapeutic advantage in CHC virus patients who achieved SVR, with a substantial delay of disease progression and comorbidities, including HCC [31]. In IFN-treated patients who achieve SVR, the presence of HCC is associated with advanced age, male gender, advanced liver fibrosis, fatty liver, and a high level of AFP in the blood following treatment [32]. IFN-based therapy was not really a suitable therapeutic option for people with chronic HCV related liver cirrhosis infection due to its limited inclusion requirements, minimal SVR rates, and extensive treatment-related toxicity. The remarkable cure rates of DAAs regimens since their introduction have generated wish that the natural advancement of HCV-related cirrhosis may be improved, including a decline in the rate of HCC [33].

DAAs are molecules that target specific nonstructural proteins of the virus and results in disruption of viral replication and infection. There are four classes of DAAs, which are defined by their mechanism of action and therapeutic target. The four classes are nonstructural proteins 3/4A (NS3/4A) protease inhibitors (PIs), NS5B nucleoside polymerase inhibitors (NPIs), NS5B non-nucleoside polymerase inhibitors (NNPIs), and NS5A inhibitors. Direct-acting antivirals are inhibitors of the NS3/4A protease, the NS5A protein, and the NS5B polymerase [34].

NS3/4A protease inhibitors are inhibitors of the NS3/4A serine protease, an enzyme involved in post-translational processing and replication of

HCV. Protease inhibitors disrupt HCV by blocking the NS3 catalytic site or the NS3/NS4A interaction [35]. The first generation protease inhibitors telaprevir and boceprevir were the first direct-acting antivirals available for the treatment of HCV, and were used in conjunction with peginterferon and ribavirin for the treatment of genotype 1 infection [36]. Other drugs in this category include glecaprevir, grazoprevir, paritaprevir, simeprevir and voxilaprevir [37].

The NS5A protein plays a role in both viral replication and the assembly of the HCV. They also result in very high SVR rates among patients with genotype 1 infection when given in combination with other direct-acting antivirals with or without ribavirin [38]. This class includes **Daclatasvir**, elbasvir, ledipasvir. ombitasvir, pibrentasvir: and velpatasvir [39].

NS5B is an RNA-dependent RNA polymerase involved in post-translational processing that is necessary for replication of HCV. The enzyme has a catalytic site for nucleoside binding and at least four other sites at which a non-nucleoside compound can bind and cause allosteric alteration. The enzyme's structure is highly conserved across all HCV genotypes, giving agents that inhibit NS5B efficacy against all six genotypes [35] .

There are two classes of polymerase inhibitors: NPIs and non-nucleoside analogues (NNPIs). The NPIs target the catalytic site of NS5B and result in chain termination, while NNPIs act as allosteric inhibitors [40].

Nucleot(s)ide polymerase inhibitors (NPIs) are activated within the hepatocyte through phosphorylation to nucleoside triphosphate, which competes with nucleotides, resulting in chain termination during RNA replication of the viral genome [41]

Sofosbuvir is the first NS5B NPIs to be available in the United States. Sofosbuvir is used in various combinations with other antivirals for different indications [40].

The objective of treatment is to cure HCV, decrease or stop fibrosis advancement and prevent cirrhosis development, allowing patients to live longer, symptom-free lives. Most studies use persistent virologic response as a surrogate parameter to evaluate treatment success, therefore DAAs is associated with better outcomes; such as a reduced chance of viral recurrence, lower mortality and decreased incidence of cirrhosis and hepatocellular carcinoma [42].

All-oral direct antivirals produce SVR in more than 95 percent of patients while maintaining a good safety profile and tolerance, and targeting viral proteins such as NS3/4A protease, NS5B polymerase, and NS5A replication complex. [19-21].

Despite the fact that DAAs has provided chronic HCV patients with a safe and effective treatment option, there are still challenges to face. These challenges include the presence of resistant variations as well as reduced efficacy in persons with cirrhosis [43]. However, outcomes from two studies published in 2016 raised issues regarding the high risk of hepatocellular carcinoma and recurrence after the use of DAAs [44, 45]. Conflicting findings extended the debate and cast doubt on the connection between DAAs therapy and HCC [46] .

