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New treatment strategies for hepatitis C infection

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Abstract

Hepatitis C infection can lead to cirrhosis and hepatocellular carcinoma and it is an important cause of mortality and morbidity. Achieving a sustained virological response has been the major aim for decades. Interferon treatment was the primarily developed therapy against the infection. Addition of the guanosine analog ribavirin to stop viral RNA synthesis increased the response rates as well as the adverse effects of the treatment. The increasing demands for alternative regimens led to the development of direct-acting antivirals (DAAs). The approval of sofosbuvir and simeprevir signaled a new era of antiviral treatment for hepatitis C infection. Although the majority of studies have been performed with DAAs in combination with interferon and resulted in a decrease in treatment duration and increase in response rates, the response rates achieved with interferon-free regimens provided hope for patients ineligible for therapy with interferon. Most DAA studies are in phase Ⅱ leading to phase Ⅲ. In the near future more DAAs are expected to be approved. The main disadvantage of the therapy remains the cost of the drugs. Here, we focus on new treatment strategies for hepatitis C infection as well as agents targeting hepatitis C virus replication that are in clinical development.

Key words: Direct-acting antivirals; Eradication; Genotype; Hepatitis C virus infection; Interferon-free; Treatment

Core tip: In this review, we focused on different treatment regimens for hepatitis C infection, especially those including the newly developed and approved direct-acting antivirals. The guidelines are constantly changing in light of new studies. The recommendations of the guidelines are reviewed and consider different genotypes of the virus in addition to the results of ongoing studies. Continuing medical need for agents that act on novel hepatitis C virus targets has resulted in new compounds targeting viral proteins, which is also highlighted in the manuscript.

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INTRODUCTION

The hepatitis C virus (HCV), discovered in 1989, affects approximately 3% of the world population, corresponding to 170 million individuals worldwide, and accounts for 500000 deaths per year[1]. Seventy-five percent of the infected patients develop chronic HCV infection, of whom 20% develop cirrhosis[2]. Hepatocellular carcinoma, liver transplantation, and an increase in cardiovascular mortality and morbidity are other outcomes of HCV infection[3]. Eradication of HCV by antiviral treatment can prevent histological deterioration and improve liver histology, along with a decrease in liver-related mortality and morbidity[4]. Pegylated-interferon (Peg-IFN) with ribavirin (RBV) was the standard therapy for hepatitis C until 2011, but new regimens are evolving at a breathtaking pace. In 2011, the first generation protease inhibitors, boceprevir and telaprevir, were approved[5]. In recent years, the Peg-IFN plus RBV regimens gave way to IFN-based strategies combining direct-acting antivirals (DAAs) with Peg-IFN and RBV. Eventually, as an understanding of the HCV life cycle increases, IFN-free combinations of DAAs have evolved to affect all steps of the HCV life cycle and cure most chronically infected patients[6]. The studies suggest use of first generation protease inhibitors (PIs), boceprevir (BOC) and telaprevir (TVR) in the treatment of patients with cirrhosis[7]. Together with the development of DAAs, treatment regimens are characterized by shorter duration, simplified dosing, improved safety profile and effectivity, with > 90% sustained virological response (SVR). Here, new treatment strategies for HCV infection, which aim to eliminate IFN and RBV from the treatment regimen in order to reduce the adverse effects of therapy, are summarized.

TREATMENT REGIMENS FOR CHRONIC HCV GENOTYPE 1 INFECTION

The purpose of HCV therapy is to eradicate the virus. The SVR, indicated by aviremia 24 wk after completion of antiviral therapy for chronic HCV infection, is used to indicate the success of therapy. For years, the standard therapy for HCV infection had been Peg-IFN and RBV for 48 wk independent of the genotype. BOC and TVR were the first NS3/4A PIs targeting NS3 (serine protease) and its cofactor NS4A to block proteolytic maturation of a large portion of the nonstructural region of the HCV polyprotein. After their approval, a combination of Peg-IFN plus RBV plus BOC/TVR began to be used, since monotherapy with BOC or TVR results in the selection of drug resistant variants. The possibility of viral resistance, even in triple combination, resulted in development of DAAs, newer second- and third-generation NS3/4A PIs, NS5B polymerase inhibitors [nucleoside inhibitors (NI) and non-NI (NNIs)], NS5A inhibitors, and inhibitors targeting cyclophilin which is the host factor with an important role in HCV RNA replication[8,9]. These DAAs target specific nonstructural proteins of the virus resulting in disruption of viral replication and infection. NS5B is a RNA-dependent RNA polymerase, essential for viral replication, while NS5A has a role in the organization and regulation of replication[10]. The DAAs in medical use and in development are listed in Table 1[8].

