Abstract
Chronic hepatitis C infection is the leading cause of chronic liver disease, cirrhosis, hepatocellular carcinoma as well as the primary indication for liver transplantation in the United States. Despite recent advances in drugs for the treatment of hepatitis C, predictive models estimate the incidence of cirrhosis due to hepatitis C infection will continue to rise for the next two decades. There is currently an immense interest in the treatment of patients with fibrosis and early-stage cirrhosis as treatment can lead to decrease in the rates of decompensated cirrhosis, hepatocellular carcinoma and need for liver transplantation in these patients. The goal of this paper is to provide clinicians and health care professionals further information about the treatment of patients with hepatitis C infection and cirrhosis. Additionally, the paper focuses on the disease burden, epidemiology, diagnosis and the disease course from infection to treatment. We provide an overview of multiple studies for the treatment of chronic hepatitis C infection that have included patients with cirrhosis. We also discuss the advantages and disadvantages of treatment in cirrhotic patients and focus on the most up to date guidelines available for treatment.

Key words: Cirrhosis; Diagnosis; Treatment; Simeprevir; Sofosbuvir; Ledipasvir; Liver transplantation; Hepatitis C virus

© The Author(s) 2015. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: The treatment of chronic hepatitis C infection has undergone a revolution with the introduction of new and highly-effective therapies allowing for high rates of cure and relatively low adverse effects. While there is strong evidence for the treatment of patients without cirrhosis, limited studies and numbers are available for patients with cirrhosis; yet this is the group likely to benefit most from treatment. This paper focuses on the current evidence and regimens for the treatment of patients with cirrhosis and addresses the advantages and disadvantages of pursuing treatment.
INTRODUCTION

Hepatitis C virus (HCV) infection is the leading cause of chronic liver disease, cirrhosis, hepatocellular carcinoma (HCC) and currently the primary indication for liver transplantation in the United States[1]. As per most recent estimates from the World Health Organization, chronic HCV infection is estimated to have a prevalence between 130 to 150 million worldwide[2]. Chronic HCV infection is defined as the persistence of HCV viremia for greater than 6 mo. While the estimated prevalence is low in developed countries (1%-2%), the less developed countries may carry a prevalence as high as 5%-10% of the adult population[3]. In United States alone, the most conservative estimates suggest the prevalence of people infected with chronic HCV to be around 2.7-5.2 million[4,5]. Amongst those who are infected with chronic HCV, studies evaluating the natural course of the disease suggest that around 55%-85% would progress to chronic liver disease, 15%-30% would progress to cirrhosis and 1%-5% are expected to die due to decompensated cirrhosis and HCC[2]. Worldwide, there are an estimated 350000 to 500000 deaths per year due to HCV related liver disease[5]. Hence, identifying the patients infected with chronic HCV infection and treating them with newly available treatments provides a unique opportunity to help decrease the morbidity and mortality from the disease. Based on these potential benefits, the center for disease control (CDC) in the United States recommends one time birth cohort screening of the population born between 1945-1965 (defined as “baby boomers”) with a HCV antibody test[6]. However, despite recent advancements in the treatment of chronic HCV infection, predictive models estimate that the prevalence of HCV cirrhosis will continue to increase through the next decade and is projected to reach 45% in 2030 of chronically infected persons[7]. The incidence of hepatic decompensation and HCC is also expected to continue to increase for an additional 10 to 13 years prior to seeing a decline due to the wider application of antiviral treatment and better responses with newer agents[7]. Currently those with cirrhosis due to chronic HCV infection are considered difficult-to-treat however may be the group that is likely to benefit most from treatment as virus eradication can potential reduce morbidity and mortality in this population.

In this manuscript, we provide an overview of chronic HCV infection in the context of disease burden, epidemiology, diagnosis and the disease course of HCV infection in the United States population. We present the current treatment regimens and trials which have included patients with cirrhosis and provide information for physicians who may be interested in learning further or pursing treatment for chronic HCV infection in patients with cirrhosis. Additionally, as cirrhotic patients represent a challenge among those with chronic HCV infection, we also discuss the advantages and disadvantages of providing treatment to patients in this pathologic stage of disease.

DISEASE BURDEN AND EPIDEMIOLOGY

Many patients with chronic HCV infection are asymptomatic and it is estimated that 45%-85% are unaware they are even infected[5]. Large population studies testing for positivity of anti-HCV antibody in non-institutionalized population in the United States have shown the prevalence to be approximately 1.8% in the general population[8]. In these studies, the strongest risk factors predicting a positive HCV infection were illegal drug use, blood transfusions prior to 1992 and high risk sexual behavior with high number of lifetime sexual partners. Other risk factors associated with a positive HCV infection included poverty, having less than twelve years of education and having been divorced or separated[8]. Surprisingly the study also showed that 15%-30% of infected patients’ reported no risk factors for the transmission of HCV infection. Additional studies examining the burden of HCV infection in the United States, show that by 2007, HCV had superseded human immunodeficiency virus (HIV) as a cause of death in the United States[9]. Several additional United States studies have also predicted a two-fold increase in HCV related deaths with direct medical expenditure exceeding $6.7 billion USD between 2010 and 2019[10] and without intervention, suggest that morbidity and mortality from HCV will peak between 2030 and 2035 forecasting for 38600 incident cases of end-stage liver disease, 3200 referrals per year for liver transplant and 36100 deaths[11].

DIAGNOSIS AND DISEASE COURSE FOR CHRONIC HCV INFECTION

HCV infection is rarely diagnosed during in the acute phase of infection. Although a variety of host-factors play a role in eradication of HCV, only 15%-25% of adults spontaneously clear the infection[12]. The remaining proportion of patients continue to have persistent viremia[8] and retrospective studies on the natural history of HCV infection, have found that about 15%-30% of people with chronic infection would progress to cirrhosis over the duration of two to three decades[13]. Progression to cirrhosis has been shown to occur at an accelerated pace in those with concomitant alcohol use (> 50 g/d), coinfection with HIV and hepatitis B virus (HBV), as well as male sex, and older age at time of infection (Figure 1)[13,14]. In the patients’ that develop HCV related cirrhosis, the risk of development of HCC has been shown to be 1%-4% per year and warrant surveillance for complications[15].

The first step in the diagnosis of HCV infection is
loss should be advised to any persons infected with disease progression to cirrhosis. Evidence that obesity may be associated with rapid development of non-alcoholic fatty liver disease and there is some syndrome have also been associated with development in infection may be beneficial. Obesity and metabolic an accelerated fibrosis in patients with chronic HCV HBV and HIV co-infections have been associated with risk of re-infection and risk factors.

Multiple studies have documented the detri-

Interventions at the time of diagnosis are aimed at reducing the progression to liver cirrhosis as well as educating the patient to prevent the transmission to others. Multiple studies have documented the detri-

chronic HCV infection due to its beneficial potential.

Once a person is diagnosed with chronic HCV infection, the decision on when to start treatment is controversial, however, generally depends on the level of fibrosis and staging. Liver biopsy is the “gold standard” for the evaluation of the level of fibrosis and can be a key factor in determining follow-up evaluation in patients. Although multiple scoring systems exist for the evaluation of the stage of liver fibrosis (Table 2)[21], a general recommendation is to initiate treatment in those with stage ≥ 3 as this stage in an important predictor of future progression to cirrhosis[22]. However, a liver biopsy carries potential risk such as excessive bleeding and injury to the liver and less invasive methods can also be utilized for determination of inflammation and fibrosis. Many clinicians use the Aspartate aminotransferase-to-platelet ratio index to determine the degree of fibrosis and studies have validated this index to be sensitive in detecting minimal fibrosis or cirrhosis in patients with HCV infection[23]. Liver elastography is also increasingly being used to determine liver stiffness; however, can only reliably distinguish cirrhosis from non-cirrhosis at this time[24]. The decision to pursue a liver biopsy over currently available non-invasive tests should be based on both the clinician and patient’s wish to gain useful information regarding fibrosis stage for prognostic purposes as well as to determine the urgency for treatment[21].

NEW PERSPECTIVE ON TREATMENTS
FOR PATIENTS WITH HCV INFECTION
AND CIRRHOSIS

The goal of treatment for HCV infection early in the disease process is to reduce all-cause mortality and prevent development of liver complications. Immediate benefits of treatment include decrease in liver inflammation as reflected by improvement in aminotransferase levels and reduction in the rate of liver fibrosis[25]. Long-term benefits include a more than 70% reduction in the risk of HCC[26] and a 90% reduction in the risk of liver related mortality and need for liver transplantation[26,27].

