The impact of the revolution in hepatitis C treatment on hepatocellular carcinoma

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Received 24 March 2016; revised 13 May 2016; accepted 18 May 2016

Hepatitis C infection represents a global health problem affecting ~200 million chronically infected patients worldwide. Owing to the development of a fibrogenic and inflammatory micromilieu in the liver, hepatitis C virus (HCV)-infected patients are at a high risk of developing fibrosis, cirrhosis and hepatocellular carcinoma (HCC). The advent of direct-acting antiviral agents (DAAs), however, has spurred a revolution in the treatment of HCV patients with sustained viral response (SVR) rates exceeding 90% in real-life settings. Recent clinical trials suggest that these novel treatments will not only alter the epidemiology of HCV infection but also the incidence of HCV-induced complications including hepatic decompensation, liver transplantation and hepatocarcinogenesis. Here, we summarize data from clinical trials carried out in HCV patients with compensated and decompensated cirrhosis and analyze the impact of viral clearance on HCC development and treatment. Finally, we review and discuss current and future treatment options of HCV patients with HCC in pre- and post-transplantation settings.

Key words: hepatitis C, antiviral therapy, hepatocellular carcinoma, liver transplantation, decompensated liver function, cirrhosis

Introduction

Chronic infection with hepatitis C affects ~3% of the world’s population and represents the most common cause of infection-related deaths [1–3]. Initially identified as a cDNA clone from the blood of infected patients and designated ‘non-A, non-B hepatitis’ [4], scientific research has come all the way from initial discovery to the most recent, compelling advances in hepatitis C virus (HCV) treatment in ~30 years. The rapid progress from the identification of the genetic organization and the structural proteins of the virus to the screening for therapeutic compounds [5] and the successful completion of phase III clinical trials represents one of only few examples of streamlined bench-to-bedside transitions in infectious diseases. With sustained viral response (SVR) rates exceeding 90% in treatment-naive and even pretreated patient populations and the prospect of numerous novel compounds in current and future clinical trials [6], a cure from HCV infection finally seems to be within reach for most if not all affected patients [7].

The anticipated success in global HCV treatment raises hopes with regard to the dreaded complications of HCV infection, namely the decompensation of liver function and the development of hepatocellular carcinoma (HCC). In contrast to the progress in HCV treatment, little progress has been made to improve liver function in patients with decompensated cirrhosis and liver transplantation remains the only hope for patients with end-stage liver disease. Similarly, attempts to improve the prognosis of patients with advanced HCC have failed as sorafenib remains the only systemic treatment option for these patients. The limited treatment options for HCV-induced complications highlight the need for efficacious HCV treatment to improve the prognosis of infected patients.

An ideal HCV treatment is expected to not only eradicate the virus but to also improve liver function, to stop or revert fibrosis and cirrhosis, and to lower or even eliminate the risk for HCC development. Direct-acting antiviral agents (DAAs) have emerged as a new group of medical compounds that hold promise to fulfill most, if not all, of these requirements. As a heterogeneous group of compounds that encompass protease inhibitors, NSSA inhibitors and NUC and non-NUC NS5B inhibitors, DAA target the HCV replication cycle at different stages, with protease inhibitors affecting post-translation protein processing, NS5B inhibitors targeting the active or allosteric sites of the RNA-dependent RNA polymerase and a not yet fully elucidated mode of action of the NSSA inhibitors.

To what extent these novel therapeutics will be able to reduce the prevalence of HCV infection and the global burden of HCV-associated complications and costs remains one of the most important questions to be answered in the decades to come.
HCV-induced HCC

Despite significant efforts to improve the prognosis of HCC patients, liver cancer still ranks fifth in global prevalence and second in mortality (http://globocan.iarc.fr) [8]. In contrast to other cancer entities, the dismal prognosis affects patients in both developed and non-developed countries and overall survival has not improved significantly in the last decades [9]. This lack of improvement stems primarily from two major problems that treating clinicians are confronted with: first, most patients are diagnosed either at advanced stages or with significant comorbidities (e.g., advanced cirrhosis) and are thus not amenable to curative treatment. In fact, curative treatment options including hepatic resection, thermal ablation or liver transplantation are mostly confined to patient populations with BCLC stage A and preserved liver function, which represents only a small fraction of the total HCC patient population. Secondly, the survival benefit of the currently available palliative treatment options is limited and lags behind the achievements made in other tumor entities (e.g., colorectal or breast cancer). The repertoire of treatment options for patients beyond BCLC stage A has remained unchanged in the last decade and is limited to locoregional therapy with transarterial chemoembolizations or selective internal radiotherapy and systemic treatment with the tyrosine kinase inhibitor sorafenib [10].

