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**Sofosbuvir and ABT-450: Terminator of hepatitis C virus?**

Zeng QL *et al*. Sofosbuvir and ABT-450: Terminator of HCV?

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**Abstract**

Combination therapy with peginterferon (pegIFN)-α and ribavirin (RBV) has been the standard of care (SOC) for chronic hepatitis C. Unfortunately, not all patients can achieve a sustained virologic response (SVR) with this regimen. SVR rates are approximately 80% in patients with hepatitis C virus (HCV) genotype 2, 3, 5, and 6 and 40%-50% in patients with genotype 1 and 4. Therefore, strategies to improve SVR rates have been an important issue for clinical physicians. Several direct acting antiviral agents (DAAs) have significantly higher SVR rates when combined with pegIFN-α and RBV than pegIFN-α and RBV alone. Treatments containing DAAs have several advantages over the previous SOC, including higher specificity and efficacy, shorter treatment durations, fewer side effects, and oral administration. Based on these advantages, treatment with pegIFN-α and RBV plus telaprevir or boceprevir has become the current SOC for patients with genotype 1 HCV infection. However, many patients are either not eligible for therapy or decline treatment due to coexisting relative or absolute contraindications as well as an inability to tolerate the hematological side effects and adverse events caused by the new SOC. These factors have contributed to the advent of pegIFN-α-free regimens. The newest therapeutic regimens containing sofosbuvir and ABT-450 have shown promising results. In this review, we summarize the development of anti-HCV agents and the clinical efficacy of sofosbuvir and ABT-450-based therapies as well as the potential for future HCV studies.

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**Key words:** Sofosbuvir; ABT-450; Hepatitis C virus; Antiviral therapy; Sustained virologic response

**Core tip:** We are entering an era in which the development of antiviral agents and successful treatment of chronic hepatitis C is rapidly escalating. In this review, we have summarized the history of anti-hepatitis C virus (HCV) agents from interferon-α (IFN-α) to the latest sofosbuvir- and ABT-450-based therapies. Although a new generation of direct acting anti-HCV agents has largely improved the sustained virologic response rates of patients, many unmet needs and questions remain, such as IFN-free regimens for difficult to treat patients, avoidance of cross-resistance, the role of IL-28B status as well as the management of some advanced and co-infected patients.

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**INTRODUCTION**

Chronic hepatitis C virus (HCV) infection is currently a major global health problem that affects 160 million people worldwide and is one of the main causes of chronic liver cirrhosis and hepatocellular carcinoma[1,2]. Compared with the former standard of care (SOC), the current SOC, consisting of peginterferon (pegIFN)-α and ribavirin (RBV) plus telaprevir or boceprevir, achieves higher rates of sustained virologic response (SVR), which is defined as undetectable HCV RNA in the serum for 24 wk after the end of treatment. SVR is associated with a better outcome for chronic hepatitis C (CHC) patients[3,4]. However, not all patients can achieve SVR[5,6]. In addition, triple therapy has many side effects and contraindications that result in a number of eligible patients refusing therapy[7,8].

Based on these complications, pegIFN-α-free regimens could be an alternative for some patients. Several pegIFN-α-free regimens containing sofosbuvir and ABT-450 have shown high SVR rates with only 12 wk of treatment and mild adverse events. These regimens have the potential to be the newest SOC for CHC in the near future. Here, we summarize the clinical development history of anti-HCV agents as well as recent studies of the efficacy and adverse event profile of sofosbuvir and ABT-450 regimens. We also discuss the future focus for HCV studies.

**BRIEF DEVELOPMENT HISTORY OF ANTI-HCV AGENTS**

***Interferon era***

Anti-HCV therapy is the backbone for the treatment of CHC. Since the late 1980s, interferon-α has gradually become the core of antiviral treatment[9-13]. However, interferon-α monotherapy achieved suboptimal efficacy until combined with RBV[14-22] (Figure 1). PegIFN-α has a higher plasma concentration and half-life than interferon, which results in an improved SVR rate as well as improved patient compliance as the pegylated form can be injected once weekly[23-25]. Higher SVR rates were achieved with combination therapy of pegIFN plus RBV than with pegIFN monotherapy, which has become the SOC during the past decade[26,27]. Meanwhile, the true meaning of SVR was unclear until a large cohort study demonstrated that patients who achieved SVR could be considered cured[28]. Unfortunately, not all patients, especially those infected with genotype 1 and 4 HCV could achieve SVR with the SOC. Furthermore, side effects, long-term treatment, contraindications and poor compliance all spurred the development of new agents with shorter treatment durations, fewer contraindications, oral administration, higher specificity, and fewer side effects.

