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## Liver-related effects of chronic hepatitis C antiviral treatment

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### Abstract

More than five years ago, the treatment of hepatitis C virus infection was revolutionized with the introduction of all-oral direct-acting antiviral (DAA) drugs. They proved highly efficient in curing patients with chronic hepatitis C (CHC), including patients with cirrhosis. The new DAA treatments were alleged to induce significant improvements in clinical outcome and prognosis, but the exact cause of the expected benefit was unclear. Further, little was known about how the underlying liver disease would be affected during and after viral clearance. In this review, we describe and discuss the liver-related effects of the new treatments in regards to both pathophysiological aspects, such as macrophage activation, and the time-dependent effects of therapy, with specific emphasis on inflammation, structural liver changes, and liver function, as these factors are all related to morbidity and mortality in CHC patients. It seems clear that antiviral therapy, especially the achievement of a sustained virologic response has several beneficial effects on liver-related parameters in CHC patients with advanced liver fibrosis or cirrhosis. There seems to be a time-dependent effect of DAA therapy with viral clearance and the resolution of liver inflammation followed by more discrete changes in structural liver lesions. These improvements lead to favorable effects on liver function, followed by an improvement in cognitive dysfunction and portal hypertension. Overall, the data provide knowledge on the several beneficial effects of DAA therapy on liver-related parameters in CHC patients suggesting short- and long-term improvements in the underlying disease with the promise of an improved long-term prognosis.

**Key words:** Chronic hepatitis C; Antiviral treatment; Inflammation; Liver fibrosis; Liver cirrhosis; Metabolic liver function; Galactose elimination capacity; Urea synthesis capacity; Portal hypertension; Hepatic encephalopathy

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**Core tip:** Antiviral therapy of chronic hepatitis C, especially the achievement of a sustained virologic response, has several beneficial effects on liver-related parameters in chronic hepatitis C patients. There seems to be a time-dependent effect of therapy. Initially, liver inflammation ameliorates, followed by more discrete changes in structural liver lesions. These improvements are followed by beneficial effects on liver function, cognitive disturbances, and portal hypertension. Together, this suggests short- and long-term improvements in the underlying liver disease with the promise of an improved prognosis.

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## INTRODUCTION

Hepatitis C virus (HCV) was isolated and named in 1989<sup>[1]</sup>, and in 2015, more than 170 million people were infected worldwide with approximately 70 million chronically infected<sup>[2,3]</sup>. The primary mode of virus transmission in Western countries is *via* percutaneous exposure to blood, and the major infection route is unsafe drug injections<sup>[4-6]</sup>. At transmission, an acute HCV infection occurs, which is often asymptomatic<sup>[7]</sup>. In 60%-80% of patients, the infection becomes chronic<sup>[8,9]</sup>, and chronic hepatitis C (CHC) is defined as positive HCV RNA for at least 6 mo. CHC holds the potential for inducing fibrosis and 10%-30% of those infected develop cirrhosis over decades, with the potential risk of complications and early death<sup>[10-12]</sup>.

HCV is a hepatotropic positive single-stranded RNA virus that translates into a single polyprotein consisting of 3011 amino acids. The HCV genome is highly diverse and is separated into seven genotypes with several subtypes<sup>[13]</sup>. HCV circulates as a lipo-viro-particle consisting of the nucleocapsid surrounded by the envelope proteins E1 and E2, and several host lipoproteins<sup>[14]</sup>. HCV is cleaved by viral and host proteases into 10 proteins with diverse functions: 3 structural proteins (*i.e.*, core, E1, and E2) and 7 nonstructural (NS) proteins (*i.e.*, p7, NS2, NS3, NS4A, NS4B, NS5A, and NS5B)<sup>[15,16]</sup>. The two viral proteases, NS2 and NS3/4A, are involved in the process of producing nonstructural proteins. Replication itself is catalyzed by the RNA polymerase NS5B, while NS5A and NS3 are important regulatory proteins. NS4B participates in membrane rearrangements, leading to the formation of a membranous web that supports continued HCV replication<sup>[16,17]</sup>.