Table 1 Centers of disease control recommendations on hepatitis C virus infection screening in the general population[17]

| Risk of HCC | Natural progression of hepatitis C virus infection in the United States. HBV: Hepatitis B virus; HCV: Hepatitis C virus; HCC: Hepatocellular carcinoma; HIV: Human immunodeficiency virus. |
|---|---|
| Birth between 1945-1965 without identifiable risk factors | Interventions at the time of diagnosis are aimed at reducing the progression to liver cirrhosis as well as educating the patient to prevent the transmission to others. Multiple studies have documented the detrimental effects of alcohol on the liver and the association between alcohol intake and development of liver fibrosis and cirrhosis, including the development of HCV[13,18,19]. HBV and HIV coinfections have been associated with an accelerated fibrosis in patients with chronic HCV infection[13] and testing patients for both HIV and HBV infection may be beneficial. Obesity and metabolic syndrome have also been associated with development of non-alcoholic fatty liver disease and there is some evidence that obesity may be associated with rapid disease progression to cirrhosis[20]. Therefore, weight loss should be advised to any persons infected with chronic HCV infection due to its beneficial potential.

Once a person is diagnosed with chronic HCV infection, the decision on when to start treatment is controversial, however, generally depends on the level of fibrosis and staging. Liver biopsy is the “gold standard” for the evaluation of the level of fibrosis and can be a key factor in determining follow-up evaluation in patients. Although multiple scoring systems exist for the evaluation of the stage of liver fibrosis (Table 2)[21], a general recommendation is to initiate treatment in those with stage ≥ 3 as this stage in an important predictor of future progression to cirrhosis[22]. However, a liver biopsy carries potential risk such as excessive bleeding and injury to the liver and less invasive methods can also be utilized for determination of inflammation and fibrosis. Many clinicians use the Aspartate aminotransferase-to-platelet ratio index to determine the degree of fibrosis and studies have validated this index to be sensitive in detecting minimal fibrosis or cirrhosis in patients with HCV infection[23]. Liver elastography is also increasingly being used to determine liver stiffness; however, can only reliably distinguish cirrhosis from non-cirrhosis at this time[24]. The decision to pursue a liver biopsy over currently available non-invasive tests should be based on both the clinician and patient’s wish to gain useful information regarding fibrosis stage for prognostic purposes as well as to determine the urgency for treatment[21].

NEW PERSPECTIVE ON TREATMENTS
FOR PATIENTS WITH HCV INFECTION
AND CIRRHOSIS

The goal of treatment for HCV infection early in the disease process is to reduce all-cause mortality and prevent development of liver complications. Immediate benefits of treatment include decrease in liver inflammation as reflected by improvement in aminotransferase levels and reduction in the rate of liver fibrosis[25]. Long-term benefits include a more than 70% reduction in the risk of HCC[26] and a 90% reduction in the risk of liver related mortality and need for liver transplantation[26,27].
Achievement of virologic cure is determined by achieving undetectable HCV RNA levels defined as sustained virologic response (SVR) at 12 wk or more following treatment completion[21,22]. SVR has been shown in multiple studies to be a good marker for cure of chronic HCV infection in patients followed for greater than five years[28] and corresponds with presence of anti-HCV antibodies but without detectable HCV RNA in the serum, in liver tissue and mononuclear cells[29]. SVR at 12 wk (SVR12) has generally been accepted as primary efficacy end-point and a marker for “virologic cure”[22]. Although previously SVR at 24 wk (SVR 24) was used as a marker for “virologic cure”, multiple new studies show high concordance rate between SVR24 and SVR12 hence allowing for its use in multiple studies for effectiveness of treatment[30].

Multiple studies have evaluated SVR rates in patients with and without cirrhosis, and all studies have concluded that patients with cirrhosis have lower SVR rates. Previous studies have provided ranges of SVR between 40%-50% in patients with Child-Pugh (CP) class A and 7%-26% in patients with CP class C[21,22]. SVR has been shown in patients with genotype 1 and 4 having suboptimal SVR rates compared with those with genotype 2 and 3. A study by Bruno et al[34] showed that in patient treated with pegylated interferon alfa-2a (peg IFN) plus ribavirin those with genotype 1 and 4 had SVR rates of 51% if they had advanced fibrosis and 33% if they had cirrhosis. Same study also showed that patients with genotype 2 and 3 had SVR rates of 61% in those with advanced fibrosis and 57% if they had cirrhosis. These studies hence show us that patients without advanced fibrosis are more likely to have an earlier response to treatment and higher rates of SVR and if affordable treatments are available, should undergo treatment prior to development of fibrosis and cirrhosis[34].

### NEW TREATMENTS FOR HCV INFECTION IN CIRRHOTIC PATIENTS

The treatment of HCV infection has evolved over the past decades and many more changes are anticipated in the treatment of patients in the coming years. The focus of this paper is to discuss treatment regimens based on recent clinical trials that have included patients with cirrhosis and discuss their success rates in achieving SVR. Although many changes are anticipated in the coming months, currently the American Association for the Study of Liver Disease (AASLD) guidelines for the treatment of cirrhotic patients recommend that treatment-naive patients with compensated cirrhosis, including those with HCC, may be treated with the same regimen as patients without cirrhosis[22]. Tables 3 and 4 provide AASLD recommendations for treatment based on genotype and peg IFN eligibility. For patients who are decompensated (moderate to severe hepatic impairment or CP-B or CP-C) who may or may not be candidates for liver transplantation including HCC, AASLD recommends referral to an experienced treatment center ideally with liver transplantation capabilities. In this paper, we present the current treatment regimens and trials which have included patients with compensated cirrhosis and provide information for physicians who may be interested in learning further or pursing treatment for chronic HCV infection in patients with cirrhosis.

### SOFOSBUVIR BASED TRIALS

Sofosbuvir (SOF) is a nucleotide analogue HCV non-structural protein (NS)5B polymerase inhibitor which has shown to have in-vitro activity against all HCV genotypes[35]. When incorporated as a substrate for viral RNA polymerase in the HCV-RNA genome, SOF leads to inhibition of viral replication. Studies have also shown pan-genotype antiviral activity against HCV and a high barrier to resistance. SOF is administered once daily via oral tablets (400 mg) with no restrictions on food intake. It enters the hepatic circulation as a pro-drug and undergoes phosphorylation to its active form in hepatocytes. While studies have shown that variables such as age, sex, body mass index (BMI), race, common concomitant medications and cirrhosis have less influence on the metabolism of the drug, it is cleared by the renal system and dose adjustment may

### Table 2 Various scoring system for the histological staging for liver fibrosis

| Stage | ISL score | Bats-Ludwig score | Metavir | Ishak score |
|-------|-----------|------------------|---------|-------------|
| 0     | No fibrosis | No fibrosis | No fibrosis | No fibrosis |
| 1     | Mild fibrosis | Fibrous portal expansion | Presence of periportal fibrotic expansion | Fibrous expansion of some portal areas with or without short fibrous septae |
| 2     | Moderate fibrosis | Rare bridges or septae | Periportal septae 1 (septum) | Fibrous expansion of most portal areas with or without short fibrous septae |
| 3     | Severe fibrosis | Numerous bridges or septae | Porto-central septae | Fibrous expansion of most portal areas with occasional portal to portal bridging |
| 4     | Cirrhosis | Cirrhosis | Cirrhosis | Marked bridging (portal to portal and portal to central) with occasional nodules (incomplete cirrhosis) |
| 5     | Cirrhosis | Cirrhosis | Cirrhosis | Cirrhosis |
| 6     | Cirrhosis | Cirrhosis | Cirrhosis | Cirrhosis |

Adapted from Ghany et al[30].
Table 3  The recommended regimen for treatment of hepatitis C virus infection by genotype in treatment-naive patients with compensated cirrhosis.[22]