Sofosbuvir was the first NS5B polymerase inhibitor approved for the treatment of chronic hepatitis C by the United States Food and Drug Administration (FDA) in December 2013 and by the European Medical Agency in January 2014. It is well tolerated. The most commonly reported side effects were fatigue, headache, nausea, insomnia, and anemia in the clinical trials performed with sofosbuvir and RBV[11]. Sofosbuvir is administered orally as a 400 mg tablet daily with or without food. Monotherapy is not recommended. Its advantages over previous DAAs are a limited drug-drug interaction profile [inhibits P-glycoprotein transporter so it is not recommended with rifampin, rifabutin, rifapentine, hypericin (a component of St John's Wort), carbamazepine, phenytoin, phenobarbital, oxcarbazepine, tipranovir/ritonavir[12]], and a lack of significant viral resistance. While no dose adjustment is needed in hepatic impairment; the drug is not recommended in end-stage renal disease.

The NEUTRINO study was a phase Ⅲ clinical trial where 327 treatment-naïve patients with HCV genotype 1, 4, 5 or 6 infection received Peg-IFN, RBV, and sofosbuvir for 12 wk, and SVR rates of 89% in genotype 1 were achieved[13]. Also, genotype 1a patients had greater SVR than patients with HCV genotype 1b (92% *vs* 82%, respectively). The SVR at 12 wk was 80% in cirrhotic patients. When the SVR of 82% with 12-wk therapy in genotype 1b subtypes is considered, it is an improvement compared to the first-generation PIs which achieved only 70% SVR with 48 wk of Peg-IFN, RBV, and BOC therapy[14]. The adverse events during the study were associated with Peg-IFN-α and RBV. The randomized phase Ⅱ ATOMIC study compared different schedules of sofosbuvir plus Peg-IFN and RBV in HCV genotype 1 treatment-naïve patients and evaluated the shortest treatment duration. The results showed that sofosbuvir plus Peg-IFN and RBV for a total of 12 wk yielded an SVR rate of 89%, equal to the SVR rate in the extended treatment regimens[15].

Simeprevir is the first available second-generation-NS3/4A- PI which also has an increased efficacy against genotype 1 HCV. The FDA approved simeprevir use in combination with Peg-IFN and RBV in December 2013. It is orally administered as a 150 mg capsule daily with food. As the drug is eliminated by the liver, its use is not recommended in patients with moderate or severe hepatic impairment[16]. The adverse effects reported with simeprevir use are photosensitivity, rash, pruritus, and nausea, which are infrequent[17]. Simeprevir is oxidatively metabolized by the CYP3A subfamily, so drugs that are significant inducers or inhibitors of CYP3A4 are expected to alter the concentration of simeprevir[18]. Because of

Table 1 Direct-acting antivirals (clinical development status in parenthesis)

NS3/4A Protease inhibitors	NS5A inhibitors	Polymerase inhibitors	
		NIs	NNIs
Telaprevir (approved)	Daclatasvir (approved)	Sofosbuvir (approved)	Dasabuvir (phase 3)
Boceprevir (approved)	Ledipasvir (phase 3)	Mericitabine (phase 2)	BMS-791325 (phase 3)
Simeprevir (approved)	Ombitasvir (approved)	VX-135 (phase 2)	PPI-383 (phase 1)
Asunaprevir (phase 3)	GS-5816 (phase 2)		GS-9669 (phase 2)
Danoprevir (phase 3)	ACH-2928 (phase 1)		TMC647055I (phase 2)
Paritaprevir (approved)	ACH-3102 (phase 2)		VX-222 (phase 2)
Vaniprevir (phase 3)	PPI-668 (phase 2)		
Sovaprevir (phase 2)	PPI-461 (phase 1)		
MK-5172 (phase 3)	GSK2336805 (phase 2)		
ACH-2684 (phase 2)	Samatasvir (phase 2)		
Narlaprevir (phase 2)	MK-8742 (phase 3)		
Vedroprevir (phase 2)	BMS-824393 (phase 2)		

NI: Nucleoside inhibitors; NNIs: Non-nucleoside inhibitors.

overlapping resistance, it should not be given to patients with treatment failure for the first-generation PIs, BOC and TVR, nor to genotype 1a patients with the Q80K variant present at baseline, since they had lower SVR rates in the trials[12].

