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# Direct-Acting Antivirals in Chronic Hepatitis C Infection with Liver Cirrhosis

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## Abstract

Chronic hepatitis C infection is a common cause of liver morbidity and mortality across the world, in part due to complications including cirrhosis and hepatocellular carcinoma. The advent of Direct-acting antiviral (DAA) therapy has the potential to change the outcome of HCV infection in the vast majority of patients. Unfortunately, the chronic nature of HCV infection means that many patients requiring direct-acting antiviral (DAA) therapy have already developed compensated cirrhosis. This chapter reviews the importance of DAAs in the treatment of HCV infection, particularly in patients with existing compensated cirrhosis. Both efficacy and safety are discussed as essential endpoints of DAA therapy. Decompensated cirrhosis, treatment failures, vitamin-D deficiency, HIV co-infection, and ethnic differences in the context of treatment response are also discussed in this chapter.

**Keywords:** direct-acting antivirals, chronic hepatitis C, hepatitis C virus, liver cirrhosis, treatment, adverse drug events

## 1. Introduction

Hepatitis C virus (HCV) is a leading cause of virologic morbidity and mortality, and afflicted individuals with HCV remain at high risk of cirrhosis, hepatic failure, and hepatocellular carcinoma [1]. The dormant nature of the Hepatitis C virus enables the virus to be both transmissible and silent. This may result in a more advanced initial presentation, as many patients are unaware of their positive infection status [2]. More advanced stages of HCV may involve cirrhosis, one of the most morbid outcomes after initial infection with HCV infection. As a result, many patients requiring HCV therapy are already cirrhotic and require a therapy which can effectively combat HCV in both non-cirrhotic and cirrhotic stages of the disease. The importance of treating the HCV virus in the compensated cirrhosis stage is paramount, to prevent the enhanced risk of worsening cirrhosis, decompensation, hepatocellular carcinoma, and death [1].

The original treatment option in chronic HCV infection was interferon-based regimens. Interferon-based regimens were once the mainstay of therapy, but it has limited effectiveness in their ability to consistently induce a sustained virologic response (SVR) in chronic HCV at high enough rates to be a plausible solution for HCV [3]. Due to the infectious and chronic nature of hepatitis C, a more successful

therapy than interferon-based therapy was warranted to reduce the global burden of disease. In addition to its ineffectiveness, interferon-based regimens had numerous side effects. The side effects are often severe and debilitating, which included bone marrow depression, neuropsychiatric symptoms, and flu-like symptoms. These side effects likely contributed to reduced patient adherence to interferon therapy [3].

The development of effective antiviral therapy for HCV infection was a difficult challenge. HCV exhibits some features which can make it difficult to treat. The HCV has a 9600-nucleotide positive sense RNA genome. The viral polymerase of HCV is unable to replicate at a high fidelity allowing for numerous errors. There is also a high viral replication rate. These two factors allow for the existence of diverse quasi-species, and in turn, the quasi-species makes both host immune response and pharmacological interventions less effective [2]. Fortunately, the new effective treatment was developed with the introduction of direct-acting antivirals (DAAs) for HCV infection. DAAs appear to meet the challenge of consistently inducing a high SVR in hepatitis C patients, including in patients who have already developed compensated cirrhosis.

## **2. The natural history of chronic hepatitis C and compensated cirrhosis**

HCV is a blood-borne virus and will result in chronic infection in 55–85% of patients. Once the infection is chronic, patients are unlikely to have spontaneous resolution of their infection and are thus at risk of fibrosis, cirrhosis, and hepatocellular carcinoma. Approximately 20–30% of patients with chronic HCV infection will develop cirrhosis [1]. There are numerous host factors in determining whether or not there will be a chronic infection, including IL-28B polymorphisms which may be associated with spontaneous resolution of the infection [2]. The development of cirrhosis at a cellular level is due to the virus inducing CD8<sup>+</sup> T cell inflammation and necrosis, which is then followed by eventual healing via fibro-genesis pathways. This cycle of insult and healing can result in cirrhosis after 10–20 years of viral hepatitis [4].

