Review

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Reversion of disease manifestations after HCV eradication

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Summary

Chronic infection with the hepatitis C virus (HCV) may lead to hepatic fibrosis and eventually cirrhosis, at which stage, patients have a substantial risk of liver failure, hepatocellular carcinoma (HCC) and liver-related death. Moreover, HCV infection is associated with several extrahepatic manifestations which impact the quality of life and increase the non-liver-related mortality rate. For patients with compensated liver disease, interferon (IFN)-based antiviral therapy has been a treatment option for over two decades. Long-term follow-up studies indicated that among those with sustained virological response (SVR) the extend of hepatic fibrosis can regress and that their risk of cirrhosis-related complications (including HCC) is reduced, also in case of cirrhosis. Recent population-based studies extended these observations for solid extrahepatic outcomes, such as end-stage renal failure and cardiovascular events. Most importantly, SVR has been associated with prolonged overall survival. These results highlight the importance of the development of new direct-acting antivirals (DAAs), by which almost all patients are able to eradicate HCV in a comfortable manner. Based on the excellent first experiences with the DAAs, physicians gained confidence to use these drugs among patients with decompensated cirrhosis on a more regular basis as well. This was not possible with interferon therapy. Also in this high risk population the DAAs show high SVR rates with improvements in biochemical parameters of liver function shortly after therapy, especially in case of SVR. In fact, some patients could actually be removed from the liver transplantation waiting list due to clinical improvement following DAA therapy. How these short-term results translate into a prolonged (long-term) survival has yet to be determined, as well as which patients with decompensated liver disease are likely or not to benefit from viral eradication. Here we review the current data regarding the beneficial clinical outcome with antiviral therapy as well the remaining uncertainties in this field, both for patients with compensated liver disease and patients with decompensated liver disease.

Keywords: Chronic hepatitis C; Antiviral therapy; Sustained virological response; Clinical outcome; Survival; Hepatocellular carcinoma; Hepatic fibrosis.

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Introduction

With approximately 150 million patients worldwide and an annual death rate of 350,000 it is no surprise that chronic infection with the hepatitis C virus (HCV) is in the center of attention within hepatology [1]. Over the last few years this viral disease even gained prime focus in medicine in general. This momentum of chronic HCV infection results from the success story of antiviral treatment development. Today, short and well-tolerated combinations of direct-acting antivirals (DAAs) have largely replaced interferon (IFN)-based therapy. Patients are hereby spared from the quality of life-reducing side-effects of IFN and frequent disappointment of treatment failure; indeed, a highly unfavorable combination. Even the accomplished pegylated (Peg)IFN and ribavirin (RBV) regimens often failed to eradicate the chronic HCV infection. In contrast, the rates of sustained virological response (SVR; defined as HCV RNA negativity in the circulation 12–24 weeks after treatment cessation) with combinations of DAAs exceed 95%. Also RBV has undesirable off-target effects and does not seem to increase the virological efficacy of DAAs in general. It remains subject to debate, however, whether this drug can be completely discarded. Although the term 'difficult-to-cure' should be taken relatively with the IFN era so close in our minds, there remain subgroups of patients in whom the firstly available DAA regimens have suboptimal efficacy. Patients with HCV genotype 3 infection are

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currently considered as such a population. Fortunately for these patients, excellent SVR rates with combination regimens including second generation DAAs have already been presented [2]. The nearby future is even looking bright for those few patients who failed to attain SVR with the currently available IFN-free regimens [3]. Although larger studies are needed, various combinations of pangenotypic and potent DAAs of various classes appear to result in SVR in almost all these patients [4,5].

We are thus quickly progressing to a situation in which there is no reason for patients to remain infected with HCV, at least not from a medical point of view. The DAAs, however, are expensive and the decision to provide or not to provide these drugs to all patients at need remains a political and cost-benefit issue. Policy-makers should weigh the estimated impact of reimbursing DAA therapy on their countries health budget against the potential clinical benefits of antiviral therapy. It is therefore highly relevant to understand how HCV eradication relates to clinical outcome. Fortunately, while the DAAs were designed and developed by the pharmaceutical companies, clinical researchers and physicians made great efforts to assess the prognosis of patients with chronic HCV infection following antiviral therapy. This review discusses the current literature in this field in terms of patient-reported outcome measures, extrahepatic disease, hepatic fibrosis, cirrhosis-related complications, and survival among patients with compensated HCV-induced liver disease, with and without liver transplantation (LT). Furthermore, we will discuss most recent data on the clinical impact of HCV eradication among patients with decompensated liver disease as our experience of antiviral treatment among this high risk population is rapidly growing due to the beneficial safety profile of IFN-free therapy.

Key point

Among patient with chronic HCV infection and compensated liver disease SVR is associated with improvement of HCV-related symptoms, improvement of the HRQoL, regression of hepatic fibrosis and a reduced occurrence of liver-related as well as non-liver-related morbidity and mortality, leading to beneficial overall survival.

Compensated liver disease

Extrahepatic disease manifestations of chronic HCV infection

Patients with chronic HCV infection may experience a variety of non-specific symptoms, including fatigue, nausea, abdominal or musculoskeletal pain, and loss of weight. With about 50% of patients reporting fatigue, this is one of the symptoms most frequently associated with HCV infection [6]. While fatigue has a profound impact on a patient's health-related quality of life (HRQoL), the HRQoL is often impaired in case of supposedly asymptomatic disease as well [7]. In absence of end-stage cirrhosis, which may result in various liver-specific symptoms, many of the reported discomforts can be attributed to the extrahepatic manifestations of HCV infection. Extrahepatic manifestations are reported in up to three quarter of patients and include mixed cryoglobulinemia vasculitis, renal disease, type II diabetes mellitus, cardiovascular disease, porphyria cutanea tarda, lichen planus and lymphoproliferative disorders such as B-cell non-Hodgkin lymphoma [8]. Irritability, malaise and other neuropsychiatric symptoms, of which depression is most frequent, have been observed among chronic HCV-infected patients as well [9]. The impact of the extrahepatic manifestations was recently highlighted by the finding that patients who are chronically infected with HCV have an increased non-liver-related mortality as compared to those who spontaneously cleared the virus upon infection or those who were never infected [10].