QUEST 1 was a randomized, double blind, placebo-controlled phase III study assessing the efficacy of simeprevir in combination with Peg-IFN and RBV[17]. Treatment-naïve genotype 1 patients randomly received simeprevir plus Peg-IFN and RBV for 12 wk and an additional 12 wk of Peg-IFN and RBV or placebo for 12 wk plus 24 wk of Peg-IFN and RBV. The overall SVR in the simeprevir and placebo group was 80% and 50%, respectively. The subanalysis showed an SVR of 71% for genotype 1a and 90% for genotype 1b patients. The baseline Q80K polymorphism present in 41% of the patients with genotype 1a was associated with lower SVR rates. In the QUEST-2 trial, similar to QUEST-1, an SVR of 81.3% was achieved in the simeprevir-treated group compared with 50% in the placebo group[19], and 91% of patients were suitable for response-guided therapy within the treatment group. The DRAGON study in Japan, assessing the efficacy of simeprevir in treatment-naïve noncirrhotic genotype 1b patients, showed an SVR of 92% in the group treated with simeprevir 100 mg/d plus Peg-IFN and RBV for 24 wk[20]. In the PILLAR phase Ⅱb study, patients received different doses of simeprevir and the highest SVR of 86.1% was achieved in the group receiving simeprevir 150 mg/d plus Peg-IFN for 24 wk[21].

Daclatasvir, the first NS5A inhibitor suppressing HCV RNA synthesis, is a once-daily administered agent approved in Japan, and awaiting FDA approval. In a study by Suzuki *et al*[22], the efficacy and safety of daclatasvir in combination with Peg-IFN and RBV were assessed in treatment-naïve genotype 1 patients where patients receiving daclatasvir 60 mg and Peg-IFN and RBV for 24 or 48 wk showed SVR rates of 90%. There are ongoing studies on daclatasvir in combination with other PIs or NNIs. As these are phase Ⅱ studies, daclatasvir is not expected to be approved by the FDA soon. However, promising results were obtained in a study of daclatasvir in combination with sofosbuvir for 12 wk, which achieved a 98% SVR in 126 treatment-naïve genotype 1 patients[23].

In the treatment of HCV genotype 1 infection, the subtypes are important as patients with genotype 1a tend to have higher relapse rates than patients with genotype 1b with certain regimens. Based on different studies, Miller *et al*[24] recommended 12 wk of IFN-α-2a or b, with RBV and sofosbuvir, or alternatively 12 wk of simeprevir plus 24 wk of Peg-IFN-α-2a or 2b and RBV, or faldaprevir 120 mg for 12 wk plus Peg-IFN-α-2a and RBV for 24 wk for HCV genotype 1-naïve patients in the 2014 United Kingdom consensus guidelines. From June 2014, the company ceased the development of the investigative HCV drug faldaprevir as there was no longer an unmet medical need for the faldaprevir IFN-based regimen[8]. The American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver (EASL) Recommendations for HCV genotype 1 infection include a combination of weekly Peg-IFN-α, daily weight-based RBV (1000 or 1200 mg in patients < 75 kg or ⩾ 75 kg, respectively), and daily sofosbuvir (400 mg), or a combination of Peg-IFN-α, daily weight-based RBV and daily simeprevir (150 mg) for 12 wk with an additional 12 wk of Peg-IFN and RBV in treatment-naïve and prior relapse patients, and for an additional 36 wk in prior partial and null responders[25,26]. For patients infected with HCV genotype 1b, a combination of weekly Peg-IFN-α, daily weight-based RBV, and daily daclatasvir (60 mg) for 12 wk and an additional 12 wk of Peg-IFN and RBV is recommended. They stated that daclatasvir should be continued in combination with Peg-IFN-α and RBV for an additional 12 wk in patients who did not achieve a HCV RNA level of < 25 IU/mL at week 4 and an undetectable level at week 10[25].