***The era of direct acting antiviral agents***

HCV is classified in the genus hepacivirus of the family flaviviridae. Once the virus is released into the cell, the viral polyprotein is translated and cleaved by host proteases and the viral NS3-4A protease into ten mature proteins. Next, viral RNA is replicated into progeny RNA by the viral NS5B polymerase. Another viral protein, HCV NS5A, is indispensable for viral replication and assembly and could be a nonenzymatic target for therapeutics. With the structures of NS3/4A protease and NS5B polymerase solved and the rapid development of different cell culture models and biotechnology[29], HCV research has been flourishing both on the bench and in industry. In particular, intensive efforts have focused on developing direct acting antiviral agents (DAAs) that can block the activity of viral enzymes.

The serine protease inhibitors telaprevir and boceprevir, approved by the US FDA in 2011, were the first and currently only DAA to make it to the clinic. Telaprevir is a linear peptidomimetic HCV NS3/4A serine protease inhibitor, and boceprevir is a protease inhibitor that binds to the HCV NS3 active site. Treatment regimens consisting of telaprevir or boceprevir plus pegIFN-α and RBV had significantly higher SVR rates in genotype 1 patients and became the SOC thereafter[30-34]. However, this new SOC has more adverse events and a similar treatment duration when compared with the former SOC[35], and monotherapy with telaprevir or boceprevir was shown to be impractical due to the rapid selection of resistant variants. In 2012, preliminary clinical data showed that combination therapy with the NS5A replication complex inhibitor daclatasvir and the NS3 protease inhibitor asunaprevir could also achieve high efficacy rates after 24 wk of treatment[36], especially in prior null responders. These results showed the potential of a pegIFN-free regimen for 24 wk treatment duration. However, some patients in this study experienced viral breakthrough due to resistant variants, which ultimately resulted in treatment failure.

In January 2013, Gane and Poordad published clinical data on the efficacy of sofosbuvir- (also known as GS-7977) and ABT-450-based oral treatment regimens for 12 wk treatment duration. The results showed that 100% of genotype 2/3 patients and 93% -95% of genotype 1 patients achieved SVR[37,38]. The sofosbuvir and ABT-450 studies were open-label clinical studies that assessed various combination and dosages of agents in previously treated and previously untreated patients. Sofosbuvir exhibits a higher barrier to resistance than ABT-450 because its target, the NS5B polymerase is highly conserved, and viral fitness is crippled if variants occur in the polymerase active site. Sofosbuvir also exhibits pan-genotypic antiviral activity compared to genotype-specific agents, such as ABT-450, asunaprevir, telaprevir and boceprevir. Although some mild adverse events were observed, these studies validated the feasibility of achieving extremely high SVR rates with a pegIFN-free regimen and a short treatment duration of 12 wk.

***General characteristics of representative DAAs***

We summarize representative DAAs from 2011 to January 2013 in Table 1. There have been several treatment evolutions during this timeframe. First, most of these agents were designed for genotype 1 patients, with genotypes 2 and 3 only being considered recently. Second, the treatment period has gradually decreased to 12 wk. Third, dosing frequency has generally improved from three times daily to once daily, which will undoubtedly contribute to better patient compliance. Fourth, combination therapy has gradually shifted away from exclusive combinations with pegIFN-α to trials with and without pegIFN-α to finally pegIFN-α-free regimens. Finally, we found that at least two representative agents were developed from bench to bedside every year. Compared with other DAAs, the sofosbuvir and ABT-450 regimens not only achieve extremely high SVR rates with 12 wk of treatment in treatment-naive patients but are also efficacious in genotype 2 and 3 patients without the need for pegIFN-α.