| Genotype | Recommended regimen and duration | Recommended regimen for compensated cirrhosis (CP-A) and duration |
|----------|----------------------------------|---------------------------------------------------------------|
| 1a       | Three options with similar efficacy:  
(1) Daily fixed dose LDP (90 mg)/SOF (400 mg) for 12 wk  
(2) Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) plus twice-daily dosed dasabuvir (250 mg) and weight-based RBV [1000 mg (< 75 kg) to 1200 mg (≥ 75 kg)] for 12 wk  
(3) Daily SOF (400 mg) plus SMV (150 mg) with or without weight-based RBV [1000 mg (< 75 kg) to 1200 mg (≥ 75 kg)] for 12 wk | Three options with similar efficacy:  
(1) Daily fixed dose LDP (90 mg)/SOF (400 mg) for 12 wk  
(2) Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) plus twice-daily dosed dasabuvir (250 mg) and weight-based RBV [1000 mg (< 75 kg) to 1200 mg (≥ 75 kg)] for 12 wk  
(3) Daily SOF (400 mg) plus SMV (150 mg) with or without weight-based RBV [1000 mg (< 75 kg) to 1200 mg (≥ 75 kg)] for 12 wk |
| 1b       | Three options with similar efficacy:  
(1) Daily fixed dose LDP (90 mg)/SOF (400 mg) for 12 wk  
(2) Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) plus twice-daily dosed dasabuvir (250 mg) for 12 wk  
(3) Daily SOF (400 mg) plus SMV (150 mg) with or without weight-based RBV [1000 mg (< 75 kg) to 1200 mg (≥ 75 kg)] for 12 wk | Three options with similar efficacy:  
(1) Daily fixed dose LDP (90 mg)/SOF (400 mg) for 12 wk  
(2) Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) plus twice-daily dosed dasabuvir (250 mg) and weight-based RBV [1000 mg (< 75 kg) to 1200 mg (≥ 75 kg)] for 12 wk  
(3) Daily SOF (400 mg) plus SMV (150 mg) with or without weight-based RBV [1000 mg (< 75 kg) to 1200 mg (≥ 75 kg)] for 12 wk |
| 2        | SOF (400 mg) and weight-based RBV [1000 mg (< 75 kg) to 1200 mg (≥ 75 kg)] for 12 wk | SOF (400 mg) and weight-based RBV [1000 mg (< 75 kg) to 1200 mg (≥ 75 kg)] for 16 wk |
| 3        | (1) SOF (400 mg) and weight-based RBV [1000 mg (< 75 kg) to 1200 mg (≥ 75 kg)] for 24 wk  
(2) Alternative for IFN eligible: SOF (400 mg) and weight-based RBV [1000 mg (< 75 kg) to 1200 mg (≥ 75 kg)] plus weekly peg IFN for 12 wk | |
| 4        | Three options with similar efficacy and 2 alternatives available:  
(1) Daily fixed dose LDP (90 mg)/SOF (400 mg) for 12 wk  
(2) Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) and weight-based RBV [1000 mg (< 75 kg) to 1200 mg (≥ 75 kg)] for 12 wk  
(3) Daily SOF (400 mg) and weight-based RBV [1000 mg (< 75 kg) to 1200 mg (≥ 75 kg)] for 24 wk  
(4) Alternative 1 for IFN eligible: Daily SOF (400 mg) and weight-based RBV [1000 mg (< 75 kg) to 1200 mg (≥ 75 kg)] plus weekly peg IFN for 12 wk  
(5) Alternative 2 for IFN eligible: Daily SOF (400 mg) and weight-based RBV [1000 mg (< 75 kg) to 1200 mg (≥ 75 kg)] for 12 wk | |
| 5        | (1) Daily SOF (400 mg) and weight-based RBV [1000 mg (< 75 kg) to 1200 mg (≥ 75 kg)] plus weekly peg IFN for 12 wk  
(2) Alternative 1 for IFN eligible: Weight-based RBV [1000 mg (< 75 kg) to 1200 mg (≥ 75 kg)] plus weekly peg IFN for 48 wk | |
| 6        | (1) Daily fixed dose LDP (90 mg)/SOF (400 mg) for 12 wk  
(2) Alternative 1 for IFN eligible: Daily SOF (400 mg) and weight-based RBV [1000 mg (< 75 kg) to 1200 mg (≥ 75 kg)] plus weekly peg IFN for 12 wk | |

LDP: Ledipasvir; SOF: Sofosbuvir; SMV: Simeprevir; Peg IFN: Pegylated interferon alfa-2a; RBV: Ribavirin; CP-A: Child-Pugh class A.

Table 4  Factors that determine ineligibility to interferon based regimens for treatment[23]

| Intolerance to IFN in the past | Autoimmune hepatitis or other autoimmune disorders | Hypersensitivity to PEG or any of its components | Decompensated hepatic disease | Major uncontrolled depression | A baseline neutrophil count below 1500/μL, a baseline platelet count below 90000/μL or baseline hemoglobin below 10 g/dL | A history of pre-existing heart disease |
|------------------------------|---------------------------------------------------|-----------------------------------------------|-------------------------------|--------------------------------|---------------------------------------------------------------------------------|-------------------------------------|
| IFN: Interferon; PEG: Percutaneous endoscopic gastrostomy. | |

be needed in patients with creatinine clearance less than 30 mL/min. Studies have also shown that despite being metabolized in the hepatocytes, no dose adjustment is recommended in patients with mild or severe hepatic impairment. The following studies evaluated the use of SOF in cirrhotic patients (summarized in Table 5).

**NEUTRINO trial[36]**

The NEUTRINO trial was a phase III single-group, open label study of SOF with peg IFN plus ribavirin in 327 treatment naïve patients infected with HCV genotype 1, 4, 5 and 6. All patients received a 12-wk treatment with SOF plus peg IFN plus ribavirin. SOF was administered once daily at a dose of 400 mg orally, with daily weight-based ribavirin (1000 mg if body weight < 75 kg
and 1200 mg if body weight ≥ 75 kg) and peg IFN administered subcutaneously once weekly at dose of 180 μg. Of the 327 patients who underwent treatment, 89% had HCV genotype 1; 9% had genotype 4, and 2% had genotype 5 or 6. Black patients represented 17% of the patients, and 17% of the patients had cirrhosis. At the end of the study, 90% of the patients overall (295/327) achieved SVR. It should be noted however that the SVR was 92% for genotype 1a and 82% for genotype 1b).

When comparing patients who were cirrhotic, SVR rates were lower (80% or 43/54 patients in cirrhotic cohort compared with 92% or 252/273 patients in non-cirrhotic cohort) (Table 5).

**FISSION trial**

The FISSION trial was a phase III randomized, open label active-control study of SOF plus ribavirin in 499 treatment naïve patients infected with HCV genotype 2 or 3. Patients were enrolled in an approximately 1:3 ratio and patients were further assigned in a 1:1 ratio to receive either 12 wk of SOF plus ribavirin or 24 wk of peg IFN plus ribavirin. HCV genotype 3 accounted for 72% of the patients and 20% of the patients in this study had cirrhosis. SOF was dosed at 400 mg daily while ribavirin was dosed daily based on weight (1000 mg if body weight < 75 kg and 1200 mg if body weight ≥ 75 kg) in group receiving SOF plus ribavirin however, in patients receiving peg IFN plus ribavirin it was dosed at 800 mg in two divided doses as per product labeling. Peg IFN was administered subcutaneously once weekly at dose of 180 μg. There were 253 patients in the treatment group with SOF plus ribavirin while there were 243 patients in the peg IFN plus ribavirin group.

At the end of the study, SOF plus ribavirin was shown to be non-inferior to peg IFN plus ribavirin and both groups had overall similar SVR of 67%. However, significant differences were present between the two genotypes. Patients with genotype 2 achieved a 93% SVR while only 56% SVR was achieved in genotype 3 patients. Liver fibrosis was one of the strongest predictors of treatment failure in the multivariate analysis and showed that presence of cirrhosis was associated with an SVR of 34% in genotype 3 patients, while did not influence SVR rates in genotype 2 patients. This trial would suggest the patients with HCV genotype 3 with advanced liver fibrosis or cirrhosis would be the “difficult to treat” patient group despite advancements in treatment regimen (Table 5).

**POSITRON trial**

The goal of the POSITRON trial was to evaluate for tolerability of the drug SOF. It was a blinded, placebo controlled trial which compared 12 wk of treatment with SOF plus ribavirin with matching placebo in patients who had previously discontinued IFN therapy due to adverse events or had a contraindication to IFN treatment. These patients had either HCV genotype 2 or genotype 3 infections. In this study, 207/278 patients were assigned to the treatment group, out of which 31 (15%) of the patients had evidence of cirrhosis. Findings of this trial showed that genotype 3 infection was associated with a lower SVR compared with those infected with HCV genotype 2. Presence of cirrhosis was associated with a lower SVR. Patients without cirrhosis achieved an SVR of