In the near future, IFN-free regimens are expected to replace IFN-based regimens for both non-responders and previously untreated patients. The patients ineligible for therapy with IFN are primary candidates for DAA therapy. Recent EASL recommendations stated that patients with HCV genotype 1 could be

treated with a combination of daily weight-based RBV or daily sofosbuvir (400 mg) for 24 wk as well as daily sofosbuvir (400 mg) and simeprevir (150 mg) for 12 wk. Although adding RBV to this regimen did not show any major advantage, it should be considered in prior non-responder and cirrhotic patients. Daily sofosbuvir (400 mg) and daclatasvir (60 mg) for 12 wk in treatment-naïve patients or for 24 wk in treatment-experienced patients is another IFN-free treatment option recommended by EASL[25]. In addition to the EASL recommendations, a fixed-dose combination of ledipasvir (90 mg/d) and sofosbuvir (400 mg/d) for 12 wk is recommended by AASLD[26].

A sofosbuvir plus RBV combination for 12 wk was evaluated in the ELECTRON trial, achieving SVR rates of 84% in treatment-naïve patients but only 10% in treatment-experienced patients[27]. The QUANTUM study evaluated treatment duration and reported SVR12 and SVR24 rates of 47% and 53%, respectively[28]. The efficacy of simeprevir plus sofosbuvir with or without RBV in prior null responders was assessed in the COSMOS trial for either 12 or 24 wk, and SVR rates of 96.3% with RBV and 92.9% without RBV were achieved[29]. The ION trial evaluated the ledipasvir and sofosbuvir combination[30,31]. Ledipasvir is a NS5A inhibitor, available as part of a fixed-dose combination with sofosbuvir: 90 mg ledipasvir and 400 mg sofosbuvir. Absorption of ledipasvir may decrease with increased gastric pH levels. ION-1 assessed the length of the treatment and SVR was achieved in 97% of patients. In the ION-3 trial treatment length was shortened to 8 wk and an SVR rate of 94% was achieved[32]. In a study by Afhdal *et al*[30], 865 patients were enrolled and divided into 4 groups, and SVR rates for the group treated with ledipasvir and sofosbuvir for 12 wk was 99%, for the group treated with ledipasvir, sofosbuvir and RBV for 12 wk was 97%, for the group treated with ledipasvir and sofosbuvir for 24 wk was 98%, and for the group treated with ledipasvir, sofosbuvir and RBV for 24 wk was 99%[30,33]. Another study by Kohli *et al*[34] tried to reduce treatment time for hepatitis C and assigned 60 patients into 3 groups of 20. High cure rates were achieved for HCV infection with 2 different 3-drug regimens that were given for 6 wk: sofosbuvir, ledipasvir and GS-9451 or GS-9669. The LEAQUE-1 phase Ⅱ study evaluated simeprevir plus daclatasvir 30 mg ± RBV for 12 wk in HCV genotype 1b treatment-naïve patients and prior non-responders[35]. Response rates were 75%-85% and 65%-95%, respectively. Another oral combination recommended by the AASLD and evaluated in SAPPHIRE-I is a combination of RBV-boosted paritaprevir (150 mg), an inhibitor of HCV NS3/4A, ombitasvir (25 mg), twice-daily dasabuvir (referred as 3-D combination) and weight-based RBV for 12 wk, which achieved an SVR of 96% in treatment-naïve genotype 1 infection[33,36].