**THE CLINICAL EFFICACY OF SOFOSBUVIR AND ABT-450**

Sofosbuvir is a direct acting nucleotide polymerase inhibitor[39], and ABT-450 is a potent macrocyclic HCV NS3 protease inhibitor. Both have been developed as oral therapies for the treatment of chronic HCV infection. Phosphorylated nucleotide analogues, such as sofosbuvir, are converted within the host hepatocyte to the active nucleoside triphosphate, which competes with natural nucleotides, thereby terminating RNA replication in the nascent viral genome. Sofosbuvir acts as a nonobligate chain terminator, targeting the highly conserved active site of the HCV-specific NS5B polymerase[38]. The mechanism of action of NS3 protease inhibitors has been thoroughly reviewed elsewhere[35]. As a potent inhibitor of CYP3A4 (the primary enzyme involved in first-pass metabolism of most protease inhibitors), ritonavir can increase the plasma concentration and half-life of ABT-450, decrease the emergence of resistance mutations in the *NS3* gene, and permit once-daily dosing of ABT-450[38,40,41].

***Clinical efficacy of sofosbuvir-******based therapy***

Gane and colleagues published an open-label clinical trial of 95 previously untreated HCV genotype 1/2/3 patients and genotype 1 null responders[37] (Table 2). The patients were divided into 8 groups: sofosbuvir monotherapy and sofosbuvir plus RBV therapy with or without pegIFN-α for 8 or 12 wk. The results showed that 100% of previously untreated genotype 2/3 patients achieved SVR based on sofosbuvir plus RBV. For previously untreated genotype 1 patients, the SVR rate was 84%. Unfortunately, the SVR rate was only 10% for genotype 1 patients who had no response to previous therapy. These results indicate that genotype 2/3 untreated patients can be completely cured with 12 wk of sofosbuvir plus RBV therapy alone.

***Clinical efficacy of*** ABT-450-***based therapy***

Poordad and colleagues published an open-label, phase 2a clinical trial of 50 genotype 1 patients, including untreated patients and patients with no or partial response to prior therapy[38] (Table 3). The patients were divided into 3 groups. Patients received a combination of ABT-333 (a nonnucleoside NS5B polymerase inhibitor), RBV and ritonavir plus two different dosages of ABT-450 for 12 wk. The results showed that 93% and 95% of previously untreated genotype 1 patients achieved SVR. Furthermore, 47% prior null and partial responders achieved SVR. These results indicate that almost all untreated patients with genotype 1 can achieve SVR with ABT-450-based regimens, and null and partial responders can achieve higher SVR rates than previously possible.

**ADVERSE EVENTS OF** **SOFOSBUVIR AND** **ABT-450 REGIMENS**

Both sofosbuvir and ABT-450 regimens have various adverse events (Table 4). The most frequent adverse events observed with sofosbuvir-based therapies were headache, fatigue, insomnia, nausea, rash, and anemia[37,42]. For ABT-450-based therapies, the most frequent adverse events were fatigue, nausea, headache, dizziness, insomnia, pruritus, rash, and vomiting. Some laboratory abnormalities were also observed during the treatment period, including anemia for sofosbuvir-based treatment and hyperbilirubinemia for ABT-450-based therapy. Some laboratory abnormalities were more common among patients receiving pegIFNα-2a. Most adverse events and abnormalities were mild, and none led to treatment interruption.

**IL-28B POLYMORPHISM IN THE SOFOSBUVIR AND ABT-450 ERA**

Genome-wide association studies have demonstrated that single nucleotide polymorphisms near the IL-28B gene that encodes IFN-λ3 are closely associated with spontaneous and treatment-induced HCV clearance[43-46]. The rs12979860 CC genotype is associated with a two-fold greater SVR rate than the TT genotype in European-American individuals. Similar ratios have been observed in both African-American and Hispanic populations of genotype 1 chronic hepatitis C patients. The presence of the C-allele is always accompanied by higher SVR rates, indicating that this allele may favor the clearance of HCV. In studies of sofosbuvir and ABT-450, five groups achieved SVR rates of 100%, independent of IL-28B status (Table 5). Therefore, lower SVR rates may not be primarily due to IL-28B genotypes. Instead, these patients may have acquired resistant variants during treatment. However, it should be noted that the sample size of these studies too small to reach a definitive conclusion on the role of IL-28B. Whether IL-28B genotype will be a predictive marker for treatment response with the new drug regimens requires further investigation with large sample sizes.

