Comparative Study of IFN-Based Versus IFN-Free Regimens and Their Efficacy in Treatment of Chronic Hepatitis C Infections

Ramesh Rana, Yizhong Chang, Jing Li, ShengLan Wang, Li Yang and ChangQing Yang

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/67214

Abstract

The hepatitis C viral (HCV) infection is a global health burden, WHO estimates 130–150 million people chronically infected with hepatitis C virus worldwide. Additional 3–4 million people become newly infected annually and more than 350,000 people die each year of HCV-related liver diseases. HCV infection exhibits higher genetic diversity with regional variations in genotypic prevalence resulting big challenges on disease management. Introduction of DAAs revolutionised the new era of all oral therapy in treatment of chronic hepatitis C infection and is the regimens of choice in present days. However, IFN-based combination therapy with sofosbuvir has promising efficacy in genotypes 3, 4, 5 or 6 infections compared to genotypes 1 and 2 infections. So, these regimens could be an option in DAAs regimen failure cases. The poor availability of data on recent DAAs (IFN-free) regimens questioned on regular use and cost effectiveness is the another challenge with DAAs regimens. So phase III trials (sofosbuvir and velpatasvir) of recent DAAs with pangenotypic actions and better tolerability in HCV infected patients are the future advances in treatment of chronic hepatitis C. After all those recent combination therapies with better SVR, the combination of pegylated interferon with ribavirin is the only option available where unavailability of other regimens still exists.

Keywords: hepatitis C virus, HCV genotypes, pegylated interferon, direct-acting antivirals, sustained virological response
1. Introduction

Hepatitis C virus (HCV) is a global public health problem causing progressive liver disease. The World Health Organization (WHO) estimates 130–150 million people chronically infected worldwide, which corresponds to 2–2.5% of world’s total population. Additional 3–4 million people becoming newly infected annually and more than 350,000 people die each year due to HCV-related diseases. Primary HCV infection causes acute hepatitis (AHC), asymptomatic in majorities; however, it can progress to chronicity in about 55–85% cases and spontaneous remission within 6 months without treatment in 15–45% [1–3]. Chronic hepatitis C (CHC) frequently presents with complications such as liver cirrhosis, liver failure, and hepatocellular carcinoma (HCC). In CHC, 15–30% have risk of cirrhosis of liver within 20 years and risk of HCC in cirrhotic is approximately 2–4% per year. Decompensated cirrhosis leads to death in 50–70% of cases without liver transplantation after 5 years. Difficulties occur in determining number of new HCV infections, as most of the acute cases are not detected clinically. Less than 25% of acute cases of hepatitis C are only clinically apparent [1, 4–6].

Hepatitis C virus (HCV) is an envelope, single-stranded RNA virus of genus hepacivirus within the Flaviviridae family. HCV has seven genotypes (GT 1–7) with 67 subtypes and 20 provisional subtypes [7]. Each genotype of HCV has its own geographical variation. GT-1 is the most prevalent worldwide, one third in East Asia followed by GT-3; GT-2, 4, and 6; and GT-5 is the least prevalent [8]. The prevalence of HCV GT-1 and 3 dominate in most of the countries irrespective of economic status while HCV GT-4 and 5 are prevalent largely in countries with lower income [7, 8]. HCV subtypes 1a and 1b are the most common genotypes in the United States and also in Europe while subtype 1b is predominant in Japan [9]. HCV subtypes 2a and 2b are relatively common in North America, Europe, and Japan, subtype 2c is common in Northern Italy. Although, GT-3 has endemic strain in South Asia, 3a is especially prevalent in intravenous drug abusers in Europe and in the United States. GT-4 is prevalent in North Africa and Middle East; GT-5 seems to be confined to South Africa and GT-6 in Southeast Asia. A newly identified GT-7 isolated from a Central African (Congolese) immigrant in Canada [9]. The increased risk of HCV is highest among persons who inject drugs (PWID), global prevalence of HCV among PWID is 67%; HIV infected person, men who have sex with men (MSM); unsafe medical procedures-recipients of infected blood products or invasive procedures in health care facilities with inadequate infection control practice. Vertical or perinatal transmission of HCV occurs in up to 4–8% of cases, and transmission risk among mothers of HIV infection is estimated 17–25% [9–11].

The HCV infection is the public health problem and global burden, and the early diagnosis and treatment are necessary. The treatment of HCV infection was begun with the approval of interferon (IFN) by the Food and Drug Administration (FDA) in 1991, followed by combined IFN with ribavirin (RBV) in 1998 and then directly acting antiviral agents (Table 1). Until approval of directly acting antiviral agents, combination of pegylated interferon alfa (PegIFN
Interferon-alfa and ribavirin (RBV) was the standard treatment for all genotypic infections (Figure 1) [4, 12]. Over the past few years, the treatment options of HCV have exponentially grown. The development of directly acting antiviral (DAA) therapy, targeting non-structural proteins involved in replication of HCV revolutionised in the treatment of HCV infection. The combination of DAAs with or without PegIFN alfa regimens is assessed in different studies, and

| Year | Generic | Genotypes (SVR) |
|------|---------|----------------|
| 1991 | Interferon-alfa-2b | Genotype 1 (9%) |
|      |         | Genotypes 2, 3 (30%) |
| 1996 | Interferon-alfa-2a | Genotype 1 (29%) |
|      |         | Genotypes 2, 3 (62%) |
| 1997 | Consensus interferon | Genotype 1 (14%) |
|      |         | Genotypes 2, 3 (47%) |
| 1998 | Interferon-alfa plus ribavirin | Genotype 1 (47%) |
|      |         | Genotypes 2-6 (75%) |
| 2001 | PegInterferon-alfa-2b | Genotype 1 (28%) |
|      |         | Genotypes 2, 3 (56%) |
| 2001 | PegInterferon-alfa-2b/ribavirin | Genotype 1 (51%) |
|      |         | Genotypes 2-6 (70%) |
|      |         | Genotypes 2, 3 (82%) |
| 2002 | PegInterferon-alfa-2a | Genotype 1 (14%) |
|      |         | Genotypes 2, 3 (47%) |
| 2003 | Pegylated alfa-2a/ribavirin | Genotype 1 (14%) |
|      |         | Genotypes 2, 3 (47%) |
| 2011 | Boceprevir/PEG/RBV | Genotype 1 (79%) |
| 2011 | Telaprevir/PEG/RBV | Genotype 1 (79%) |
| 2013 | Simeprevir/PEG/RBV | Genotype 1 (up to 80%) |
| 2013 | Sofosbuvir/PEG/RBV | Genotype 1 (up to 92%) |
|      |         | Genotype 4 (92%) |
| 2013 | Sofosbuvir/RBV | Genotype 2 (up to 100%) |
|      |         | Genotype 3 (up to 92%) |
| 2014 | Sofosbuvir/simeprevir/RBV | Genotype 1 (up to 92%) |
| 2014 | Sofosbuvir/ledipasvir | Genotypes 1, 4, 5, 6 (up to 100%) |
| 2014 | Ombitasvir/paritaprevir/ritonavir/dasabuvir with/without RBV | Genotype 1 (up to 100%) |
| 2015 | Daclatasvir for use with sofosbuvir | Genotype 3 (up to 98%) |
| 2015 | Ombitasvir, paritaprevir and ritonavir plus RBV | Genotype 4 (up to 100%) |

PEG, pegylated interferon by injection; RBV, ribavirin (pills); HCV inhibitors are pills; SVR, sustained virological response; SVR 12, 24-viral cure.

Reference: http://hcvadvocate.org/treatment/drug-pipeline/#Quick

Table 1. FDA approved medications for treatment of Hepatitis C infections.
their efficacies in treatment of different HCV genotypes are evaluated individually. Recently, the combination of IFN-free DAAs regimens with or without ribavirin is evaluated as “All oral regimens” for treatment of HCV infection in different genotypes with better efficacy and tolerability [13]. The current treatment strategies for HCV are based on HCV genotyping; and HCV RNA load determination before, during, and after antiviral therapy; then selection of agents that are active against the isolated specific HCV genotype [4, 12, 14]. The aim of this review is to compare the efficacy of IFN-based and IFN-free regimens (DAAs combination therapy) on the basis of sustained virological response (SVR) rates in HCV genotypic infections.

Figure 1. Combination of PegIFN-alfa and ribavirin for the treatment of HCV infections according to genotypes [4]. HCV, hepatitis C virus; RNA, ribonucleic acid; RVR, rapid virological response; DAAs, directly acting antivirals; cEVR, complete early virological response.

2. Treatment

The primary goal of HCV treatment is to cure the infection. The obtaining sustained virological response (SVR) is defined as undetectable HCV RNA in 12 weeks (SVR 12) or 24 weeks (SVR 24) after treatment completion. Cure rate, which achieves SVR, is more than 99%. SVR is generally associated with resolution of liver disease in patient without cirrhosis, but the patient with cirrhosis remains risk of life-threatening complications. However, the hepatic fibrosis may regress, and risk of complications like hepatic failure and portal hypertension is reduced. The risk of HCC and all causes of mortality are significantly reduced, nevertheless, not eliminated in cirrhotic patients who clear HCV compared to untreated patients and non-sustained
virological responders [4, 15–17]. The endpoint of therapy is an SVR after therapy as assessed by sensitive molecular method with the lower limit of HCV RNA detection ≤15 International Units/ml (IU/ml) [4, 12, 14].