SVR and reduced extrahepatic morbidity

Eradication of HCV infection has been shown to decrease both the frequency as well as the severity of fatigue [6]. Among 401 patients with chronic HCV infection, the percentage reporting fatigue reduced from 53% at baseline to 33% at 24 weeks after successful antiviral therapy (p <0.001). Among those with SVR the median visual analog scale fatigue score was 13 mm, as compared to a median score of 27 mm at baseline (p <0.001). In absence of a sustained off-treatment virological response nor the percentage with fatigue nor the severity of fatigue showed a statistically significant improvement. Being less fatigue is likely to contribute to an improved perception of the HRQoL, which was observed upon SVR in a large meta-analysis including 9 studies who stratified their data by virological response [11]. While the HRQoL is not generally assessed in daily clinical practice, patients will definitely experience these benefits more directly as compared to any reduction in the risk of hard clinical events. Thus, to fully appreciate the true burden of HCV infection and the potential benefits of successful antiviral therapy, these patient-reported outcomes (PROs) should not be underestimated. The potential impact of antiviral therapy on the PROs are discussed in more detail elsewhere in this issue of the *Journal* by Younossi *et al.* [12].

Several recent cohort studies focused on the association between antiviral therapy and solid extrahepatic outcome measures. After Romero-Gómez *et al.* showed that the extend of insulin resistance reduced among patients with chronic HCV infection who attained SVR, a large cohort study including 2842 patients from Japan assessed the occurrence of type 2 diabetes mellitus during a mean follow-up duration of 6.4 years [13,14]. The cumulative 10-year occurrence of type 2 diabetes mellitus in this cohort was 8% and multivariable Cox regression analysis indicated that achievement of SVR was independently associated with a reduced risk (hazard ratio (HR) 0.37, p <0.001). More recently, Gragnani *et al.* showed that treatment-induced HCV eradication led to a sustained disappearance of cryoglobulinemia in nearly all patients

(97%), with a complete and persistent resolution of all initial signs and symptoms of the mixed cryoglobulinemia syndrome in 56% [15]. None of the patients with SVR in this cohort progressed to malignant lymphoma, which is in line with a prior report from Japan in which the 15-year cumulative lymphoma development rates were 0% and 2.6% among IFN-treated patients with SVR and without SVR, respectively ($p = 0.016$) [16]. When considering antiviral therapy and extrahepatic outcome there are two recent large cohort studies which should be addressed. The first study, from Taiwan, found that the 8-year cumulative incidence rates of end-stage renal disease (0.15% and 1.32%), acute coronary syndrome (2.21% and 2.96%), and ischemic stroke (1.31% and 1.76%) were statistically significantly lower among 12,384 IFN-treated patients compared to 24,768 propensity score-matched untreated controls, respectively ($p < 0.05$ for all) [17]. In multivariate analysis, antiviral therapy remained independently associated with a lower occurrence of these clinically important outcome events. Although data on the virological response were not available, it should be noted that the majority of the Taiwanese patients with chronic HCV infection will have attained SVR with IFN-based therapy. The second study, among 3,385 IFN-treated patients with chronic HCV infection from Scotland (followed for a median duration of 5.3 years), confirmed these findings and did link the improved extrahepatic prognosis to SVR [18]. Another interesting finding by Innes *et al.* was that patients with SVR were less frequently hospitalized due to acute alcohol intoxication or violence-related injuries [18]. Whether this is merely a psychological effect or has some sort of neurobiological basis remains to be elucidated [19]. It is probably because of these effects on extrahepatic morbidity that patients with SVR were found to have a reduced liver-unrelated mortality [18,20]. This beneficial association with SVR was firstly described among patients with a HCV and human immunodeficiency virus (HIV) coinfection [21]. Taken together, these results indicate that the stage of liver disease should not be the only parameter when considering the indication for antiviral therapy among patients with chronic HCV infection.

Hepatic manifestations of chronic HCV infection

Chronic HCV infection often leads to low grade hepatic inflammation. The inflammatory processes stimulate and activate hepatic stellate cells to transdifferentiate into myofibroblasts. These myofibroblasts are central in fibrogenesis as they produce many of the extracellular matrix components as well as the mediators which lead to accumulation of these proteins [22]. As a result, chronic HCV infection is often accompanied by the development of hepatic fibrosis. The degree of hepatic fibrosis is usually assessed by semi-quantitative histopathological scoring systems, such as the METAVIR or Ishak classification [23,24]. In both these scores, cirrhosis represents the most advanced stage of disease, at which point the normal architecture of the liver parenchyma is completely compromised. Cirrhosis is characterized by nodules of regenerating hepatocytes surrounded by fibrotic septa, which stretch between portal areas or between the portal areas and the central veins. A key concept in the pathophysiology of cirrhosis is the vascularization of these septa by which blood shunts through porto-caval anastomoses so that functional hepatocytes are bypassed [25,26]. The consequent relative hypoxemia in the liver parenchyma may further contribute to liver injury and neovascularization; a vicious circle is the result [27].

In case of HCV-induced cirrhosis, it is clear that the prognosis of the patient is impaired [28,29]. Among these patients, the overall estimated annual risk for liver failure, HCC or liver-related death were 2.9%, 3.2% and 2.7%, respectively [30]. Based on older natural history studies, which have several limitations, it has been estimated that approximately 16% of the patients with chronic HCV infection will develop cirrhosis within 20 years of infection [31]. A more recent report, however, showed a substantial higher cumulative cirrhosis development rate of approximately 15% at 5-years of follow-up [32]. Although this study may be biased as it was conducted in the special population of American veterans, it should be realized that fibrosis progression can accelerate over time while the majority of Western patients with chronic HCV infection are thought to have been infected in the 1960s and '70s [33]. The estimates of fibrosis progression as derived from the historic cohorts may thus underestimate the incidence rate of cirrhosis among the population with chronic HCV infection today. An accelerated course of disease was indeed highlighted by a recent follow-up analysis in a unique cohort of Irish women who were diagnosed with chronic HCV genotype 1b infection following a single-source outbreak of HCV (due administration of contaminated anti-D immunoglobulin) from 1977 to 1979 [34]. Either way, it is expected that the number of patients with HCV-induced cirrhosis, and consequently the number with cirrhosis-related complications, will rise during the upcoming years [35,36].

