Published in final edited form as:

Expert Opin Pharmacother. 2015 March ; 16(4): 617–624. doi:10.1517/14656566.2015.1012493.

Dasabuvir: a new direct antiviral agent for the treatment of hepatitis C

Juan Pablo Trivella, MD¹, Julio Gutierrez, MD², Paul Martin, MD^{†,3}

¹University of Miami/Jackson Memorial Hospital, Department of Gastroenterology and Hepatology, 1500 NW 12 Ave, Jackson Medical Tower E-1101, Miami, FL 33136, USA

²University of Texas Health Science Center, The Texas Liver Institute, San Antonio Department of Hepatology, 607 Camden, San Antonio, TX 78215, USA

³University of Miami, Miller School of Medicine, Department of Gastroenterology and Hepatology, 1500 NW 12 Ave, Jackson Medical Tower E-1101, Miami, FL 33136, USA

Abstract

Introduction: Treatment of hepatitis C virus (HCV) infection with direct-acting antivirals (DAAs) has revolutionized the care of infected patients. Among these novel compounds are non-nucleoside analogs, which bind viral RNA- dependent RNA polymerase resulting in a conformational change inhibiting RNA synthesis.

Areas covered: Efficacy and tolerability of treatment regimens containing the non-nucleoside analog polymerase inhibitor dasabuvir (ABT-333).

Expert opinion: Dasabuvir-containing regimens achieve high rates of sustained virologic response in HCV genotype 1a and 1b--infected patients when combined with other DAAs, namely paritaprevir (ABT-450), ritonavir and ombitasvir (ABT-267). In the populations studied, dasabuvir seems to be well tolerated and safe. The major limitations of this novel drug are its genotype-restricted activity, the necessity to include ribavirin for HCV genotype 1a and the emergence of resistance if not combined with other DDAs.

Keywords

ABT-333; antiviral agents; dasabuvir; hepatitis C; polymerase inhibitor; sustained virological response

1. Introduction

More than 180 million people worldwide are chronically infected with the hepatitis C virus (HCV) [1]. The current estimated global prevalence is around 2.3% but this proportion varies considerably among different regions [2].

[†]Author for correspondence: pmartin2@med.miami.edu.

Declaration of interest

P Martin acts as a consultant and investigator for Abbvie. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

“*The Global Burden of Diseases, Injuries and risk factors study*” [3] identified Central and East Asia and North Africa/Middle East as regions with the highest prevalence of HCV (> 3.5%), whereas Asia Pacific, Tropical Latin America and North America had lower disease prevalence (< 1.5%). The estimated HCV prevalence in European countries varies between 2.4% for Western and Central Europe to 2.9% for Eastern Europe [4].

In the United States, the calculated HCV prevalence is 1.3% of the general population but this percentage may be an underestimate since a significant proportion of infected individuals remain undiagnosed [5].

Twenty to thirty years after the initial exposure to the virus, 10 - 20% of chronically infected individuals will develop cirrhosis. Once cirrhosis has developed, the risk of hepatocellular carcinoma increases annually between 1 and 5% and the risk of hepatic decompensation increases 3 - 6% per year [6].

Until recently, antiviral therapy for HCV was based on peginterferon α and ribavirin (RBV) [7]. In 2011, the first-generation direct-acting antivirals (DAAs) boceprevir and telaprevir were approved by the FDA for therapy of HCV genotype 1 infection. Two years later, sofosbuvir, a nucleotide analog inhibitor of the HCV NS5B polymerase [8], and simeprevir, a selective HCV NS3/4A-protease inhibitor [9], were introduced for treatment of HCV genotype 1a and 1b. When combined, treatment with sofosbuvir and simeprevir for 12 weeks led to sustained virologic response (SVR) in 93% of prior null-responders with HCV genotype 1a and 1b [10].

Several additional DAAs are currently in advanced clinical testing. Among these, the non-structural (NS) NS3/4A serine proteases, NS5A protein and NS5B RNA-dependent RNA polymerase inhibitors are particularly promising [11].

Dasabuvir (Box 1), a non-nucleoside polymerase inhibitor, is one of these novel compounds. It was recently approved by the FDA for its use in combination with other DAAs for the treatment of hepatitis C genotype 1a and 1b.

2. Dasabuvir

Once HCV enters the hepatocyte, the RNA-composed viral genome is translated by the NS5B polymerase into a single protein. This structure is cleaved by the host and viral proteases into 10 individual proteins that are either part of the virion structure or exert functions in the replication cycle of the HCV [12].