Chronic infection with hepatitis C is one of the main risk factors for HCC development [11]. While hepatitis B is the main risk factor for HCC development in the Asian-Pacific region and Africa, hepatitis C infection plays a major role in HCC development in the United States [12, 13], the UK [14], Europe, Egypt and Japan [15]. Following the natural course of infection, 20%–30% of the infected patients will develop liver cirrhosis within 20–30 years after infection [16]. Of these patients with HCV-induced liver cirrhosis, ~67%–91% will die due to liver-related causes and 1%–8%/year will develop HCC [17–20]. These data imply that only a fraction of HCV patients will develop cirrhosis, but this subpopulation carries a particularly high risk for HCC development. This is in stark contrast to HBV infection, where HCC develops more frequently in non-cirrhotic patients.

Compared with HBV, which as a DNA virus is able to integrate into genomic DNA, the HCV genome consists of RNA and requires a constant replication intermediate for persistent infection. Both HBV and HCV have been shown to exert virus-intrinsic carcinogenic effects, but this effect seems to be more pronounced in HBV- than in HCV-infected liver cells. These observations imply that HCV-induced carcinogenesis is more dependent on a chronic inflammatory milieu induced by a fibrotic/cirrhotic liver architecture after long-term HCV infection. The frequent coexistence of viral infection, a cirrhotic liver milieu and multifocal HCC poses a major obstacle to the treatment of infected patients and highlights the need for HCV treatments that improve both the liver function and the procarcinogenic liver micromilieu.

Nevertheless, the fact that HCV-induced development of HCC is a gradual process that is strictly dependent on the continuous presence of infectious HCV particles offers a unique chance to stop the process of hepatocarcinogenesis by clearing the viral infection. At the moment, it is unclear to what extent HCV clearance is able to alter the procarcinogenic cirrhotic liver milieu. In fact, one study showed that SVR induced a decrease in fibrosis and a regression of cirrhosis, but failed to improve portal inflammation and sinusoidal capillarization [21], warranting further investigations of the long-term histopathological changes induced by HCV clearance.

Impact of HCV therapy on liver function in patients with compensated or decompensated cirrhosis

When left untreated, chronic HCV infection can lead to continuous deterioration of liver function and ultimately liver failure. Globally, the percentage of patients with cirrhosis or HCC that is attributable to HCV infection has been estimated at 27% and 25%, respectively, resulting in a total of 211 000 deaths for cirrhosis and 155 000 deaths for HCC in 2002 [22]. The natural course of the infection, however, differs considerably between infected individuals and ranges from stable liver function for lifetime to rapid liver failure. In a large prospective study in 214 patients with compensated cirrhosis, 32% of patients developed HCC, 23% ascites, 17% jaundice and 1% encephalopathy during an average follow-up period of 10 years [23].

The reasons for the differential course of HCV infection have been examined in a number of studies and predictive scores have been developed to identify patient subpopulations that are at high risk of hepatic decompensation. The risk factors described in these studies differ considerably and include, among others, consumption of alcohol, transaminase levels, age, low platelet count and decreased serum albumin content [19, 24]. Compared with other causes of hepatitis, the risk of hepatic decompensation and HCC development seems to be increased in HCV patients. In head-to-head comparisons with HBV-infected patients or patients with non-alcoholic steatohepatitis, HCV patients tended to be older, had higher transaminase levels, lower albumin levels and decreased platelet counts [19] and developed HCC more frequently [25].