HCV is a major challenge for the immune system, and host factors play important roles in the potential clearance of HCV and long-term disease progression<sup>[18,19]</sup>. An initial vigorous immune response is considered crucial, and both initial and consistent innate and adaptive immune responses are important determinants of whether the infection can be cleared or becomes chronic. The innate immune responses include the activation of proinflammatory pathways<sup>[20-23]</sup>, and adaptive immune factors include weak or absent HCV-specific T-cell responses<sup>[24,25]</sup>. If HCV infection is not cleared, these mechanisms lead to sustained liver inflammation with the activation of macrophages, which subsequently activate or transdifferentiate hepatic stellate cells into myofibroblast-like cells with proinflammatory, contractile, and profibrogenic properties. This may initiate a vicious cycle where inflammatory and fibrogenic cells consistently stimulate each other<sup>[26]</sup>, resulting in the accumulation of excessive extracellular matrix proteins and fibrosis progression<sup>[27]</sup>.

## TREATMENT OF CHRONIC HEPATITIS C

The ultimate treatment goal of CHC is a sustained virologic response (SVR), defined as undetectable HCV RNA 12-24 wk after treatment cessation, corresponding to "cure" or, in other words, HCV eradication. The treatment has evolved drastically over the last decades. For years, CHC treatment was based on subcutaneous interferon treatments that had inadequate efficacy and severe adverse effects, leaving this type of treatment intolerable for many patients, especially those with cirrhosis<sup>[28-30]</sup>. Interferon treatment acts *via* a direct immune-stimulating mechanism and has several derivative effects on innate and adaptive immunity<sup>[31]</sup>. In 2001,

pegylated interferon was introduced; it has a longer half-life and a more favorable pharmacokinetic profile, and it improved the SVR rate slightly, while the majority of the adverse effects remained<sup>[32-34]</sup>. In addition to interferon treatment, ribavirin was required. Ribavirin is a nucleoside analog of guanosine that is used to potentiate the effects of antiviral treatments<sup>[35]</sup> and is still used as a potential addition to some DAA regimens.

In 2011, the first DAA treatments were introduced, and as the name infers, the DAAs are specific inhibitors of the viral proteins. Boceprevir and telaprevir were the first generation of DAAs; they inhibit the NS3/4A protease, are effective against only genotype 1, and were approved as an add-on to the established pegylated interferon and ribavirin treatment. The treatment duration was between 24 and 48 wk, and the drugs improved the SVR rates<sup>[36-39]</sup> and held promise for a new era of all-oral DAA therapy.

In 2014, sofosbuvir was marketed in Europe. Sofosbuvir is a uridine nucleotide analog that inhibits NS5B RNA polymerase by competing with natural nucleotides and by inducing viral RNA chain termination. Sofosbuvir is orally administered for 12-24 wk, is pangenotypic, and may be combined with other DAAs that are genotype-specific<sup>[40]</sup>. With the introduction of sofosbuvir, high SVR rates, in general above 90%, were reached even in difficult-to-treat patient groups, *e.g.*, patients with cirrhosis and nonresponders to previous therapy<sup>[41-44]</sup>. Several other DAAs were introduced starting in 2013, including ledipasvir (an NS5A inhibitor), daclatasvir (an NS5A inhibitor), and simeprevir (a second-generation NS3/4A inhibitor), and 3D combination [ombitasvir (an NS5A inhibitor), paritaprevir (an NS3/4A inhibitor), and ritonavir with the potential addition of dasabuvir (an NS5B inhibitor)], all of which contributed to increasing SVR rates, ultimately reaching 100%<sup>[43-47]</sup>.

With the introduction of all-oral DAA therapy, a new era of CHC treatment commenced. Not only was it possible to successfully treat the “healthiest” patients, but treatment was suddenly a possibility for all patients with CHC. Rapidly, the scientific discussions changed focus to special groups such as cirrhosis patients and non-responders, and to the biological effects of HCV eradication.