Inhibitors of NS5B are classified into two main categories: i) nucleotide analogs compete with physiological nucleotides for the incorporation in the RNA strand, blocking further protein assembly. Drugs from this class have pangenotypic activity since the active site is well preserved among the different HCV genotypes; and ii) non-nucleoside analogs attach directly to the enzyme, producing an allosteric modulation that renders it nonfunctional [13].

Dasabuvir as a non-nucleoside NS5B polymerase inhibitor binds the enzyme outside its active site producing a conformational change that inhibits its activity [13]. A limitation of

dasabuvir is the lower potential for cross-genotypic activity as the binding sites are poorly preserved across HCV genotypes. For this reason, use of dasabuvir is limited to genotype 1 patients and it also must be used in combination with other agents. However, in genotype 1a and 1b infection, it exhibits highly potent and selective activity [11] and is safe and well tolerated in single and multiple ascending doses in healthy volunteers [14,15].

With regard to pharmacokinetics, studies in human hepatocytes indicate that dasabuvir does not affect CYP. Its metabolism is mainly oxidative and it is followed by product conjugation into a glucuronide. *In vivo*, dasabuvir has good bioavailability and distribution through liver and is eliminated primarily by biliary excretion [16].

2.1 IFN-containing regimens

2.1.1 Dasabuvir, PEG and RBV—To assess its safety, pharmacokinetics and antiviral activity, dasabuvir was evaluated as initial monotherapy for 2 days followed by 26 days of combination with peginterferon and RBV in treatment-naïve genotype 1a and 1b HCV-infected subjects (total n = 24, 21G1a + 3G1b). Patients were divided into three groups, each of which received a fixed dose of dasabuvir (300, 600 or 1200 mg twice daily [b.i.d]) until completion of the 28 days. Placebo group (Total n = 6, 5G1a + 1G1b) received the combination of peginterferon and RBV alone. 79.2% (19/24) of the patients in the dasabuvir group had an HCV RNA maximal decrease superior to 2 log₁₀, whereas in the placebo group only 16.7% (1/6) had similar results. At day 28, 10 patients in the treatment group had an HCV RNA < 25 IU/ml, whereas none in the placebo group achieved this viral load [17].

Another double-blind, randomized Phase IIa trial [18] investigated the dose-dependent efficacy and safety of dasabuvir and P/R in a 12-week study of treatment-naïve HCV genotype 1 patients. The first group (8 patients: 5G1a + 3G1b) received 400 mg of dasabuvir b.i.d for 3 days followed by a regimen of dasabuvir with pegylated IFN and RBV (400 mg dasabuvir b.i.d, 180 mg/week peginterferon, 1000 -- 1200 mg weight-based RBV). Group 2 (8 patients: 6G1a + 2G1b) received the analogous treatment regimen with dasabuvir at 800 mg b.i.d. The control group (11 patients: 9G1a + 2G1b) received a matched placebo for dasabuvir alongside the P/R treatment. After 12 weeks of treatment, group 1 demonstrated an 87.5% virologic response, the group 2 virologic response was 62.5%, whereas the placebo group achieved only a total virologic response of 18.2%. Even though the sample size was small, there was a numerically greater HCV RNA decrease in subjects infected with subtype 1b than in subjects with subtype 1a (1.45 vs 0.82). Dasabuvir was well tolerated, without patients discontinuing treatment. Mild adverse events included headache and fatigue. Although the addition of dasabuvir showed modest improvement in SVR when combined with IFN/RBV over standard care alone, it is unlikely to be a commonly prescribed regimen given the availability of IFN-free regimens.

2.2 IFN-free regimens

2.2.1 Dasabuvir, paritaprevir, ombitasvir—The efficacy of combining DAAs targeting HCV had been studied *in vitro*. The pairwise combination of paritaprevir (a potent HCV NS3/4A protease inhibitor), ombitasvir (NS5A inhibitor) and dasabuvir has shown

additive and synergistic activity in cellular models. This translates into an improved resistance barrier when compared with any single DAA alone [19].

2.2.2 Dasabuvir, paritaprevir/r and RBV—An open-label Phase IIa study of 50 patients with HCV genotype 1 used a 12-week regimen of dasabuvir (400 mg b.i.d dose) with RBV (1000 -- 1200 mg daily dose).

A subgroup of 33 previously untreated patients also received two daily doses of either 150 mg (group 1) or 250 mg (group 2) of paritaprevir (including 100 mg of ritonavir), while the remaining 17 patients (group 3; either null or partial response to previous peginterferon/RBV treatment) received a single daily dose of 150 mg paritaprevir (including 100 mg of ritonavir). All patients received weight-derived doses of RBV. Twelve weeks post-treatment, SVR was 95% for group 1 patients, 93% for group 2 patients and 47% for group 3 patients. Common adverse events included fatigue, nausea, headache and insomnia. One patient discontinued treatment due to abnormal elevation of aminotransferases [20].