**PERSPECTIVES**

***Genotype 1 patients with no or partial response to prior therapy will be the focus of future studies***

Currently, the highest SVR rate observed in genotype 1 patients who have no response to prior therapy is 90%, which was achieved with daclatasvir and asunaprevir-based therapy (Table 6). SVR rates in this patient population treated with telaprevir and boceprevir regimens were only 33% and 52%, respectively, which was significantly inferior to the rates in treatment-naive patients. Sofosbuvir plus RBV has achieved an excellent SVR rate in untreated genotype 1 patients compared with genotype 1 patients who had no response to previous treatment. While the ABT-450 regimen achieved high efficacy in genotype 1 patients with no or partial response to prior treatment, the SVR rate was still less than 50%. All of the above-mentioned results suggest that genotype 1 patients with no or partial response should be the focus of further investigation.Furthermore, genotype 1a patients have more opportunities to develop resistance to the DAAs combination from Poordad’s study[38]. Genotype 1a accounts for 89%, 8 out of 9 patients with virologic failure in group 3 who have been analyzed for the presence of resistance-associated variants. The genetic barrier to resistance of protease inhibitors is relatively lower for subtype 1a because this subtype only requires one nucleotide substitution to generate resistance, whereas the 1b virus requires two. Accordingly, genotype 1a patients may be more difficult to treat in new DAAs era.

***DAA combinations with less*** ***cross-resistance may be the solution for genotype 1 patients with no or partial response to prior therapy***

Although it has not been investigated in a head-to-head study, genotype 1 patients with no or partial response to prior therapy have different SVR rates (10% *vs* 90%) with different DAA combinations (Table 6)[37,38], indicating that different DAA combinations might be important to successfully treating these types of patients. Various combinations of DAAs are now under investigation[47,48]. However, why a particular combination may lead to an improved SVR rate in these patients remains unclear. It is possible that adding another DAA could complement the mechanisms of action of other agents in the regimen as well as decrease the appearance of cross-resistant variants. As Table 6 shows, 90% of genotype 1 patients with no response to prior therapy can achieve SVR[33], suggesting that a potent DAA combined with pegIFN-α and RBV may be one choice for those patients who can endure the adverse events and long period of treatment.

***Combinations with less cross-resistance are the goal for the future***

Various DAA combinations have now been investigated, such as asunaprevir plus daclatasvir; sofosbuvir plus RBV; sofosbuvir plus daclatasvir; faldaprevir plus BI207127; ABT-450/ritonavir plus ABT-333; ABT-450, ritonavir plus ABT-072; miracitabine, danoprevir plus ritonavir; and alisporivir plus RBV[47]. DAA combinations not only have the potential to increase antiviral efficacy but also to reduce the risk of viral breakthrough. When combining DAAs, it is important to consider combinations that have a low propensity for cross-resistance. The genetic barriers to resistance of DAAs appear to be an important factor during the development of resistance. When two agents with a low genetic barrier to resistance are combined, breakthrough occurs more quickly[49]. Adding on pegIFN-α or RBV[36] as well as nucleoside analogues with a higher genetic barrier might be better tactics for overcoming resistance[37,50]. For example, 90% of difficult-to-treat patients can achieve SVR with a combination of daclatasvir, asunaprevir, pegIFN-α2a and RBV for 24 wk of treatment[36]. Furthermore, 84%-100% of patients can achieve SVR with a combination of sofosbuvir plus RBV for 12 wk of therapy[37].

***PegIFN-α: to be with or not to be with***

Whether or not to include pegIFN-α is a key issue in the DAA era. Several years ago, many hepatologists believed that HCV treatment would be IFN free. Now, however, the ability to do away with IFN is not so clear, especially in some difficult-to-treat patients. Although not compared in a head-to-head study, the SVR rate was relatively lower in refractory patients treated with a pegIFN-free regimen, as shown in Table 6. This information indicates that IFN-free regimens may be available for easy-to-treat patients in the near future, whereas IFN might be necessary for difficult-to-treat patients.