## ASSESSMENT OF LIVER DISEASE SEVERITY

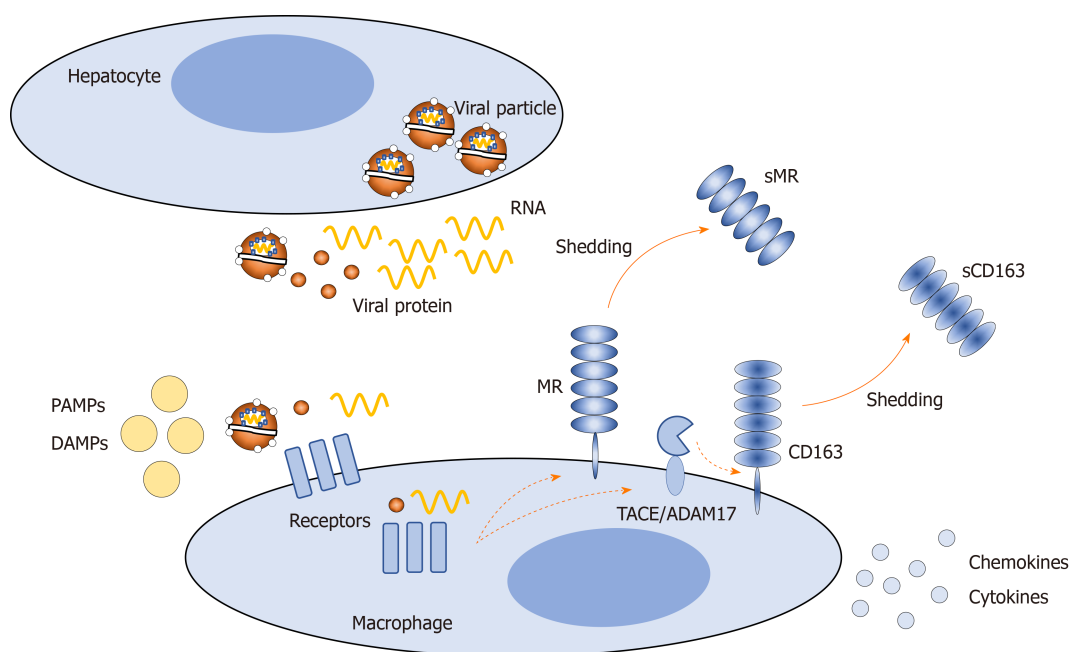
Assessment of liver disease severity is crucial in CHC as it is related to morbidity and mortality<sup>[48-50]</sup>. Several components affect the prognosis of chronic liver disease and the three major factors are inflammation, fibrosis, and liver function<sup>[51]</sup>. As described above, the presence of inflammation drives the process of fibrogenesis, with structural changes leading to portal hypertension. In addition, liver function may be compromised, probably due to both ongoing hepatic inflammation and structural liver changes, with the loss of functional liver mass.

### Macrophage activation

In HCV infection, hepatocytes release viral particles and components, which may bind directly to surface or endosomal macrophage receptors or interfere indirectly with these receptors<sup>[52]</sup>. In addition, other factors may act on macrophage receptors, such as pathogen-associated molecular patterns, including lipopolysaccharide, which may enter the circulation from the gut due to increased intestinal permeability, and damage-associated molecular patterns released from damaged hepatocytes. These factors activate macrophages, causing an altered proinflammatory phenotype and amplifying hepatic inflammation<sup>[53,54]</sup>. One way to assess hepatic inflammation noninvasively is to evaluate the presence of specific macrophage activation markers in the blood. Two such markers are soluble (s)CD163 and soluble mannose receptor (sMR)<sup>[55-57]</sup> (Figure 1). sCD163 and sMR are well-established markers of liver disease severity, portal hypertension, and prognosis in several liver and infectious diseases<sup>[58-68]</sup>. Furthermore, significant associations between macrophage activation and histological inflammatory activity and fibrosis have been observed in CHC<sup>[69-71]</sup>. After antiviral therapy of chronic hepatitis B and interferon treatment of CHC, macrophage activation is diminished in parallel with the amelioration of hepatic inflammation<sup>[72,73]</sup>.