Cirrhosis is a significant cause of detriment in the chronic HCV infection and ultimately can lead to the end stages of HCV infection, including decompensation, hepatocellular carcinoma (HCC), death, or the need for transplantation [5]. Decompensated cirrhotic patients HCV develop encephalopathy, ascites, or variceal bleed. Both variceal hemorrhage and HCC represent the fatal consequences of chronic HCV and cirrhosis [5]. Numerous studies done on DAAs and prevention of hepatocellular carcinoma indicate that DAA therapy does ultimately decrease the overall risk of HCC [6–8]. However, even with DAA therapy there still may be an increased risk of HCC in patients with treated HCV infection, so the exact benefit of DAAs on the reduction of HCC in patients who have existing HCV infection is unknown [9, 10]. Due to the uncertainty of the exact benefit of DAAs on HCC, patients with HCV and compensated cirrhosis should undergo HCC screenings, including those who have already completed a DAA regimen and achieved SVR.

DAA therapy is a relatively new concept and was designed to directly inhibit the viral lifecycle. In addition to the antiviral benefit, there is early evidence to indicate that DAA therapy is concurrently reducing HCV-associated manifestations including cirrhosis and cirrhosis-related complications [6]. Evidence of DAA therapy's protective benefit from HCV cirrhosis-related complications can be seen in transplant databases. There is a relationship between DAA therapy and the decreased need for HCV-associated liver transplants [11]. This is of significant benefit, as a liver transplant represents the most expensive financial burden HCV can place on a

healthcare system, and by being able to mitigate this expense, DAAs may not only prove to be effective therapeutically but also economically [12].

While one of the most important goals of treating HCV is to prevent cirrhosis; a significant portion of HCV patients already have existing cirrhosis in need of DAA therapy. Furthermore, these patients are more likely to have DAA treatment failure versus their non-cirrhotic counterparts [13]. This makes DAA therapy of paramount significance for clinicians, in both preventing HCV cirrhosis and emphasizing the importance of selecting an appropriate DAA regimen in HCV patients with compensated cirrhosis.

### 3. Direct-acting antiviral agents

DAAs were first approved by the Food and Drug Administration (FDA) in 2011 and were used initially with the old standard of care interferon-based regimens [14]. DAAs can be classified into four different groups; protease inhibitors, polymerase inhibitors, NS5B inhibitors, and NS5A inhibitors [14]. The primary mechanism of DAAs is to directly inhibit the lifecycle replication of HCV virus. There are also specific methods of resistance that the HCV virus may develop, and it is essential to consider the possibility of resistance when starting HCV therapy [15].

There are numerous regimens available involving DAAs. The American Association for the Study of Liver disease (AASLD) have developed HCV guidelines to assist in selecting a particular DAA regimen based on variables including the genotype of HCV infection, treatment naïve status, existing compensated cirrhosis, decompensated cirrhosis, and co-infection with HIV (**Table 1**) [16]. DAA is typically 8 or 12 weeks depending on the indication given in the AASLD guidelines along with the regimen being given. Overall, SVR rates appear high with DAA regimens [13]. The benefits of DAAs can also be observed in histological

Genotype	Drug	Treatment duration (weeks)
Genotype 1	Elbasvir/Grazoprevir	12
	Glecaprevir/Pibrentasvir	12
	Ledipasvir/Sofosbuvir	12
Genotype 2	Sofosbuvir/Velpatasvir	12
	Glecaprevir/Pibrentasvir	12
Genotype 3	Sofosbuvir/Velpatasvir	12
	Glecaprevir/Pibrentasvir	12
Genotype 4	Sofosbuvir/Velpatasvir	12
	Elbasvir/Grazoprevir	12
	Glecaprevir/Pibrentasvir	12
	Ledipasvir/Sofosbuvir	12
Genotype 5/6	Sofosbuvir/Velpatasvir	12
	Glecaprevir/Pibrentasvir	12
	Ledipasvir/Sofosbuvir	12

**Table 1.**  
 DAA regimens for each HCV major genotype in the treatment of patients with compensated cirrhosis, according to current AASLD guidelines.

studies. Patients who have achieved remission with DAAs show a lessened degree of inflammation on tissue specimen examination. Interestingly, there is no decrease in fibrosis noted at a histological level [17].