The knowledge of these potentially lethal HCV-related complications triggered early clinical trials that utilized interferon (IFN) in patients with compensated liver function [26, 27]. Long-term low-dose IFN therapy did not reduce disease progression, although serum transaminase levels, viral load and histologic inflammation scores decreased significantly. In a large cohort study of more than 3000 naïve patients, the combined IFN–ribavirin treatment reduced fibrosis effectively and prevented fibrosis progression in 92% of patients [28]. This study clearly identified low baseline fibrosis, SVR, a body mass index <27 kg/m², minimal baseline activity and low viral load as positive prognostic factors, a result that has been confirmed ever since.

Regression of cirrhosis has been shown to reduce disease-related morbidity and the necessity for liver transplantation [29] but was only present in a minority of patients due to the low response rates in early studies. Recently, a large observational cohort study that examined more than 28 000 patients between 1999 and 2014 assessed the death rates in patients with versus patients without an SVR [30]. In this study, viral clearance resulted in a 45% risk reduction for death and decreased hepatic morbidity. In another cohort of patients with either advanced fibrosis or cirrhosis that were treated with IFN-based regimens, a sustained virological response reduced the all-cause mortality rate by 74% and the liver-related mortality rate by 94% [31].
Nevertheless, the overall benefit in the intention-to-treat population was largely reduced due to the low SVR rates of 16% and 36% in these studies. Whether IFN-free regimens are equally able to improve liver function of HCV patients has recently been investigated in a number of clinical trials [32–37]. The first report of patient cohorts in real-world settings seemed to support this hypothesis by showing a significant improvement of liver function (MELD score) in nearly half of the patients treated with DAA while achieving SVR rates of more than 60% [34]. Owing to the increase in SVR rates in these studies, the number needed to treat to prevent one death declined accordingly, from 1052 at a 2% SVR rate with IFN monotherapy to 43 at a response rate of 50% with triple therapy [38].

Owing to the lower risk of hepatic decompensation with modern DAAAs compared with IFN therapy, several trials have recently examined the therapeutic effects of DAA-based treatment regimens in patients with decompensated cirrhosis (Child Pugh Score B and C, MELD score >18), reviewed in [34, 39, 40]. In early clinical trials, the addition of protease inhibitors to regimens containing IFN and ribavirin resulted in higher SVR rates in patients with both Child A and B cirrhosis [41], although several serious adverse events (SAEs) were reported. More recently, studies using IFN-free DAA regimens have been published that extended the spectrum of treated patients to Child–Pugh B and C cirrhotics (Table 1). In two recent studies, treatment of two cohorts with either Child B or Child C cirrhosis with ledipasvir and sofosbuvir plus ribavirin was equally effective, with SVR rates exceeding 90% [32, 36]. In another study, a combination of sofosbuvir and velpatasvir was successfully used to treat Child–Pugh B patients, achieving overall SVR rates of 83% with SAE frequencies below 20% [33]. A fourth study that subjected patients ranging from Child A to C to daclatasvir, sofosbuvir and ribavirin treatment reported similarly high SVR rates for Child A and B status, but not for Child C patients (SVR 56%) [37]. In another study, one of two cohorts containing decompensated cirrhotics was successfully treated with an IFN-free regimen of sofosbuvir and ribavirin [35].

A pivotal question remains to what extent liver function can still improve in patients with advanced cirrhosis. While long-term outcomes of morbidity and mortality are still lacking, all published studies have shown improvement of liver function at least in a subset of patients with Child B/C cirrhosis. However, in all studies examining patients with decompensated cirrhosis, another subpopulation of patients did not show improvement of liver function and some even showed further deterioration of liver function despite viral clearance. A major task will therefore be the identification of predictive parameters that allow for the discrimination between patients ‘beyond the point of no return’ and those that will truly benefit from HCV treatment.

Taken together, the most recent clinical trials suggest that DAA treatment may achieve high SVR rates without comprising quality of life [42] and with limited side-effects even in patients with decompensated cirrhosis. Nevertheless, severe liver toxicity has been described in patients treated with DAA [43] and the FDA has issued a safety warning for the use of proteasome inhibitors in patients with advanced liver disease. More clinical trials will be needed in decompensated patients to fully evaluate the clinical safety of DAA treatment in patients with end-stage liver disease.