Regression of hepatic fibrosis and cirrhosis following SVR

Stories with respect to the regenerative ability of the liver date back to the Greek myth of Heracles and the eagle Theon. Yet, hepatologist have been only been able to experience the damage-repairing qualities of the liver since two decades. Our ability to eradicate or suppress viral hepatitis, which is the predominant etiology of liver disease worldwide, has been the basis for this observation. Most histological studies with paired liver biopsies from before

Key point

Viral eradication following liver transplantation is associated with significant histologic and clinical benefits.

and after antiviral therapy have been performed among patients with chronic HCV infection [37]. The largest histological study to date already dates back to 2002 and combined the results of 4 large prospective studies in which patients underwent their second liver biopsy 24 weeks after cessation of IFN therapy [38]. While patients with significant fibrosis who did not attain SVR showed stable liver disease, those with SVR had, on average, a negative estimated annual fibrosis progression rate (−0.591) suggesting fibrosis regression. The most impressive result of this study, especially at that time, was that almost 50% of the 153 patients with cirrhosis at baseline no longer scored METAVIR F4 in their post-treatment liver biopsy. Hereafter, other studies in which the post-treatment biopsy was obtained after a longer duration have confirmed these findings, with even higher percentages of patients who reversed the highest fibrosis score [39,40]. Fibrosis regression following SVR has been described for HCV-HIV co-infected patients as well.

As fibrosis takes so long to develop, it seems only natural that it takes a long time to regress. Indeed, Shiratori *et al.* showed this with their analyses among 593 Japanese patients with chronic HCV infection in whom the time to the post-treatment liver biopsy ranged from 1 to 10 years [41]. Following SVR, regression of fibrosis was significantly more evident in case the paired liver biopsy was obtained after more than 3 years of follow-up. In line with this finding a repeated measurement analysis including over 3,000 platelet count measurements during the follow-up of a large cohort of HCV-infected patients with advanced fibrosis showed a gradual and rather linear increase in platelets for many years following SVR [42].

Even with longer follow-up, however, not all patients with the highest fibrosis scores show fibrosis regression. While this fuels the discussion regarding the infamous 'point of no return', it may also be that the fibrosis scores used to evaluate fibrosis regression (which have never been validated for this purpose) are somewhat too crude. A recent Italian study among 38 patients with HCV-induced cirrhosis and SVR, in whom the median time between the liver biopsies was 5.6 years, showed that the total area of fibrosis significantly regressed even among those 15 patients who still score a METAVIR F4 in their liver biopsy after HCV eradication [43]. Although regression of the highest fibrosis score has tempted researchers to conclude that cirrhosis is reversible, this conclusion was heavily argued on the basis that cirrhosis represents more than merely severe fibrosis [44]. Indeed, the important vascular abnormalities within cirrhosis liver have not been shown to revert, fibrosis is not evenly distributed throughout the liver which may lead to sampling error, and micro-nodular cirrhosis may convert into macro-nodular cirrhosis which is more difficult to diagnose for the pathologist. On the other hand, persisting factors such as alcohol use, diabetes mellitus and/or overweight can maintain hepatic inflammation and fibrosis following HCV eradication [33]. Recently, higher body mass index (BMI) was negatively associated with the post-SVR platelet count improvement among patients with advanced hepatic fibrosis [42].

Regression of fibrosis following antiviral therapy among patients with cirrhosis was, nevertheless, found to be relevant as this was linked to a beneficial clinical outcome in a French study among 96 patients with chronic HCV infection who were followed for a median duration for 9.8 years [45]. While cirrhosis-related complications did not occur among patients who regressed from METAVIR F4 to ⩽F2, the incidence of cirrhosis-related complications per 100 person-years was 4 among those who remained with F3 or F4 after therapy ($p = 0.002$). Although limited by the use of transient elastography for fibrosis regression assessment, the link between fibrosis regression and beneficial clinical outcome was recently confirmed among patients with a HCV-HIV coinfection [46]. Histological improvement may also explain the reduction in the hepatic venous pressure gradient (HVPG) which has been observed following HCV eradication with IFN-based therapy [47,48]. Even though both studies included a limited number of patients, which may be explained by the invasive nature of the measurement, the HVPG remains one of the best surrogate markers within hepatology and therefore suggestive of clinical benefit [49]. At the latest European Association for the Study of the Liver (EASL) meeting a reduction in HVPG was also described shortly after DAA therapy, although the decline in HVPG was not always achieved in the subgroup of patients with highest portal pressure (HVPG >16 mmHg) at baseline [50,51]. Although the follow-up in this study was too short for any definite conclusions, it may indeed be that in some patients the liver damage is too extensive to expect histological (and subsequent clinical) improvements.

SVR and reduced liver-related morbidity

Whether or not there is histological improvement upon SVR, patients and physicians are more interested in the clinical prognosis following antiviral therapy. Over the recent years, various large Western cohort studies, with substantial follow-up duration, included patients with chronic HCV infection who were treated with IFN-based therapy. Even though patients with cirrhosis were included in these cohorts, all had compensated liver disease as IFN therapy is not generally applied to patients with signs of hepatic decompensation. In 2007, the results of a cohort of 479 patients with HCV-induced advanced hepatic fibrosis who were

followed for a median duration of 2.1 years were presented [52]. An important observation of this study was that liver failure, defined as an episode of jaundice, ascites, hepatic encephalopathy or variceal bleeding, did not occur among patients who attained SVR while the liver failure rate was 365 per 10,000 patient-years in case of unsuccessful IFN-based therapy ($p = 0.001$). Although extension of the follow-up to 8.4 years in this cohort did reveal a few patients with decompensation of cirrhosis following SVR, the association with a reduced event rate remained strong and statistically significant in multivariable analyses (hazard ratio [HR] 0.07, $p < 0.001$) [53]. The most important finding of the study by Veldt *et al.*, however, was that liver-related mortality occurred less often among those with SVR as opposed to those without SVR [52]. Later, both these findings were confirmed in the partially prospective analyses within the Hepatitis C Antiviral Long-Term Treatment Against Cirrhosis (HALT-C) study cohort [54]. In a cohort study including 339 HCV-HIV co-infected patients who were followed for a mean duration of 70.5 months after IFN-based therapy, hepatic decompensation events or liver-related deaths occurred in only 4 (2.9%) with SVR as compared to 28 (13.9%) without SVR [55].