Successful DAA therapy is defined as a sustained virologic remission at 12 weeks (SVR12) post-treatment in the infected patient. The success of DAA therapy has a lot of variables, which is addressed in the AASLD guidelines. Corroborating an appropriate regimen based on a specific genotype, the presence of existing cirrhosis, HIV co-infection, treatment naivety, and treatment failure is all addressed in the AASLD guidelines [16]. In addition to the factors addressed in the AASLD guidelines, there appear to be some genetic examples influencing SVR in DAA therapy, include IL-28B polymorphisms, low-density lipid receptor genetic variants, vitamin D receptor, and bile salt export pump polymorphisms [18].

#### **4. DAAs in the role of combating HCV as a public health problem**

DAAs in conjunction with appropriate global health strategies provides us with the possibility to diminish HCV as a public health problem [19]. Analytical data collected from a treat-all model indicate there is a cost-effective benefit to treating all HCV infected individuals with DAA regimens [20]. Urbanization is another crucial factor to consider as increased rates of urbanization may be associated with the risk of HCV [21]. Not all endemic areas with HCV are countries of means, so it remains necessary to consider the price of antiviral regimens and eliminate any economic barriers towards achieving comprehensive treatment response. One study analyzing the cost of HCV treatment stated the current DAA price point appears to be affordable to treat most populations at an extensive level, similar to HIV. The same study concluded that genotype testing remains a significant cost until a consistent pan-genotypic DAA regimen can be developed [22]. The current DAA regimens and guidelines are contingent on knowing the genotype being treated. This is because much of the existing data in the literature shows a particular regimen's treatment success rates as a function of the genotype being treated [16].

Public health programs should also be instituted alongside DAA therapy to help reduce the burden of HCV infection. In the United States, intravenous drug users are responsible for a new increase in HCV infections; before this rise, the incidence of HCV had been decreasing [1]. Being able to both reduce the rate of new infections while treat existing infections with DAA regimens would make the most logistical sense in reducing the global burden of disease associated with HCV. In addition to the benefit of lowering HCV infections, the advent of DAAs could also reduce the global incidence of HCC as both hepatitis B and C are prominent identifiable risks for the development of HCC globally [23].

#### **5. Hepatitis C genotypes**

There are six major genotypes of HCV virus. There is a geographical component in HCV genotypes, as different regions of the world have a varying rate of the six different HCV genotypes. The information about HCV genotyping is significant, as it helps dictate therapy. The current AASLD guidelines rely primarily on genotype when assisting clinicians to select a particular DAA regimen. The genotype also provides pre-treatment success probabilities when selecting a DAA regimen for the achievement of SVR in patients with existing compensated cirrhosis. One study noted that HCV Genotype 1 patient with cirrhosis tend to have high SVR regardless of their cirrhosis status, but Genotype 3 patients have a more diminished response



and are therefore more difficult to treat in existing cirrhosis [24]. Ribavirin may be used as an adjunct with DAA regimens to help achieve SVR in patients with specific characteristics, including the genotype. Below are the major six genotypes of HCV, and the current AASLD guidelines for each one with an emphasis on the management with compensated cirrhosis.

## 5.1 Genotype 1

Genotype 1 infection is the most common genotype globally, and it is also the most common genotype seen in developed countries [25]. Community-based studies conducted in the United States are often reflective of Genotype 1 infections as it is the predominant subtype in the United States, and Genotype 1 infections demonstrate a high overall SVR with DAA including in patients with existing cirrhosis [26].

### 5.1.1 *Elbasvir/Grazoprevir*

The C-WORTHY trial included patients that were both non-cirrhotic and existing compensated cirrhosis, with both groups being treated with Elbasvir/Grazoprevir. The SVR reflected the success rate in both patients without cirrhosis and with compensated cirrhosis. The conclusion can be made that compensated cirrhosis is not a hindrance in the achievement of SVR in patients taking Elbasvir/Grazoprevir [27]. The AASLD guidelines indicate 12 weeks of Elbasvir/Grazoprevir treatment is warranted in HCV Genotype 1 infections in both non-cirrhotic patients and in patients who have compensated cirrhosis [16].

### 5.1.2 *Glecaprevir/Pibrentasvir*

The EXPEDITION-1 study examined patients with compensated cirrhosis across genotypes 1, 2, 4, 5, and 6. Only genotype 3 was not represented among the six major genotypes. All 5 of the genotypes showed a high overall treatment response, with the genotype 1 patients with cirrhosis showing an SVR of 100% [28].