---

**Table 5  Summary of sofosbuvir trials and enrollment of cirrhotic patients**

| Trial     | Regimen                  | Duration (wk) | Patient population (patients with cirrhosis in treatment group) | SVR and additional findings | SVR for cirrhotic patients |
|-----------|--------------------------|---------------|-----------------------------------------------------------------|----------------------------|---------------------------|
| NEUTRINO  | SOF + peg IFN + RBV      | 12            | 327 treatment naïve (54) with G1, 4-6                           | 90% overall                | 80%                       |
|           |                          |               | G1: 292                                                         | 89%                       |                           |
|           |                          |               | G4: 28                                                          | 96%                       |                           |
|           |                          |               | G5: 6-7                                                         | 100%                      |                           |
| FISSION   | SOF + RBV                | 12            | 253/499 treatment naïve with G2, G3 (49 cirrhotic) assigned to treatment arm | 67%                       | 47%                       |
|           |                          |               | G2: 70/253                                                     | 97%                       | 91%                       |
|           |                          |               | G3: 183/253                                                    | 56%                       | 34%                       |
| POSITRON  | SOF + RBV                | 12            | 207/278 IFN intolerant or ineligible with G2, G3 (31 cirrhotic) assigned to treatment group | 78%                       | 61%                       |
|           |                          |               | G2: 109                                                        | 93%                       | 94%                       |
|           |                          |               | G3: 98                                                          | 61%                       | 21%                       |
|           |                          |               | 100 treatment experienced with G2, G3 (26)                     | 50%                       | 42%                       |
|           |                          |               | G2: 36                                                          | 86%                       | 60%                       |
|           |                          |               | 95 treatment experienced with G2, G3 (32)                      | 30%                       | 19%                       |
| FUSION    | SOF + RBV                | 12            | 100 treatment naïve                                            | 75%                       | 66%                       |
|           |                          |               | G2: 32                                                          | 94%                       | 78%                       |
|            |                          |               | G3: 63                                                         | 62%                       | 61%                       |
|            |                          |               | 73 patients with G2 (10)                                       | 95%                       | 90%                       |
|            |                          |               | Treatment naïve G2: 32                                        | 97%                       | 100%                      |
|            |                          |               | Treatment experienced G2: 41                                   | 90%                       | 88%                       |
|            |                          |               | 250 patients with G3: 58                                       | 85%                       | 67%                       |
|            |                          |               | Treatment naïve G3: 105                                        | 95%                       | 92%                       |
|            |                          |               | Treatment experienced G3: 145                                 | 79%                       | 60%                       |
| VALENCE   | SOF + RBV                | 12            | 250 patients with G3: 58                                       | 85%                       | 67%                       |
|           |                          |               | Treatment naïve G3: 41                                        | 95%                       | 92%                       |
|           |                          |               | Treatment experienced G3: 145                                 | 79%                       | 60%                       |

SOF: Sofosbuvir; Peg IFN: Pegylated interferon alfa-2a; RBV: Ribavirin; G: Hepatitis C virus genotype; SVR: Sustained virologic response.
93% for HCV genotype 2 and 61% for HCV genotype 3 while patients with cirrhosis achieved an SVR of 94% for HCV genotype 2 and 21% for HCV genotype 3 infection. The trial also showed that the combination of SOF plus ribavirin was an optimal regimen with better tolerability. Most frequent adverse effects included fatigue (44%), nausea (22%), headache (21%), insomnia (19%) and pruritus (11%) with these symptoms likely from ribavirin than SOF. The drop in hemoglobin to < 10 g/dL occurred in only 7% of the patients and no reduction in platelets or neutrophil values were reported. Additionally, the discontinuation rate due to adverse effects was low at only 2%.

**FUSION trial**[37]

The FUSION trial evaluated the efficacy of SOF plus ribavirin in patients with mainly HCV genotype 2 and 3 who had failed prior treatment with Peg IFN plus ribavirin. Two hundred and one patients with HCV genotype 2 and 3 were included in the FUSION trial with 76% of patients having prior relapse. Treatment was continued for either 12 or 16 wk. Approximately 35% of the patients had compensated cirrhosis although the majority of them had HCV genotype 3 (62%). The results of the study showed an overall SVR in treatment experienced patients with SOF plus ribavirin to be significantly lower in the 12 wk (100 patients included in analysis with SVR of 50%) when compared with 16 wk arm (95 patients included in analysis with SVR of 73%). HCV genotype 2 patients had SVR of 86% with 12-wk treatment regimen and 94% for 16-wk treatment regimen, however HCV genotype 3 had SVR of only 30% with 12-wk and 62% with 16-wk regimen. Cirrhosis was associated with poor SVR rates with only 60% (12-wk regimen) and 78% (16-wk regimen) in patients with HCV genotype 2 and with 19% (12-wk regimen) and 61% (16-wk regimen) in patients with HCV genotype 3. Although the trial demonstrated efficacy in HCV genotype 2 treatment with a shorter and all oral regimen in patients with prior treatment failure, it identified both cirrhosis and HCV genotype 3 as a major predictors of SVR failures. The trials also showed that extension to a 16 wk regimen was associated with higher SVR and further studies may be needed to evaluate for a longer treatment regimen for treatment in HCV genotype 3 patients.

**VALENCE trial**[38]

The VALENCE trial was a multi-center phase 3 clinical trial with European patients with genotype 2 and 3 HCV infection who were randomly assigned in a 4:1 ratio to either receive SOF plus ribavirin or matching placebo. Randomization was stratified according to status with respect to prior therapy (defined either a previous therapy or no previous therapy), and the presence or absence of cirrhosis. Although initially planned to treat patients with only a 12-wk regimen of SOF plus ribavirin, results of the FUSION trial led to an amendment of the protocol to allow for extending treatment beyond 12 wk. The study protocol was amended to allow for study-group assignment such that they were unblended and the placebo group was removed and only patients with HCV genotype 3 were extended treatment to 24 wk. Patient with HCV genotype 3 who had finished 12 wk of treatment before the amendment were not candidates to receive additional duration of treatment. Subgroup analysis in this trial showed that among patients with HCV genotype 2, the response were consistently high across subgroups as seen in previous studies (SVR rates of 93% after 12 wk of treatment) (Table 5). Rates of SVR for HCV genotype 3 patients (identified as the “difficult-to-treat”) however depended on treatment history, cirrhosis status and length of treatment. Patients with HCV genotype 3 who received 24 wk of treatment, 213/250 (85%) achieved SVR 12 after cessation of treatment. At 24 wk however 2 patients had virologic relapse while 4 were lost to follow-up and 1 patient had invalid HCV RNA result. Among patients who had not received prior treatment who were treated for 24 wk, the rates of SVR were 92% among those with cirrhosis and 93% among those without cirrhosis. However, if patient had received prior treatment, the rates SVR were 60% among those with cirrhosis compared with 79% among those without cirrhosis. The presence of cirrhosis had an overall lower SVR (67%) compared with non-cirrhotic patients who had higher SVR (85%).

**SIMEPREVIR BASED TRIALS**

Simeprevir (SMV) is an oral, reversible HCV NS3/4A protease inhibitor which has been shown to have in-vivo activity against all genotype except for HCV genotype 3[39]. Studies show that SMV is extensively metabolized in the liver and intestinal tract and has bioavailability of 44% after a single oral administration. It is a CYP3A4 substrate and hence its concentration is significantly affected based on drugs that are either inhibitors or inducers of the CYP3A4. Additionally, its efficacy is decreased in patients with certain mutations, most concerning in-vivo studies being the Q80K polymorphism at baseline in patients with genotype 1a who are now advised to seek alternative therapy. The following studies evaluated the use of SMV in cirrhotic patients.

**QUEST trials**

Two trials evaluated the use of SMV in phase III clinical trials for genotype 1 infection. Both QUEST-1 and QUEST-2 were global phase III, randomized, double blind, placebo controlled clinical trials which were designed to assess the safety, efficacy and tolerability of SMV with combination with peg IFN and ribavirin in treatment naïve patients with genotype 1 HCV infection with compensated liver disease.

In QUEST-1 trial[40], 394 patients with chronic HCV genotype 1 who were treatment naïve were stratified
by HCV subtype and interleukin-28B genotype and were randomly assigned in a 2:1 ratio to receive SMV (150 mg orally once daily) with peg IFN plus ribavirin for 12 wk followed by peg IFN plus ribavirin for 12 or 36 wk (SMV group) or placebo orally plus peg IFN with ribavirin for 12 wk, followed by peg IFN plus ribavirin for 36 wk (placebo group). In this randomized double-blind multicenter trial undertaken in 13 countries, the treatment duration was 24 wk or 48 wk in the SMV group based on criteria for response. Treatment was stopped at week 24 if HCV RNA was less than 25 IU/mL (detectable or undetectable) at week 4 and undetectable at week 12, otherwise continued with peg IFN plus ribavirin until week 48. Both groups were followed up to 72 wk after the start of treatment. This study included 48 patients with cirrhosis (defined as METAVIR score of F4), in whom SVR12 was achieved in 58% (18/31) in the SMV group while only 29% (5/17) in the placebo group. For comparison, in the same trial, 82% (188/229) of the non-cirrhotic patients treated in the SMV group achieved SVR12 while 53% (60/113) of non-cirrhotic patients in the placebo group achieved SVR12. Similar treatment criteria was used in QUEST-2 trial[41], which included 32 patients with cirrhosis (METAVIR score F4) of which 17 were in the SMV group and 15 in the placebo group. In the SMV group, 11/17 patients (65%) achieved SVR12 compared with 6/15 (40%) in the placebo group. In comparison, 209/257 (81%) of non-cirrhotic patients treated in the SMV group achieved SVR12 while 67/134 (50%) of non-cirrhotic patients in the placebo group achieved SVR12.