Patients with prior treatment failure and non-responder patients are still the most difficult group awaiting treatment. In the phase Ⅱ COSMOS trial, 400 mg sofosbuvir and 150 mg simeprevir were given to non-responders or previously untreated patients, and 92%-96% of patients responded to treatment without additional need of RBV[37]. SVR rates did not improve with longer treatment duration or addition of RBV even in the presence of Q80K baseline drug-resistant variants. Daclatasvir is also recommended in treatment-experienced patients. Although mutations associated with resistance to daclatasvir occur at several positions (mutation sites are M28T, Q30E/H/R, L31M/V, P32L, and Y93C/H/N for HCV genotype 1a, and L31F/V, P32L and Y93H/N for HCV genotype 1b), its viral resistance profile does not overlap with that of other DAAs[38,39]. This makes it a good candidate to suppress emerging resistance when combined with other DAAs. The efficacy of daclatasvir 60 mg in combination with sofosbuvir 400 mg with and without RBV for 24 wk was assessed in an open label phase Ⅱ study in patients who failed treatment with TVR or BOC plus Peg-IFN and RBV. The SVR rates were 100% and 98%, respectively, with and without RBV[23]. Although HCV genotype 1a is associated with lower SVR rates, there was no difference between HCV genotype 1a and 1b in this study. The ASPIRE trial evaluated 7 different schedules of simeprevir (100 mg or 150 mg) in combination with Peg-IFN and RBV for the treatment of 452 treatment-experienced patients (16%-20% with cirrhosis)[40]. The SVR rates were 77%-89% in the relapse group and 38%-59% in the non-responder group. The phase Ⅲ PROMISE trial patients (260 treatment-experienced) received simeprevir (150 mg) plus Peg-IFN and RBV for 12 wk followed by Peg-IFN and RBV alone for 12 or 36 wk based on response-guided therapy criteria. An SVR of 79% was achieved and most patients were able to shorten therapy to 24 wk[41]. The ledipasvir and sofosbuvir combination is another treatment option for treatment-experienced patients with HCV genotype 1. Three phase Ⅲ studies were performed in patients who did not respond to IFN therapy with or without a PI[42]; 12 wk of the ledipasvir and sofosbuvir combination ± RBV was given to patients without cirrhosis while 24 wk of therapy was given to patients with cirrhosis. SVR rates were 94% and 96% with and without RBV, respectively. Twenty four wk of therapy was recommended for patients with decompensated cirrhosis while equal efficacy was gained with both 12 and 24 wk of therapy in patients with compensated cirrhosis (96% and 97%, respectively).

Overall, the AASLD-recommended therapy options for treatment-experienced patients are; ledipasvir plus sofosbuvir combination, sofosbuvir plus simeprevir combination with or without RBV, or the triple combination of direct-acting antivirals (3-D) with or without RBV, based on the existence of cirrhosis[42]. The SAPPHIRE-Ⅱ trial included non-cirrhotic patients who failed treatment with Peg-IFN/RBV. The patients received a 3-D combination plus RBV for 12 wk and achieved 96.3% SVR[39]. The PEARL-Ⅱ study evaluated 12 wk of the 3-D regimen with and without RBV in treatment-experienced HCV genotype 1b patients. All patients

in the RBV-containing group and 96% of patients in the RBV-free group achieved an SVR with 12 wk of treatment. Adverse effects were tolerable and fewer in the RBV-free group[43].

TREATMENT REGIMENS FOR CHRONIC HCV GENOTYPE 2 INFECTION

Peg-IFN and RBV had been the standard care of therapy for chronic HCV genotype 2. The duration of treatment was 24 wk and 85%-90% of the patients achieved SVR[44]. With the introduction of DAAs, daclatasvir has been given with Peg-IFN and RBV for 12 wk to treatment-naive HCV genotype 2 patients and 83% of the patients achieved SVR. Since most patients are ineligible, intolerant or unwilling for Peg-IFN, 12 wk of sofosbuvir and RBV combination was found to be highly effective on patients with HCV genotype 2 and was recommended by AASLD and EASL. The FISSION study compared 12 wk of sofosbuvir and RBV with 24 wk of Peg-IFN and RBV where sofosbuvir was found to be superior in the included treatment-naive patient group[12]. 20%-21% of the 499 patients had cirrhosis and the SVR12 rate was 91% for cirrhotic patients with genotype 2 patients and 34% for cirrhotic patients with genotype 3. The FUSION study on the other hand evaluated the treatment duration on treatment-experienced patients of HCV genotype 2. Patients received sofosbuvir plus weight-based RBV for 12 or 16 wk. The SVR rates were 86% and 93%, respectively. 35% of the patients had cirrhosis and the SVR rates were 78% *vs* 60% for genotype 2 (16 wk *vs* 12 wk of treatment) and 61% and 19% for genotype 3 cirrhotic patients, respectively[45]. Although there is no clear benefit shown with 16 wk of treatment, guidelines offer extending treatment to 16 wk in the presence of cirrhosis. The VALENCE study assessed treatment-naive and treatment-experienced patients receiving sofosbuvir and RBV and reported an overall SVR of 93%; 97% (29/30) in treatment-naive noncirrhotic individuals, 100% (2/2) in treatment-naive cirrhotics, 91% (30/33) in treatment-experienced noncirrhotics, and 88% (7/8) in treatment-experienced cirrhotics[46]. The POSITRON study is another phase Ⅲ study involving treatment-experienced patients or patients ineligible for IFN. The efficacy of sofosbuvir and RBV for 12 wk was assessed and the noncirrhotic and cirrhotic patients with genotype 2 achieved 92% and 94% SVR rates, respectively[45]. Based on these studies AASLD and recent EASL guidelines recommend daily sofosbuvir and weight-based RBV for 12 wk for patients with HCV genotype 2 infection in whom prior Peg-IFN and RBV treatment has failed[25,43]. Alternative regimen is a combination of sofosbuvir with Peg-IFN and RBV for 12 wk and it was studied in LONESTAR-2 phase Ⅲ trial where 50% of patients had compensated cirrhosis. Unexpectedly, the results were similar to IFN-free regimen with SVR rates close to 100%[47]. Considering the adverse effects of IFN, sofosbuvir regimen seems like the highly effective and well-tolerated regimen for patients with genotype 2[12].