***The role of IL-28B in reducing treatment duration***

In Table 2 and Table 5, groups 4 and 6 differ with respect to treatment duration (12 wk and 8 wk, respectively). In group 4, 81% (9/11) of patients were genotype CC or CT. In group 6, 90% (9/10) of patients were genotype CC or CT. It will be interesting to investigate whether IL-28B polymorphisms could predict treatment duration in the DAA era, especially in patients with the potential to reduce the treatment course.

***Other aspects***

In addition to above-mentioned situations, results from group 5 patients who received sofosbuvir monotherapy suggested the crucial role of RBV in maintaining an antiviral response (Table 2). However, the exact mechanism by which RBV contributes to SVR in the DAA era remains uncertain. Another area of important research in the future will likely be treatment of patients with cirrhosis, and hepatitis B virus and human immunodeficiency virus co-infected patients. Although the sofosbuvir- and ABT-450-based therapies were well tolerated, the safety profile of other combination treatments remains to be seen.

**CONCLUSION**

A series of clinical trials have demonstrated that we are currently experiencing a “watershed moment” for the treatment of hepatitis C[51,52]. Despite some unresolved questions, the recent achievements demonstrating DAAs as potent new HCV clearing agents with improved SVR rates appear to be encouraging, and it may be possible to cure nearly all HCV-infected patients in the near future.The progress of new anti-HCV agents might indicate that agents with specificity, sensitivity and a high barrier to resistance are the mainstay for conquering pathogen-related disease. Future studies may focus on the improvement of SVR rates in genotype 1 patients who have no or partial response to prior therapy as well as special patient populations, such as those with cirrhosis or co-infected patients. Furthermore, determining an optimal combination therapy with little cross-resistance and few adverse events as well as better understanding the status of IL-28B polymorphism and the potential mechanism of how RBV may synergize with DAAs are also areas of future study.

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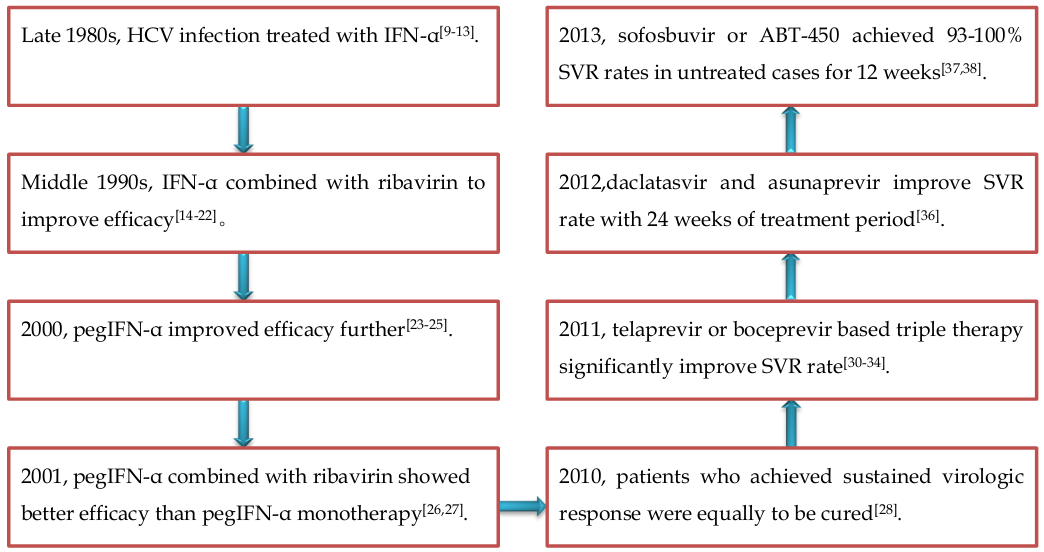
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**Figure 1** **Brief development history of the anti-hepatitis C virus agents.** HCV: Hepatitis C virus; INF-α: Interferon-α.