The most common adverse events seen in patients receiving SMV in QUEST-1 were fatigue (42% vs 41% for placebo), itching (26% vs 16% for placebo), and headache (33% vs 39% for placebo). The most common adverse events seen in patients receiving SMV in QUEST-2 were fatigue (37% vs 42% for placebo), itch (25% vs 25% for placebo), headache (39% vs 37% for placebo), fever (31% vs 40% for placebo), and influenza-like illness (26% vs 26% for placebo). In QUEST-1, in both the SMV and placebo arms, 3% of patients discontinued treatment due to an adverse event. In QUEST-2, 2% of patients in the SMV arm and 1% of patients in the placebo arm discontinued treatment due to an adverse event[42].

### Table 6 Sustained virologic response achieved in the COSMOS study[43]

| Cohort | Regimen | Duration (wk) | SVR12 |
|--------|---------|---------------|-------|
| Cohort 1: Prior non-responder HCV patients with METAVIR scores (F0-F2) | SMV/SOF + RBV | 24 | 79% |
| | SMV/SOF | 24 | 93% |
| | SMV/SOF + RBV | 12 | 96% |
| | SMV/SOF | 12 | 93% |
| Cohort 2: Prior non-responder and treatment native HCV patients with METAVIR scores (F3-F4) | SMV/SOF + RBV | 24 | 93% |
| | SMV/SOF | 24 | 100% |
| | SMV/SOF + RBV | 12 | 93% |

SOF: Sofosbuvir; SMV: Simeprevir; RBV: Ribavirin; SVR12: Sustained virologic response at 12 wk; HCV: Hepatitis C virus.

### SMV PLUS SOF: COSMOS TRIAL[43]

The COSMOS study evaluated the efficacy of combined SOF plus SMV in patients with HCV genotype 1 infection who had previously not responded to peg IFN and ribavirin or were treatment naïve. Patients in this study were assigned in a 2:2:1:1 ratio to receive 150 mg SMV and 400 mg SOF orally and once daily for 12 or 24 wk with ribavirin or without ribavirin in two cohorts - Cohort 1 (non-cirrhotic - METAVIR score F0-F2) and Cohort 2 (previous non-responders and treatment naïve patients with METAVIR scores F3-F4). Table 6 shows the results of the COSMOS study demonstrating SVR in patients in each cohort. The most common side effects in the pooled groups were fatigue [n = 52 (31%)], headache [n = 33 (20%)], jaundice [n = 26 (16%)]. This study also showed that the combination of SOF plus SMV achieved excellent SVR rates in all subgroups regardless of duration of therapy (12 or 24 wk) or co-administration of ribavirin in difficult to treat patients. Although, it should be noted that this study was not powered to show non-inferiority of ribavirin (RBV)-free regimens and hence benefit from RBV is not apparent from the results of the study.

### SOF PLUS LEDIPASVIR ± RBV

Ledipasvir is a NS5A inhibitor with potent antiviral activity against HCV genotype 1a and 1b[44]. Inhibition of NS5A viral phosphoprotein leads to disruption in viral replication, assembly and secretion. Most drug interactions with ledipasvir involve drugs that are Pgp-inducers such as rifampin or St. John’s wort. The following studies evaluated the use of ledipasvir in combination with SOF.

### ION-1 trial[45]

The ION-1 study was a phase 3 open label study with previously untreated patients with HCV genotype 1 infection and randomly assigned patients in a 1:1:1:1 ratio to receive either 12- or 24-wk of SOF/ledipasvir (400/90 mg daily) with or without RBV. Up to 16% of patients had cirrhosis, 12% were black and 67% had HCV genotype 1a infection. Overall the rates of SVR12 were 99% in the group that received 12 wk of
ledipasvir/SOF and 97% in the group that received 12 wk of ledipasvir-SOF with RBV. The SVR was 98% in the group that received 24 wk of ledipasvir-SOF and 99% in the group that received 24 wk of ledipasvir-SOF with RBV. Adverse reactions commonly included fatigue, headache, insomnia and nausea and were tolerable by most patients. Presence of cirrhosis was associated with slightly reduced SVR but rates were still 94%-100% within each treatment group. ION-1 trial has been summarized in Table 7.

**ION-2 trial**

ION-2 study was a phase 3 randomized control trial which involved patients with HCV genotype 1 infection who had not achieved SVR after treatment with peg IFN and ribavirin with or without protease inhibitor. Similar to the ION-1, the study randomly assigned patients in a 1:1:1:1 ratio to receive either 12- or 24-wk of SOF/ledipasvir (400/90 mg daily) with or without RBV. In the study, 20% of the patients had cirrhosis and 79% were HCV genotype 1a. Overall rates of SVR were 94% in the group that received 12 wk of ledipasvir/SOF and increased to 96% in the group that received 12 wk of ledipasvir/SOF and RBV. SVR rates were 99% with 24 wk of ledipasvir/SOF and 99% in the group with 24 wk of ledipasvir/SOF with RBV. No patient in the study discontinued the drug due to adverse event. Among patients' with cirrhosis who were assigned to 12 wk of treatment, rates of SVR were 86% for those receiving ledipasvir/SOF and 82% with those receiving ledipasvir/SOF with RBV for 12 wk. For the patients in the 24 wk arm of treatment, the response rates were similar among cirrhotic and non-cirrhotic patients. However in patients with cirrhosis those who received 12 wk of treatment compared with those who received 24 wk of treatment, the difference in SVR was significant ($P = 0.007$). ION-2 trial has been summarized in Table 7.

**ION-3 trial**

ION-3 study was a phase 3 open label trial that evaluated treatment of patients with HCV genotype 1 infection without cirrhosis who had not received any prior treatment. Although the study did not include any patients with cirrhosis, the aim of the study was to evaluate shorter duration of treatment with achievement of SVR. The study included 647 previously untreated patients who were randomized to receive ledipasvir/SOF for 8 wk, ledipasvir/SOF plus ribavirin for 8 wk or ledipasvir/SOF for 12 wk. The rates of SVR12 were 94% in ledipasvir/SOF for 8 wk group, 93% in ledipasvir/SOF plus ribavirin for 8 wk and 95% in ledipasvir/SOF for 12 wk. The trial confirmed that non-inferiority of the 8 wk regimen when compared with 12 wk of ledipasvir/SOF. ION-3 trial has been summarized in Table 7 and allow treatment regimens to be shortened to 8 wk in non-cirrhotic patients based on clinician’s judgement and patient situation.

Based on these studies, the Food and Drug Administration (FDA) in the United States approved the first combination pill to treat HCV genotype 1 infection which is a blend of SOF and ledipasvir. It is also the first approved regimen that does not require administration with interferon or ribavirin for the treatment of HCV genotype 1 infection.

**ABT-450/R (PARITAPREVI/RITONAVIR)-OMBITASVIR AND DASABUVIR**

ABT-450 (Paritaprevir) is an inhibitor of NS3/4A protease and is administered with ritonavir (ABT-450/r). Addition of ritonavir leads to inhibition of ABT-450 metabolism increasing drug levels and allowing for once daily dosing, however, ritonavir by itself does not have any activity against HCV. Ombitasvir on the other hand is a NS5A inhibitor and dasabuvir is a non-nucleoside inhibitor of the HCV NS5B RNA polymerase. Although trials have evaluated the efficacy of this regimen in HCV genotype 1 patients without cirrhosis (SAPPHIRE-I [48], SAPPHIRE-II [49], PEARL-III and IV [50]), the trial that included cirrhotic patients was the TURQUOISE-II [51] trial which evaluated treatment-naïve and treatment experienced patients with CP-A cirrhosis. The trial included 380 patients with CP-A cirrhosis and randomized them to either a 12 or 24 wk of treatment with ABT-450/r-Ombitasvir and Dasabuvir + RBV according to body weight. SVR12 rates were 91.8% (191/208) in the 12

### Table 7  Summary of sofosbuvir and ledipasvir trials and enrollment of cirrhotic patients

| Trial   | Regimen                  | Patient population (% with cirrhosis) | Duration (wk) | SVR12 |
|---------|--------------------------|--------------------------------------|---------------|-------|
| ION-1   | SOF + LDP                | 214 naïve (16%)                      | 12            | 99%   |
|         | SOF + LDP + RBV          | 211 naïve (15%)                      | 12            | 97%   |
|         | SOF + LDP                | 214 naïve (15%)                      | 24            | 98%   |
|         | SOF + LDP + RBV          | 215 naïve (17%)                      | 24            | 99%   |
| ION-2   | SOF + LDP                | 109 treatment experienced (20%)     | 12            | 94%   |
|         | SOF + LDP + RBV          | 111 treatment experienced (20%)     | 12            | 96%   |
|         | SOF + LDP                | 109 treatment experienced (20%)     | 24            | 99%   |
|         | SOF + LDP + RBV          | 111 treatment experienced (20%)     | 24            | 99%   |
| ION-3   | SOF + LDP                | 215 naïve (0%)                       | 8             | 94%   |
|         | SOF + LDP + RBV          | 216 naïve (0%)                       | 8             | 93%   |
|         | SOF + LDP                | 216 naïve (0%)                       | 12            | 95%   |

SOF: Sofosbuvir; LDP: Ledipasvir; RBV: Ribavirin; SVR12: Sustained virologic response at 12 wk.