### Table 1. Studies addressing hepatitis C virus treatment in patients with compensated and decompensated cirrhosis

<table>
<thead>
<tr>
<th>Treatment regimen</th>
<th>Child–Pugh score</th>
<th>SVR12 rates (%)</th>
<th>Changes in liver function</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple regimens</td>
<td>CHILD A: 46/80 (57%)</td>
<td>63% of the total population</td>
<td>44% improved</td>
<td>Deterding et al.</td>
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<td></td>
<td>CHILD B: 30/80 (38%)</td>
<td></td>
<td>15% worsened</td>
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<td></td>
<td>CHILD C: 4/80 (5%)</td>
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<tr>
<td>Ledipasvir, sofosbuvir, ribavirin</td>
<td>Pre-transplantation Cohort A: Group 1: Child B</td>
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<td></td>
<td>Group 1: 87%–89%</td>
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<td></td>
<td>Charlton et al.</td>
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<td>Group 2: 86%–87%</td>
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<td>Pre-transplantation cohort A: CHILD B 56/107 (52%)</td>
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<td>Manns et al.</td>
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<td>CHILD C 51/107 (48%)</td>
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<td></td>
<td>CHILD B: 46/51</td>
<td>58/81 (72%) improved</td>
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<td>CHILD C: 36/46</td>
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<td>Ledipasvir, sofosbuvir, ribavirin</td>
<td>CHILD A: 20%</td>
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<td>Poordad et al.</td>
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<td>CHILD B: 53%</td>
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<td>CHILD C: 27%</td>
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<td></td>
<td>CHILD A: 92%</td>
<td>60% improved</td>
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<td></td>
<td>CHILD B: 94%</td>
<td>25% stable</td>
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<td></td>
<td>CHILD C: 36%</td>
<td>15% worsened</td>
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<tr>
<td>Daclatasvir, sofosbuvir, ribavirin</td>
<td>CHILD A: 77%</td>
<td>93% total population</td>
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<td>Siederdissen et al.</td>
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<td>CHILD B: 17%</td>
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<td>CHILD C: 4%</td>
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<tr>
<td>Sofosbuvir, velpatasvir (+/− ribavirin)</td>
<td>CHILD A: 6%</td>
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<td></td>
<td>CHILD B: 90%</td>
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<td>CHILD C: 4%</td>
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<td>sof/vel 12 weeks: 83%</td>
<td>47% improved</td>
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<td>sof/vel 24 weeks: 86%</td>
<td>42% stable</td>
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<td>Curry et al.</td>
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<td>sof/vel/riba 12 weeks: 94%</td>
<td>11% worsened</td>
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**risk of HCC development before and after HCV treatment**

HCV infection has early been recognized as a major risk factor for HCC development, causing approximately one-third of all...
HCC cases globally [11]. The risk of cancer development among HCV patients, however, varies considerably among patient sub-populations and between studies [44]. Therefore, a number of clinical trials have aimed at developing clinical scores that reliably allow for the identification of high-risk patient cohorts. These studies confirm that the risk of HCC development is primarily dependent on the level of fibrosis/cirrhosis present at diagnosis. In addition, a number of risk factors have been identified, including AFP levels, gender, age and platelet count [45]. In another study, carcinogenesis was associated with HCV RNA levels, ALT levels and genotype 1 infection [46].

Since these studies suggest that chronically active HCV infection with persistent inflammation and destruction of the hepatic architecture is a main risk factor for HCC development, clinicians have used IFN-based regimens for more than 20 years to temper inflammation and to fight viral infection. As a fact, IFN was early recognized as an ideal drug to prevent both HCV replication and HCC development since the drug exerts direct antiviral and antitumoral effects. Accordingly, early clinical trials showed not only a reduction in HCV RNA levels, but also an improvement in liver function and a strongly reduced risk for HCC development [47]. These results have been confirmed in a large number of studies subsequently with different treatment regimens and in heterogeneous patient populations [48]. In addition, a number of meta-analyses have been published, all of which confirm a reduced risk for HCC development, albeit with different results regarding the hazard ratio and the overall risk [49–51]. In the most recent of these meta-analyses, 30 studies were included, demonstrating a relative risk of 0.24 [95% confidence interval (CI) 0.18–0.31] with an overall evidence level of moderate quality [51].