2.2.3 Dasabuvir, ombitasvir, paritaprevir/r and RBV—A randomized, open-label, Phase IIb trial of IFN-free therapy with dasabuvir, ombitasvir, paritaprevir/r and RBV [21] included 571 HCV genotype 1 patients, treatment naïve, as well as previous nonresponders to therapy (438 untreated patients and 133 previously nonresponder patients). A total of 14 treatment subgroups included combinations of paritaprevir/r (100, 150 or 200 mg daily doses, each with 100 mg of daily ritonavir), ombitasvir (25 mg daily dose) and dasabuvir (400 mg b.i.d dose) along with weight-dependent doses of RBV. Treatment duration varied from 8, 12 to 24 weeks (Table 1). Results at 24 weeks posttreatment showed that 88% of previously untreated patients in the 8-week group had SVR while 95% of previously untreated patients in the 12-week groups demonstrated SVR (primary efficacy analysis on subgroups administered 150 mg of paritaprevir). SVR among all treatment subgroups ranged from 83 to 100%. The most common adverse events were fatigue, headache, nausea and insomnia. Only 1% (8 patients) discontinued treatment prior to completion of the study.

The SAPHIRE I trial [22] included 631 naïve to treatment, non-cirrhotic, genotype 1 HCV-infected patients that were randomly assigned to receive paritaprevir/r-ombitasvir (single tablet co-formulation, once daily) and dasabuvir (b.i.d) in combination to RBV (weight based) or matching placebo. In the genotype 1a patients receiving RBV, the rate of SVR at 12 weeks was 95.3% and for those with genotype 1b the SVR was as high as 98%. The rate of discontinuation of therapy due to adverse events was significantly low (0.6%) in both treatment and placebo group. The SAPHIRE II trial [23] looked at the efficacy of combining paritaprevir/r-ombitasvir once daily and dasabuvir b.i.d in association to RBV or matching placebo in patients who *failed* prior treatment with peginterferon-RBV. The overall SVR at 12 weeks in the treatment group (combination therapy + RBV) was 96.3% (genotype 1a: 96% and genotype 1b: 96.7%). All patients who had a prior partial response to peginterferon-RBV responded to the new combination therapy + RBV, whereas 95.3% of patients with prior relapse and 95.2% of patients with prior null response achieved SVR after 12 weeks of treatment.

In the PEARL III study [24], 419 HCV genotype 1b patients were treated with paritaprevir (150 mg), ritonavir (r) (100 mg), ombitasvir (25 mg) and dasabuvir (250 mg) with either RBV (1000 -- 1200 mg weight-dependent) or a matched placebo for 12 weeks. The SVR for the RBV and placebo groups was 99.5 and 99%, respectively. In this trial, 9% of patients in the RBV group required RBV dose reduction due to anemia. Most recently, an Austrian study presented at the 2014 ACG meeting [25] showed similar results (99% SVR in HCV genotype 1B patients treated with the combination paritaprevir/r, ombitasvir, dasabuvir but no RBV), suggesting that RBV does not enhance the efficacy of this regimen in HCV genotype 1b patients.

The combination of paritaprevir/r, ombitasvir, dasabuvir and RBV was further evaluated in patients with cirrhosis due to HCV genotype 1 (A and B) who were naïve to HCV treatment or who failed prior therapy with peginterferon-RBV. In this study, 380 patients with Child-Pugh class A cirrhosis were randomly assigned to receive either 12 or 24 weeks of treatment with the three-drug combination and RBV. 91.8% of the patients in the 12-week treatment arm achieved SVR at posttreatment week 12, whereas the SVR with 12 weeks in the 24-week arm was 95.9%. The difference in rates of SVR between the two groups was not significant ($p = 0.09$) but for both groups the response was superior to the historical control rate [26]. During the course of this study it was also noted that there was an early improvement in standard laboratory tests (ALT, AST, GGT, bilirubin, albumin, PT and platelets) reflecting a reduction in hepatic injury and normalization of liver synthetic capabilities [27].

In liver transplant recipients with recurrent HCV genotype 1 infection, the three-drug combination with RBV was highly effective. In a recent publication, 34 liver transplant recipients with no or mild fibrosis were treated for either 12 or 24 weeks. At the end of the study, no viral load was evidenced in 97% of the patients. The most common adverse events experienced were fatigue, headache and cough [28].