### Fibrosis staging

Fibrosis staging is important in CHC patients, as fibrosis stage is a strong predictor of complications and mortality<sup>[74,75]</sup>. Historically, liver biopsy has been the method of choice as it brings insight into the exact structure of the liver and yields information on inflammation and fibrosis as well as potential differential diagnoses. Liver histology from CHC patients covers a wide spectrum of abnormalities, from acute inflammation to lasting structural changes, often in combination<sup>[76,77]</sup>. Moreover, a liver



**Figure 1** Release of viral particles, viral proteins, and RNA from hepatocytes in hepatitis C infection, and subsequent shedding of soluble CD163 and soluble mannose receptor from the surface of macrophages in response to exogenous and endogenous stimuli. PAMP: Pathogen-associated molecular pattern; DAMP: Damage-associated molecular pattern; MR: Mannose receptor; sMR: Soluble mannose receptor; sCD163: Soluble CD163.

biopsy may be used to assess fibrosis progression over time<sup>[11]</sup>. However, the biopsy represents a small portion of the liver, which may be heterogeneous. Some studies have shown sampling error in up to 30% of biopsies<sup>[78,79]</sup>, with adequate biopsy length being of primary importance<sup>[80]</sup>. Liver biopsy may further be limited by inter- and intraobserver variation in histological assessment<sup>[81]</sup>; is invasive, with a small but significant risk of complications (*e.g.*, pain, bleeding, and even mortality)<sup>[82]</sup>; and is disliked by many patients, which limits its use in follow-up studies. The lack of histological verification of structural liver changes is one of the major limitations in many studies.

Due to the limitations of liver biopsy, noninvasive methods for grading and staging liver inflammation and fibrosis have become increasingly sought and used. Noninvasive methods include biomarkers and imaging techniques, many of which were developed and validated in CHC patients. The biomarkers include scores such as the aspartate aminotransferase-to-platelet ratio index (APRI) based on aspartate transaminase (AST) and platelets<sup>[83]</sup>; the fibrosis-4 (FIB-4) index based on age, AST, alanine transaminase (ALT), and platelets<sup>[84]</sup>; the enhanced liver fibrosis test<sup>[85]</sup>; and the FibroTest<sup>[86]</sup>, which have all been extensively investigated in CHC patients, yielding “good or decent” prediction of fibrosis and especially cirrhosis<sup>[85,87-92]</sup>. In addition, the APRI and FIB-4 predict HCV liver-related death<sup>[93]</sup>.

The majority of the imaging techniques used for liver fibrosis assessment are based on the detection of the velocity of a propagating wave through liver tissue, where the velocity of the shear wave reflects tissue stiffness, with the highest velocity in the stiffest tissue. Many methods have been developed and tested, including transient elastography (TE) using the FibroScan<sup>®</sup> device (Echosens, Paris, France) and shear-wave elastographies (SWE), divided into point (p)-SWE, also known as acoustic radiation force impulse (ARFI) scans, and 2D-, and 3D-SWE. Last, magnetic resonance imaging elastography has been used in CHC patients<sup>[94]</sup>. FibroScan TE provides a measure of liver stiffness by Young’s modulus of elasticity and is expressed in kPa, whereas the ARFI scans yield the velocity of the shear wave reported in m/s.

The major quality of noninvasive fibrosis assessment inherently lies in the term noninvasive. In addition, the methods overall have practical advantages, including high applicability and good reproducibility and availability<sup>[94-97]</sup>. However, the methods also have several limitations. The performance of noninvasive methods to diagnose fibrosis or cirrhosis will depend on the prevalence of the disease stage in the cohort. This is known as spectrum bias and is especially relevant when comparing methods between cohorts. In addition, the use of noninvasive methods may be limited because most are not liver specific, and may be influenced by other factors<sup>[94,98-104]</sup>.

Currently, the best validated method in CHC patients is TE using the FibroScan



device. Several studies have shown good concordance between liver stiffness by FibroScan and histological stage<sup>[105,106]</sup>, with good reproducibility, especially in patients with higher stages of fibrosis<sup>[107]</sup>. The ARFI method is becoming widely used and is in good agreement with liver histology in CHC patients<sup>[108,109]</sup>.

### **Metabolic liver function**

The liver is an extraordinary organ with numerous and highly complex functions, several of which are exclusive to the liver. In routine clinical practice, standard blood parameters such as albumin and coagulation factors are often used to assess liver function. However, a more detailed analysis can be obtained by using other methods. Some metabolic liver functions are decreased in patients with chronic hepatitis, but data on improvements after interferon therapy are conflicting<sup>[110-113]</sup>. Assessment of these functions can provide insight into CHC by linking pathophysiological events such as inflammation and fibrosis with changes in liver function and can aid understanding of how prognosis is affected after antiviral treatment<sup>[114-117]</sup>.