Although long-term low dose IFN did not prevent HCC development, a *post-hoc* analysis of the HALT-C trial confirmed two prior large retrospective follow-up studies from Italy and France in which the incidence of HCC among patients with SVR was significantly lower as compared to those with ongoing HCV infection after antiviral therapy [54,56,57]. These results were all included in a recent meta-analysis of observational studies, in which the average adjusted hazard effect of SVR with respect to HCC was 0.23 (95% confidence interval (CI) 0.16–0.35) among those with advanced liver disease [58]. With a separate analysis, although predominantly including studies from Asia where the risk of HCC is substantially higher, Morgan *et al.* described a similar relative HCC risk reduction with SVR among patients with all stages of fibrosis (HR: 0.24, 95% CI: 0.18–0.31). Noticeably, in all cohort studies the risk of HCC was not eradicated upon SVR, especially in case of cirrhosis. Based on these observation, Western investigators recently combined their data and found that the overall residual risk of HCC among 1,000 patients with cirrhosis and IFN-induced SVR was 1% per year [59]. Higher age, lower platelet count, higher aspartate aminotransferase (AST)/alanine aminotransferase (ALT) ratio and diabetes mellitus were independent risk factors, indicating that HCC after SVR should be expected more frequently in the era of DAAs as these new drugs are able to cure older patients with more advanced cirrhosis. All patients with HCV-induced cirrhosis and SVR are currently advised to remain included in HCC surveillance programs.

Overall survival

Based on the hepatic as well as the extrahepatic disease manifestations, chronic HCV infection increases the all-cause mortality rate [10]. Improving the overall survival is thus the primary goal of anti-HCV therapy. Even though the clinical efficacy of antiviral therapy in terms of survival (or any other endpoint for that matter) has never been established in a randomized placebo-controlled clinical trial, there is general consensus that this goal is achieved.

In 2011, Backus *et al.* indicated, that SVR was associated with reduced all-cause mortality (HR: 0.70 for HCV genotype 1, HR: 0.64 for HCV genotype and HR: 0.51 for HCV genotype 3, $p < 0.01$ for all) within a large population of HCV-infected American veterans with various stages of hepatic fibrosis and many comorbidities [60]. Shortly after, this was confirmed in a more general population with chronic HCV infection and advanced hepatic fibrosis, who are at highest risk of clinical sequelae of the infection [53]. After 10 years of follow-up, the cumulative all-cause mortality rate was 26% among those without SVR *vs.* 9% among those with SVR in this cohort ($p < 0.001$). Although the possibility of confounding was heavily discussed, both these studies have performed extensive multivariable analyses including important baseline variables that are linked to both the success of antiviral therapy as well the long-term clinical outcome [61,62]. A causal relation between HCV eradication and prolonged survival can also be considered plausible based on the (above-described) extensive body of evidence in favor of SVR as a patient-relevant endpoint. Moreover, after these first two publications, others have published similar findings among patients with chronic HCV infection in general as well as among patients with cirrhosis specifically, also after employing more advanced statistical methods [18,20,63]. A recent meta-analysis estimated that the average adjusted HR of SVR for all-cause mortality was 0.50 (95% CI: 0.37–0.67) among cohorts including patients with all stages of fibrosis and 0.26 (95% CI: 0.18–0.37) among cohorts including solely patients with advanced hepatic fibrosis [64]. Still, in contrast to these strong relative risk reduction, it is noteworthy that the absolute clinical efficacy of antiviral therapy may be limited, especially in case a mild natural history may be expected [18,65]. The clinical relevance of successful antiviral therapy was further substantiated by two groups who showed that the survival of patients who attained SVR did not deviate from the survival of an age- and gender-matched general population, despite the presence of cirrhosis prior to antiviral treatment initiation [66,67]. Further studies need to assess whether this holds for all subpopulations.

Even in case HCC has developed, patients with SVR seem to have a beneficial survival as compared to those without SVR, both in case of successful IFN-based therapy before or after the diagnosis of liver

cancer [68,69]. While antiviral therapy should thus be considered as part of the treatment of patients with HCV-induced HCC, we were recently alarmed about an exceptionally high early HCC recurrence rate after DAA therapy in this specific population [70]. The rapid viral load decline was hypothesized to misbalance the HCV-stimulated immune control over small metastasis, thereby altering the biological behavior of the tumor cells. This early report got a lot of attention and caused quite some stress and uncertainty among both patients and physicians. Fortunately, our fears were quickly attenuated as the observation in Spain could not be confirmed in three large prospective studies among DAA-treated patients with HCC from France [71]. Still, more data on this specific matter are urgently needed.

Key point

In a substantial proportion of patients with chronic HCV infection and decompensated cirrhosis show functional improvement as witnessed by a decrease in MELD and CTP scores upon antiviral therapy with DAAs, both before and after liver transplantation.

Decompensated liver disease

As the population with chronic HCV infection continues to age and the duration of infection increases, the prevalence of advanced liver disease, HCC and need for liver transplant (LT) is rising. Indeed, the prevalence of cirrhosis and hepatic decompensation has doubled over the last decade, and HCV-related liver disease, particularly in the setting of HCC, remains the leading indication for LT in many countries [72]. In the IFN era, antiviral therapy was contraindicated in a significant proportion of patients on the LT waiting list. When IFN-based therapy was used, only patients with low Child-Turcotte-Pugh (CTP) scores (<B8) and Model for End-Stage Liver Disease scores (MELD; <16–17) were treated. The major aim of antiviral treatment among those patients who were able to tolerate it was to achieve SVR or on-treatment undetectable HCV RNA at time of LT in order to avoid HCV reinfection thereafter [73]. The severe side-effects and low chance of SVR made physicians reluctant, however, to initiate IFN therapy among those with decompensated cirrhosis. Still, also in this specific population with most advanced cirrhosis, successful IFN-based therapy was suggested to be clinically relevant. A study in which 66 patients with advanced liver disease (6% CTP-A, 71% CTP-B, 23% CTP-C; 24% MELD >18) were treated with PegIFN and RBV for 6 months showed a beneficial clinical outcome during the median follow-up of 30 months in case of SVR. When compared to patients without SVR, and a cohort of untreated control patients, those with SVR had less ascites (46% and 66% *vs.* 8%), less encephalopathy (52% and 63% *vs.* 15%), less bleeding episodes (21% and 31% *vs.* 0%), and reduced HCC development (21% and 10% *vs.* 0%) or liver-related deaths (19% and 30% *vs.* 0%). Moreover, there was a hint for an improved overall survival among patients with SVR as compared to those without SVR and controls (20-months survival rates of 80%, 78% and 72%, respectively, $p = 0.07$) [74]. Extending the follow-up to a little over 4 years confirmed that SVR represents a positive prognostic factor among patients with decompensated cirrhosis, as 8 of 24 (33%) patients with SVR *vs.* 49 of 51 (96%) patients without SVR experienced hepatic decompensation ($p < 0.0001$) [75]. However, as could be anticipated, only a minority of patients in this study attained SVR and these patients are likely to represent a group with beneficial clinical outcome in absence of viral eradication as well. Nowadays, the excellent safety profile of the DAAs has led to the treatment of patients who would not have received IFN-based therapy, including waitlisted patients with decompensated liver disease. And with success! SVR rates greater than 95% are now reached in patients with compensated cirrhosis undergoing transplantation for coexistent HCC and very good, albeit slightly lower response rates, of about 80% are achieved in case of decompensated cirrhosis (Table 1) [76–78]. With these developments hepatologists are now able to assess more accurately whether eradication of HCV can still benefit those with most advanced cirrhosis.