2.1. Efficacy of IFN-based versus IFN-free regimens for treatment of HCV genotype 1 infections

HCV genotype 1 infection is the most prevalent genotype among all genotypes [8]. So, the drug trials are also largely assessed on this genotype. Previously, the combination of PegIFN alfa with ribavirin was widely used. However, after the introduction of directly acting antiviral (DAA) agents, either they were used in combination with PegIFN and ribavirin or they were used in combination with themselves as two DAAs or four DAAs regimen. The efficacy and tolerability were superior to the previously standard regimen (PegIFN alfa and ribavirin) and also duration was significantly reduced from 24–72 to 12–24 weeks. The IFN-free regimens were better preferred due to higher efficacy rate and fewer adverse effects compared to combination of PegIFN regimens. However, we cannot exclude the fact that PegIFN and ribavirin remain the ultimate option in setting where no other options are available [4, 12, 14]. The different regimens and their efficacy for treatment of genotype 1 infection are given in Table 2.

| Treatment regimens | Naïve (SVR) | Treatment-experienced (SVR) | Partial responders | Null responders | Relapsers |
|--------------------|-------------|-----------------------------|--------------------|----------------|----------|
| PegIFN alfa/ribovirin | SVR 24/48: 42–46% SVR: 49% in North America and 50% Western Europe | – | – | – | – |
| PegIFN/RBV + boceprevir | SVR 24/44wks (NB): 67–68% (B): 42–53% | SVR32: 59–66% SVR44: 88% | – | – | – |
| PegIFN/RBV + telaprevir (in previously untreated patients) | T12PR: 75% T8PR: 69% T12PR24: 61% T12PR48: 67% PWID: 71% Non-PWID: 72% | – | 68% | 46% | – |
| PegIFN alfa/RBV + simeprevir | SVR12: 80% (overall) (1a–71%, 1b–90%) NCN: 81% | – | SVR 24: 48–86% (1a-42%, 1b-58%) | SVR 24: 38–59% (1a-42%, 1b-58%) | SVR24: 77–89% C: 73% NCN: 44% NCN: 79.2% |
| PegIFN alfa/RBV + sofosbuvir | SVR12: 89% (overall) (1a-92%, 1b-82%) | – | – | | – |
The combination of pegylated interferon alpha and ribavirin was a standard regimen previously in treatment of hepatitis C genotype 1 infection. The main drawback with this regimen was longer duration of treatment course, that is, 24–72 weeks. With this regimen, HCV genotype 1 infected patient had SVR rates of approximately 40% in North America and 50% in Western Europe. The SVR rate was comparatively lower in genotype 1 than other genotypes.

### Table 2. Efficacy of IFN-based vs. IFN-free regimens for treatment of HCV genotype 1 infections.

| Treatment regimens                  | Naive (SVR)                  | Treatment-experienced (SVR) | Partial responders | Null responders | Relapers |
|-------------------------------------|------------------------------|----------------------------|--------------------|-----------------|----------|
| Sofosbuvir+ simeprevir              | SVR12: 91% (+RBV) 95% (−RBV)| SVR12: 87% (NC) 76% (C)    | –                  | Non-responders 91% | –        |
|                                     | SVR12: 88% (NC) 75% (C)     |                            |                    |                 |          |
| Sofosbuvir + ledipasvir             | SVR8 (NC): 94% (−RBV) 93% (+RBV) 95% (+RBV* 12wks) | SVR12: 94% (−RBV) 96% (+RBV) | SVR24: 99% (−RBV) 99% (+RBV) | –      | –       |
|                                     | SVR12: 99% (−RBV) 97% (+RBV) |                            |                    |                 |          |
|                                     | SVR24: 98% (−RBV) 99% (+RBV) |                            |                    |                 |          |
| Sofosbuvir + daclatasvir            | NC: 100% (±RBV)              |                            | –                  | NC: 100% (+RBV) | –        |
|                                     | Cirrhotic:                   |                            |                    |                 |          |
|                                     | SVR12: 84.9%                 |                            |                    |                 |          |
|                                     | SVR24: 93.4%                 |                            |                    |                 |          |
| Sofosbuvir + velpatasvir            | –                            | SVR12 (overall): 98% (1a) 99% (1b) | –                  | –              | –        |
| Ritonavir-boosted paritaprevir, ombitasvir, dasabuvir ± RBV | SVR12-1a (NC): 95–97% (±RBV) 90% (−RBV) 91% (+HIV) | SVR12 (NC): 96% (1a) 97% (1b) | NC: 100% | NC: 95% | NC: 95% |
|                                     | SVR12-1b (NC): 98–100% (−RBV) 97–100% (±RBV) | CC: SVR12: 92% SVR24: 96% |                    |                 |          |
|                                     | SVR12 (C): 92% (1a) 99% (1b) |                            |                    |                 |          |

PegIFN alfa-pegylated interferon-alfa; RBV-ribavirin; T12PR-telaprevir, pegylated interferon-alfa and ribavirin for 12 weeks; T12PR24-telaprevir, pegylated interferon-alfa and ribavirin for 12 weeks, then pegylated interferon-alfa and ribavirin for remaining 12 weeks (total 24 weeks); T12PR48-telaprevir, pegylated interferon-alfa and ribavirin for 12 weeks then pegylated interferon alfa and ribavirin for remaining 36 weeks (total 48 weeks); NCN, non-cirrhotic naïve; C, cirrhotic; CC, compensated cirrhosis; NB, non-black patients; B, Black patients; PWID, people who inject drugs; SVR 4/8/12/24/48, sustained virological response at 4 weeks, 8 weeks, 12 weeks, 24 weeks or 48 weeks; (+) RBV, with ribavirin; (−) RBV, without ribavirin; (±) RBV, with or without ribavirin

2.1.1. Pegylated interferon alpha and ribavirin

The combination of pegylated interferon alpha and ribavirin was a standard regimen previously in treatment of hepatitis C genotype 1 infection. The main drawback with this regimen was longer duration of treatment course, that is, 24–72 weeks. With this regimen, HCV genotype 1 infected patient had SVR rates of approximately 40% in North America and 50% in Western Europe. The SVR rate was comparatively lower in genotype 1 than other genotypes. The
previous studies showed SVR of 42–46% infected with genotype 1, treated for 24 or 48 weeks [18, 19]. The HIV co-infected patients had SVR of 40% with this regimen [20]. This regimen is contraindicated in patients with uncontrolled depression, psychosis, or epilepsy, pregnant women or couples unwilling to comply with adequate contraception, severe concurrent medical diseases and co-morbidities including retinal disease, autoimmune thyroid disease, and decompensated liver disease. In patient with hepatitis B co-infection, this regimen is used as monoinfected patients, although there is a potential risk of hepatitis B infection reactivation during HCV clearance [12].

2.1.2. Boceprevir in combination with pegylated interferon alfa and ribavirin

Boceprevir is a first generation NS3/4A protease inhibitors (PIs) approved by FDA in 2011. Introduction of PIs constituted a milestone in treating CHC infection, achieved SVR rates of up to 75% in naïve and 29–88% in treatment-experienced patients with GT-1 infection [21, 22]. However, low genetic barrier to resistance is the main limitation. Introduction of newer DAAs replaced the choice of this regimen. The phase 1 and 2 double blind studies carried out for untreated HCV genotype 1 infection in non-black and black populations who were treated for 24–44 weeks showed SVR of 67–68 and 42–53%, respectively [23]. Another study of 403 patients previously treated with PegIFN alfa/RBV regimen, the triple therapy with boceprevir for 32–44 weeks showed SVR of 59–66%. Among patients with an undetectable HCV RNA level at week 8, SVR was 86 and 88% after 32 and 44 weeks of triple therapy, respectively [24]. A study done in 179 cases who inject drugs (PWID) versus non-PWID with this regimen showed SVR of 71 and 72%, respectively. Among them, 53% were advanced stage (F3–4) and 44% were on antiviral therapy [25]. The main side effect of this regimen was anaemia 21–46% for which erythropoietin has to be used or treatment had to discontinue 1–2% [24].

2.1.3. Telaprevir in combination with pegylated interferon alfa and ribavirin

Telaprevir is a first generation NS3/4A protease inhibitors (PIs) approved by FDA in 2011. Telaprevir, a protease inhibitor specific to the HCV non-structural 3/4A serine protease, rapidly reduced HCV RNA levels in early studies. A study with this regimen grouped into Telaprevir/PegIFN alfa/RBV (TPR) 12 weeks; T12PR24; and T12PR48 showed sustained virological response of 35, 61 and 67%, respectively [26]. In phase 3 trial with triple therapy in previously untreated genotype 1 infected cases showed T12PR and T8PR SVR of 75 and 69%, respectively [27]. Previously in non-responders and partial responders, the SVR of 44 and 70%, respectively, was achieved [28]. A study done in 179 cases who inject drugs (PWID) versus non-PWID with this regimen showed SVR of 71 and 72%, respectively. Among them, 53% were advanced stage (F3–4) and 44% were on antiviral therapy [25]. The main adverse effect 10–21% with telaprevir was anaemia, gastrointestinal side effect, and skin rash. Rash was the most common reason for discontinuation of therapy [26, 27].

2.1.4. Simeprevir in combination with pegylated interferon alfa and ribavirin

Simeprevir (TMC435) is an oral HCV NS3/4A protease inhibitor used in combination with PegIFN alfa and ribavirin to treat HCV genotype 1 infected patients. This combination is
generally well tolerated with potent antiviral activity and pharmacokinetic profile. In ASPIRE phase IIb trial done in previously treated patients with PegIFN and ribavirin, the SVR at 24 weeks was 38–59% (1a-42 and 1b-58%) in prior null responders, 48–86% (1a-56 and 1b-88%) in prior partial responders, and 77–89% (no difference) in prior relapsed cases. There were same SVR rates in patient with or without Q80K polymorphism at baseline 60.9%. In patients with cirrhosis (METAVIR score F4), combination therapy with 150 mg of simeprevir had SVR rate at 24 weeks was 73% in prior relapsers, 82% in prior partial responders, and 31% in prior null responders [29]. Another phase 3 trial on partials and null responders showed SVR of 70 and 44%, respectively [28]. According to QUEST 1 & 2 phase 3 study, overall SVR 12 in previously untreated and treated naïve patients was 81 (209/257) and 80% (1a-71 and 1b-90%). On subtype analysis, SVR rates on with or without Q80K polymorphism at baseline in 1a were 52–75 and 80–85%, respectively, and 82% in 1b. The SVR rates were comparatively higher in F0–2 83–85% than F3–4 66–70% [30, 31]. In patients who relapsed on previous therapy, the SVR 12 was 79.2%. Among them, 92.7% were enabled to shorten therapy with PR at 24 weeks [32]. The cause of treatment failure with this regimen was viral breakthrough in 10.6–13%. The main side effects were fatigue, headache, pruritus, and influenza like illness and anaemia. Skin rash and photosensitivity were also very common with simeprevir [29–32].

2.1.5. Sofosbuvir in combination with pegylated interferon alfa and ribavirin

Sofosbuvir is a nucleotide analogue HCV NS5B polymerase inhibitor with similar in vitro activity against pan-HCV genotypes. This therapy is used for HCV pan-genotype infections (1–6 genotypes) treatment-naïve patients with or without cirrhosis but no evidence on treatment-experienced patients. In the NEUTRINO phase III trial in treatment-naïve patients, the overall SVR rate was 89% (259/291), 92% (207/225) for subtype 1a and 82% (54/66) for subtype 1b. Cirrhotic patients had a lower SVR rate than non-cirrhotic patients (80 vs. 92%, respectively) [33]. According to two large-scale US real-life studies, the overall SVR4 rate was 85% (140/164, treatment-naïve—55% and treatment-experienced—45%). SVR4 rate was 90% (114/127) in non-cirrhotic compared to 70% (26/37) in cirrhotic patients [34]. In TRIO real-life study including treatment-naïve (58%) and treatment-experienced (42%), SVR12 was 81 (112/138) and 81% (25/31) in non-cirrhotic and cirrhotic treatment-naïve patients, respectively, and 77% (30/39) in non-cirrhotic treatment-experienced and 62% (53/85) in cirrhotic treatment-experienced patients [21].