One exclusive liver function is galactose elimination, which depends on the enzyme galactokinase, primarily located in the hepatocyte cytoplasm<sup>[118]</sup>. The test evaluates the total functional capacity of the liver to eliminate galactose from the bloodstream, reflecting functional liver cell mass; and therefore, is decreased in patients with cirrhosis<sup>[114,119]</sup>.

Another exclusive, and in addition vital liver function is ureagenesis, which covers the final and irreversible transformation of amino nitrogen to urea nitrogen<sup>[120]</sup>. Ureagenesis plays a key regulatory role in whole-body nitrogen homeostasis, and disturbances in ureagenesis are associated with hepatic encephalopathy due to reduced nitrogen clearance<sup>[121]</sup>. The ureagenesis capacity also depends on functional liver mass and is compromised in cirrhosis patients<sup>[122,123]</sup>.

In addition, several other methods may be used to investigate diverse liver functions. The <sup>13</sup>C-aminopyrine breath test assesses microsomal cytochrome P450 activity of the liver<sup>[124]</sup>, whereas excretory liver function may be assessed through the measurement of plasma elimination of indocyanine green (ICG)<sup>[125]</sup>.

### **Complications of CHC infection**

Complications of CHC infection include cirrhosis development with esophageal varices that may bleed, ascites and hepatorenal syndrome, hepatic encephalopathy (HE), and hepatocellular carcinoma (HCC). Portal hypertension is a major risk factor for an unfavorable disease course<sup>[126]</sup>. Portal hypertension may be assessed by liver vein catheterization, where wedged hepatic venous pressure is obtained in a hepatic vein and free hepatic venous pressure is measured in the right hepatic vein close to the inferior vena cava. The hepatic venous pressure gradient (HVPG) is thus determined as the difference between wedged hepatic venous pressure and free hepatic venous pressure<sup>[127]</sup>. Portal hypertension is then defined as HVPG > 5 mmHg and clinically significant portal hypertension by HVPG > 10 mmHg, which comes with a significantly increased risk of varices<sup>[128]</sup>.

The presence of even minimal HE affects the quality of life, poses an increased risk of developing clinically manifest HE and is associated with a more unfavorable prognosis<sup>[129,130]</sup>. It should be noted that CHC in itself may affect cognition irrespective of HE<sup>[131]</sup>. The detection of minimal HE relies on psychometric testing, and to evaluate cognitive function in a quantitative way, several methods may be applied. The major limitation of any test to assess HE is the fact that it is only one test. Minimal HE represents complex cognitive disturbances with no single manifestation, and one test will not be able to encompass the entire spectrum of deficits in patients with HE. This is mirrored in studies showing low concordance between the continuous reaction time test and the psychometric hepatic encephalopathy score or critical-flicker frequency<sup>[132,133]</sup>.

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## **HEPATIC EFFECTS OF ANTIVIRAL TREATMENT**

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### **Amelioration of inflammation**

Amelioration of inflammation is the first critical step in stopping the vicious cycle of fibrosis progression in any chronic liver disease. With viral clearance, inflammation diminishes, and this is probably required before the reversal of fibrosis and improved function can occur. Currently, it is well established that antiviral therapies, interferon- or DAA-based resolve inflammation, as indicated by biomarkers<sup>[43,44,73]</sup> and liver biopsies<sup>[33,134-137]</sup>. In addition, liver damage diminishes with reductions in ALT levels following DAA therapy, but liver-specific enhanced macrophage activation resolves rapidly with treatment<sup>[138]</sup> (Figure 2). This is supported by results from chronic

hepatitis B patients, where a treatment-induced decrease in circulating sCD163 parallels diminished CD163 expression in liver biopsies<sup>[72]</sup>. In addition, it is not the effect of the treatment *per se* or the different mechanisms of action of the respective treatments but the clearance of the virus that reduces inflammation, as only patients who achieve an SVR have a decrease in sCD163<sup>[139]</sup> and achieve inflammation resolution in liver biopsies<sup>[134,136]</sup>.