Although these studies clearly demonstrate a risk reduction for HCC development after SVR, HCC may still develop after viral clearance [52]. In a study with patients who had cleared viral infection after treatment, patients who continued to follow a surveillance schedule had significantly higher survival rates compared with patients who discontinued surveillance [53]. Patients benefited most from a 3-month surveillance interval that allowed for detection of recurrent HCC at early stages. With more and more patients achieving an SVR with modern therapeutics, this specific patient cohort has been examined for risk factors for HCC development, similar to the studies carried out with HCV-infected patients. The risk factors identified in SVR patients overlap in part with HCV-infected patients (low platelets, fibrotic stage, age, male gender, steatosis, lower serum albumin) but additionally reveal an important role for the serum AFP value for the long-term prognosis of SVR patients [54–56]. In patients who developed liver-related complications and HCC after viral clearance, these events tended to occur early and long-term complications were predominantly found in non-SVR patients. This result could suggest that short-term follow-up studies of SVR patients could underestimate the benefit achieved by viral clearance and that long-term follow-up studies could be required to fully assess the benefit from HCV treatment.

**Prevention of HCC recurrence in HCV patients**

After curative treatment, HCC frequently recurs due to the underlying liver disease. In HCV patients, disease-free survival rates after hepatic resections are as low as 12% after 10 years, a rate that is much lower compared with other etiologies, including HBV infection [57]. Negative prognostic factors for recurrence in HCV patients treated with either hepatic resection or radiofrequency ablation are well established and include TNM stage, resection margin, Edmonson’s grade, age, low serum albumin levels, blood transfusion, absence of tumor capsule and microvascular invasion [57–60].

To reduce the risk for recurrence in HCV patients, a number of treatments have been employed with limited success. As two examples, supplementation with both vitamin K and branched-chain amino acid granules has been shown to lower the recurrence frequency in small cohorts of HCV-infected patients [61, 62]. Given the potent antiviral effects of type I IFN, both IFN α and β have been used in a large number of clinical trials as an adjuvant treatment to improve the prognosis of HCV patients. While some of these trials did not achieve clearance of the virus, most but not all of them demonstrated a long-term benefit for the treated patients by delaying or preventing HCC recurrence [63–65]. Again the benefit from IFN treatment was greater in HCV than in HBV patients [66], resulting not only in reduced recurrence but also in decreased mortality in the published meta-analyses [65, 67–70]. As expected for long-term IFN treatment, adherence to therapy was rather low with dropout rates exceeding two-thirds of the treated patients in some of the studies. In more recent studies with higher percentages of patients with SVR, the positive prognostic effects of HCV clearance could be confirmed [71–73]. In comparison with untreated patients, time to beyond Milan criteria was significantly prolonged in HCV patients, a finding of particular importance for patients listed for liver transplantation [71]. Of interest, the number needed to treat in these studies to prevent one case of HCC recurrence was as low as 8 [72].

A second series of studies addressed the effect of antiviral treatment before curative treatment, a therapeutic setting that may become more relevant with the most recent treatment advances. In these studies, SVR before hepatic resection improved liver function, recurrence-free survival and overall survival [74, 75], and viral clearance delayed not only primary, but also secondary recurrences [75].