2.1.6. Sofosbuvir and simeprevir plus ribavirin

In COSMOS study, the combination of sofosbuvir and simeprevir with or without ribavirin for 12 or 24 weeks was assessed in naïve or null responders infected with genotype 1 patient without severe fibrosis. SVR12 was achieved in 91% (98/108) with ribavirin vs. 95% (56/59) of those who did not. SVR rates were similar by treatment status, treatment-naïve 95% (38/40) vs. previous non-responders 91% (116/127) or treatment duration 94% (77/82) after 12 weeks vs. 91% (77/85) after 24 weeks. Neither ribavirin nor treatment duration had clear effect on sustained virological response in HCV-infected patients with Gln80Lys polymorphism at baseline [22]. In TRIO real-life study, SVR12 achieved in 88% (68/88) of non-cirrhotic treatment-naïve and
75% (41/55) of cirrhotic treatment-naïve patients, whereas 87 (64/74) and 76% (53/70) in non-cirrhotic and cirrhotic treatment-experienced patients, respectively [21].

2.1.7. **Sofosbuvir and ledipasvir plus ribavirin**

Three phase III trials ION-1-3 have assessed the combination of sofosbuvir with ledipasvir, an NS5A inhibitor with or without ribavirin in genotype 1 infected populations. In naïve patients, including 16% compensated cirrhotic populations in ION-1 showed SVR12 in 99 (211/214) and 97% (211/217) patients after 12 weeks combination therapy without or with RBV, respectively. The SVR12 rate was 98% (212/217) in without RBV and 99% (215/217) in with RBV after 24 weeks [35]. In ION-3, non-cirrhotic treatment-naïve patients, SVR12 was 94% (202/215) without RBV for 8 weeks, 93% (201/216) with RBV for 8 weeks, and 95% (205/216) without RBV for 12 weeks. However, relapse rates were higher in 8 weeks compared to 12 weeks therapy [36]. In ION-2, in treatment-experienced patients including 20% cirrhotic patients, overall SVR12 rates were 94 (102/109) and 96% (107/111) without or with RBV, respectively. The SVR rates were 99 (108/109) and 99% (110/111) without or with RBV after 24 weeks, respectively [37]. The different phase III studies were not powered to compare responses to regimens with or without RBV or to 12 weeks or 24 weeks of treatment [38].

2.1.8. **Sofosbuvir and daclatasvir**

Daclatasvir is a potent, pan-genotypic NS5A inhibitor with antiviral activity against HCV genotypes 1–6 in vitro [39], combined with sofosbuvir for treatment of hepatitis C. In phase IIb trial in patient without cirrhosis, the 24 weeks of therapy achieved SVR rates of 100% (14/14 and 15/15) without or with ribavirin, respectively, in treatment-naïve patients, and 100% (21/21) without ribavirin and 95% (19/21) with ribavirin non-responders to combination therapy of PegIFN alfa, ribavirin, and either telaprevir or boceprevir. Whereas SVR rates were achieved in 98% (40/41) of treatment-naïve without ribavirin after 12 weeks of therapy [40]. In phase II clinical trial, the efficacy of sofosbuvir plus daclatasvir with or without ribavirin for 12 or 24 weeks has been evaluated in large real-life cohort including genotype 1 cirrhotic patients. The SVR12 rates were 84.9% after weeks and 93.4% after 24 weeks of treatment. However, majority of analyses performed on data available after 4 weeks of follow up showed SVR4 rates of 85.2% with 12 weeks and 95.1% with 24 weeks of treatment without RBV, whereas 100% with 12 weeks and 98.7% with 24 weeks treatment with RBV [41]. In cirrhosis, the addition of RBV improved SVR, SVR4 of 76.5% with 12 weeks vs. 94% with 24 weeks without RBV treatment, which rose to 100 and 98.3%, respectively, with RBV. In non-cirrhotic patients, SVR4 achieved in all regardless of use of RBV or treatment duration. Without RBV, SVR4 in treatment-naïve after 12 or 24 weeks was 87.1 vs. 88.7%; however, rates increased to 100% (for both duration) with addition of RBV. In treatment-experienced patients, SVR4 without or with RBV after 12 weeks was 82.6 vs. 100%, and after 24 weeks 96.7 vs. 98.5% [41].

2.1.9. **Sofosbuvir and velpatasvir**

Velpatasvir is a new pangenotypic HCV NS5A inhibitor with antiviral activity against HCV replicons in genotype 1–6 infections. The combination of sofosbuvir and velpatasvir for
12 weeks has been assessed in ASTRAL phase 3 trial in previously treatment-experienced patients (PegIFN/RBV with PIs) including cirrhosis, relapsed cases, patients who had detectable HCV RNA after PegIFN and ribavirin treatment. The overall sustained virological response rate was 98% in subtype 1a and 99% in subtype 1b infected patients [42]. In phase II trial in treatment-experienced patients including 50% cirrhosis and treatment failure, the combination of sofosbuvir and velpatasvir with or without ribavirin was assessed. The SVR showed 100% in without ribavirin and 96% in with ribavirin treatment patients [43]. The overall relapse rate was very low, and this regimen was well tolerated in treatment-experienced patient including cirrhosis [42, 43].

2.1.10. Ritonavir boosted paritaprevir, ombitasvir, and dasabuvir

In seven phase III trials, in non-cirrhotic treatment-naïve patients, SAPPHIRE-I trial with combination therapy with RBV for 12 weeks showed SVR of 95% (307/322) in subtype 1a and 98% (148/151) in subtype 1b infected patients [44]. In PEARL-IV trial, the combination therapy without or with RBV showed SVR of 90 (185/205) vs. 97% (197/100) in subtype 1a treatment-naïve patients, respectively [45]. In PEARL-III trial in non-cirrhotic treatment-naïve of subtype 1b patients, SVR12 rates were 99% (207/209) without RBV vs. 99% (209/210) with RBV [45]. TURQUOISE-I study in non-cirrhotic treatment-naïve patients co-infected with HIV-1 (stable on antiviral treatment – atazanavir or raltegravir), SVR12 rates were 93% (29/31) after 12 weeks vs. 91% (29/32) after 24 weeks of treatment. The SVR12 rates based on subtypes 1a and 1b were 91 (51/56) and 100% (7/7), respectively [46]. In SAPPHIRE-II trial, non-cirrhotic treatment-experienced patients (PegIFN-alfa and RBV failures) were treated with this regimen in combination with RBC for 12 weeks. The SVR12 rates were 96% (166/173) in subtype 1a vs. 97% (119/123) in subtype 1b. The overall SVR12 rates were 95% (82/86) in prior relapers, 100% (65/65) in partial responders, and 95% (139/146) in null responders [47]. In PEARL-II trial, SVR12 achieved in 100% (91/91) without RBV vs. 97% (85/88) with RBV in subtype 1b infected patients [48]. In compensated cirrhotic treatment-naïve and treatment-experienced patients, the SVR rates were 92% (191/208) after 12 weeks vs. 96% (165/172) after 24 weeks of treatment with RBV in TURQUOISE-II trial. The SVR12 rates were 92% (239/261) in subtype 1a vs. 99% (118/119) in subtype 1b infected patients [49].

2.2. Efficacy of IFN-based versus IFN-free regimens for treatment of HCV genotype 2 infections

HCV genotype 2 is the third most prevalent genotype worldwide [8]. Although PegIFN alfa with ribavirin used previously, IFN-free combination of sofosbuvir with ribavirin is the best first line treatment option in genotype 2 infection [12]. Other regimens, IFN-based or IFN-free could be an option in cases who fail with this regimen (Table 3). The combination of PegIFN alfa and ribavirin remains acceptable when all other options are not available [12, 14].

2.2.1. Pegylated interferon alfa and ribavirin

The initial treatment of HCV genotype 2 began with PegIFN alfa alone or combination of PegIFN alfa and ribavirin. Although sustained virological response rate was lower than recent
newer regimens, this regimen remains acceptable for treatment of genotype 2 where other options are not available [12]. In randomised study, the sustained virological response rates were 62% (232/372) in 16 weeks vs. 75% (268/356) in 24 weeks treatment course. The chances of relapse rates were higher among 16 weeks than 24 weeks [30]. In phase IV single arm study, 24 weeks therapy with this regimen in previously untreated naïve patients showed end of treatment (EOT) and SVR of 100 and 93%, respectively [51]. In phase III multicenter study in prior relapers who were retreated for 24–48 weeks showed a sustained virological response rates of 53–81% in 48 weeks retreated patients vs. 75% in 24 weeks retreated patients [52].

| Treatment regimens | Naïve | Treatment-experienced | Partial responders | Null responders | Relapers |
|--------------------|-------|-----------------------|--------------------|----------------|----------|
| PegIFN alfa/ribavirin | SVR 24: 62% (16 weeks) 75% (24 weeks) | SVR24: 75% SVR48: 53–81% (48 weeks) | – | – | – |
| PegIFN/RBV + sofosbuvir | SVR12: 92% | SVR12: 96% (overall) | – | – | – |
| Sofosbuvir + ribavirin | SVR12: 93–100% (overall) 93–97% (NC) 83–100% (C) | SVR12: 91% (NC) 88% (C) | SVR12: 94% (overall) | – | – |
| | SVR12: 82% (NC) 60% (C) | SVR16: 89% (NC) 78% (C) | – | – | – |
| Sofosbuvir + daclatasvir | SVR12: 92% | – | – | – | – |
| Sofosbuvir + velpatavir | – | SVR12: 99% (overall) | – | – | – |

PegIFN, pegylated interferon-alfa; RBV, ribavirin; EOT, end of treatment; SVR12/16/24, sustained virological response at 12 weeks, 16 weeks and 24 weeks; NC, non-cirrhotic; C, cirrhotic.

Table 3. Efficacy of IFN-based vs. IFN-free regimens for treatment of HCV genotype 2 infections.