### **Subtle changes in liver fibrosis**

To date, many studies have assessed changes in noninvasive measures after DAA therapy; improvements in several biomarker-based fibrosis panels have been shown, including APRI and FIB-4<sup>[140,141]</sup>. Several studies have also shown decreasing liver stiffness with DAA therapy<sup>[138,140,142,143]</sup>. In a 2018 review and meta-analysis of liver stiffness changes after interferon or DAA therapy, the authors showed a mean decrease of 2.4 kPa at the end of treatment, 3.1 kPa within the first 6 mo after the end of treatment, and 4.1 kPa more than 1 year after treatment. The authors speculate that the initial decrease is due partly to the resolution of inflammation and that the subsequent decrease pertains to fibrosis regression, which is supported by a larger decrease in patients with high baseline inflammation<sup>[144]</sup>. However, a consistent decrease from the end of treatment to the 1-year follow-up may represent fibrosis regression (Figure 2).

After the introduction of DAA therapy, there are only limited data from paired biopsies assessing fibrosis regression. In one study, cirrhosis resolved in seven of 14 patients<sup>[137]</sup>. In another study evaluating 10 patients with paired biopsies and liver stiffness measurements after DAA therapy, the results indicated that fibrosis regression occurs but is not as prominent as liver stiffness measurements might indicate<sup>[145]</sup>. Thus, data on changes in liver fibrosis after DAA therapy are scarce, and follow-up is still relatively short. Therefore, one can only speculate on the real effect based on the relevant literature from interferon-based studies and those using noninvasive measures. As shown by data from the interferon era, fibrosis regression or resolution takes place but is a slow process taking years<sup>[33,134-136,146]</sup>, and the regression of cirrhosis is less common<sup>[136,147,148]</sup>. Additionally, it is known that fibrosis will progress without treatment<sup>[149]</sup>, and progression holds an increased risk of clinical decompensation and HCC<sup>[150]</sup>.

### **Improved metabolic liver function**

Data on the effects of interferon treatment on galactose metabolism are conflicting. In one study where disease severity at baseline was unclear, the galactose elimination capacity (GEC) improved 3 mo after the initiation of interferon therapy<sup>[151]</sup>. This was paralleled by findings in another study with GEC improvement after 3 mo of interferon treatment, although only in responders to treatment<sup>[110]</sup>, whereas others have found no effect of treatment response on the GEC<sup>[112,152]</sup>.

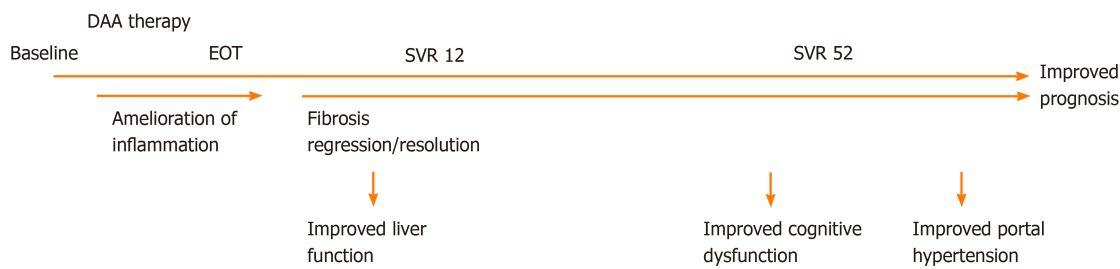
Data on the GEC after successful DAA therapy are limited but the GEC seems to improve 12 wk post-treatment<sup>[138]</sup> (Figure 2). In these patients, GEC reflects liver disease severity and fibrosis but not inflammation<sup>[111,153]</sup>.

Conversely, the amelioration of inflammation seems to improve the capacity for ureagenesis, as has also been shown in acute alcoholic hepatitis<sup>[117]</sup>, which also seems to be the case in CHC patients after DAA therapy (Authors' unpublished data). Other data concerning treatment effects on functional hepatic nitrogen clearance (FHNC) are limited, but the acceleration of the urea cycle after successful interferon therapy was demonstrated in a metabolomics study<sup>[154]</sup>.