**Management of HCV in patients before and after liver transplantation**

HCV infection represents the major cause for liver transplantation in the United States, EU and other developed countries. While the prognosis of patients transplanted for HCC is excellent, the outcome of transplanted HCV-infected patients is impaired by graft infection and progressive organ dysfunction [76, 77]. The survival of HCV+/HCC+ patients after transplantation is lower than the survival of HCV−/HCC+ patients, suggesting that HCV treatment is of high priority in HCV patients awaiting transplantation [78]. The treatment of HCV-infected patients with IFN-based regimens, however, has been hampered by severe hepatic dysfunction before transplantation and the immunosuppressive therapy required thereafter. The treatment with DAA thus represents a unique chance for HCV-infected patients to preserve graft function and to prevent secondary complications.
The ideal timing of HCV treatment currently remains a matter of intensive debate. While treatment before transplantation seems to be a straightforward answer, none of the therapeutic regimens have been tested sufficiently in patients with end-stage liver disease (MELD score >30, Child–Pugh Score C) or impaired renal function (GFR <30 ml/min). Secondly, in HCV patients without HCC and moderate fibrosis or cirrhosis, HCV treatment may ameliorate liver function and therefore delay liver transplantation. Thirdly, HCV treatment could be interrupted by liver transplantation, jeopardizing successful treatment or inducing viral resistance to therapy. Nevertheless, a recent study demonstrated convincingly that DAA treatment before transplantation is a valid option for patients with HCV and HCC on the transplant waiting list [79]. In this study, administration of sofosbuvir and ribavirin successfully prevented HCV recurrence in 70% of the transplanted patients. Most interestingly, viral clearance correlated with the number of consecutive days of undetectable viral DNA before transplantation, and none of the patients with more than 4 weeks of undetectable RNA before transplantation experienced recurrence. These results suggest that even without long-term SVR, HCV+/HCC+ patients may benefit substantially from treatment before transplantation. In many ways, HCV+/HCC+ patients represent an ideal population for pre-transplantation treatment, since these patients are generally transplanted due to high matchMELD scores in the absence of end-stage liver disease, in contrast to HCV+/HCC− patients who typically are transplanted in a decompensated state.

Since not all transplanted HCV patients display progressive graft dysfunction and fibrosis, starting treatment after transplantation in all or selectively in patients with progressive fibrosis may constitute an alternative strategy. In fact, IFN-free regimens have been used successfully and with low rates of SAEs in transplanted patients [36, 76, 80–88]. Sofosbuvir and ribavirin was one of the first and most frequently used combinations, but current trials include multiple combinations including simeprevir, boceprevir, telaprevir, ledipasvir, velpatasvir and others (Table 2). Most notably, these trials demonstrate unprecedented rates of SVR even in rapid progressors with cholestatic hepatitis and in the absence of allograft rejections. Despite this encouraging treatment success, some studies have reported SAEs in up to 50% of patients treated with sofosbuvir and ribavirin [83]. Since most of these SAEs are related to hepatic decompensation, some authors have advocated antiviral treatment as early as possible if treatment is planned after transplantation [89].

In summary, DAA-based treatments are able to improve the outcome of HCV-infected patients in both pre- and post-transplantations settings. While pre-transplantation HCV treatment could be more favorable in patients with compensated cirrhosis, post-transplantation treatment may be the method of choice in patients with end-stage liver disease (Child–Pugh C).

**Table 2.** Studies addressing hepatitis C virus treatment before and after liver transplantation

<table>
<thead>
<tr>
<th>Treatment regimen</th>
<th>Time of treatment</th>
<th>SVR12 rates (%)</th>
<th>Adverse events</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sofosbuvir, ribavirin</td>
<td>Before transplantation</td>
<td>12 weeks post-LT: 30/43 (70%)</td>
<td>Fatigue (38%) Headache (23%) Anemia (21%)</td>
<td>Curry et al.</td>
</tr>
<tr>
<td>Sofosbuvir, ribavirin</td>
<td>Post-transplantation (6–150 months)</td>
<td>28/40 (70%)</td>
<td>Fatigue (30%) Diarrhea (28%) Headache (25%)</td>
<td>Charlton et al.</td>
</tr>
<tr>
<td>Ombrtavisir/ABT-450/ritonavir, dasabuvir, ribavirin</td>
<td>Post-transplantation (at least 12 months)</td>
<td>33/34 (97%)</td>
<td>Fatigue, headache, cough</td>
<td>Kwo et al.</td>
</tr>
<tr>
<td>Simeprevir, sofosbuvir, ribavirin</td>
<td>Post-transplantation (mean 5 years, after LT)</td>
<td>133/151 (88%)</td>
<td>SAE frequency 11.9%</td>
<td>Brown et al.</td>
</tr>
<tr>
<td>Sofosbuvir, ribavirin</td>
<td>Post-transplantation (average 16 months)</td>
<td>54/92 (59%)</td>
<td>SAE frequency 47%, most frequent: hepatic decompensation</td>
<td>Forns et al.</td>
</tr>
<tr>
<td>Simeprevir, sofosbuvir, ribavirin</td>
<td>Post-transplantation (median 32 months)</td>
<td>94/105 (90%)</td>
<td>Fatigue (13%), Skin complaints (6%), Headache (5%)</td>
<td>Pungpapong et al.</td>
</tr>
<tr>
<td>Sofosbuvir, simeprevir</td>
<td>Post-transplantation (mean 71 months)</td>
<td>28/30 (93%)</td>
<td>Decrease in hemoglobin, lymphocytes, increase in bilirubin and glucose</td>
<td>Saab et al.</td>
</tr>
<tr>
<td>Ledipasvir, sofosbuvir, ribavirin</td>
<td>Post-transplantation (0.2–12 years)</td>
<td>217/226 (96%)</td>
<td>Decrease in hemoglobin, lymphocytes, increase in bilirubin and glucose</td>
<td>Manns et al.</td>
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</tbody>
</table>