3. DAAs and the risk of HCC development

The majority of research found that DAAs treatment can lower the chance of developing HCC. From 2006 to 2012, a comprehensive prospective research including 1270 CHC patients with hepatitis C infection was conducted at 35 locations in France and found that DAAs were not associated with a significant increase in the probability of HCC growth [47]. In another large retrospective cohort study, at baseline, DAAs-treated patients were older, mostly males, and had more cirrhosis than untreated CHC patients comparing 30,183 DAAs-treated patients to 137,502 untreated patients. The research revealed that DAAs treatment was linked to a substantially decrease incidence of HCC when it became in comparison to no treatment after being adjusted for age, gender, co-morbidities, and medication usage [48].

A prospective multicenter cohort trial in Latin America comprised 1400 F1-F4 patients treated with DAAs. The median time of follow-up from the start of DAAs therapy was 16 months and reaching SVR with DAAs protocols was linked with a 73% decrease in the relative risk for newly diagnosed HCC [33, 49].

Waziry et al., (2017) reported that according to a meta-analysis of 26 trials, DAAs medication is not associated with a higher risk of HCC in individuals with chronic HCV and cirrhosis. Despite certain methodological constraints, the authors reach the conclusion that there is no proof to support the theory that DAAs therapy raises the risk of HCC [50].

Ioannou et al., (2018) conducted a study that included almost 60,000 CHC patients who began antiviral medication with DAAs-only regimens. DAAs-induced SVR was linked to a 71% decrease in the prevalence of recently diagnosed HCC [51]. **Kanwal et al., (2017)** examined a retrospective

group of DAA-treated HCV patients**.** And found that Individuals who had an SVR had a considerably reduced incidence of HCC than those who did not [52]**.**

Shiha et al., (2020) evaluated 2400 patients in Egypt with advanced fibrosis to determine the prevalence of HCC in chronic hepatitis C patients' genotype 4 with liver cirrhosis and extensive hepatic fibrosis after achieving SVR with DAAs (F3-F4). He discovered that chronic hepatitis C genotype 4 patients with liver cirrhosis (F4) and severe hepatic fibrosis (F3) who achieved SVR with DAAs had a lower risk of HCC [53].

On the other hand, in two distinct research studies, DAAs were shown to increase the risk of hepatocellular cancer [54, 55]. Authors, one from Portugal and the other from Austria, reported an exceptionally high prevalence of HCC after DAAs-based HCV eradication. **Cardoso et al. (2016)** found that 7.4 percent of patients developed HCC after a year of viral clearance [54]. **Kozbial et al. (2016)** showed that 5.2 percent of patients developed de novo HCC after SVR with DAAs during a 48-week follow-up [55].

Calvaruso et al. (2018) who conducted his study on cirrhotic patients with HCV showed that (3.5 percent) had HCC over a 14-month average follow-up. In this cohort, a lack of SVR was associated with an increased risk of HCC [56.] In the research done by **Conti *et al.* (2016)** the potential for HCC risk was assessed in 285 cirrhotic individuals who had no history of HCC and who were treated with DAAs. Regardless of the fact that DAAs achieve SVR in 91% of patients, the researchers note that DAAs-induced SVR did not diminish the risk of HCC in the near run [45]. According, **Huang et al. (2018)** exposed the density of HCC formation and recurrence with DAAs and showed a higher risk of HCC incidence or recurring following DAAs treatments [57]

Hassany et al. (2020) reported that the incidence of HCC is considerably greater in patients with non-SVR (23.8 percent) and (6.7 percent) in patients having SVR in a sample of 350 HCV-related liver cirrhosis (LC) patients treated with DAAs [58]

4. Characteristics of tumour after DAAs therapy

Romano *et al.* (2015) found that, following DAAs, the tumour became more aggressive and was accompanied by a rise in the number of focal lesions and extrahepatic metastases, indicating the tumour growth is more rapid than normal in these patients [59]. Furthermore, **Renzulli *et al.* (2018)** discovered that HCC occurred at greater incidence after DAAs therapy and that microvascular invasion was aggressive in individuals with HCV-related cirrhosis [60].

Another study, conducted by **Faillaci *et al.*** (2018) showed that DAAs were linked to elevated levels of aggressiveness and tumour recurrence [61].

In their study, **Reig *et al.* (2016**) discovered the increased aggressiveness of HCC in individuals with HCV infection and a history of successfully treated HCC were included in the trial, who achieved full response and lacked 'non-characterized nodules' at the time of starting all-oral direct acting antiviral medication for their HCV infection [44].