---

**Khullar V et al.** HCV cirrhosis - New perspectives
wk group and 95.9% (165/172) in the 24-wk group. Based on this trial, the FDA has approved this drug regimen for patients with compensated cirrhosis as an alternative to other regimens.

As per most recent guidelines, the first line recommended treatment for patients with decompensated HCV genotype 1 and genotype 4 cirrhosis (defined as CP-B or C) who may or may not be candidates for liver transplantation, including those with HCC, includes a daily fixed-dose combination of ledipasvir/SOF and ribavirin for 12 wk. If the patient has anemia or is ribavirin intolerant, the recommended regimen is fixed combination of ledipasvir/SOF for 24 wk. For patients with HCV genotype 2 and 3 cirrhosis (defined as CP-B or C) who may or may not be candidates for liver transplantation, including those with HCC, the AASLD recommends daily SOF and weight-based ribavirin for up to 48 wk. Treatment of patients with decompensated cirrhosis is recommended only by highly experienced HCV practitioners, ideally in a center with liver transplantation capabilities. Table 2 includes the current recommendations by AASLD for treatment of non-cirrhotic and compensated cirrhotic patients with chronic HCV infection.

**ADVANTAGES TO TREATMENT OF HCV INFECTION IN CIRRHOTIC PATIENTS**

There are multiple advantages to treating HCV infection in the cirrhotic liver and in those with advanced fibrosis. Studies have shown that treatment of patients with CP-A and CP-B can result in slowing of disease progression, decrease all-cause mortality, prevent the formation of esophageal varices, decrease the risk of development of HCC as well as prevent the need for liver transplantation. Although there are numerous studies on the benefit of treatment of patients with compensated HCV cirrhosis who achieve SVR, limited data is available for the treatment of patients with decompensated cirrhosis. A study of seventy-five decompensated HCV cirrhosis patients treated with peg IFN and ribavirin demonstrated significant lower rates of decompensation events and hospitalizations, however, this regimen needs to be used with extreme caution given the high incidence of serious adverse effects including life-threatening infection, worsening hepatic decompensation and death. With the new treatment regimens which are peg IFN free, it is important to note that many studies exclude patients with decompensated cirrhosis or have a limited number. Metabolism of the drugs is significantly different in those with cirrhosis and hence caution needs to be exercised when prescribing certain regimens. For example, SMV has not been studied in patients with decompensated cirrhosis (CP-B or CP-C) and it is unclear how hepatic impairment would affect its drug metabolism. On the other hand although limited data is available for treatment with SOF and ribavirin, it appears to be well-tolerated in patients with advanced liver disease.

HCV infection is the leading indication of liver transplantation in the United States and recurrence of the graft liver post-transplantation is nearly universal. Studies show that the patients who undergo liver transplantation and have HCV-RNA viral titers \( \geq 1 \times 10^6 \) copies/mL had a five year survival of 57% vs 84% for patients with lower viral RNA titers \( P = 0.0001 \). Additionally, studies indicate that pre-transplant treatment prevents post-transplant recurrence in selected patients and efficacy is higher with > 16 wk between treatment and transplantation. A recent phase 2, open-label study evaluated if SOF and ribavirin treatment before liver transplantation can prevent recurrence post-transplantation. This study had 61 patients with chronic HCV infection with any genotype and cirrhosis who were on wait-list for liver transplantation and were treated with 48 wk of SOF and ribavirin prior to transplantation. Forty-six received liver transplantation and forty-three patients had HCV-RNA level of less than 25 IU/mL. Of these forty-three patients, 30 (70%) had a post-transplantation SVR at 12 wk, 10 (23%) had recurrent infection and 3 (7%) died from complications of transplantation. Recurrence was related inversely to the number of consecutive days of undetectable HCV RNA before transplantation and among 26 patients with undetectable HCV RNA for at least 30 d prior to transplantation, only one had recurrence post-transplant.

**DISADVANTAGES TO TREATMENT IN HCV CIRRHOSIS PATIENTS**

The treatment of patients with HCV cirrhosis has shown to have lower SVR rates than in patients who are non-cirrhotic. Studies show that treatment with peg IFN plus ribavirin in patients with advanced fibrosis or cirrhosis leads to a significantly lower SVR when compared with patients with mild to moderate fibrosis. Additionally, previous studies evaluating the use of triple therapy (peg IFN plus ribavirin with either boceprevir or telaprevir) in patients with cirrhosis showed not only a lower SVR but also a high incidence of significant adverse events including worsening of liver disease, severe infection and difficult to manage anemia. Hence due to the risk of adverse effects, treatment of these patients requires significant oversight and should be considered only at experienced centers with transplantation capabilities leading to increasing cost and accessibility issues. Unfortunately, the treatment in some transplant centers is also controversial. There may be a tendency in some liver transplant centers to wait until transplantation and pursue treatment post-transplant. Additionally, having positive HCV infection in a cirrhotic liver may also provide access to HCV positive liver transplant options in such patients given the paucity of available organs.
CONCLUSION
With the availability of newer, shorter duration and simpler therapies with high SVR rates, HCV infection today has become a curable disease. Although the costs of treatment are still prohibitive for many patients, those with cirrhosis are likely to derive the most benefit from treatment. Earlier eradication of HCV viremia in those with cirrhosis can potentially reduce the need for liver transplantation, risk of development of HCC and reduce HCV associated morbidity and mortality both pre-and post-transplantation. Treatment in this patient population should be considered especially given the emergence of newer and safer therapies. Due to the rapid advances and new therapies being available, the Infectious Disease Society of America and AASLD have jointly developed a clinical guidance tool[39] that should be considered by clinicians as a reference tool for treatment of patients with HCV infection(www.hcvguidelines.org).