The CERTAIN-1 studied Japanese patients with genotype 1 infections, and also documented an excellent treatment response. The SVR remained high in patients with compensated cirrhosis, with all 38 cirrhotic patients achieving SVR [29]. The current AASLD guidelines mandate that non-cirrhotic, treatment naïve patients taking Glecaprevir/Pibrentasvir require 8 weeks of therapy, but the duration of therapy extends to 12 weeks with the presence of compensated cirrhosis [16].

### 5.1.3 *Ledipasvir/Sofosbuvir*

The ION-1 study showed high SVR rates in all treatment naïve patients with genotype 1 infection. The effect of cirrhosis on efficacy was difficult to determine, but there was no negative effect on the safety profile [30]. Ledipasvir/Sofosbuvir is an 8-week therapy in non-cirrhotic, non-black, non-HIV positive patients, but the presence of compensated cirrhosis changes the guidelines therapy to 12 weeks [16].

### 5.1.4 *Sofosbuvir/Velpatasvir*

Sofosbuvir/Velpatasvir is a 12-week regimen regardless of cirrhosis status [16]. The ASTRAL-1 examined patients who received Sofosbuvir/Velpatasvir for 12 weeks across genotype 1, 2, 4, 5, 6 with genotype 3 not being represented. Across all 5 genotypes studied, there were 121 patients in ASTRAL-1 with compensated

cirrhosis. All but 1 achieved SVR (120/121), indicating a high success rate [31]. This may also help support the idea that Sofosbuvir/Velpatasvir could potentially be a pan-genotypic drug in compensated cirrhosis, as 5 of the six major genotypes were in this study.

## 5.2 Genotype 2 infection

Genotype 2 infection is most commonly seen in East Asia [25]. There are currently 2 AASLD recommended therapies for treatment naïve Genotype 2 infections [16].

### 5.2.1 Glecaprevir/Pibrentasvir

The EXPEDITION-1 trial examined genotype 2 patients, and similar to the genotype 1 patients, genotype 2 patients with compensated cirrhosis achieved SVR at a high rate of 100% with Glecaprevir/Pibrentasvir [28]. These findings were reproduced in the CERTAIN-1 trial in Japan, with all 18 genotype 2 patients with compensated cirrhosis achieving SVR without any adverse drug reactions [32].

### 5.2.2 Sofosbuvir/Velpatasvir

The Sofosbuvir/Velpatasvir regimen to combat genotype 2 infections was studied in the ASTRAL-1 and ASTRAL-2 studies. The results showed that Sofosbuvir/Velpatasvir was effective at achieving SVR in genotype 2 infections (99%) and that SVR rates were not affected by cirrhosis [31].

## 5.3 Genotype 3 infection

After Genotype 1 infections, Genotype 3 infections are the most common type of HCV worldwide. Genotype 3 remains the most predominant type of HCV infection in South Asia [25]. Genotype 3 infections are a particular challenge when it comes to compensated cirrhosis. It is the second most common infection, but it does not respond well to first generation sofosbuvir-based regimens in the presence of cirrhosis. The ALLY-3 trial, involving the daclatasvir/sofosbuvir showed a response rate of 96% in patients without any cirrhosis. However, among patients with existing compensated cirrhosis, the response rate plummeted to a mere 63% [33].

### 5.3.1 Glecaprevir/Pibrentasvir

The Surveyor II study showed that with 12 weeks of therapy, treatment response was observed in 98% of Genotype 3 treatment naïve patients who had compensated cirrhosis [34]. The AASLD guidelines call for an 8-week therapy in treatment naïve patients without cirrhosis, but the presence of cirrhosis extends the Glecaprevir/Pibrentasvir therapy to 12 weeks.

### 5.3.2 Sofosbuvir/Velpatasvir

The ASTRAL-3 study showed a high overall SVR for genotype 3 patients taking Sofosbuvir/Velpatasvir. However, there was a reduction in SVR from 97% in patients with no cirrhosis down to 91% in patients with cirrhosis [35]. Although there was a decrease in efficacy due to the presence of cirrhosis, it was a far less drastic decrease when comparing the outcomes in Genotype 3 treatment with Daclatasvir/Sofosbuvir in the presence of cirrhosis [33]. The standard of treatment is 12 weeks, regardless of cirrhosis status [16].