TREATMENT REGIMENS FOR CHRONIC HCV GENOTYPE 3 INFECTION

Until the development of DAAs, HCV genotype 2 and 3 infections were accepted as easy to treat. Today, with IFN-free regimens, patients with HCV genotype 3 are the most difficult to treat[12]. The recommended regimen for treatment-naïve patients with HCV genotype 3 infection is daily sofosbuvir and weight-based RBV for 24 wk, and was studied in the VALENCE phase Ⅲ trial. SVR rates of 94% for treatment-naïve noncirrhotic patients, 92% for treatment-naïve cirrhotics, 77% for treatment-experienced noncirrhotics, and 60% for treatment-experienced cirrhotics were achieved[48]. The FISSION, FUSION and POSITRON studies assessed the effectiveness of sofosbuvir and RBV in patients with HCV genotype 2 and 3 for 12 and 16 wk, and concluded that previous exposure to Peg-IFN and RBV and disease severity were significant factors in patients with HCV genotype 3 infection[49]. The results were better in treatment-naïve patients and also better with 16 wk of therapy. Taking the VALENCE trial into account, extension of therapy duration as well as addition of another anti-HCV drug should be considered in order to improve the effectiveness of the therapy. Sofosbuvir and daclatasvir combination for 12 wk in treatment-naive or 24 wk in treatment-experienced patients is recommended by EASL guidelines based on the ALLY-3 study, in which 91% treatment-naïve and 86% treatment-experienced patients achieved an SVR with 12 wk of sofsobuvir and daclatasvir combination[50]. Adding RBV is recommended in patients with predictors of poor response to anti-HCV therapy, especially prior non-responders and/or patients with cirrhosis[25]. An alternative regimen for patients with HCV genotype 3 infection in whom prior Peg-IFN and RBV treatment has failed, is retreatment with daily sofosbuvir, RBV and weekly Peg-IFN for 12 wk. In the LONESTAR-2 study, a sofosbuvir, Peg-IFN, and RBV combination resulted in an SVR in 83% of patients infected with genotype 3. The presence of cirrhosis did not affect the response, so genotype 3 treatment-experienced patients with cirrhosis may need IFN-based regimens for a better response[33].

TREATMENT REGIMENS FOR CHRONIC HCV GENOTYPE 4-6 INFECTION

Forty-eight weeks of Peg-IFN and RBV had been the mainstay therapy for patients with genotype 4 infection until the development of DAAs. Recent AASLD and EASLD guidelines recommend the FDA-approved sofosbuvir, Peg-IFN, and RBV regimen for 12 wk[12,25,42]. The genotype 4 cohort of the NEUTRINO study evaluating the efficacy of 12 wk of sofosbuvir and Peg-IFN plus RBV combination achieved a 96% SVR[13]. In a

study conducted in subjects of Egyptian ancestry, 32 treatment-experienced patients were treated with sofosbuvir and RBV for 12 or 24 wk and 87% SVR was achieved in the 24 wk group suggesting this therapy as an effective choice of treatment, especially for patients ineligible for IFN[39]. Simeprevir is effective against HCV genotype 4 infection and the ongoing phase 3 trials including treatment-naïve and treatment-experienced patients have promising results[25]. Therefore, sofosbuvir and simeprevir for 12 wk is an acceptable choice of treatment for patients with HCV genotype 4 infection.