**Table 1 Representative direct acting antiviral agent from 2011 to January, 2013**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **DAA** | **HCV genotype** | **Course of DAA** | **Course of therapy** | **Dose** | **With or without pegIFN-α** | **Publishd year** | **References** |
| **Telaprevir** | 1a/1b/1c/unknown | 12/8wk | 20/24/44/48 wk | 750 mg(*tid*) | With | 2011 | 30-32 |
| **Boceprevir** | 1a/1b/unknown | 24/32/44wk | 28/36/48 wk | 800mg(*tid*) | With | 2011 | 33-34 |
| **Daclatasvir** | 1a/1b | 24 wk | 24 wk | 60 mg (*qd*) | With or without | 2012 | 36 |
| **Asunaprevir** | 1a/1b | 24 wk | 24 wk | 600 mg (*bid*) | With or without | 2012 | 36 |
| **Sofosbuvir** | 1/2/3 | 8/12 wk | 8/12 wk | 400 mg (*qd*) | Without | 2013 | 37 |
| **ABT-450** | 1a/1b | 12 wk | 12 wk | 250/150 mg (*qd*) | Without | 2013 | 38 |

*qd*: Once daily; *bid*: Twice daily; *tid*: Thrice daily. DAA: Direct acting antiviral agent; pegIFN-α: Peginterferon-α.

**Table 2 Overview of 95 hepatitis C patients under sofosbuvir regimen**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Group** | **Number** | **Genotype(*n*)** | **Status before treatment** | **Therapeutic schedule** | **SVR rate** |
| **1** | 10 | 2/3(4/6) | Untreated | Sofosbuvir+RBV 12wk | 100% |
| **2** | 9 | 2/3(3/6) | Untreated | (Sofosbuvir+RBV 12 wk)+pegIFNα-2a 4 wk | 100% |
| **3** | 10 | 2/3(4/6) | Untreated | (Sofosbuvir+RBV 12 wk)+ pegIFNα-2a 8 wk | 100% |
| **4** | 11 | 2/3(4/7) | Untreated | Sofosbuvir+RBV+ pegIFNα-2a 12 wk | 100% |
| **5** | 10 | 2/3(3/7) | Untreated | Sofosbuvir 12 wk | 60% |
| **6** | 10 | 2/3(0/10) | Untreated | Sofosbuvir+RBV+pegIFNα-2a 8 wk | 100% |
| **7** | 10 | 1a/1b(9/1) | No response to prior therapy | Sofosbuvir+RBV 12 wk | 10% |
| **8** | 25 | 1a/1b(22/3) | Untreated | Sofosbuvir+RBV 12 wk | 84% |

*qd*: Once daily; *bid*: Twice daily; *tid*: Thrice daily. *qw*: Once weekly; SVR: Sustained virologic response; The dose of sofosbuvir is 400 mg (*qd*), Peginterferon α (pegIFN α)-2a is 180 μg (*qw*), ribavirin (RBV) is 500mg (*bid*) for patients with body weight < 75 kg, and RBV is 600 mg (*bid*) for patients with body weight > 75 kg.

**Table 3 Overview of 50 hepatitis C patients under ABT-450 regimen**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Group** | **Number** | **Genotype(*n*)** | **Status before treatment** | **Therapeutic schedule** | **Usage** | **SVR2 rate** |
| **1** | 19 | 1a/1b (17/2) | Untreated | ABT-450+Ritonavir+  ABT-333+RBV 12 wk | ABT-450 250mg *qd*  Ritonavir 100mg *qd*  ABT-333 400mg *bid*  RBV 1000 or 1200mg/d1 | 95% |
| **2** | 14 | 1a/1b (11/3) | Untreated | ABT-450+Ritonavir+  ABT-333+RBV12 wk | ABT-450 150mg *qd*  Ritonavir+ABT-333+RBV Ditto | 93% |
| **3** | 17 | 1a/1b (16/1) | No or partial response to prior therapy | ABT-450+Ritonavir+  ABT-333+RBV12 wk | ABT-450 150mg *qd*  Ritonavir+ABT-333+RBV Ditto | 47% |

1Body weight < 75 kg 1000 mg/d, divided into doses of 400 mg and 600 mg, bid; Body weight ≥ 75 kg 1200mg/d, 600 mg bid; 2Sustained virologic response (SVR) in this study was defined as an hepatitis C virus RNA level of less than 25 IU per milliliter 12 wk after treatment. *qd*: Once daily; *bid*: Twice daily; RBV: Ribavirin.