## **5.4 Genotype 4 infection**

Genotype 4 infections are seen in Africa and the Middle East, with Egypt, in particular, shouldering a high rate of HCV genotype 4 infections [25]. The response rate in genotype 4 infections appears to be high in some real-world studies, regardless of cirrhosis status [36].

### *5.4.1 Elbasvir/Grazoprevir*

The current AASLD guidelines recommend a 12-week therapy, regardless of whether or not there is existing cirrhosis.

### *5.4.2 Glecaprevir/Pibrentasvir*

EXPEDITION-1 showed that Genotype 4 patients with compensated cirrhosis still had a high SVR [28]. The AASLD guidelines dictate an 8-week regimen in patients with no history of cirrhosis, but the Glecaprevir/Pibrentasvir regimen becomes 12 weeks within patients with compensated cirrhosis.

### *5.4.3 Ledipasvir/Sofosbuvir*

One study examined the success rate of Ledipasvir/Sofosbuvir with Genotype 4 infection; with all patients achieving SVR regardless of any underlying fibrosis or cirrhosis [37].

### *5.4.4 Sofosbuvir/Ledipasvir*

ASTRAL-1 showed all patients with Sofosbuvir/Ledipasvir and a Genotype 4 infection achieved SVR12 [31]. The population studied had both patients with compensated cirrhosis and without cirrhosis patients, but both groups had an SVR of 100%. The AASLD mandates a 12-week therapy as the recommended regimen regardless of cirrhosis status.

## **5.5 Genotype 5 and genotype 6 infection**

The current AASLD guidelines have HCV genotype 5 and genotype 6 infections grouped, but they remain 2 distinct major genotypes of HCV infection. Genotype 5 represents the least commonly observed genotype of the major HCV genotypes and is most commonly seen in Sub-Saharan Africa and East Africa. Genotype 6 infections are most commonly seen in East Asia [25].

### *5.5.1 Glecaprevir/Pibrentasvir*

The EXPEDITION-1 trial showed that patients with compensated cirrhosis and both genotype 5 and genotype 6 infection achieved remission at high rates [28].

### *5.5.2 Ledipasvir/Sofosbuvir*

Genotype 5 compensated cirrhosis patients had studied in one trial had a lower response rate than their non-cirrhotic counterparts [38]. However, there was just one non-responder in each group, with 8/9 cirrhotic patients achieving SVR (89%) and 31/32 patients without cirrhosis achieving SVR (97%). Both non-responders had an IL-28B polymorphism.



### 5.5.3 Sofosbuvir/Velpatasvir

Overall SVR12 was observed in patients with Genotype 5 and Genotype 6 infections at rates of 97% and 100%, respectively in ASTRAL-1. Compensated cirrhosis was included in both groups of patients, and across all 5 genotypes (1, 2, 4, 5, 6) studied in ASTRAL-1, 120/121 (99%) of patients with compensated cirrhosis achieved SVR [31].

## 6. Decompensated cirrhosis and direct acting anti-viral therapy

Patients with cirrhosis are at risk of hepatic decompensation, which includes ascites, encephalopathy, spontaneous bacterial peritonitis and variceal bleed [1]. The development of any one of these features represents increase mortality, and decompensation represents an end stage of HCV infection, with patients having a 5-year survival rate of 51% [39]. Decompensation also remains an independent risk factor for the development of HCC [40].

Selecting an appropriate DAA therapy in patients with compensated cirrhosis is therefore important, as it may help to avoid the morbidity and mortality associated with decompensated cirrhosis. There are a few DAA regimens which show benefit in patients who have decompensated cirrhosis.

Before DAAs, interferon-based regimens were the only option, and in particular, when discussing the decompensated population, interferon-based regimens were both ineffective and poorly tolerated [41].

The ALLY-1 study looked at the effects of Daclatasvir/Sofosbuvir along with ribavirin on patients with advanced cirrhosis, including decompensated cirrhosis across 5 of the 6 major HCV genotypes, with genotype 5 being the only one not represented [42]. They noted a high treatment response with Child-Pugh A or B cirrhosis (93%), but once progression to Child-Pugh C cirrhosis occurred, the efficacy of Daclatasvir/Sofosbuvir was significantly diminished with a treatment response of 56%.