Improvement of liver function tests and measurements of decompensation

Interestingly, an improvement of liver function (albumin and bilirubin levels) and measurements of decompensation including MELD and CTP scores have been reported during and shortly after therapy among patients with advanced liver disease treated with sofosbuvir (SOF)/ledipasvir (LDV) [77,78], SOF/daclatasvir (DCL) [76], and SOF/velpatasvir (VPV) [79] (Table 2). These results have been confirmed in real-world studies of patients treated with DAA regimens, and parallel observations among patients with chronic hepatitis B virus (HBV) infection and advanced liver disease who were treated with oral antiviral therapy [80–84]. Virological suppression, or eradication, thus seems to result in improved hepatic function.

In the real-world UK study (HCV Research UK registry), the outcome of patients at high risk of death from chronic HCV infection (median baseline MELD score of 11, range: 6–32) who were treated for 12 weeks with DAA-combination regimens was set against that of a comparable group of untreated patients [80]. As in prior open label studies, SVR was achieved in over 80% of this highly diseased population. Six months after DAA initiation, liver function was found to be superior in treated patients as compared to untreated patients, as the median MELD score decreased among treated patients (−0.85) and increased among untreated patients (+0.75; $p < 0.001$). In line with these results, a greater proportion of treated patients showed an improvement in MELD scores. Among those with a worsened MELD score despite antiviral therapy, the degree of worsening was lower as compared to those who

Table 1. Characteristics of studies including patients with chronic HCV infection and decompensated cirrhosis treated with DAAs.

	Regimen	Duration (wk)	n	SVR	MELD >15 (n)	MELD >20 (n)
SOLAR [77, 78]	LDV/SOF ± RBV	12-24	140	57-89%	54	5
ALLY-1 [76]	SOF + DCV + RBV	12	60	56-94%	14	3
CUP [80]	SOF + DCV or SOF + LDV	12	467	81.6% (68.8-90.9%)	89	15
ASTRAL-4 [79]	SOF/VEL ± RBV	12-24	267	50-100%	13	n.a.

DAAs, direct-acting antivirals; DCV, daclatasvir; HCV, hepatitis C virus; LDV, ledipasvir; MELD, Model for End-Stage Liver Disease; n, number; RBV, ribavirin; SOF, sofosbuvir; SVR, sustained virological response; VEL, velpatasvir.

did not receive DAAs. Significantly fewer treated patients developed a profound worsening in MELD (increase of 2 points or more) over 6 months as compared to untreated patients (23.0% *vs.* 37.9%, $p = 0.05$). Thus, these results suggest that DAA therapy may already benefit patients with chronic HCV infection and decompensated liver disease within 6 months. A decrease in mean MELD score was even observed among patients who failed to attained SVR, but did experience several months of non-viremia prior to virological relapse (−0.63). Nevertheless, patients with SVR had considerably better functional outcomes than those who were not successfully treated, with adverse outcomes reported in 45.0% and 82.5%, respectively. The proportion of patients with "re-compensated" disease who had at least one decompensating event during the study period was reduced in the treated compared to untreated cohort (3.7% *vs.* 10.0%, $p = 0.0009$), apart from the subgroup with baseline MELD score >14. Additional analyses suggested that patients above the age of 65 with reduced hepatic synthetic function (serum albumin ⩽35 g/L) were less likely to benefit from DAA therapy as well, although these factors were not sufficiently discriminative to identify a subgroup in which antiviral therapy should be deferred in favor of LT. Although findings are suggestive of a point of no return, after which antiviral treatment may be too late to influence the natural history of HCV-related liver disease, more data is needed before any definite conclusions can be drawn.

Delisting patients from the LT waiting list

Data regarding clinical benefits and potential delisting from the LT waiting list in HCV-infected patients treated with the new DAA combinations are scarce. One anecdotal case on a successfully treated woman was recently reported [85]. The patient, 67 years of age, waitlisted for decompensated cirrhosis (CTP 12, MELD 16) with refractory ascites and chronic hepatic encephalopathy achieved complete functional (CTP 5, MELD 12) and clinical recovery (no ascites, no encephalopathy). She could be removed from the waiting list. In a recent retrospective multicenter European study, waitlist outcome was evaluated in 103 consecutive LT candidates with decompensated cirrhosis without HCC treated with different DAA combinations. The cumulative incidences of inactivation and delisting were 16% and 0% at 24 weeks after the start of therapy and 35% and 20% at 48 weeks after the start of therapy. The 25 patients who were inactivated showed a median improvement of 4 points for the MELD score (p <0.0001) and a median improvement of 3 points for CTP score (p <0.0001). Three variables emerged as independent predictors of inactivation due to clinical improvement, namely, baseline MELD (HR: 0.819, $p = 0.0004$), delta MELD (HR: 1.311, p <0.0001) and delta-albumin (HR: 0.419, $p = 0.0041$) (the latter two assessed after 12 weeks of DAAs therapy). The more relevant biochemical changes after 24 weeks from start of therapy were a median increase of albumin by 0.4 g/dl and a median reduction of bilirubin by 0.8 mg/dl. In addition, the percentage of patients with refractory ascites halved from 28% at baseline to 14.1% after 24 weeks following treatment initiation, while stage 2 hepatic encephalopathy regressed in almost two thirds of affected patients. Inactivation occurred at a median of 22.6 weeks (16.4–35.2) from start of therapy while the decision to delist a patient from the waiting list required 6 additional months (44.3 weeks, range: 36.3–53.3), possibly reflecting the (understandable) caution of physicians to delist a re-compensated cirrhotic patient. Thus, as for chronic HBV infection, it emerges that among patients with decompensated HCV-induced cirrhosis who are listed for LT, second generation DAAs favors the inactivation and delisting of about one third and one fifth of patients

Table 2. Changes in measurements of hepatic decompensation following DAA therapy among patients with chronic HCV infection and advanced liver disease.