2.2.2. Pegylated interferon alfa and ribavirin plus sofosbuvir

In LONESTAR-2 phase IIb study, in treatment-experienced patients infected with HCV genotype 2 patients including 14 with cirrhosis received therapy for 12 weeks, the sustained virological response rates were 96% [53]. Another study showed that the relapsed cases of sofosbuvir and ribavirin regimen treated for 12 weeks were retreated with this regimen for 12 weeks, achieved SVR [54]. In phase II study in previously untreated naïve patients, the sustained virological responses in 12 or 24 weeks treatment were 92% (23/25) [55]. The main side effects with this regimen were fatigue, headache, nausea, pain, and insomnia [55].
2.2.3. Sofosbuvir and ribavirin

This IFN-free combination therapy is the best first-line treatment option in HCV genotype 2 infected patients [12]. In FISSION trial in treatment-naïve patients who were treated for 12 weeks, the SVR was 95% (69/73). The virological response rate was higher in non-cirrhotic patients, 97 vs. 83% in cirrhotic patients [33]. In POSITRON trial, who were intolerant or ineligible to IFN, treated for 12 weeks, SVR was 93% (101/109) [56]. The 12 vs. 16 weeks therapy was in FUSION trial showed SVR of 82 (32/39) vs. 89% (31/35) in non-cirrhotic and 60 (6/10) vs. 78% (7/9) in cirrhotic cases, respectively. The longer than 12 weeks therapy was beneficial in cirrhotic population [56]. In VALENCE trial, the treatment was given for 12 weeks in treatment-naïve and treatment-experienced patients with or without cirrhosis. In treatment-naïve patients, the SVR rates were 97% (29/30) in without cirrhosis and 100% (2/2) in with cirrhosis. In treatment-experienced patients, SVR rates were 91 (30/33) vs. 88% (7/8) in without cirrhosis and with cirrhosis, respectively [57]. This combination therapy was well tolerated, and no virological breakthroughs were observed in treatment adherent patients [12].

2.2.4. Sofosbuvir and daclatasvir

Daclatasvir, NS5A replication complex inhibitor, is active against HCV genotype 2 in vitro. The combination of sofosbuvir with daclatasvir therapy was observed in phase II trial showed sustained virological response of 92% (24/26) after 12 weeks of therapy and overall 93% after 24 weeks of therapy [40]. Based on data with other, 12 weeks is probably sufficient to treat more difficult-to-cure HCV genotypes. This regimen should be kept reserved for patients who failed with other options in HCV genotype 2 infections [12, 40].

2.2.5. Sofosbuvir and velpatasvir

In 2 phase III trial (open label studies), the combination of sofosbuvir (400 mg) and velpatasvir (100 mg) was assessed in patients infected with HCV genotype 2 who previously received treatment and who did not received previous treatment including compensated cirrhosis. The sustained virological response was achieved in 99% of cases with this regimen [58]. In ASTRAL phase III double blind trial in treatment-experienced patients including cirrhosis, treatment relapsed, and detectable HCV RNA under PegIFN and ribavirin therapy, the SVR12 was 100% in genotype 2 infected patients [42]. From the data available, this regimen was well tolerated with higher SVR in treatment of genotype 2 infection. However, these data have to be compared with the blind trials or studies.

2.3. Efficacy of IFN-based versus IFN-free regimens for treatment of HCV genotype 3 infections

There are four treatment options available for treatment of hepatitis C genotype 3 infection including one phase III trial drug (Table 4). The IFN-based combination therapy-PegIFN alfa and ribavirin regimen remains acceptable only in settings where none other options are available [12]. The triple combination of PegIFN alfa, ribavirin and sofosbuvir appears to be valuable even in, who failed on sofosbuvir and ribavirin combinations. However, it has to be done
in larger population infected with HCV genotype 3 patients [54]. The IFN-free combination therapy—sofosbuvir and ribavirin—appears to be suboptimal particularly in cirrhotic HCV genotype 3 infected patients, although it is the best first line treatment option for genotype 2 infection [12]. Sofosbuvir and daclatasvir with or without ribavirin are a new attractive option for patients infected with genotype 3. Ledipasvir is considerably less potent against genotype 3 in vitro than daclatasvir. In clinical trials, the combination of ledipasvir with sofosbuvir or other agents is not recommended in patients infected with HCV genotype 3 [12, 14].

| Treatment regimens | Naïve | Treatment-experienced Partial responders | Null responders | Relapsers |
|--------------------|-------|------------------------------------------|-----------------|-----------|
| PegIFN alfa/ribavirin | 24 weeks: SVR-79% EOT-93% | – | – | – |
| PegIFN/RBV + sofosbuvir | – | SVR12: 83% (+C) | – | – | SVR12: 91% |
| Sofosbuvir and ribavirin | SVR12: 56–61% (overall) 61% (NC) 34% (C) SVR12 vs. SVR16: 30 vs. 62% (NC) 19 vs. 61% (C) SVR24: 94% (NC) 92% (C) | SVR24: 80% (overall) 87% (NC) 60% (C) | – | – | SVR24: 63% |
| Sofosbuvir and daclatasvir | SVR24: 89% (NC) SVR12 (−RBV): 94% (NC) 69% (C) | SVR12 (−RBV): 94% (NC) 69% (C) | – | – | – |
| Sofosbuvir and velpatasvir | SVR12 (overall): 95% SVR12 (NC): 100% (+RBV) SVR12 (C): 88% (−RBV) 96% (+RBV) | – | – | – |

PegIFN, pegylated interferon-alfa; RBV, ribavirin; SVR 12/24, sustained virological response at 12 weeks and 24 weeks; EOT, end of treatment; NC, non-cirrhotic; C, cirrhotic.

Table 4. Efficacy of IFN-based vs. IFN-free regimens for treatment of HCV genotype 3 infections.

2.3.1. Pegylated interferon alfa and ribavirin

This combination therapy remained acceptable for treatment of genotype 3 infections until the development of other regimens with higher sustained virological response and also in setting where other options are not available [12]. In this regimen, the treatment is given for 24 weeks in genotype 3 infected patients. In phase 4 single arm study in 182 HCV genotype 3
infected population and treatment was given with this regimen for 24 weeks; the overall sustained virological response rate was observed and also at end of treatment (EOT). It showed EOT and SVR were of 93 and 79%, respectively [51]. Baseline viremia, treatment duration >16 weeks, and steatosis were independent predictors of SVR. The relapsed rate were higher among male and older age >55 years [51].

2.3.2. Pegylated interferon alfa and ribavirin plus sofosbuvir

In LONESTAR-2 phase IIb trial, in treatment-experienced patients infected with HCV genotype 3, the sustained virological response rate was 83% (20/24) including (10/12) patients with cirrhosis [53]. However, pangenotypic activity of sofosbuvir together with higher SVR in other genotypes 89% (overall in genotype 1, 4 or 6) indicates this regimen can be safely used in patients with genotype 3 infections [53]. In phase 2 trial, in non-cirrhotic treatment-naïve patients were treated for 12 weeks, the sustained virological response was achieved in 92% (23/25) cases [55]. In another study, patients who relapsed after treatment with sofosbuvir and ribavirin regimens were retreated with this triple combination therapy for 12 weeks, and the SVR was achieved in 91% (20/22) cases [54].

2.3.3. Sofosbuvir and ribavirin

The combination of sofosbuvir with daily fixed dose ribavirin is used for treatment of genotype 3 infection for 24 weeks. In FISSION trial, in treatment-naïve patients who were treated for 12 weeks, the SVR rate was 56% (102/183). The non-cirrhotic patients had better SVR of 61 vs. 34% in cirrhotic patients [33]. In POSITRON trial, patients were also treated for 12 weeks with this regimen who were ineligible or intolerant to interferon. The SVR rate was 61% (60/98) of cases. In FUSION trial, the 12 vs. 16 weeks treatment was compared. The SVR rate was significantly higher, 62% in non-cirrhotic and 61% in cirrhotic patients with 16 weeks treatment compared to 30% in non-cirrhotic and 19% in cirrhotic patient with 12 weeks treatment [56]. In VALENCE trial, treatment was given for 24 weeks in both treatment-naïve and treatment-experienced without or with cirrhosis. In treatment-naïve, the SVR24 was 94% (86/92) in non-cirrhotic and 92% (12/13) in cirrhotic patients. Whereas, in treatment-experienced, SVR 24 was 87% (87/100) in non-cirrhotic and 60% (27/45) in cirrhotic patients [57]. So based on these studies, 24 weeks treatment is appropriate for the HCV genotype 3 infected patients. Another study, in relapsed cases with sofosbuvir and ribavirin, patients were retreated for 24 weeks, achieved SVR only of 63% (24/38) of cases, indicating the regimen is suboptimal in such patients with HCV genotype 3 infection [54].

2.3.4. Sofosbuvir and daclatasvir

In treatment of HCV genotype 3 infected patients, this regimen is given for 12 weeks in non-cirrhotic patients and 24 weeks with daily weight-based ribavirin for 24 weeks in cirrhotic patients. In phase IIb trial, after 24 weeks of combination therapy, SVR rate was 89% (16/18) in treatment-naïve without cirrhosis [40]. In ALLY-3 phase III trial, after 12 weeks of combination therapy without ribavirin, SVR12 was 97% (73/75) in non-cirrhotic and 58% (11/19) in cirrhotic treatment-naïve patients, whereas SVR12 was 94 (32/34) and 69% (9/13) in treatment-experienced patients without or with cirrhosis, respectively [59]. This regimen was well tolerated with rare adverse events, and none of them discontinued treatment [12].
2.3.5. *Sofosbuvir and velpatasvir*

In phase II trial, the combination of sofosbuvir (400 mg) and velpatasvir (100 mg) with or without daily fixed dose ribavirin for 12 weeks was assessed in treatment-experienced patients with or without cirrhosis infected with HCV genotype 3. The sustained virological response was achieved 100% with or without ribavirin in non-cirrhotic patients. However, SVR of 88% without ribavirin and 96% with ribavirin was achieved in compensated cirrhotic patients \[43\]. In another 2 phase III trial (open label studies), in patients infected with genotype 3 who have previously received treatment and who did not receive treatment including compensated cirrhosis, 12 weeks of this regimen without ribavirin achieved SVR of 95% \[58\]. Based on these studies, this regimen was well tolerated in treatment of HCV genotype 3 infections.