ASTRAL-4 also demonstrated a diminished response to DAAs in decompensated cirrhosis. Among patients who received Sofosbuvir/Velpatasvir alone, the SVR was 83%. The addition of ribavirin however improved the SVR to 94% [43].

The adjunct use of ribavirin therapy and extending the duration may also be indicated in the treatment of HCV with decompensation according to current AASLD guidelines. Insulin resistance and protein malnutrition are two associated risks with the development of decompensated cirrhosis, so clinicians should be aware and attempt to address these issues to prevent further worsening of HCV into decompensation [44].

## 7. Direct-acting antivirals in HCV/HIV co-infected patients and compensated cirrhosis

The Human Immunodeficiency Virus (HIV) and Hepatitis C (HCV) are both blood-borne infections which share common risk factors with regards to routes of transmission. Intravenous drug users may be at risk of both infections, and intravenous drug users represent the most common cause of new HCV infections [1]. Co-infection with HCV and HIV also appears to alter the host immune system, with strong evidence of decreased natural killer cells [45]. Clinicians also must exercise caution as there remains a possibility of drug-drug interaction, including hepatotoxicity between Highly Active-Antiretroviral Therapy (HAART) and DAA

[2]. This is a stark contrast from interferon-based regimens, which both struggled to consistently induce SVR and had numerous patient discontinuations due to adverse events [46]. Daclatasvir/Sofosbuvir appears to have a high success across genotypes 1–4 as observed in the ALLY-2 study; with the success of Daclatasvir/Sofosbuvir being possibly contingent on favorable pharmacokinetics when interacting with HAART in HIV treatment. The SVR rates remained high even in patients with compensated cirrhosis, with a reported SVR of 92% in co-infected and cirrhotic patients. The SVR was low with 8 weeks of therapy, and to achieve SVR of 92% patients required 12 weeks of treatment [47]. Community-based literature involving reiterate the idea that there may be a slightly diminished response in the HCV/HIV co-infected cohort in real-world studies [48].

## **8. Direct-acting antivirals in substance abuse patients with pre-existing cirrhosis**

Substance abuse is a noteworthy variable when discussing hepatitis C virus and cirrhosis. Intravenous drug use and contaminated needles are now the most common way in which new cases of hepatitis C are contracted [1]. As a result, it is important to target the most common cause of new infections to help reduce the spread of hepatitis C virus. The AASLD guidelines currently recommend annual testing for the HCV virus alongside counseling on measures to reduce HCV transmission [16].

## **9. Direct-acting antivirals in the African-American population**

The African-American population is an important population when it comes to chronic hepatitis C infection, as they have an infection rate three times higher than the non-Hispanic White population [49]. Interferon-based treats were less effective in African-Americans than other groups, so there is some historical significance in finding a consistently effective treatment [50]. Fortunately, DAAs appears to be effective in the African-American population with response rates being high and treatment not having a significant variation with a history of compensated cirrhosis [51, 52]. Ethnicity is a factor seen in the AASLD guidelines; for instance, patients who would otherwise need 8 weeks of Ledipasvir/Sofosbuvir would require 12 weeks due to African-American ethnicity [16].

## **10. Association of vitamin D level and HCV treatment response**

Vitamin D deficiency appears to be a marker of hepatic dysfunction in patients who have the chronic liver disease and may be predictive of decompensation and mortality [53]. Vitamin D also has some molecular implications in the development of HCV related HCC [54]. Vitamin D deficiency is also noted to be more likely in patients with cirrhosis versus non-cirrhotic counterparts; although the levels of pre-treatment vitamin D does not appear to significantly influence SVR [55].

## **11. Management of non-responders**

The AASLD treats patients who have failed interferon-based therapy in the same group as DAA naïve patients. DAAs remain effective treatment in the vast majority

of patients with compensated cirrhosis. However, there remains a portion of the hepatitis C patient population who do not respond to DAA therapy. These patients pose a unique challenge.