REFERENCES
1 Davis GL, Albright JE, Cook SF, Rosenberg DM. Projecting future complications of chronic hepatitis C in the United States. Liver Transpl 2003; 9: 331-338 [PMID: 12682882 DOI: 10.1034/j.1365-8321.2003.00773X]
2 WHO. Hepatitis C: Fact sheet N°164. [Accessed 2015 Feb 2]. Available from: URL: http://www.who.int/mediacentre/factsheets/fs164/en/
3 Global surveillance and control of hepatitis C. Report of a WHO Consultation organized in collaboration with the Viral Hepatitis Prevention Board, Antwerp, Belgium. J Viral Hepat 1999; 6: 35-47 [PMID: 10847128]
4 Chak E, Talal AH, Sherman KE, Schiff ER, Saab S. Hepatitis C virus infection in USA: an estimate of true prevalence. Liver Int 2011; 31: 1090-1101 [PMID: 21745274 DOI: 10.1111/j.1478-3231.2011.02494.x]
5 Armstrong GL, Wasley A, Simard EP, McQuillan GM, Kuhnert WL, Alter MJ. The prevalence of hepatitis C virus infection in the United States, 1999 through 2002. Ann Intern Med 2006; 144: 705-714 [PMID: 16702586 DOI: 10.7326/0003-4819-144-10-200605160-00004]
6 Smith BD, Morgan RL, Beckett GA, Falek-Ytet Y, Holtzman D, Teo CG, Jewett A, Baack B, Rein DB, Patel N, Alter M, Yartel A, Ward JW. Recommendations for the identification of chronic hepatitis C virus infection among persons born during 1945-1965. MMWR Recomm Rep 2012; 61: 1-32 [PMID: 22885429]
7 Davis GL, Alter MJ, El-Serag H, Poyart N, Jennings LW. Aging of hepatitis C (HCV)-infected persons in the United States: a multiple cohort model of HCV prevalence and disease progression. Gastroenterology 2010; 138: 513-521, 521.e1-6 [PMID: 19861128 DOI: 10.1053/j.gastro.2009.09.067]
8 Alter MJ, Kruszon-Moran D, Nainan OV, McQuillan GM, Gao F, Moyer LA, Kaslow RA, Margolis HS. The prevalence of hepatitis C virus infection in the United States, 1988 through 1994. N Engl J Med 1999; 341: 556-562 [PMID: 10451460 DOI: 10.1056/NEJM199908193410802]
9 Ly KN, Xing J, Kleves RM, Jiles RB, Ward JW, Holmberg SD. The increasing burden of mortality from viral hepatitis in the United States between 1990 and 2007. Ann Intern Med 2012; 156: 251-278 [PMID: 22351712 DOI: 10.7326/0003-4819-156-4-20120221-00004]
10 Wong JB, McQuillan GM, McHutchison JG, Poyart N. Estimating future hepatitis C morbidity, mortality, and costs in the United States. Am J Public Health 2000; 90: 1562-1569 [PMID: 11029980 DOI: 10.2105/AJPH.90.10.1562]
11 Rein DB, Wittenborn JS, Weinbaum CM, Sabin M, Smith BD, Lesesne SB. Forecasting the morbidity and mortality associated with prevalent cases of pre-cirrhotic chronic hepatitis C in the United States. Dig Liver Dis 2011; 43: 66-72 [PMID: 20739252 DOI: 10.1016/j.dld.2010.05.006]
12 Seeff LB. Natural history of hepatitis C. Am J Med 1999; 107: 10S-15S [PMID: 10655449 DOI: 10.1016/S0002-9344(99)00374-5]
13 Thein HH, Yi Q, Dore GJ, Krahn MD. Estimation of stage-specific fibrosis progression rates in chronic hepatitis C virus infection: a meta-analysis and meta-regression. Hepatology 2008; 48: 418-431 [PMID: 18563841 DOI: 10.1002/hep.22375]
14 Poyart T, Bedossa P, Opolon P. Natural history of liver fibrosis progression in patients with chronic hepatitis C. The OBSVIRC, METAVIR, CLINIVIR, and DOSVIRC groups. Lancet 1997; 349: 825-832 [PMID: 9121257 DOI: 10.1016/S0140-6736(96)67642-8]
15 Fattovich G, Giustina G, Degos F, Tremolada F, Diodati G, Almasio P, Nevens F, Solinas A, Mura D, Brouwer JT, Thomas H, Njpoum C, Casarin C, Bonetti P, Fuschini P, Bascho J, Tocco A, Bhalia A, Galussini R, Varenta F, Schalm SW, Realdi G. Morbidity and mortality in compensated cirrhosis type C: a retrospective follow-up study of 384 patients. Gastroenterology 1997; 112: 463-472 [PMID: 9024300 DOI: 10.1016/gast.1997.v112.pn0924300]
16 Pawlotsky JM. Use and interpretation of virological tests for hepatitis C. Hepatology 2002; 36: S65-S73 [PMID: 12407578 DOI: 10.1038/jhep.2002.36815]
17 Centers for Disease Control and Prevention (CDC). Testing for hepatitis C infection: an update of guidance for clinicians and laboratories. MMWR Mortal Wkly Rep 2013; 62: 362-365 [PMID: 23657112]
18 Saldaar K, Schiff ER. Alcohol and hepatitis C. Semin Liver Dis 2004; 24: 305-315 [PMID: 15349807 DOI: 10.1055/s-2004-832942]
19 Harris DR, Gonin R, Alter HJ, Wright EC, Buskell ZJ, Hollinger FB, Seeff LB. The relationship of acute transfusion-associated hepatitis to the development of cirrhosis in the presence of alcohol abuse. Ann Intern Med 2001; 134: 120-124 [PMID: 11177315 DOI: 10.7326/0003-4819-134-2-20010610-00002]
20 Ortiz V, Berenguer M, Rayon JM, Carrasco D, Berenguer J. Contribution of obesity to hepatitis C-related fibrosis progression. Am J Gastroenterol 2002; 97: 2408-2414 [PMID: 12358265 DOI: 10.1111/j.1572-0241.2002.05995.x]
21 Ghany MG, Strader DB, Thomas DL, Seeff LB; American Association for the Study of Liver Diseases. Diagnosis, management, and treatment of hepatitis C: an update. Hepatology 2009; 49: 1335-1374 [PMID: 19330875 DOI: 10.1002/hep.22759]
22 Recommendations for Testing, Managing, and Treating Hepatitis C. [Accessed Feb 2 2015]. Available from: URL: http://hcvguidelines.org/full-report-view
23 Wai CT, Greenenson JK, Fontana RJ, Kalbfeisch JD, Marrero JA, Conjeevaram HS, Lok AS. A simple nonsensitive index can predict both significant fibrosis and cirrhosis in patients with chronic hepatitis C. Hepatology 2003; 38: 518-526 [PMID: 12883497 DOI: 10.1053/jhep.2003.50486]
24 Castella L. Noninvasive methods to assess liver disease in patients with hepatitis B or C. Gastroenterology 2012; 142: 1293-1302.e4 [PMID: 22537436 DOI: 10.1053/j.gastro.2012.02.017]
25 Poyart N, McHutchison J, Manns M, Trepo C, Lindsay K, Goodman Z, Ling MH, Albrecht J. Impact of pegylated interferon alfa-2b and ribavirin on liver fibrosis in patients with chronic hepatitis C. Gastroenterology 2002; 122: 1303-1313 [PMID: 11984517 DOI: 10.1016/gastro.2002.33023]
26 Morgan RL, Baack B, Smith BD, Yartel A, Pitas M, Falek-Ytet Y. Eradication of hepatitis C virus infection and the development of hepatocellular carcinoma: a meta-analysis of observational studies. Ann Intern Med 2013; 158: 329-337 [PMID: 23460056 DOI: 10.7326/0003-4819-158-5-201303050-00005]
27 van der Meer AJ, Veldt BJ, Feld JJ, Wedemeyer H, Dufour JF, Lammert F, Duarte-Rojo A, Heathcote EJ, Manns MP, Kuske L, Zeuzem S, Hofmann WP, de Knecht RJ, Hansen BE, Janssen HL.
D2'-deoxy-2'-fluoro-2'-C-methyluridine monophosphate, is a alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomized, double-blind, placebo-controlled trial. *Lancet* 2014; 384: 403-413 [DOI: 10.1016/S0140-6736(14)60494-3]

36 Manns M, Marcellin P, Poodrad F, de Araujo ES, Buti M, Horsmans Y, Janczewska E, Villamil F, Scott I, Poeters M, Lenz O, Owerker-Mahadevan S, De La Rosa G, Kalmeijer R, Scott J, Sinha R, Beaumont-Mauvel M. Simeprevir with pegylated interferon alfa 2a plus ribavirin in treatment-naive patients with chronic hepatitis C virus genotype 1 infection (QUEST-1): a phase 3, randomised, double-blind, placebo-controlled trial. *Lancet* 2014; 384: 403-413 [DOI: 10.1016/S0140-6736(14)60494-3]

37 Lawitz E, Sulkowski MS, Ghalib R, Rodriguez-Torres M, Younossi ZM, Corregidor A, DeJesus E, Pearlman B, Rabinovitz M, Gitlin N, Lim JK, Pockros PJ, Scott JD, Fievery LB, Lambrecht T, Owerker-Mahadevan S, Callewaert K, Symonds WT, Picchio G, Lindsay KL, Beaumont M, Jacobson IM. Simeprevir plus sofosbuvir, with or without ribavirin, to treat chronic infection with hepatitis C virus genotype 1 infection (QUEST-2): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet* 2014; 384: 414-426 [DOI: 10.1016/S0140-6736(14)60538-9]

38 Ghany MG, Gara N. QUEST for a cure for hepatitis C virus: the end is in sight. *Lancet* 2014; 384: 381-383 [DOI: 10.1016/S0140-6736(14)60807-2]

39 Lawitz E, Sulkowski MS, Ghalib R, Rodriguez-Torres M, Younossi ZM, Corregidor A, DeJesus E, Pearlman B, Rabinovitz M, Gitlin N, Lim JK, Pockros PJ, Scott JD, Fievery LB, Lambrecht T, Owerker-Mahadevan S, Callewaert K, Symonds WT, Picchio G, Lindsay KL, Beaumont M, Jacobson IM. Simeprevir plus sofosbuvir, with or without ribavirin, to treat chronic infection with hepatitis C virus genotype 1 infection (QUEST-1): a phase 3, randomised, double-blind, placebo-controlled trial. *Lancet* 2014; 384: 403-413 [DOI: 10.1016/S0140-6736(14)60494-3]

40 Manns M, Marcellin P, Poodrad F, de Araujo ES, Buti M, Horsmans Y, Janczewska E, Villamil F, Scott I, Poeters M, Lenz O, Owerker-Mahadevan S, De La Rosa G, Kalmeijer R, Scott J, Sinha R, Beaumont-Mauvel M. Simeprevir with pegylated interferon alfa 2a plus ribavirin in treatment-naive patients with chronic hepatitis C virus genotype 1 infection (QUEST-1): a phase 3, randomised, double-blind, placebo-controlled trial. *Lancet* 2014; 384: 403-413 [DOI: 10.1016/S0140-6736(14)60494-3]

41 Lawitz EJ, Gruener D, Hill JM, Marbury T, Moorhead L, Mathias A, Cheng G, Link JO, Wong KA, Mo H, McHutchison JG, Brainard DM. A phase 1, randomized, placebo-controlled, 3-day, dose-ranging study of GS-5885, an NS5A inhibitor, in patients with genotype 1 hepatitis C. *J Hepatol* 2012; 57: 24-31 [PMID: 22331425 DOI: 10.1016/j.jhep.2011.12.029]