2.4. Efficacy of IFN-based versus IFN-free regimens for treatment of HCV genotype 4 infections

There are seven treatment options available for treatment of hepatitis C genotype 4 infections, including two IFN-based regimens and four IFN-free regimens (Table 5). The combination of PegIFN alfa and ribavirin remains acceptable only in that case where other options are not available \[12\].

| Treatment regimens | Naïve | Treatment-experienced | Partial responders | Null responders | Relapsers |
|--------------------|-------|-----------------------|-------------------|----------------|-----------|
| PegIFN alfa/ribavirin | SVR24: 29% | SVR36: 66% | SVR48: 69% | SVR48: 60% | SVR48: 40% | SVR24: 86% |
| PegIFN/RBV + simeprevir | SVR24: 93% | – | – | – | – |
| PegIFN/RBV + sofosbuvir | SVR 12: 96% | – | – | – | – |
| Sofosbuvir + simeprevir | SVR12: >98% (F1–2) | SVR12: 98–100% (F1–2) | 80–97.7% (F3–4) | 88–94.7% (F3–4) | – | – | – |
| Sofosbuvir+ledipasvir | SVR12: 95% (+RBV) | – | – | – | – |
| Sofosbuvir+daclatasvir | – | – | – | – | – |
| Sofosbuvir and velpatasvir | – | SVR12 (overall): 100% (+C/R) | – | – | – |
| Ritonavir boosted paritaprevir, ombitasvir | SVR12: 100% (+RBV) | 90.9% (−RBV) | SVR12 (+RBV): 100% | – | – | – |

PegIFN, pegylated interferon-alfa; RBV, ribavirin; SVR 12/24/36/48, sustained virological response at 12 weeks, 24 weeks, 36 weeks and 48 weeks; (+)C/R, with cirrhosis and relapse; (−)RBV, with ribavirin; (+) RBV, with ribavirin.

Table 5. Efficacy of IFN-based vs. IFN-free regimens for treatment of HCV genotype 4 infections.
2.4.1. Pegylated interferon alfa and ribavirin

The combination of PegIFN alfa and ribavirin is still the option for treatment of HCV genotype 4 when other options are not available [12]. In prospective randomised controlled trial, the combination of PegIFN alfa and ribavirin was used for 24–48 weeks. The sustained virological response rates were 29 vs. 66 vs. 69% in 24 vs. 36 vs. 48 weeks of treatment, respectively [60].

2.4.2. Pegylated interferon alfa and ribavirin plus simeprevir

Simeprevir is active against HCV genotype 4 in vitro. So, this combination therapy can be used in genotype 4 infection. However, the duration of therapy is 24 weeks (SPR 12 + PR 12 weeks) in treatment-naïve or prior relapsers including cirrhosis and 48 weeks (SPR12 + PR 36 weeks) in prior partial or null responders including cirrhosis. In phase III study, SVR12 was achieved in 83% (29/35) in treatment-naïve patients, 86% (19/22) in prior relapsers, 60% (6/10) in prior partial responders, and 40% (16/40) in prior null responders. This regimen was effective in treatment-naïve and prior relapsers, however, suboptimal in prior partial and null responders [61].

2.4.3. Pegylated interferon alfa and ribavirin plus sofosbuvir

In NEUTRINO phase III in treatment-naïve patients, this combination therapy for 12 weeks was evaluated. The SVR rate was 96% (27/28) in HCV genotype 4 infected patients [33]. Those who failed in this combination therapy did not select HCV variants resistant to sofosbuvir. No data were available in treatment-experienced or HIV-coinfected patients [12].

2.4.4. Sofosbuvir and ledipasvir

Sofosbuvir in combination with ledipasvir is used in treatment-naïve and treatment-experienced patients with or without cirrhosis for 12 weeks. Addition of ribavirin to this therapy has beneficial effect in cirrhotic individuals. In SYNERGY trial, efficacy and safety of combination of sofosbuvir and ledipasvir without ribavirin are assessed in patient with genotype 4 infection. The sustained virological response was achieved in 95% (20/21) of cases [62]. The shorter 8 weeks treatment duration as in patients infected with genotype 1 infections is not clear due to lack of data in genotype 4 infected cases [12].

2.4.5. Sofosbuvir and simeprevir

The unavailability of data on treatment of HCV genotype 4 infection had questioned the use of this IFN-free regimen (sofosbuvir plus simeprevir) as an option previously, however, according to a very recently published two studies, sofosbuvir (SOF) plus simeprevir (SIM) regimen with or without ribavirin, can be a good option in treating HCV genotype 4 infected cases [12, 63, 64]. A retrospective multicentre observational study in 53 patients (naïve or experienced patients) including advanced liver fibrosis or liver cirrhosis treated with SOF and SIM with or without ribavirin showed a SVR12 of 92% (49/53). In this study, treatment failures were observed in those who didn’t receive ribavirin and interferon non-responders except one naïve patient [63]. Another multicentre observational study in 583 patients infected with HCV
genotype 4 showed the overall SVR rates of 95.7% (558/583) with SOF/SIM regimen. Based on fibrosis stages in naïve patients, mild fibrosis score had better SVR12 of 98.9% (94/95) in F1 and 98.1% (105/107) in F2 stage than severe fibrosis score with SVR12 of 97.7% (86/88) in F3 and 80.8% (42/52) in F4 stage. While in treatment-experienced patients with severe fibrosis score, SVR12 was 94.7% (72/76) in F3 and 88.9% (40/45) in F4 stage. In addition, patients who were previously treated with interferon had SVR of 100% (45/45) in F1 and 98.7% (74/75) in F2 mild fibrosis score [64]. Therefore, this regimen can be efficacious and well tolerated in treatment-naïve and experienced patients including severe fibrosis score or liver cirrhosis. Furthermore, the addition of ribavirin could be considered especially in treatment-experienced and advanced cirrhosis patients as recommended by recent AASL and EASL guidelines [12, 14, 63, 64].

2.4.6. Sofosbuvir and daclatasvir

Daclatasvir has its antiviral activity against genotype 4 in vitro. The combination of sofosbuvir and daclatasvir with or without ribavirin is effective in treating patients infected with HCV genotype 4. However, there is no data available with this combination in treatment of this genotype. Nevertheless, both sofosbuvir and daclatasvir have antiviral effectiveness against genotype 4 in vitro. So, the results in patients infected with genotype 1 can be extrapolated [12].

2.4.7. Sofosbuvir and velpatasvir

Velpatasvir and sofosbuvir have a pangenotypic action for treatment of HCV genotype 1–6 infections. The combination of sofosbuvir and velpatasvir assessed in ASTRAL phase 3 trial in previously treatment-experienced patients (PegIFN/RBV with PI) including cirrhosis, relapsed cases, patients who had detectable HCV RNA after PegIFN and ribavirin treatment. The overall sustained virological response rate was 100% in genotype 4 infected patients. The overall relapse rate was very low, and this regimen was well tolerated in treatment-experienced patient including cirrhosis [42].

2.4.8. Ritonavir-boosted paritaprevir and ombitasvir

A fixed dose ritonavir, paritaprevir, and ombitasvir with or without ribavirin treatment for 12–24 weeks were assessed in treatment-naïve and treatment-experienced patients with or without compensated cirrhosis infected with HCV genotype 4. According to PEARL-I trial in non-cirrhotic chronic HCV genotype 4 infected patients, sustained virological response rates were 100% in treatment-naïve (42/42) and treatment-experienced patients (49/49) with ribavirin regimen, whereas 90.9% (40/44) in treatment-naïve patients without ribavirin regimen for 12 weeks [65]. In AGATE-I trial with a fixed dose ritonavir, paritaprevir, and ombitasvir plus ribavirin in chronic HCV genotype 4 infected treatment-naïve and treatment-experienced patients including compensated cirrhosis, post-treatment sustained virological response rates were 97% (57/59) in 12 weeks and 98% (60/61) in 16 weeks group [66]. In addition, AGATE-II trial in Egyptian patients, SVR12 was 94% (94/100) in patients without cirrhosis, whereas SVR12 of 97% (30/31) and SVR24 of 93% (27/29) in patients with cirrhosis [67]. Extension of this treatment regimen beyond 12 weeks (16 and 24 weeks) for HCV genotype 4 infected patients.
patients with compensated cirrhosis seemed to have no additional benefits [66, 67]. This regimen was generally well tolerated by chronic HCV genotype 4 infected patients with or without compensated cirrhosis in clinical trials, so this regimen is a valuable option, although having postmarking reports of hepatic decompensation and hepatic failure mainly in patients with advanced cirrhosis [68].

2.5. Efficacy of IFN-based versus IFN-free regimens for treatment of HCV genotypes 5 or 6 infections

HCV genotype 5 is the least prevalent worldwide and then genotype 6 infection [8]. The treatment options for these genotypes are one IFN-based triple combination of PegIFN alfa, ribavirin, and sofosbuvir; and three IFN-free combination therapy: sofosbuvir and ledipasvir, sofosbuvir and daclatasvir, and sofosbuvir and velpatasvir (Table 6). IFN-based combination of PegIFN-alfa and ribavirin remains acceptable in setting where other treatment options are not available [12].

| Treatment Regimens | Naïve | Treatment-experienced | Partial responders | Null responders | Relapsers |
|--------------------|-------|-----------------------|-------------------|----------------|-----------|
| PegIFN/RBV + sofosbuvir | SVR12: 90% | – | – | – | – |
| Sofosbuvir and ledipasvir | SVR (GT-5): 95% | SVR12 (TN+TE): 96% (overall) | SVR (GT-5): 95% | – | – |
| Sofosbuvir and daclatasvir | – | – | – | – | – |
| Sofosbuvir and velpatasvir | SVR12 (overall): 96% | SVR12 (overall): 97% (GT-5) 100% (GT-6) | – | – | – |

PegIFN, pegylated interferon alfa; RBV, ribavirin; GT-5, genotype 5; GT-6, genotype 6; SVR12, sustained virological response at 12 weeks; TN+TE, treatment-naïve and treatment-experienced.

Table 6. Efficacy of IFN-based vs. IFN-free regimens for treatment of HCV genotype 5 or 6 infections.

2.5.1. Pegylated interferon alfa and ribavirin plus sofosbuvir

In NEUTRINO phase III trial, this combination therapy has been evaluated in treatment-naïve patients. There were total seven patients (one infected genotype 5 and six infected with genotype 6), all patients achieved sustained virological response [33]. However, no data have been presented with this regimen in treatment-experienced patients. So, it is not clear whether longer duration of treatment is needed [12].

2.5.2. Sofosbuvir and ledipasvir

Ledipasvir is active against both genotype 5 or 6 in vitro. The combination of sofosbuvir and ledipasvir is used in treatment of these genotypes. Those patients without cirrhosis,
including treatment-naïve and treatment-experienced should be treated for 12 weeks without ribavirin. Addition of ribavirin is recommended in cirrhotic cases. However, 24 weeks combination of sofosbuvir and ledipasvir is recommended, when ribavirin is contraindicated or with poor tolerance [12]. In multicentre open label phase II trial, in treatment-naïve and treatment-experienced patients infected with genotype 5 including cirrhosis, the overall SVR was 95% (39/42). The SVR was 95% (20/21) in treatment-naïve and 95% (19/20) in treatment-experienced patients. However, SVR was 97% (31/32) in non-cirrhotic vs. 89% (8/9) in cirrhotic patients [69]. In phase 2 clinical trial, in treatment-naïve and treatment-experienced patients infected with HCV genotype 6, the 12 weeks treatment with this regimen without ribavirin had a sustained virological response of 96% (24/25) [12, 70].