In addition, **Khalid *et al.*, (2020)** in their study, which was conducted on 234 HCC patients, the final analysis included 171 HCV-related HCC patients labelled as "TN" (HCV Treatment Naïve) without a history of therapy or health file prior to HCC diagnosis) (n = 120) and "TH" (HCV infection was treated with a DAAs-based strategy) (n = 51) using Aggressiveness Index termed AgI score. According to the findings of the study, patients over the age of 55 in the TH group exhibited tumor aggressiveness (AgI score > 4) with proportion more than the TN group (57.7 vs. 42.3 percent) [62]

Abdelaziz *et al.* (2019) found that in patients who received DAAs, the pattern of tumor formation or recurrence was characterized by greater AFP levels and is more infiltrative, suggesting the presence of substantial lymphadenopathy and malignant PVT [63].

Fouad et al. (2019) conducted a study which comprised of two groups: group I (HCC patients with a DAAs history) and group II (HCC patients who never had DAAs treatment). The data demonstrated that HCC was much more multifocal in group I patients than in group II patients individuals. Furthermore, at the time of diagnosis, the tumour diameters of HCCs in group I patients were larger than those of HCCs in group II patients. More specifically, although less than 1% of patients in Group I had tumors smaller than 2 cm, more than 15% of patients in Group II had tumors less than 2 cm (P value 0.001), demonstrating more aggressive tumor behavior linked with a DAAs history. In both cases, the right lobe was the principal sufferer. Radiology found portal vein thrombosis (PVT) in 45 percent of group I patients in comparison to only 21 percent of group II patients (P value 0.001) [64].

Some studies have connected the beginning of HCC to underlying abnormalities like high levels of fibrosis, HBV co - infection, or old age. [65]. Another viewpoint suggests that DAAs cause immune surveillance mechanisms to become dysregulated as a result of the rapid clearance of viral particles, and this behavior has been confirmed by a number of investigations [66,67].

This dysregulation may lead to the restoration of innate immunity as a consequence of the down regulation of type II and III IFNs, their receptors, and IFN-stimulated genes. A reduction in IFN activation may promote the proliferation of malignant cells because IFN possesses the ability to inhibit angiogenesis and cell proliferation, whereas DAAs do not. In addition, after HCV eradication, one of the changes that is observed in the immune system is a decrease in the number of cytotoxic activity of natural killer cells in the liver, which favors a faster progression of HCC foci. This is one of the alterations that has been observed.[65, 68].

5. Limitations:

The main limitations of the included studies is that they didn't include all the types of available DAAs, as the studies followed in most cases a certain protocol applied in the institution or the country where the study was performed. This could lead to inconclusive results due to difference in the virus genotypes that could affect the process of HCC development. Some of the studies didn't illustrate the effect of long term follow up that couldn't reflect the effect of DAAs on development of HCC along more prolonged period. The results of most of these studies couldn't be generalized due to inclusion of a single race only in the analysis. The racial variations could also affect the development of HCC.

6. Conclusion:

The study finds that DAAs therapy does not increase the risk of de novo HCC following SVR However, patients with HCV cirrhosis who achieve SVR with DAAs, are still at risk of developing de novo HCC. HCC which occurs after DAAs therapy seem to be more aggressive and it's growth is faster than usual.

A Follow-up strategy must tackle these uncertainties concerning DAAs. Therefore, there should be careful monitoring of cirrhotic patients taking DAAs. In addition, future studies should be conducted to find ways of preventing HCC after DAAs.

Data collection: The following databases were searched: PubMed, Web of Science and Scopus. The search included all the papers published since 2010 and later on. The following keywords were during the search process "HCC", "DAAs", "HCV", "De novo". The systematic reviews and meta-analyses were excluded. The search included cases series and case control studies.

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Ethical Statement: institutional review board Mansoura faculty of medicine Mansoura universityunder code number :MS.19.04.560 .

Author Contribution: the authors developed the theoretical formalism and contributed to the final version of the manuscript .

List of Abbreviations: interferon(IFN), sustained virological response (SVR) , direct acting anti-viral therapy (DAAs) hepatocellular carcinoma (HCC), Hepatitis C virus (HCV), National Committee for Control of Viral Hepatitis (NCCVH), world health organization (WHO), hepatitis B viral (HBV), alpha fetoprotein (AFP), protease inhibitors (PIs), nucleoside polymerase inhibitors (NPIs), non-nucleoside polymerase inhibitors (NNPIs), liver cirrhosis (LC) , portal vein thrombosis (PVT)

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