The POLARIS-1 and POLARIS-4 trials involve patients who have failed DAA regimens across 4 genotypes (genotype 1, 2, 3, 4) and were given Sofosbuvir/Velpatasvir/Voxilaprevir. POLARIS-1 had an SVR of 96% in patients taking for re-treatment, with a 99% success in patients with no cirrhosis and 93% in patients with compensated cirrhosis. POLARIS-4 had an SVR of 98% and did not differ based on cirrhosis status [56]. The regimen of Sofosbuvir/Velpatasvir/Voxilaprevir appears to be an effective therapy in DAA treatment failures.

## **12. Safety and tolerability of direct-acting antivirals**

The development of DAAs not only improved the efficacy of HCV treatment but also enhanced the safety and tolerability of HCV therapy. The improved safety profile and increased tolerability can be observed in both patients with and without compensated cirrhosis. It is important to continue documenting data on adverse events and DAAs, as DAA regimens are a novel concept and require continued monitoring.

### **12.1 Elbasvir/Grazoprevir**

In the C-WORTHY study looking at Genotype 1 patients, both with and without cirrhosis, Elbasvir/Grazoprevir commonly cause asthenia (14%), fatigue (26%), and headache (23%). However, serious events were far less common, occurring in only 3% of patients [27].

### **12.2 Glecaprevir/Pibrentasvir**

The EXPEDITION-1 study evaluated Glecaprevir/Pibrentasvir in compensated cirrhosis across all genotypes except for Genotype 3 and noted that adverse events occurred in 69% of patients, most commonly fatigue and headaches. Severe adverse reactions occurred in 8% of patients, but there was no evidence of a direct drug-induced adverse event [28]. In Genotype 3 patients, either with cirrhosis or prior treatment history, treatment with Glecaprevir/Pibrentasvir was well tolerated with no serious adverse event attributable to the regimen; nor any discontinuations because of an adverse drug reaction [34].

### **12.3 Ledipasvir/Sofosbuvir**

ION-1 examined Genotype 1 patients without cirrhosis and in patients with compensated cirrhosis. Fatigue, headache, insomnia, and nausea were commonly observed adverse events. However, the overall safety profile was excellent, with no patients discontinuing the study due to adverse events [30]. Another study involving Genotype 4 patients, both with compensated cirrhosis and no history of cirrhosis also showed that Ledipasvir/Sofosbuvir is well-tolerated, with no serious adverse events and no discontinuations noted [37]. Genotype 5 patients receiving Ledipasvir/Sofosbuvir commonly had mild symptoms including asthenia, fatigue, and headache. One patient had a serious adverse reaction, but that was judged to be unrelated to DAA therapy [38].

## **12.4 Sofosbuvir/Daclatasvir**

The ALLY-1 trial involved the use of sofosbuvir/daclatasvir and ribavirin in patients with advanced cirrhosis across all major genotypes. Few serious adverse events were noted in the study, none of which could be directly attributable as a consequence of a drug. Anemia is a common side effect of ribavirin [42].

## **12.5 Sofosbuvir/Velpatasvir**

A large study involving genotypes 1, 2, 4, 5,6 and patients with both compensated cirrhosis and no history of cirrhosis showed a good safety profile. Less than 1% of patients discontinued therapy due to adverse reactions. There was no significant difference between the placebo group and the experimental group when it came to adverse events. The most common adverse events noted were fatigue, headache, nasopharyngitis, and nausea [31]. Another study examining Genotype 3 infections, 2% of patients had adverse events severe enough to cause discontinuation. Common adverse events were fatigue, headache, insomnia, and nausea [35].

## **13. Summary**

Direct-acting antivirals represent a breakthrough in the treatment of hepatitis C virus. It has the potential to reduce the global burden of disease caused by the natural hepatitis C history, including cirrhosis, decompensation, and hepatocellular carcinoma. It may also reduce the economic burden of liver transplants. The patient's with existing compensated cirrhosis remain at an elevated risk of numerous other complications, so it is imperative to have an appropriate therapy to help mitigate poor patient outcomes. There are numerous options with the new DAA and being able to appropriately select a regimen will allow for optimal sustained virologic responses in patients with compensated cirrhosis. The AASLD guidelines provide an excellent tool to help dictate a therapy which is tailored to each patient and genotype. As more research is collected on this novel therapy, DAA regimens have the potential to improve on its already remarkable efficacy.

### **Conflict of interest**

None.

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