Regarding the aminopyrine breath test and ICG, no data are available after DAA therapy. However, some studies have shown improvements after interferon therapy, while others could not detect any differences<sup>[110,151]</sup>.

## **IMPLICATIONS FOR CLINICAL OUTCOME AND PROGNOSIS**

Treatment-naïve CHC patients have a higher risk of death compared with the background population<sup>[155,156]</sup>, and the risk may be even higher in patients consuming moderate or excessive amounts of alcohol<sup>[157]</sup>. The achievement of an SVR with interferon-based treatments was associated with reduced mortality<sup>[158]</sup>, in some studies, to a level comparable to the background population<sup>[159,160]</sup>; however, others find that it is still significantly higher<sup>[161]</sup>. Some have suggested that any potential outcome advantage wanes when patients are matched for liver function at baseline<sup>[162]</sup>. However, in one study in patients matched for liver function at baseline, the SVR was still associated with better survival<sup>[163]</sup>. After the development of cirrhosis, mortality is increased, and in one study of patients with CHC cirrhosis who achieved an SVR by interferon treatment, the authors showed a substantial remaining risk of HCC and



**Figure 2** Proposed time-line for liver-related effects of direct-acting antiviral therapy. DAA: Direct-acting antiviral; EOT: End of treatment; SVR12: Sustained virologic response at 12 wk post-treatment; SVR52: Sustained virologic response 1 year after treatment.

clinical disease progression<sup>[164]</sup>. DAA therapy is still “new” on the market, and long-term follow-up studies are limited. Based on the first studies, it seems that DAA therapy leads to an improved prognosis with decreased mortality<sup>[165-167]</sup>, potentially with a significant survival benefit as soon as 18 mo post-treatment<sup>[168]</sup>. Interestingly, patients without advanced liver disease also experience reduced mortality after DAA therapy<sup>[169]</sup>, while potential issues including increases in MELD scores were observed after treatment of, *e.g.*, decompensated cirrhosis patients<sup>[170]</sup>. From these studies, there seems to be a prognostic benefit in CHC patients following an SVR induced by DAA therapy, although the reasons for the benefit are not entirely clear. The available data do not provide causality; however, there are some indices suggesting that the beneficial effects of treatment on different aspects of liver disease and function may in fact lead to improved outcome.

First, low liver stiffness is a predictor of a good prognosis in patients with CHC, at least prior to therapy<sup>[171,172]</sup>, but studies of noninvasive measures and associations with prognosis after DAA therapy are lacking.

Second, several studies have indicated that metabolic liver function is associated with prognosis. In one study, patients with a severely compromised GEC had a high risk of liver-related clinical outcomes<sup>[152]</sup>. Others have shown that the GEC is a strong predictor of mortality<sup>[114,173]</sup> and has prognostic value additive to the use of the Child-Pugh score<sup>[174]</sup>. Conversely, the GEC does not outperform established scores for the prediction of prognosis<sup>[175]</sup>, even though the GEC was shown to be significantly higher in survivors of acute liver failure<sup>[176]</sup>. Disturbances in the urea cycle and related enzymes are associated with the severity of liver disease and potentially precede histological deterioration in chronic hepatitis<sup>[177-179]</sup>. On the basis of these results and the higher FHNC in survivors of alcoholic hepatitis<sup>[117]</sup>, we speculate that improvements in metabolic liver functions may be succeeded by a better outcome in CHC patients.

Third, improvements of neurocognitive dysfunction are observed after interferon-based SVR<sup>[180]</sup>. This finding is corroborated by DAA-induced improvements in brain MR spectroscopy<sup>[181]</sup> and continuous reaction time (CRT)<sup>[138]</sup> but is not corroborated by the findings of others<sup>[182]</sup>. These discrepancies may reflect the different modalities used to assess cognitive dysfunction and the timing of the tests, *e.g.*, the CRT was not significantly improved until 1 year after treatment cessation (Figure 2). Another factor in favor of improvement in cognitive functions is self-reported mood outcomes, which are indeed improved after antiviral therapy<sup>[183]</sup>.