	Solar-1 [78]	Solar-2 [77]	Ally-1 [76]	Astral-4 [79]
Number of patients evaluated	93	81	39	250
Time at evaluation	SVR-4	SVR-24	SVR-12	SVR-12
MELD changes				
Improvement	67%	73%	40%	54%
In CTP-B cirrhosis	64%	65%	43%	54%
In CTP-C cirrhosis	70%	83%	67%	-
Worsening	17%	16%	40%	25%
In CTP-B cirrhosis	17%	20%	43%	25%
In CTP-C cirrhosis	18%	11%	0%	-
CTP changes				
Improvement	67%	77%	76%	47%
Worsening	8%	8%	12%	11%

CTP, Child-Turcotte-Pugh score; DAA, direct-acting antiviral; HCV, hepatitis C virus; MELD, Model for End-Stage Liver Disease; SVR, sustained virological response (at 4; 12 or 24 weeks after DAA therapy).

Key point

Clinical improvements following antiviral therapy with DAAs can result in the withdrawal of patients with chronic HCV infection from the liver transplantation waiting list.

within 1 year, respectively. Logically, patients with lower MELD scores have higher chances of being delisted and patients with higher baseline MELD scores need greater MELD score reductions before there is sufficient functional and clinical improvement for LT waiting list inactivation. As such, among patients with a baseline MELD score <16, the probability of inactivation was 26.3, 66.7 and 83.3% in case of a delta MELD score of <2, 2 to 4 and >4, respectively, after 12 weeks of therapy. In contrast, among patients with baseline MELD score ranging from 16 to 20, the probability of inactivation was 0% in case of a week 12 delta MELD <2, *vs.* 40 and 60% in patients with week 12 delta MELD of 2 to 4 or >4. Among patients with baseline MELD score >20, inactivation was only observed among those with a delta MELD >4 at week 12 [86]. Another French cohort study among 183 patients awaiting transplantation showed that approximately a third (36%) of patients with decompensated cirrhosis had a complete clinical and biological response with regression to CPT-A cirrhosis at the end of antiviral therapy [87]. Also in this cohort improvements were less likely among those with most advanced cirrhosis. Interestingly, in case DAA therapy results in sufficient long-term clinical improvements and patients may indeed be inactivated or even delisted, this might not only benefit the HCV-infected population. Patient with cirrhosis due to other etiologies may see their chance on a donor liver increase as the proportion of waiting list registrants due to HCV (a group that represents a large proportion of those awaiting LT in many centers) is reduced.

Open questions regarding the clinical benefit of DAAs in decompensated cirrhosis

While a lot of expertise has been gained with antiviral therapy among patients with compensated liver disease over the last decades, antiviral therapy among chronic HCV-infected patients with decompensated cirrhosis is rather new. Even though hepatologists may consider their experiences in patients with chronic HBV infection, for whom there is more data on antiviral therapy in the setting of liver failure, there remain uncertainties regarding the clinical outcome of therapy in such patients with chronic HCV infection. These uncertainties include whether DAA therapy is safe among those with advanced liver insufficiency, whether meaningful functional hepatic recovery is possible in most HCV-infected individuals with advanced cirrhosis and how long such recovery would take, whether there is indeed a point of no return after which antiviral therapy is futile, and, finally, whether short-term positive effects on MELD will indeed translate into long-term clinical benefits.

One of the key limitations with respect to these questions is the lack of control groups in open label studies. Furthermore, in most studies, patients with significant advanced liver disease were either excluded or, if included, their numbers were extremely low. In the 2 Solar studies patients were treated with SOF/LDV/RBV for 12 *vs.* 24 weeks, but patients with CTP scores greater than 12 were excluded due to their high near-term mortality [77,78]. In the Ally-1 study, in which patients were treated with SOF + DCV + RBV for 12 weeks, MELD score ranged from 8 to 27, but only 3 had a meld score >20 [76]. Finally, in the above-discussed UK real-world study only 19.1% had MELD scores >15 and only 15 patients had a MELD score >20 [80]. While in all these reports it appears that the DAA regimens are relatively safe and that the majority of adverse events are caused by the underlying natural disease process, it is still not absolutely clear whether the protease inhibitors, NS5A and polymerase inhibitors cause adverse events, particularly in patients with unstable cirrhosis. Reports of hepatic decompensation during dasabuvir, ombitasvir, and paritaprevir/ritonavir therapy among those with most advanced liver disease led the Food and Drugs Administration (FDA) to discourage the use of this specific IFN-free combination regimen among those patients with CTP-B/C cirrhosis [88]. In one recent report from Welker *et al.*, lactic acidosis developed in 5 out of 35 patients with advanced liver disease treated with SOF-based therapy, which the authors attributed to mitochondrial toxicity of the oral agents [89]. While on closer inspection, mitochondrial toxicity was unlikely and not adequately documented in these patients, it contributes to the uncertainty whether these new oral agents are safe in this vulnerable population, which is already at risk to develop severe complications including liver decompensating events [90]. Obviously, a clear understanding of the risk *vs.* benefit ratio of DAA-driven therapy is not only relevant for waitlisted patients, in whom antiviral therapy may be postponed to after LT, but also for those in whom LT is not an option at all.

Clearly if antiviral therapy was able to reverse liver dysfunction and, in doing so, avoid the need for LT, it should be recommended in all waitlisted patients. But how soon may liver function improvement be expected? In decompensated HBV-related cirrhosis, clinical improvements lag behind virologic responses [83]. The severity of liver disease at the time of lamivudine initiation was shown to be related to the time it takes for liver function to recover [84]. Chronic HBV-infected patients of CTP-B cirrhosis needed shorter time to achieve a 2-point reduction in CTP score (5.9 *vs.* 14 months) and to gain a 0.5 g/dl increment in albumin (5.8 *vs.* 14 months) as compared to patients with CTP-C cirrhosis [91]. Furthermore, not all patients with decompensated HBV-cirrhosis survive during treatment with the oral antivirals. In the large prospective multicenter study from the US, 21% of lamivudine-treated patients died of liver failure

with 78% of the deaths occurring within the first 6 months of therapy. The severity of liver disease at the time of antiviral treatment initiation seems a more relevant determinant of early mortality than the virological response and should thus be considered to guide patient prioritization for LT. The same seems to hold true for chronic HCV-infected patients as a proportion does not gain immediate benefit from DAA therapy. In fact, in the Solar 2 study of SOF/LDV/RBV, the most common reason for not attaining SVR among patients with CTP-C cirrhosis was death due to progressive liver failure [78]. Also, continuing analyses from the real-world UK cohort, for which the follow-up was extended to 15 months post-treatment initiation, showed that the adverse event free survival among treated patients with CTP-C or a MELD score >14 at baseline remained poor [92]. Even more alarming, the change in MELD score after 12 weeks of DAA therapy was not statistically significantly associated with the adverse event free survival at 15 months. Although these analyses may be preliminary and would benefit from more power on solid clinical endpoints, they do require our attention. If anything, these results highlight that the clinical relevance of the expensive DAA regimens among patients with most advanced cirrhosis has yet to be determined.