2.5.3. Sofosbuvir and daclatasvir

Daclatasvir and sofosbuvir are active against genotype 5 or 6 in vitro. This regimen is given for 12 weeks with or without ribavirin in these genotypes. However, in cirrhotic patients with contraindications or intolerance to ribavirin, combination therapy can be extended to 24 weeks. There were no data available with this regimen for these rare genotypes [12].

2.5.4. Sofosbuvir and velpatasvir

The combination of sofosbuvir (400 mg) and velpatasvir (100 mg) for 12 weeks was assessed in ASTRAL phase III trial for treatment of genotypes 5 and 6. In this double blind, placebo controlled trial, patients were previously treatment-experienced (PegIFN and ribavirin or PegIFN, ribavirin and protease inhibitors), relapsed cases, and who had persistent detectable HCV RNA on PegIFN alfa and ribavirin therapy. The sustained virological response achieved in patients infected with genotypes 5 and 6 were 97 and 100%, respectively. This regimen was well tolerated, with very low failure rate in treatment of HCV genotype 5 and 6 infections [42]. In another randomised trial, the overall sustained virological response was 95% in treatment-naïve patients [71].

3. Discussion

The development of DAAs was the milestone in the treatment of chronic hepatitis C, and their combination therapy became the first option for almost all genotypes. However, the IFN-based combination therapies have their own role in treatment of chronic hepatitis C infections when DAAs combination regimens are unavailable or fails [12]. In genotype 1 infections, the IFN-based combination therapy: PegIFN alfa, RBV, and simeprevir, and PegIFN, RBV, and sofosbuvir combination had higher overall SVR of 60–90% including relapers or partial/null responders compared to other three regimens. In IFN-free regimens, all the DAAs combination regimens (2/4 DAAs ± RBV) have overall SVR of above 90% [12, 14]. The combination of sofosbuvir with ledipasvir or daclatasvir velpatasvir or 4DAAs (ritonavir, paritaprevir, ombitasvir, & dasabuvir) had superior SVR rates compared to IFN-based regimens [35, 36, 40, 42, 44]. In HCV genotype 2 infections, though PegIFN alfa with RBV and sofosbuvir has higher SVR >90%, the combination of sofosbuvir and ribavirin is the first line regimen for its treatment [33]. Although combination of sofosbuvir with daclatasvir or velpatasvir has SVR > 90%, they are reserved for treatment
failed options with first line drugs [40–43]. In genotype 3 infections, the combination of sofosbuvir and ribavirin is suboptimal [54], so IFN-based PegIFN/RBV/SOF regimen or IFN-free combination of SOF and daclatasvir becomes the choice of treatment [40, 54, 59]. The phase 3 trials, sofosbuvir and velpatasvir have higher SVR, so it might be the choice of regimen in future [43, 58]. In genotype 4 infections, IFN-based PegIFN, RBV with simeprevir or sofosbuvir have SVR > 90% in treatment-naïve cases. However, SVR in partial or null responders is suboptimal [33, 61]. The IFN-free two DAAs or three DAAs with or without RBV has overall SVR > 90%, although no data available for partial or null responders or relapsers cases [42, 62, 65, 72]. In genotype 5 or 6 infections, IFN-based PegIFN/RBV/SOF has SVR of 90% in treatment-naïve [33]. However, two DAAs combinations have better SVR of > 95% [12, 43, 69, 70]. In this review, it showed that IFN-free DAAs regimens have better SVR and well tolerated compared to IFN-based regimen. The combination of DAAs with or without ribavirin has almost replaced the IFN-based combination therapy in present context. Nevertheless, we cannot exclude the fact that the combination of PegIFN alfa and ribavirin still leaves us an ultimate option in setting where all other options are not available [12, 14].

4. Conclusion

The combination of IFN-free DAAs regimens has superior in their efficacy and tolerability compared to IFN-based regimens in case of treatment of chronic hepatitis C in all genotypes. However, in genotypes 3, 4, 5 or 6, the IFN-based combination of pegylated interferon alfa, ribavirin, and sofosbuvir can be an option in case of treatment failure with DAAs first line regimens. Nevertheless, this is not mentioned in the retreatment guidelines, and this is just an assumed recommendation that needs to be evaluated in trials.

Authors’ contributions

All the authors have equally contributed to research design, editing, and finalising of this chapter.

Conflict of interest statement

The authors declared that there is no conflict of interest regarding the publication of this chapter.

Acknowledgements

This study was supported by the grants from the National Natural Science Foundation of China (No. 81370559), Shanghai major joint project for important diseases (2014ZYJB0201), and Shanghai joint project with advanced technology (SHDC12014122).
Abbreviations

HCV                    hepatitis C virus  
WHO                    World Health Organisation  
DAA                    directly acting antivirals  
IFN                    interferon  
SVR                    sustained virological response  
CHC                    chronic hepatitis C  
AHC                    acute hepatitis C  
HCC                    hepatocellular carcinoma  
GT                     genotype  
PWID                   persons who inject drugs  
MSM                    men who have sex with men  
HIV                    human immunodeficiency virus  
RBV                    ribavirin  
SVR12/24/48            sustained virological response at 12, 24, and 48 weeks  
PegIFN alfa             pegylated interferon alfa  
PIs                    protease inhibitors  
TPR                    telaprevir/pegylated interferon alfa/ribavirin  
EOT                    end of treatment  

Author details

Ramesh Rana, Yizhong Chang, Jing Li, ShengLan Wang, Li Yang and ChangQing Yang*

*Address all correspondence to: cqyang@tongji.edu.cn

Division of Gastroenterology and Hepatology, Digestive Disease Institute, Tongji Hospital, Tongji University School of Medicine, Shanghai, PR China

References

[1] World Health Organization. WHO Guidelines Approved by the Guidelines Review Committee. In: Guidelines for the Screening Care and Treatment of Persons with Chronic Hepatitis C Infection: Updated Version. Edn. Geneva: World Health Organization. 2016. PMID: 27227200.

[2] Chopp S, Vanderwall R, HUIT A, Klepser M: Simeprevir and sofosbuvir for treatment of hepatitis C infection. Am J Health Syst Pharm 2015, 72(17), p1445–1455. DOI: 10.214/ajhp140290
[3] Thomson EC, Fleming VM, Main J, Klenerman P, Weber J, Eliahoo J, Smith J, McClure MO, Karayiannis P: Predicting spontaneous clearance of acute hepatitis C virus in a large cohort of HIV-1-infected men. Gut 2010:gut. 2010, 60(6): 837–845. DOI: 10.1136/gut.2010.217166

[4] Mauss S, Berg T, Rockstroh J, Sarrazin C, Wedemeyer H: Hepatology – A Clinical Textbook 2016, 356. http://www.hepatologytextbook.com/download/hepatology2016.pdf.

[5] Coppola N, Pisaturo M, Zampino R, Macera M, Sagnelli C, Sagnelli E: Hepatitis C virus markers in infection by hepatitis C virus: In the era of directly acting antivirals. World J Gastroenterol 2015, 21(38):10749. DOI: 10.3748/wjg.v21.i38.10749

[6] 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(2):418–431. DOI: 10.1002/hep.22375

[7] Smith DB, Bukh J, Kuiken C, Muerhoff AS, Rice CM, Stapleton JT, Simmonds P: Expanded classification of hepatitis C virus into 7 genotypes and 67 subtypes: Updated criteria and genotype assignment web resource. Hepatology 2014, 59(1):318–327. DOI: 10.1002/hep.26744

[8] Messina JP, Humphreys I, Flaxman A, Brown A, Cooke GS, Pybus OG, Barnes E: Global distribution and prevalence of hepatitis C virus genotypes. Hepatology 2015, 61(1):77–87. DOI: 10.1002/hep.27259

[9] Wasitthankasem R, Vongpunsawad S, Siripon N, Suya C, Chulothok P, Chaiear K, Rujirojindakul P, Kanjana S, Theamboonlers A, Tangkijvanich P: Genotypic distribution of hepatitis C virus in Thailand and Southeast Asia. PLoS One 2015, 10(5):e0126764. DOI: 10.1002/hep.26744

[10] Magiorkinis G, Magiorkinis E, Paraskevis D, Ho SY, Shapiro B, Pybus OG, Allain J-P, Hatzakis A: The global spread of hepatitis C virus 1a and 1b: A phylodynamic and phylogeographic analysis. PLoS Med 2009, 6(12):e1000198. DOI: 10.1371/journal.pmed.1000198

[11] Murphy DG, Sablon E, Chamberland J, Fournier E, Dandavino R, Tremblay CL: Hepatitis C virus genotype 7, a new genotype originating from Central Africa. J Clin Microbiol 2015, 53(3):967–972. DOI: 10.1128/JCM.02831

[12] European Association for Study of L: EASL recommendations on treatment of hepatitis C 2015. J Hepatol 2015, 63(1):199–236. DOI: 10.1016/j.jhep.2015.03.025

[13] Hézode C, Bronowicki J-P: Ideal oral combinations to eradicate HCV: The role of ribavirin. J Hepatol 2016, 64(1):215–225. DOI: 10.1016/j.jhep.2015.09.009

[14] Panel A: Hepatitis C guidance: AASLD-IDSA recommendations for testing, managing, and treating adults infected with hepatitis C virus. Hepatology 2015, 62:932–954. DOI: 10.1002/hep.27950

[15] Solbach P, Wedemeyer H: The new era of interferon-free treatment of chronic hepatitis C. Viszeralmedizin 2015, 31(4):290–296. DOI: 10.1159/000433594
[16] Arase Y, Kobayashi M, Suzuki F, Suzuki Y, Kawamura Y, Akuta N, Kobayashi M, Sezaki H, Saito S, Hosaka T, et al.: Effect of type 2 diabetes on risk for malignancies includes hepatocellular carcinoma in chronic hepatitis C. Hepatology 2013, 57(3):964–973. DOI: 10.1002/hep.26087

[17] van der Meer AJ, Veldt BJ, Feld JJ, Wedemeyer H, Dufour J-F, Lammert F, Duarte-Rojo A, Heathcote EJ, Manns MP, Kuske L: Association between sustained virological response and all-cause mortality among patients with chronic hepatitis C and advanced hepatic fibrosis. JAMA 2012, 308(24):2584–2593. DOI: 10.1001/jama.2012.144878

[18] Manns MP, McHutchison JG, Gordon SC, Rustgi VK, Shiffman M, Reindollar R, Goodman ZD, Koury K, Ling M-H, Albrecht JK: Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: A randomised trial. Lancet 2001, 358(9286):958–965. DOI: 10.1016/S0140-6736(01)06102-5

[19] Fried MW, Shiffman ML, Reddy KR, Smith C, Marinos G, Gonçales FL, Häussinger D, Diago M, Carosi G, Dhumeaux D, et al.: Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. N Engl J Med 2002, 347(13):975–982. DOI: 10.1056/NEJMoa20047

[20] Torriani FJ, Rodriguez-Torres M, Rockstroh JK, Lissen E, Gonzalez-García J, Lazzarin A, Carosi G, Sasadeusz J, Katlama C, Montaner J, et al.: Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection in HIV-infected patients. N Engl J Med 2004, 351(5):438–450. DOI: 10.1056/NEJMoa040842

[21] Dieterich D, Bacon BR, Flamm SL, Kowdle KV, Milligan S, Tsai N, Younossi Z, Lawitz E: Evaluation of sofosbuvir and simeprevir-based regimens in the TRIO network: Academic and community treatment of a real-world, heterogeneous population. Hepatology 2014, 2014 (60): 220A.