**summary**

The recent advances in HCV treatment represent an unprecedented ‘medical triumph’ in the treatment of chronic infections [1]. Modern DAA-based therapies promise high SVR rates in patients with both compensated and decompensated liver function with manageable side-effects. In HCV-infected patients in developed countries, these novel antiviral therapies will reduce the incidence of hepatic decompensation and the development of HCC in the years to come [90, 91]. Nevertheless, a number of facts suggest that HCV treatment will only have a moderate impact on global HCC prevalence. First, HCV infection accounts only for ~30% of all HCC cases worldwide. Secondly, most of the chronic HCV carriers are unaware of their infection. This applies to patients in third-world countries which are...
unable to offer appropriate HCV diagnostics as well as to developed countries in which, as an example, up to 50% of patients in US National Health Surveys were unaware of their positive HCV status [92]. Thirdly, even if infected patients are diagnosed and treated successfully, some of them might not benefit from treatment. Studies suggest that up to 20% of HCV patients are diagnosed with concomitant cirrhosis and sometimes shortly before or even after their first hepatic decompensation [93]. At this stage, HCV clearance might not change the dismal prognosis of the advanced cirrhosis and the treated cirrhotic patients remain at high risk for the development of HCC. Fourthly, treatment of HCV patients with state-of-the-art drugs is costly and can currently be only offered to a fraction of the global HCV patient population. Lastly, possible negative effects of DAA treatment on secondary HCC development have to be considered. As an example, the role of HCV treatment with DAA in patients with already established HCC remains a matter of debate. In these patients, HCV-induced inflammation could play a role in local tumor control, prevention of distant metastases and recurrence of HCC after curative treatments. In support of this view, an unexpected high rate of early HCC recurrences has been reported in patients with complete responses who were subjected to DAA treatment [94], thus warranting further studies in this patient population.

These facts point out some of the major disadvantages of treating an established disease and its complications compared with cost-effective primary prevention measures [15] and call for the development of an HCV vaccine to ideally complement the treatment of chronic HCV infections with DAA.

funding

This work was supported by grants from the Deutsche Forschungsgemeinschaft (WI 3308/3-1) and the Deutsche Krebshilfe (111150) to TCW.

disclosure

The authors have declared no conflicts of interest.

references

Current management of newly diagnosed acute promyelocytic leukemia

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Received 8 February 2016; revised 29 March 2016; accepted 4 April 2016

The management of acute promyelocytic leukemia (APL) has considerably evolved during the past two decades. The advent of all-trans retinoic acid (ATRA) and its inclusion in combinatorial regimens with anthracycline chemotherapy has provided cure rates exceeding 80%; however, this widely adopted approach also conveys significant toxicity including severe myelosuppression and rare occurrence of secondary leukemias. More recently, the advent of arsenic trioxide (ATO) and its use in association with ATRA with or without chemotherapy has further improved patient outcome by allowing to minimize the intensity of chemotherapy, thus reducing serious toxicity while maintaining high anti-leukemic efficacy. The advantage of ATRA–ATO over ATRA chemotherapy has been recently demonstrated in two large randomized trials.