Potential paradoxical consequence of DAA therapy

Anti-HCV therapy may also have an apparent paradoxical consequence. Indeed, patients with decompensated cirrhosis may eliminate the virus, stabilize their disease and not progress to a stage where LT is indicated. In these circumstances, such patients might lose their eligibility or priority for LT as their MELD score decreases. Even if their life-expectancy improves in the short-term, they may not recover to any meaningful extent and, post-therapy, these patients may be left without access to transplantation but with a poor quality of life (so called 'MELD purgatory') [93]. Furthermore, given the advanced age of many patients waitlisted for LT for end-stage HCV-related liver disease, complications such as HCC or further decompensation could arise in the mid to long-term where LT may no longer be a viable option. So far, it still has to be shown whether DAA therapy can reduce the incidence of HCC, which was comparable between DAA-treated (6.1%) and untreated patients (8.0%) with HCV-induced decompensated cirrhosis over a 24-week study period [80].

Surely, studies with longer follow-up duration are needed to assess whether patients with no immediate gain are slower to improve in liver function, as well as whether patients have a reduced occurrence of HCC or all-cause mortality following DAA therapy. Considering the DAAs were only recently implemented, these studies have to be awaited.

Post liver transplantation

Recurrent HCV infection of the allograft is universal if the virus is detectable at time of LT. Due to immunosuppression and the increasing use of low-quality grafts, an accelerated progression of fibrosis in the transplant is often observed. Approximately one third of the patients will progress to cirrhosis within 5 years after LT, leading to an impaired graft and patient survival [94]. In the IFN era, the most common approach was to treat graft hepatitis after histological damage was confirmed and before clinical decompensation had developed. Overall SVR rates were low, ranging between 30 and 40% across different series, and toxicity was a significant concern with high rates of treatment discontinuation and/or dose reductions [95]. Despite these results, the positive impact of SVR on clinical outcome was well demonstrated. Indeed, sustained viral eradication was clearly shown to result in decreased risk of fibrosis progression, hepatic decompensation, graft loss, as well as a decrease in portal pressure, ultimately resulting in enhanced survival [96–101]. This beneficial effect was more pronounced in patients treated prior to the development of advanced post-transplant liver disease [101].

Regarding histologic parameters, patients attaining SVR were significantly more likely to experience improvement in necroinflammatory activity and fibrosis stage as compared to patients who did not attain SVR. However, histologic benefit (particularly fibrosis change) was not always apparent early after viral clearance, but was rather confirmed in subsequent "long-term biopsies" (recently reviewed in: [94]). In one study based on 29 patients with SVR, the stage of fibrosis at 2 years improved by at least 1 stage in 27%, remained unchanged in 38%, and worsened in 35%. After 3 to 5 years, the fibrosis stage had improved in 67%, remained unchanged in 13%, and worsened in 20% [102]. In another study, a comparison of fibrosis scores between pre-treatment and the last post-treatment biopsy showed an overall stabilization and/or improvement in 57.5% of cases; 75% in case of SVR as compared to 50% in case of no SVR. Also in the post-LT setting the relation between time and improvement of hepatic fibrosis seems evident. While the rate with fibrosis stabilization/improvement did not differ between those with SVR and those without SVR at the end of therapy (64% *vs.* 63%, $p = 1.0$), patients with SVR significantly more frequently showed fibrosis stabilization/improvement when the paired liver biopsies was performed at least 12 months after antiviral therapy (92% *vs.* 41%, $p = 0.005$) [101]. In case histologic improvement is not observed, clinicians should be aware for additional hepatic