Fourth, one of the strong predictors of adverse outcomes in cirrhosis patients is portal hypertension, and thus, its reduction is warranted. In a small study of eight patients treated with pegylated interferon, ribavirin, and boceprevir, there was a significant improvement in HVPG at 24 wk of follow-up after treatment<sup>[184]</sup>. Whereas some did not observe an improvement in HVPG at the end of DAA treatment<sup>[185]</sup>, other studies indicate that DAA therapies ameliorate portal hypertension at least in long-term follow-up<sup>[186,187]</sup> (Figure 2). In addition, follow-up HVPG measurements may predict the risk of hepatic decompensation<sup>[188]</sup>.

Last, the development of HCC is a risk in CHC patients, especially in those with cirrhosis<sup>[189]</sup>, and the risk increases in parallel with cirrhosis severity and portal hypertension<sup>[190]</sup>. In recent years, an intense debate regarding HCC risk after successful DAA therapy has flourished. In 2016, a study showed a greatly increased risk of HCC after DAA therapy, especially HCC recurrence<sup>[191]</sup>. This was followed by other studies with similar results<sup>[192,193]</sup>. However, over recent years, more data have appeared, and the general consensus is that DAA therapy does not increase the risk of HCC<sup>[194,195]</sup>, but probably decreases the risk similar to interferon-based treatments<sup>[158]</sup>. At the same time, it seems clear that the risk of HCC does not disappear after treatment and that continued and probably life-long surveillance is needed at least in

cirrhosis patients or until studies have defined which patients remain at risk<sup>[196,197]</sup>.

Taken together, the evidence suggests a health benefit in patients who achieve an SVR. In our opinion, causality between the improvements and improved prognosis cannot be established from the available literature. However, as reviewed above, several studies indicate such associations. The magnitude and timing of the benefit, as well as its mechanisms, remain elusive, but the data indicate that there is an association between improvements in liver inflammation, fibrosis, and metabolic function and improved outcome after an SVR.

## FUTURE ASPECTS

Several questions to be addressed in future studies can be raised. A major question discussed in this review is whether the beneficial effects of DAA therapy on the liver in fact lead to improvements in prognosis. We speculate that liver-related improvements precede clinical benefits and improve prognosis, but confirmation is needed. Such studies require long-term follow-up and large cohorts for high enough power in terms of achieving “enough” events.

Next, one could ask: how good does it get? It would be very interesting to evaluate metabolic liver function after longer follow-up to see, first, whether the improvements are sustained and second, whether further improvement occurs. Such a study would also be useful in terms of the associations between improvements in liver function and liver-related events/clinical benefit.

In addition, it is not entirely clear what happens with structural liver damage. A large study with liver biopsies after DAA therapy is warranted. In addition, such a study should include a noninvasive method to determine the degree of fibrosis. The results might enable clinicians to predict the severity of liver fibrosis after DAA therapy without the need for liver biopsies.

Another very interesting aspect is the determination of cirrhosis severity without the use of invasive methods. There is a large gap between the mere presence of cirrhosis (compensated cirrhosis) and the more severe decompensated cirrhosis, with the occurrence of clinical events. These two groups may respond differently to treatment in regard to the amelioration of liver-related effects. This needs further clarification in a study including decompensated cirrhosis patients.

Portal hypertension is a good predictor of liver-related events in cirrhosis, and a large study with liver vein catheterizations before and at long-term follow-up after DAA therapy to assess the timing and extent of improvement in portal hypertension is also in high demand.

Future studies should be designed with the usual major limitations in mind, thereby trying to minimize these limitations. They include lack of histological verification of the disease severity before treatment but especially after treatment, and in addition, the metabolic studies are often limited by sample size, as this study type is often logistically comprehensive and time-consuming.

## CONCLUSION

From the literature, it seems clear that antiviral therapy, especially the achievement of an SVR, has several beneficial effects on liver-related parameters in CHC patients. There seems to be a time-dependent effect of DAA therapy. Initially, liver inflammation ameliorates, followed by more discrete changes in structural liver lesions. These improvements are followed by beneficial effects on metabolic liver function, cognitive disturbances, and portal hypertension (Figure 2).

In conclusion, the published data suggest short- and long-term improvements in the underlying liver disease with the promise of an improved prognosis after DAA therapy in patients with CHC and advanced liver disease.

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