In the PEARL-I study, a 3-D regimen plus RBV was evaluated in 49 treatment-experienced patients without cirrhosis for 12 wk, and 100% of the patients achieved an SVR in the intention-to-treat analysis with no serious adverse events reported[51]. There are not enough studies of DAAs in genotype 4 infection, but the ledipasvir plus sofosbuvir combination for 12 wk is also accepted as effective and recommended by the AASLD based on the SYNERGY trial of 20 patients with HCV genotype 4 where 40% of patients were treatment-experienced and 40% had advanced fibrosis. The overall SVR achieved was 95%[52].

The clinical trials including genotypes 5 and 6 infection are inadequate; in fact no phase Ⅲ data have been presented in treatment-experienced or cirrhotic patients. The only study evaluating treatment-naïve patients with genotype 5 and 6 was the NEUTRINO study where only one patient with genotype 5 and 6 patients with genotype 6 were enrolled[13]. SVR rates achieved for both genotypes were 100% with 12 wk of sofosbuvir and the Peg-IFN and RBV combination. As a result, this combination is the recommended regimen by the AASLD and EASL guidelines.

In addition, ledipasvir is known to have *in vitro* activity against HCV genotype 6 so the ledipasvir plus sofobusvir combination was evaluated in a small, 2-center, open 2 - label study in 25 treatment-naïve and treatment-experienced patients, of whom 2 had cirrhosis. The SVR rate was 96%[53]. This daily fixed-dose combination of ledipasvir and sofosbuvir for 12 wk is a recommended regimen for patients with HCV genotype 6 in whom prior therapy has failed[42].

TREATMENT REGIMENS FOR PATIENTS WITH HUMAN IMMUNODEFICIENCY VIRUS/HCV CO-INFECTION

HCV infection is one of the important causes of comorbidity in patients with human immunodeficiency virus (HIV). Since liver-related mortality became the second highest cause of death in HIV-positive patients, HCV eradication has become obligatory. BOC and TVR were already approved in HCV/HIV co-infection, but since 2013 both sofosbuvir and simeprevir were approved by the FDA to be used in combination with Peg-IFN and RBV to treat patients co-infected with HIV/HCV genotype 1, and sofosbuvir was approved to be used in combination with RBV to treat patients with HIV/HCV genotype 2 and 3[54]. Sofosbuvir plus ledipasvir combination is another alternative for co-infected patients[53]. The limitation of DAAs is pharmacokinetic interactions with antiretroviral drugs. In particular, efavirenz, etravirine, and nevirapine are not recommended with daclatasvir, simeprevir, or sofosbuvir. In addition, daclatasvir dose adjustment is needed in case of ritonavir-boosted atazanavir use[45].

In a study done in Puerto Rico, 12 wk of sofosbuvir plus the Peg-IFN and RBV combination achieved an SVR in 91% of patients[55]. Furthermore, 12 wk of simeprevir plus the Peg-IFN and RBV combination was investigated in HIV/HCV co-infected patients and resulted in a 74% SVR rate in patients with HCV genotype 1[56]. Ledipasvir plus sofosbuvir combination with or without RBV was administered to 12 HIV/HCV genotype 1 patients in a small trial and showed a 100% SVR12 rate[57]. The only study evaluating IFN-free treatment on HIV/HCV co-infected patients is the PHOTON study where sofosbuvir plus RBV was administered to HIV/HCV genotype 1, 2, and 3 patients for 24, 12, and 12 wk, respectively[58]. SVR was achieved in 76% of the patients with genotype 1, 88% of the patients with genotype 2, and 67% of the patients with genotype 3. Studies on treatment regimens including other DAAs are still in progress.

TREATMENT STRATEGIES IN DEVELOPMENT

Commonly used DAAs targeting viral proteins NS3, NS4A, NS5A, and NS5B are mentioned above. One other least characterized viral protein essential for viral replication is NS4B, a 27-kDa integral membrane protein[59]. Several compounds targeting HCV NS4B in antiviral treatment have been mentioned in recent studies. Chen *et al*[60] identified several new azaindole sulfonamides targeting HCV NS4B, and 5-substituted 7-azaindole sulfonamides had the most potent activity with a favorable liver to plasma ratio and excellent oral exposure in rats. Also, NS4B was found to be essential for NS5A phosphorylation[61]. Domain I of NS5A and the C-terminal domain of NS4B were found to be the major determinants mediating the NS5A-NS4B interaction in a study by David *et al*[62]. They suggested that modulation of this interaction could be added to the list of potential NS5A DAA targets.