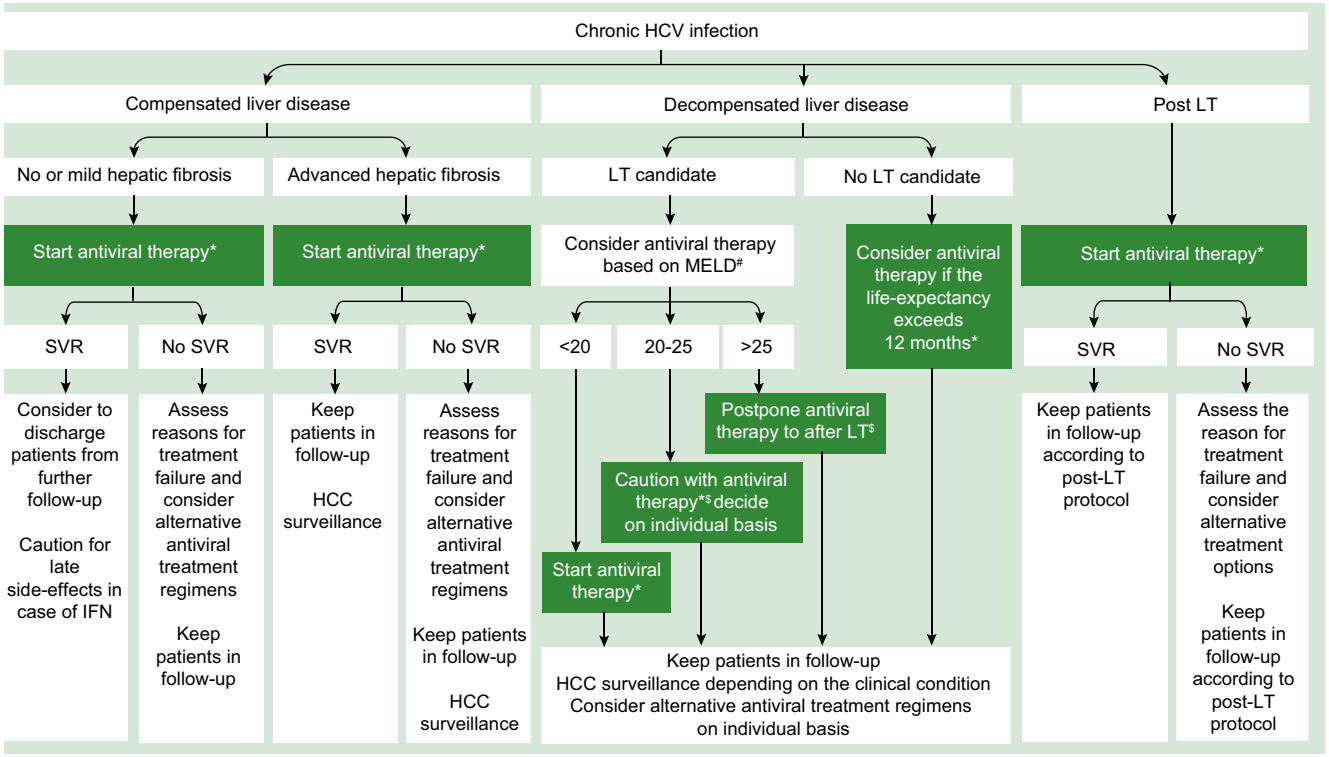

Fig. 1. Simplified scheme for indication of antiviral therapy and follow-up of patients with chronic HCV infection. *Consider drug-specific and/or psychosocial contraindications for antiviral treatment. #This concerns a suggested approach. There is no data for any hard clinical recommendations. $Take the center-specific waiting time for liver transplantation into account. HCC, hepatocellular carcinoma; HCV, hepatitis C virus; LT, liver transplantation; MELD, Model for End-Stage Liver Disease; SVR, sustained virological response.

pathologies such as non-alcoholic steatohepatitis, de novo autoimmune hepatitis, biliary complications, or chronic rejection. While there are no studies which evaluated fibrosis progression or regression following antiviral therapy with DAAs in the post-LT setting, there is currently no reason to assume that these results will differ from those in the IFN era.

With the DAAs there are no limitations to treat post-transplant recurrence, including patients with decompensated cirrhosis or those with fibrosing cholestatic hepatitis (FCH) – a life-threatening form of HCV recurrence. Excellent SVR rates are achieved, greater than 95%, even in the FCH group [73,76–78,103–106]. From a safety point of view, very few severe adverse events have been reported throughout studies. As in the immune competent setting, most deaths have occurred in cirrhotic patients and are drug-unrelated. In terms of clinical benefits, results parallel to the situation as described in the immune competent setting. Most importantly, in FCH, where recurrence is characterized by rapid portal fibrosis and cholestasis leading to fast deterioration of the liver, short series of patients treated with the DAAs have shown that the vast majority of patients survive without the need of re-transplantation, with rapid and profound improvements in clinical status [104,105].

In case of decompensated graft cirrhosis, treatment with DAAs is associated with a reduced likelihood of SVR [76–78,103,106,107]. Despite these lower success rates, improvements in MELD score and CTP have been observed. In the Solar 1 study, 6 of the 30 patients with CTP-B cirrhosis treated for 12 weeks had a worsening in MELD score at 4 weeks post-therapy. This rate was significantly lower among those treated for 24 weeks (3 out of 29), so that one could again argue that these findings indicate that time is needed to observe functional changes [77]. In the Solar 2 study, 28% of CTP-B patients reversed to CTP-A status (n = 14/50), while this percentage increased to 68% (21/31) in the CTP-C score improving to CTP-B status [78]. In the Ally-1 study, these percentages were 50% (15/30) and 46% (6/13), respectively [76]. Further studies should focus on the demand for liver re-transplantation, reduced liver graft-related mortality, as well as reversibility of clinical liver failure.

Conclusions

With lots of recent, high-quality data, there is cumulative evidence for a clinical benefit of successful antiviral therapy among patients with chronic HCV infection and compensated liver disease, both before

as well as after LT. Viral eradication is not only associated with a reduction of liver-related consequences of HCV infection, but also with a reduction of relevant extrahepatic disease manifestations. As a result, SVR is associated with an improved overall survival. With all the newly available DAAs, having excellent virological efficacy, these results are most timely and form the basis for DAA reimbursement. Still, the beneficial outcome with IFN-induced SVR should be confirmed for DAA-induced SVR as our experience with these drug prolongs. In the short-term, however, there do not seem to be major issues with the DAA regimens, at least not among those with compensated HCV-related liver disease. With tens of thousands of patients being treated worldwide, these would have surfaced. Still, as we were recently warned by several reported observations in *the Journal* for those patients with a history of HCC, we need to remain alert for unexpected off-target effects. The next challenge, in order to make a real impact on the burden of HCV infection, is to get these drugs to the patients. This requires us to diagnose HCV infection, perhaps through efficient screening programs. Another hurdle, which has been extensively discussed all over, concerns the costs of treatment. Ironically, the prices of the DAAs are partly based on the same investigator-initiated studies (which showed strong risk reductions upon SVR) by which antiviral therapy was justified in the first place. Although the importance of SVR is thus currently reflected in these high prices, SVR should perhaps be considered as too important to be this expensive.

Unlike for patients with compensated liver disease, uncertainties still remain with respect to the clinical efficacy of antiviral therapy among patients with chronic HCV infection and decompensated cirrhosis. Recent studies with the DAAs demonstrated that SVR can now be achieved in the majority of these patients, unlike the situation with IFN, with short-term improvements in measures of decompensation. Indeed, modest improvements in MELD score have been documented, but also inactivation and even delisting of some patients from the LT waiting list was reported. How these short-term results of liver function improvement relate to an improved quality of life and prolonged overall survival needs further clarification. Long-term studies are also required to delineate the extend of improvement which can be expected in those with most significant portal hypertension and synthetic dysfunction. As suggested in Fig. 1, it might be better to proceed with LT and treat the HCV infection thereafter as MELD increases, although specific MELD or CTP score cutoffs for futile DAA therapy surely need more study (Fig. 1). This is especially relevant for patients who are able to undergo LT in a timely manner given the very high rates of SVR achieved when treating individuals after LT. Considering the high event rate among those with decompensated cirrhosis, we should be able answers these remaining questions on relative short notice.

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Conflict of interest

The authors declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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