**Table 4 Major adverse events during sofosbuvir and ABT-450** **regimens**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Adverse events** | **Sofosbuvir regimen** | **ABT-450 regimen1** | **Adverse events** | **Sofosbuvir regimen** | **ABT-450 regimen1** |
| **Headache** | 32%-90% | 14%-26% | **Vomiting** | No data | 0%-21% |
| **Fatigue** | 10%-70% | 35%-47% | **Irritability** | 0%-36% | No data |
| **Insomnia** | 10%-67% | 0%-26% | **Pruritus** | 0%-33% | 0%-21% |
| **Nausea** | 0%-44% | 21%-24% | **Decreased appetite** | 0%-50% | No data |
| **Rash** | 10%-60% | 6%-21% | **Upper respiratory tract infection** | 0%-20% | No data |
| **Anemia** | 0%-44% | No data | **Arthralgia** | 0%-30% | No data |
| **Dizziness** | 4%-44% | 5%-29% | **Back pain** | 0%-22% | No data |
| **Myalgia** | 0%-40% | No data | **Pyrexia** | 0%-18% | No data |
| **Diarrhea** | 0%-30% | No data |  |  |  |

1Adverse events during ABT-450 regimen were only listed those that occurred in more than 20% of patients.

**Table 5 IL-28B polymorphism in sofosbuvir and ABT-450 era**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Group (sofosbuvir)** | **Status before treatment** | **IL-28B CC (*n)*** | **IL-28B CT (*n*)** | **IL-28B TT (*n*)** | **SVR rate (*n*)** |
| **1** | Untreated | 5 | 4 | 1 | 100% |
| **2** | Untreated | 4 | 4 | 1 | 100% |
| **3** | Untreated | 4 | 4 | 2 | 100% |
| **4** | Untreated | 4 | 5 | 2 | 100% |
| **5** | Untreated | 2 | 6 | 2 | 60% |
| **6** | Untreated | 3 | 6 | 1 | 100% |
| **7** | No response to  prior therapy | 2 | 5 | 3 | 10% |
| **8** | Untreated | 11 | 12 | 2 | 84% |
| **Group(ABT-450)** |  |  |  |  |  |
| **1** | Untreated | 10/9 | 7/7 | 2/2 | 95% |
| **2** | Untreated | 5/4 | 7/7 | 2/2 | 93% |
| **3** | No or partial response to prior therapy | 0/0 | 12/6 | 5/2 | 47% |

SVR: Sustained virologic response.

**Table 6 The outcome of representative direct acting antiviral agent-based therapy for genotype 1 null responders**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Authors** | **Number** | **Therapeutic schedule** | **SVR rate** | **References** |
| Zeuzem *et al*[24] | 37 | (pegIFN-α2a+RBV)4W+(pegIFN-α2a+RBV+Telaprevir)12W+(pegIFN-α2a+RBV)32 wk | 33% | 32 |
| Bacon *et al*[33] | 58 | (pegIFN-α2b+RBV)4W+(pegIFN-α2b+RBV+Boceprevir)44 wk | 52% | 33 |
| Lok *et al*[36] | 11 | Daclatasvir+Asunaprevir 24 wk | 36% | 36 |
| Lok *et al*[36] | 10 | Daclatasvir+Asunaprevir+pegIFN-α2a+RBV 24 wk | 90% | 36 |
| Gane *et al*[37] | 10 | Sofosbuvir+RBV 12 wk | 10% | 37 |
| Poordad *et al*[38] | 7 | ABT-450+Ritonavir+ABT-333+RBV 12 wk | 43% | 38 |

pegIFN α: Peginterferon α; SVR: Sustained virologic response.