[22] Lawitz E, Sulkowski MS, Ghalib R, Rodriguez-Torres M, Younossi ZM, Corregidor A, DeJesus E, Pearlman B, Rabinovitz M, Gitlin N: Simeprevir plus sofosbuvir, with or without ribavirin, to treat chronic infection with hepatitis C virus genotype 1 in non-responders to pegylated interferon and ribavirin and treatment-naïve patients: The COSMOS randomised study. Lancet 2014, 384(9956):1756–1765. DOI: 10.1016/S0140-6736(14)61036

[23] Poordad F, McConie J, Bacon BR, Bruno S, Manns MP, Sulkowski MS, Jacobson IM, Reddy KR, Goodman ZD, Boparai N, et al.: Boceprevir for untreated chronic HCV genotype 1 infection. N Engl J Med 2011, 364(13):1195–1206. DOI: 10.1056/NEJMoa1010494

[24] Bacon BR, Gordon SC, Lawitz E, Marcellin P, Vierling JM, Zeuzem S, Poordad F, Goodman ZD, Sings HL, Boparai N, et al.: Boceprevir for previously treated chronic HCV genotype 1 infection. N Engl J Med 2011, 364(13):1207–1217. DOI: 10.1056/NEJMoa1009482

[25] Arain A, Bourgeois S, de Galocys C, Henrion J, Deltenre P, d’Heygere F, George C, Bastens B, Van Overbeke L, Verrando R, et al.: Belgian experience with triple therapy with boceprevir and telaprevir in genotype 1 infected patients who inject drugs. J Med Virol 2016, 88(1):94–99. DOI: 10.1002/jmv.24308
[26] McHutchison JG, Everson GT, Gordon SC, Jacobson IM, Sulkowski M, Kauffman R, McNair L, Alam J, Muir AJ: Telaprevir with peginterferon and ribavirin for chronic HCV genotype 1 infection. N Engl J Med 2009, 360(18):1827–1838. DOI: 10.1056/NEJMoa0806104

[27] Jacobson IM, McHutchison JG, Dusheiko G, Di Bisceglie AM, Reddy KR, Bzowej NH, Marcellin P, Muir AJ, Ferenci P, Flisiak R, et al.: Telaprevir for previously untreated chronic hepatitis C virus infection. N Engl J Med 2011, 364(25):2405–2416. DOI: 10.1056/NEJMoa1012912

[28] Reddy KR, Zeuzem S, Zoulim F, Weiland O, Horban A, Stanciu C, Villamil FG, Andreone P, George J, Dammers E, et al.: Simeprevir versus telaprevir with peginterferon and ribavirin in previous null or partial responders with chronic hepatitis C virus genotype 1 infection (ATTAIN): A randomised, double-blind, non-inferiority phase 3 trial. Lancet Infect Dis 2015, 15(1):27–35. DOI: 10.1016/S1473-3099(14)71002

[29] Zeuzem S, Berg T, Gane E, Ferenci P, Foster GR, Fried MW, Hezode C, Hirschfield GM, Jacobson I, Nikitin I: Simeprevir increases rate of sustained virologic response among treatment-experienced patients with HCV genotype-1 infection: A phase IIb trial. Gastroenterology 2014, 146(2):430–441.e436. DOI: 10.1053/j.gastro.2013.10.058

[30] Manns M, Marcellin P, Poordad F, de Araujo ESA, Buti M, Horsmans Y, Janczewska E, Villamil F, Scott J, Peeters M: Simeprevir with pegylated interferon alfa 2a or 2b plus ribavirin in treatment-naive patients with chronic hepatitis C virus genotype 1 infection (QUEST-2): A randomised, double-blind, placebo-controlled phase 3 trial. Lancet 2014, 384(9941):414–426. DOI: 10.1016/S0140-6736(14)60538

[31] Jacobson IM, Dore GJ, Foster GR, Fried MW, Radu M, Rafalsky VV, Moroz L, Craxi A, Peeters M, Lenz O: 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(9941):403–413. DOI: 10.1016/S0140-6736(14)60494-3

[32] Forns X, Lawitz E, Zeuzem S, Gane E, Bronowicki JP, Andreone P, Horban A, Brown A, Peeters M, Lenz O: Simeprevir with peginterferon and ribavirin leads to high rates of SVR in patients with HCV genotype 1 who relapsed after previous therapy: A phase 3 trial. Gastroenterology 2014, 146(7):1669–1679.e1663. DOI: 10.1053/j.gastro.2014.01.051

[33] Lawitz E, Mangia A, Wyles D, Rodriguez-Torres M, Hassanain T, Gordon SC, Schultz M, Davis MN, Kayali Z, Reddy KR: Sofosbuvir for previously untreated chronic hepatitis C infection. N Engl J Med 2013, 368(20):1878–1887. DOI: 10.1056/NEJMoa1214853

[34] Jensen DM, O’Leary JG, Pockros PJ, Sherman KE, Kwo PY, Mailliard ME, Kowdley KV, Muir AJ, Dickson RC, Ramani A: Safety and efficacy of sofosbuvir-containing regimens for hepatitis C: Real-world experience in a diverse, longitudinal observational cohort. Hepatology 2014, 2014:219A–220A.

[35] Afdhal N, Zeuzem S, Kwo P, Chojkier M, Gitlin N, Puoti M, Romero-Gomez M, Zarski J-P, Agarwal K, Buggisch P: Ledipasvir and sofosbuvir for untreated HCV genotype 1 infection. N Engl J Med 2014, 370(20):1889–1989. DOI: 10.1056/NEJMoa1402454
[36] Kowdley KV, Gordon SC, Reddy KR, Rossaro L, Bernstein DE, Lawitz E, Shiffman ML, Schiff E, Ghalib R, Ryan M: Ledipasvir and sofosbuvir for 8 or 12 weeks for chronic HCV without cirrhosis. N Engl J Med 2014, 370(20):1879–1888. DOI: 10.1056/NEJMoa1402555

[37] Townsend KS, Osinusi A, Nelson AK, Kohli A, Gross C, Polis MA, Pang PS, Sajadi MM, Subramanian M, McHutchison JG: High efficacy of sofosbuvir/ledipasvir for the treatment of HCV genotype 1 in patients coinfected with HIV on or off antiretroviral therapy: results from the NIAID ERADICATE trial. Hepatology 2014, 2014:240A–241A.

[38] Bourliere M, Sulikowski MS, Omata M, Zeuzem S, Feld JJ, Lawitz E, Marcellin P, Hyland RH, Ding X, Yang JC: An integrated safety and efficacy analysis of >500 patients with compensated cirrhosis treated with ledipasvir/sofosbuvir with or without ribavirin. Hepatology 2014, 2014 (60): 239A.

[39] Gao M: Antiviral activity and resistance of HCV NS5A replication complex inhibitors. Curr Opin Virol 2013, 3(5):514–520. DOI: 10.1016/j.coviro.2013.06.014

[40] Sulikowski MS, Gardiner DF, Rodriguez-Torres M, Reddy KR, Hassanein T, Jacobson I, Lawitz E, Lok AS, Hinestrosa F, Thuluvath PJ: Daclatasvir plus sofosbuvir for previously treated or untreated chronic HCV infection. N Engl J Med 2014, 370(3):211–221. DOI: 10.1056/NEJMoa1306218

[41] Pol S, Bourliere M, Lucier S, De Ledinghen V, Zoulim F, Dorival-Mouly C, Métivier S, Larrey D, Tran A, Hezode C: Safety and efficacy of the combination daclatasvir-sofosbuvir in HCV genotype 1-mono-infected patients from the French observational cohort ANRS CO22 HEPATHER. J Hepatol 2015, 62(Suppl 2):S258.

[42] Feld JJ, Jacobson IM, Hézode C, Asselah T, Ruane PJ, Gruener N, Abergel A, Mangia A, Lai C-L, Chan HLY, et al.: Sofosbuvir and velpatasvir for HCV genotype 1, 2, 4, 5, and 6 infection. N Engl J Med 2015, 373(27):2599–2607. DOI: 10.1056/NEJMoa1512610

[43] Pianko S, Flamm SL, Shiffman ML, Kumar S, Strasser SI, Dore GJ, McNally J, Brainard DM, Han LL, Doehle B, et al.: Sofosbuvir plus velpatasvir combination therapy for treatment-experienced patients with genotype 1 or 3 hepatitis C virus infection a randomized trial. Ann Intern Med 2015, 163(11):11. DOI: 10.7326/M15-1014

[44] Feld JJ, Kowdley KV, Coakley E, Sigal S, Nelson DR, Crawford D, Weiland O, Aguilar H, Xiong J, Pilot-Matias T: Treatment of HCV with ABT-450/r–ombitasvir and dasabuvir with ribavirin. N Engl J Med 2014, 370(17):1594–1603. DOI: 10.1056/NEJMoa1315722

[45] Ferenci P, Bernstein D, Lalezari J, Cohen D, Luo Y, Cooper C, Tam E, Marinho RT, Tsai N, Nyberg A: ABT-450/r–ombitasvir and dasabuvir with or without ribavirin for HCV. N Engl J Med 2014, 370(21):1983–1992. DOI: 10.1056/NEJMoa1402338