42 Afdhal N, Zeuzem S, Kwo P, Chojkier M, Gitlin N, Puoti M, Romero-Gomez M, Zarski JP, Agarwal K, Buggisch P, Foster GR, Bräu N, Buti M, Jacobson IM, Subramanian GM, Ding X, Mo H, Yang JC, Pang PS, Symonds WT, McHutchison JG, Muir AJ, Mangia A, Marcellin P. Ledipasvir and sofosbuvir for untreated HCV genotype 1 infection. *N Engl J Med* 2014; 370: 1889-1898 [PMID: 24725239 DOI: 10.1056/NEJMoa1402454]

43 Afdhal N, Reddy KR, Nelson DR, Lawitz E, Gordon SC, Schiff E, Nahas R, Ghalib R, Gitlin N, Hering R, Lalezier J, Younes ZH, Pockros PJ, Di Bisceglie AM, Arora S, Subramanian GM, Zha Y, Dvorob-Soh Y, Yang JC, Pang PS, Symonds WT, McHutchison JG, Muir AJ, Sulkowski M, Kwo P. Ledipasvir and sofosbuvir for previously treated HCV genotype 1 infection. *N Engl J Med* 2014; 370: 1899-1909 [PMID: 24725238 DOI: 10.1056/NEJMoa1402355]

44 Feld JJ, Kowdley KV, Coakley E, Sigal S, Nelson DR, Crawford D,
Weiland O, Aguilar H, Xiong J, Pilot-Matias T, DaSilva-Tillmann B, Larsen L, Podsadecki T, Bernstein B. Treatment of HCV with ABT-450/r-ombitasvir and dasabuvir with ribavirin. N Engl J Med 2014; 370: 1594-1603 [PMID: 24720703 DOI: 10.1056/NEJMoai315722]

Zeuzem S, Jacobson IM, BAYkal T, Marinho RT, Poordad F, Bourlière M, Sulkowski MS, Wedemeyer H, Tam E, Desmond P, Jensen DM, Di Bisceglie AM, Varunok P, Hassanein T, Xiong J, Pilot-Matias T, DaSilva-Tillmann B, Larsen L, Podsadecki T, Bernstein B. Retreatment of HCV with ABT-450/r-ombitasvir and dasabuvir with ribavirin. N Engl J Med 2014; 370: 1604-1614 [PMID: 24720679 DOI: 10.1056/NEJMoai401561]

Ferenci P, Bernstein D, Lalaziti J, Cohen D, Luo Y, Cooper C, Tam E, Marinho RT, Tsai N, Nyberg A, Box TD, Younes Z, Enayati P, Green S, Baruch Y, Bhandari BR, Caruntu FA, Sepe T, Chulanov V, Jancezwieksa E, Rizzato G, Gervain J, Planas R, Moreno C, Hassanein T, Xie W, King M, Podsadecki T, Reddy KR. ABT-450/r-ombitasvir and dasabuvir with or without ribavirin for HCV. N Engl J Med 2014; 370: 1983-1992 [PMID: 24795200 DOI: 10.1056/NEJMoai402338]

Poordad F, Zeuzem C, Trinh R, Kowdley KV, Zeuzem S, Agarwal K, Shiffman ML, Wedemeyer H, Berg T, Yoshida EM, Foras X, Lovell SS, Da Silva-Tillmann B, Collins CA, Campbell AL, Podsadecki T, Bernstein B. ABT-450/r-ombitasvir and dasabuvir with ribavirin for hepatitis C with cirrhosis. N Engl J Med 2014; 370: 1973-1982 [PMID: 24725237 DOI: 10.1056/NEJMoai402869]

Bruno S, Crosisniani A, Facceitio C, Rossi S, Roffi L, Redaelli A, de Franchis R, Almasio PL, Mainesonneuve P. Sustained virologic response prevents the development of esophageal varices in compensated, Child-Pugh class A hepatitis C virus-induced cirrhosis. A 12-year prospective follow-up study. Hepatology 2010; 51: 2069-2076 [PMID: 20196120 DOI: 10.1002/hep.23528]

Alemi M, Rahbin N, Weiland O, Davidsdottir L, Hedenstierna M, Rose N, Verbaan M, Stål P, Carlsson T, Norrgren H, Ekbom A, Granath F, Hultcrantz R. A risk for hepatocellular carcinoma persists long-term after sustained virologic response in patients with hepatitis C associated liver cirrhosis. A 12-year prospective follow-up study. Hepatology 2010; 51: 2069-2076 [PMID: 20196120 DOI: 10.1002/hep.23528]

Singal AG, Volk ML, Jensen D, Di Bisceglie AM, Schoenfeld PS. A sustained viral response is associated with reduced liver-related morbidity and mortality in patients with hepatitis C virus. Clin Gastroenterol Hepatol 2013; 57: 230-236 [PMID: 23616492 DOI: 10.1016/j.cgh.2012.09.018]

D’Ambrosio R, Aghemo A, Rumi MG, Ronchi G, Donato MF, Paradis V, Colombo M, Bedossa P. A morphometric and immunohistochemical study to assess the benefit of a sustained virological response in hepatitis C virus patients with cirrhosis. Hepatology 2012; 56: 532-543 [PMID: 22271347 DOI: 10.1002/hep.25606]

Iacobelli A, Siciliano M, Perri F, Annicchiarico BE, Leandro G, Caruso N, Accadia L, Bombardieri G, Andruilli A. Peginterferon alfa-2b and ribavirin in patients with hepatitis C virus and decompensated cirrhosis: a controlled study. J Hepatol 2007; 46: 206-212 [PMID: 17125876 DOI: 10.1016/j.jhep.2006.08.020]

Hézode C, Fontaine H, Dorival C, Larrey D, Zoulam F, Canva V, de Ledinghen V, Poynard T, Samuel D, Bourlière M, Zarski JP, Raabe JJ, Alric L, Marcellin P, Riachi G, Bernard PH, Louisad Ratti V, Metivier S, Tran A, Serfaty L, Abergel A, Causse X, Di Martino V, Guyader D, Lucidarme D, Grando-Lemaire V, Hillon P, Feray C, Dao T, Cacoub P, Rosa I, Attali P, Petrov-Sanchez V, Barthe Y, Pawlotsky JM, Pol S, Carrat F, Bronowicki JP. Triple therapy in treatment-experienced patients with HCV-cirrhosis in a multicentre cohort of the French Early Access Programme (ANRS CO20-CUPIC) - NCT01514890. J Hepatol 2013; 59: 434-441 [PMID: 23669289 DOI: 10.1016/j.jhep.2013.04.035]

Forns X, Charlton M, Denning J, McHutchison JG, Symonds WT, Brainard D, Brandt-Sarifi T, Chang P, Kivett V, Castells L, Prieto M, Fontana RJ, Baumert TF, Coilly A, Londono MC, Habersetzer F. Sofosbuvir compassionate use program for patients with severe recurrent hepatitis C after liver transplantation. Hepatology 2015; 61: 1485-1494 [PMID: 25557906 DOI: 10.1002/hep.27681]

Charlton M, Seaberg E, Wisser R, Everhart J, Zetterman R, Lake J, Detre K, Hoofnagle J. Predictors of patient and graft survival following liver transplantation for hepatitis C. Hepatology 1998; 28: 823-830 [PMID: 9731579 DOI: 10.1002/hep.510280333]

Everson GT, Terrault NA, Lok AS, Rodrigo del R, Brown RS, Saab S, Shiffman ML, Al-Osaimi AM, Kulik LM, Gillespie BW, Everhart JE. A randomized controlled trial of pretransplant antiviral therapy to prevent recurrence of hepatitis C after liver transplantation. Hepatology 2013; 57: 1752-1762 [PMID: 22821361 DOI: 10.1002/hep.25976]

Curry MP, Forns X, Chung RT, Terrault NA, Brown R, Fenkel JM, Gordon F, O’Leary J, Kuo A, Schiano T, Everson G, Schiff E, Befeler A, Gane E, Saab S, McHutchison JG, Subramanian GM, Symonds WT, Denning J, McNair L, Arturburn S, Svarovskai E, Moonka D, Adibh N, Sofosbuvir and ribavirin prevent recurrence of HCV infection after liver transplantation: an open-label study. Gastroenterology 2015; 148: 100-107.e1 [PMID: 25261839 DOI: 10.1053/j.gastro.2014.09.023]

Forns X, Garcia-Retortillo M, Serrano T, Feliu A, Suarez F, de la Mata M, Garcia-Valdecasas JC, Navasa M, Rimola A, Rodés J. Antiviral therapy of patients with decompensated cirrhosis to prevent recurrence of hepatitis C after liver transplantation. J Hepatol 2003; 39: 389-396 [PMID: 12927925 DOI: 10.1016/S0168-8278(03)00310-6]

P- Reviewer: Grassi A, Jin B, Komatsu H, Onyewke CA
S- Editor: Tian YL  L- Editor: A  E- Editor: Liu SQ

Khullar V et al. HCV cirrhosis - New perspectives