Another target of antiviral therapy is the ion channel activity of HCV p7. The p7 channel is crucial for virus replication *in vitro*, playing a role in virus assembly and release[63]. BIT225 is a novel small molecule identified as an inhibitor of the p7 ion channel that completed 2 phase I human trials. Phase IIa studies are still ongoing. Luscombe *et al*[64] reported the inhibitory effect of BIT225 as well as its strong synergy with Peg-IFN and RBV, which makes it a good candidate for use in combination therapy. Although the mechanism of action is not fully understood, amantadine and rimantadine

are known to inhibit the HCV p7 ion channel[65]. In the p7 channel, there are 6 equivalent hydrophobic pockets and nearby there are 3 aromatic amino acids (His17, Phe20, and Trp21). Du *et al*[66] focused on the nuclear magnetic resonance structure of HCV p7 and found that the best binding site of amantadine was Trp21. The binding sites and interactions mentioned in their study may help the future development of p7 channel inhibitors. Clinical data is only available for amantadine[67] while other compounds are reported to inhibit the HCV p7 ion channel, including long alkylchain iminosugars and hexamethylene amiloride[68,69].

HCV genomic RNA holds genetic information for viral proteins and contains regions of sequences required for HCV replication or translation. Antisense oligonucleotides (ASOs) have been identified in order to inhibit HCV RNA replication and viral polyprotein synthesis *in vitro*. Studies on HCV-infected patients show that modified ASOs can result in decrease in viral load of > 2 log units[70]. A new generation of ASOs, locked nucleic acids (LNA), show improved affinity of binding to RNA targets, increased sequence specificity, and lower toxicity[71]. An internal ribosome entry site (IRES) is a nucleotide sequence that allows translation initiation in the middle of a messenger RNA (mRNA) sequence in HCV[72]. Host microRNA (miR-122) plays a role in HCV replication *in vitro* and is joined directly to a region in the IRES[73]. Studies in primates demonstrated that LNA-based ASOs targeting miR-122 can be delivered to the liver for 12 wk with no adverse effects and result in a virological response of > 2 log units in plasma HCV RNA levels, and decreased expression of cellular mRNA carrying the miR-122 region[74,75]. In a study by Laxton *et al*[76], 47 ASOs were screened and 7 hits with selectivity index higher than 10 were identified; 5 hits targeting NS5a and 2 hits targeting IRES (seq132 and seq207-250a). Seq132 ASO showed potent antiviral activity (95% to 98% antiviral activity) with low cytotoxicity. The possible antiviral mechanisms of seq132 were highlighted as antagonism of miR122 binding, loss of HCV sequences due to RNase H activity, and local destabilization of the IRES secondary structure. In addition, Bhat *et al*[77] revealed the interaction between ribosomal protein S5 (RPS5) and HCV IRES. They found that blocking RPS5 in 40S ribosome subunits results in inhibition of HCV IRES activity. Therefore, HCV translation is inhibited. This may help in designing potential peptide mimics as potential antiviral molecules.

CONCLUSION

Development of DAAs represents significant progress in the treatment of HCV infection. IFN-based regimens cause adverse events, which make tolerance and compliance an important issue. Therefore, the new era of IFN-free regimens is highly accepted in the treatment of treatment-naïve and treatment-experienced patients, especially in individuals in whom IFN is absolutely contraindicated. Current IFN-free regimens offer SVR rates above 90% and 12-wk treatment duration in both groups. Recently, sofosbuvir, found to be effective against all genotypes, and simeprevir, daclatasvir, and ledipasvir are the most promising DAAs. The once daily dosing, low pill burden, pan-genotypic activity, lower rate of drug-drug interactions, fewer side effects, and shorter treatment duration makes these regimens more tolerable.

The most important issue of DAA treatment is the cost and availability. The regimens are extremely expensive so the cost should be reduced to provide universal access in all patients with HCV, especially in developing countries. In these regions, as for HIV treatment, International Health Organizations may help with free drug distribution and treatment follow-up.

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