[46] Wyles DL, Sulikowski MS, Eron JJ, Trinh R, Lalezari J, Slim J, Gathe JC, Wang CC, Elion R, Bredeek F: TURQUOISE-I: 94% SVR12 in HCV/HIV-1 coinfected patients treated with ABT-450/r/ombitasvir, dasabuvir and ribavirin. Hepatology 2014, 2014:1136A–1137A.
Zeuzem S, Jacobson IM, Baykal T, Marinho RT, Poordad F, Bourliere M, Sulkowski MS, Wedemeyer H, Tam E, Desmond P, et al.: Retreatment of HCV with ABT-450/r-ombitasvir and dasabuvir with ribavirin. N Engl J Med 2014, 370(17):1604–1614. DOI: 10.1056/NEJMoa1401561

Andreone P, Colombo MG, Enejosa JV, Koksal I, Ferenci P, Maieron A, Mullhaupt B, Horsmans Y, Weiland O, Reesink HW, et al.: ABT-450, ritonavir, ombitasvir, and dasabuvir achieves 97% and 100% sustained virologic response with or without ribavirin in treatment-experienced patients with HCV genotype 1b infection. Gastroenterology 2014, 147(2):359.e1. DOI: 10.1053/j.gastro.2014.04.045

Poordad F, Hezode C, Trinh R, Kowdley KV, Zeuzem S, Agarwal K, Shiffman ML, Wedemeyer H, Berg T, Yoshida EM: ABT-450/r–ombitasvir and dasabuvir with ribavirin for hepatitis C with cirrhosis. N Engl J Med 2014, 370(21):1973–1982. DOI: 10.1056/NEJMoa1402869

Shiffman ML, Suter F, Bacon BR, Nelson D, Harley H, Sola R, Shafran SD, Barange K, Lin A, Soman A, et al.: Peginterferon alfa-2a and ribavirin for 16 or 24 weeks in HCV genotype 2 or 3. N Engl J Med 2007, 357(2):124–134. DOI: 10.1056/NEJMoa066403

Zeuzem S, Hultcrantz R, Bourliere M, Goeser T, Marcellin P, Sanchez-Tapias J, Sarrazin C, Harvey J, Brass C, Albrecht J: Peginterferon alfa-2b plus ribavirin for treatment of chronic hepatitis C in previously untreated patients infected with HCV genotypes 2 or 3. J Hepatol 2004, 40(6):993–999. DOI: 10.1016/j.jhep.2004.02.007

Lagging M, Rembeck K, Rauning Buhl M, Christensen P, Dalgard O, Farkkila M, Hellstrand K, Langeland N, Lindh M, Westin J, et al.: Treatment with peg-interferon and ribavirin in patients with chronic hepatitis C virus genotype 2 or 3 infection with prior relapse. Scand J Gastroenterol 2013, 48(7):839–847. DOI: 10.3109/00365521.2013.793389

Lawitz E, Poordad F, Brainard DM, Hyland RH, An D, Symonds WT, McHutchison JG, Membreno FE: Sofosbuvir in combination with pegIFN and ribavirin for 12 weeks provides high SVR rates in HCV-infected genotype 2 or 3 treatment experienced patients with and without compensated cirrhosis: Results from the LONESTAR-2 study. Hepatology 2013, 58(Suppl 1):1380A.

Esteban R, Nyberg L, Lalezari J, Ni L, Doehle B, Kanwar B, Brainard D, Subramanian M, Symonds W, McHutchison J: O8 successful retreatment with sofosbuvir-containing regimens for HCV genotype 2 or 3 infected patients who failed prior sofosbuvir plus ribavirin therapy. J Hepatol 2014, 1(60):S4–S5. DOI: 10.1016/S0168-8278(14)60010-6

Lawitz E, Lalezari JP, Hassanein T, Kowdley KV, Poordad FF, Sheikh AM, Afdhal NH, Bernstein DE, Defejes E, Freilich B, et al.: Sofosbuvir in combination with peginterferon alfa-2a and ribavirin for non-cirrhotic, treatment-naive patients with genotypes 1, 2, and 3 hepatitis C infection: A randomised, double-blind, phase 2 trial. Lancet Infect Dis. 2013; 13(5):401–408. DOI: 10.1016/S1473-3099(13)70033-1
[56] Jacobson IM, Gordon SC, Kowdley KV, Yoshida EM, Rodriguez-Torres M, Sulkowski MS, Shiffman ML, Lawitz E, Everson G, Bennett M: Sofosbuvir for hepatitis C genotype 2 or 3 in patients without treatment options. N Engl J Med 2013, 368(20):1867–1877. DOI: 10.1056/NEJMoa1214854

[57] Zeuzem S, Dusheiko GM, Salupere R, Mangia A, Flisiak R, Hyland RH, Illeperuma A, Svarovskaia E, Brainard DM, Symonds WT: Sofosbuvir and ribavirin in HCV genotypes 2 and 3. N Engl J Med 2014, 370(21):1993–2001. DOI: 10.1056/NEJMoa1316145

[58] Foster GR, Afdhal N, Roberts SK, Bräu N, Gane EJ, Pianko S, Lawitz E, Thompson A, Shiffman ML, Cooper C: Sofosbuvir and velpatasvir for HCV genotype 2 and 3 infection. N Engl J Med 2015; 373 (27): 2608–2617. DOI: 10.1056/NEJMoa1512612

[59] Nelson DR, Cooper JN, Lalezari JP, Lawitz E, Pockros PJ, Gitlin N, Freilich BF, Younes ZH, Harlan W, Ghalib R, et al.: All-oral 12-week treatment with daclatasvir plus sofosbuvir in patients with hepatitis C virus genotype 3 infection: ALLY-3 phase III study. Hepatology 2015, 61(4):1127–1135. DOI: 10.1002/hep.27726

[60] Kamal S, El Tawil A, Nakano T, He Q, Rasenack J, Hakam S, Saleh W, Ismail A, Aziz A, Madwar MA: Peginterferon α-2b and ribavirin therapy in chronic hepatitis C genotype 4: Impact of treatment duration and viral kinetics on sustained virological response. Gut 2005, 54(6):858–866. DOI: 10.1136/gut.2004.057182

[61] Moreno C, Hézode C, Marcellin P, Bourgeois S, Francque S, Samuel D, Zoulim F, Grange J-D, Shukla U, Lenz O: Efficacy and safety of simeprevir with PegIFN/ribavirin in naïve or experienced patients infected with chronic HCV genotype 4. J Hepatol 2015, 62(5):1047–1055. DOI: 10.1016/j.jhep.2014.12.031

[62] Kapoor R, Kohli A, Sidharthan S, Sims Z, Petersen TL, Osinusi A, Nelson AK, Silk R, Kotb C, Sugarman K: All oral treatment for genotype 4 chronic hepatitis C infection with sofosbuvir and ledipasvir: Interim results from the NIAID SYNERGY trial. Hepatology. 2014, 60: 321A.

[63] Willemse S, Baak L, Kuiken S, Sluys Veer A, Lettinga K, Meer J, Depla A, Tuynman H, Nieuwkerk C, Schinkel C: Sofosbuvir plus simeprevir for the treatment of HCV genotype 4 patients with advanced fibrosis or compensated cirrhosis is highly efficacious in real life. J Viral Hepat 2016; 23 (12): 950–954. DOI: 10.1111/jvh.12567

[64] El-Khayat HR, Fouad YM, Maher M, El-Amin H, Muhammed H: Efficacy and safety of sofosbuvir plus simeprevir therapy in Egyptian patients with chronic hepatitis C: A real-world experience. Gut 2016: gutjnl-2016. DOI: 10.1136/gutjnl-2016-312012

[65] Hézode C, Asselah T, Reddy KR, Hassanein T, Berenguer M, Fleischer-Stepniewska K, Marcellin P, Hall C, Schnell G, Pilot-Matias T, et al.: Ombitasvir plus paritaprevir plus ritonavir with or without ribavirin in treatment-naive and treatment-experienced patients with genotype 4 chronic hepatitis C virus infection (PEARL-I): A randomised, open-label trial. Lancet. 2015; 385(9986):2502–2509. DOI: 10.1016/S0140-6736(15)60159-3
[66] Asselah T, Hézode C, Qaqish RB, ElKhashab M, Hassanein T, Papatheodoridis G, Feld JJ, Moreno C, Zeuzem S, Ferenci P: Ombitasvir, paritaprevir, and ritonavir plus ribavirin in adults with hepatitis C virus genotype 4 infection and cirrhosis (AGATE-I): A multicentre, phase 3, randomised open-label trial. Lancet Gastroenterol Hepatol 2016, 1(1):25–35. DOI: 10.1016/S2468-1253(16)30001-2

[67] Waked I, Shiha G, Qaqish RB, Esmat G, Yosry A, Hassany M, Soliman R, Mohey MA, Allam N, Zayed N: Ombitasvir, paritaprevir, and ritonavir plus ribavirin for chronic hepatitis C virus genotype 4 infection in Egyptian patients with or without compensated cirrhosis (AGATE-II): A multicentre, phase 3, partly randomised open-label trial. Lancet Gastroenterol Hepatol 2016, 1(1):36–44. DOI: 10.1016/S2468-1253(16)30002-4

[68] Keating GM: Ombitasvir/paritaprevir/ritonavir: A review in chronic HCV genotype 4 infection. Drugs 2016, 76(12):1203–1211. DOI: 10.1007/s40265-016-0612-1

[69] Abergel A, Asselah T, Metivier S, Kersey K, Jiang D, Mo H, Pang PS, Samuel D, Loustaud-Ratti V: Ledipasvir-sofosbuvir in patients with hepatitis C virus genotype 5 infection: An open-label, multicentre, single-arm, phase 2 study. Lancet Infect Dis. 2016; 16 (4): 459–464. DOI: 10.1016/S1473-3099(15)00529-0

[70] Gane EJ, Hyland RH, An D, Svarovskaia E, Pang PS, Brainard D, Stedman CA: Efficacy of ledipasvir and sofosbuvir, with or without ribavirin, for 12 weeks in patients with HCV genotype 3 or 6 infection. Gastroenterology 2015, 149(6):1454-e1. DOI: 10.1053/j. gastro.2015.07.063

[71] Everson GT, Towner WJ, Davis MN, Wyles DL, Nahass RG, Thuluvath PJ, Etzkorn K, Hinestrosa F, Tong M, Rabinovitz M, et al.: Sofosbuvir with velpatasvir in treatment-naive noncirrhotic patients with genotype 1 to 6 hepatitis C virus infection a randomized trial. Ann Intern Med 2015, 163(11):818–826. DOI: 10.7326/M15-1000

[72] Pol S, Reddy KR, Baykal T, Hezode C, Hassanein T, Marcellin P, Berenguer M, Fleischer-Stepniewska KM, Hall C, Collins C: Interferon-free regimens of ombitasvir and ABT-450/r with or without ribavirin in patients with HCV genotype 4 infection: PEARL-I study results. Hepatology 2014, 2014:1129A–1130A.