The TURQUOISE I trial assessed the safety and tolerability of the three-drug combination plus RBV in patients coinfecting with HCV genotype 1 and HIV-1 at 12 or 24 weeks. Both groups achieved high SVR (93.5% in the 12-week group and 96.9% in the 24-week group) and the majority of adverse events, when present, were mild to moderate in intensity (fatigue, insomnia, headache). No patient discontinued therapy due to symptoms. The HIV viral load remained below 200 c/ml in all patients after completion of treatment. This study suggests that there is no significant difference regarding adverse events, tolerability or virologic response between patients coinfecting with HIV/HCV and those with HCV monoinfection [29].

2.3 Adverse events associated with dasabuvir

Adverse events associated with second-generation DAAs are generally mild and do not typically require discontinuation of therapy [30]. The most common adverse events related to regimens containing dasabuvir have included headache, fatigue, nausea and dizziness (Table 2). Dasabuvir combined with IFN and RBV has more frequent adverse events than its use in IFN-free regimens. In IFN-free regimens incorporating RBV, dose reductions of the latter due to toxicity (anemia) have been required in up to 10% of the patients [30].

However, RBV dose reduction does not appear to diminish SVR in all oral DAA regimens. Baseline patient characteristics, including race, ethnicity, gender or IL28b, do not affect the likelihood of experiencing adverse events during dasabuvir treatments or SVR [31].

The potential drug--drug interactions associated with dasabuvir-containing regimens also reflect the inclusion of ritonavir. This antiviral is added to the three-drug treatment in order to increase paritaprevir plasma concentrations, allowing its once-daily dosing administration [32]. Ritonavir causes CYP3A inhibition, a key mechanism in pharmacologic drug metabolism. Thus, ritonavir may prolong pharmaceutical half-lives of concomitant medications, including immunosuppressants, benzodiazepines, antipsychotics and antidepressants, statins and others [33,34].

3. HCV resistance

Due to the lack of proofreading capability, the HCV polymerase enzyme has relatively poor fidelity. Hence, a wide variety of spontaneous viral mutations are synthesized constantly by the reproducing virus [7]. Viral resistance patterns to non-nucleoside inhibitors reflect the viral protein-binding site.

Viral polymorphisms that have been shown to affect the performance of dasabuvir include C316Y, M414T/V, Y448H/C, G554S, S556G and D559G. *In vitro* studies have shown that these resistant variants experience a loss of susceptibility to dasabuvir that ranges from less than 10-fold to more than a 1000-fold when compared to the nonmutant variants [35]. *In vivo*, the resistant variants are commonly detected in patients who have failed previous treatment with pegIFN/RBV even if naïve to DAA [20,36,37].

In a study of dasabuvir in combination with paritaprevir/r and RBV, relapse primarily occurred in genotype 1a patients. Prior to the addition of ombitasvir to this regimen, relapse was associated with resistance variants to both paritaprevir and dasabuvir. Addition of ombitasvir (an NS5A inhibitor) improved SVR; however, virologic failure continues to be more prevalent in genotype 1a patients, likely due to resistance patterns including those seen with dasabuvir [20].

The resistance profile to dasabuvir was evaluated in another trial in which naïve-to-treatment patients with HCV genotype 1 (a and b) received dasabuvir as monotherapy for 2 days and then continued on dasabuvir, PEG-INF and RBV for another 26 days. In this study, the most frequently seen mutation was S556G but the mutation that conferred the highest level of resistance was C316Y. The presence of C316Y did not alter the response to IFN/RBV except for 1 out of 24 patients in which IFN levels were not detectable [17].

Most recently, the SAPHIRE-I trial showed that one patient (0.2%) treated with dasabuvir, ombitasvir, paritaprevir/r and RBV had virologic failure and seven (1.5%) had relapse at posttreatment week 12. Each of the eight patients described above had at least one amino acid variant known to confer resistance to DAAs. The variant S556G in the protein NS5B was seen in three patients [22]. In the SAPHIRE II trial, no patient had virologic failure while on treatment but seven of them (2.4%) had posttreatment relapse. In five of these patients (4 G1a + 1 G1b), at least one amino acid known to confer resistance to DAAs was

detected. Three of these patients (2 G1a + 1G1b) had the S556G variant in the NS5B protein [23].

4. Conclusion

Dasabuvir achieves an SVR of > 90% in patient with HCV genotype 1 (a and b) when combined with other DAAs. It was recently approved by the FDA in combination with ombitasvir, paritaprevir and ritonavir with or without RBV for treatment of patients with chronic hepatitis C infection including those with compensated cirrhosis (Table 3).

As a non-nucleoside polymerase inhibitor, the threshold for resistance is low and its mechanism of action is limited to genotype 1 virus alone. Dasabuvir is not a substrate for CYP (minimizing the likelihood of interaction with other drugs) but the requirement for ritonavir boosting does.

Clinical trials indicate that the most common side effects seen with dasabuvir-containing regimens are headaches, fatigue and nausea. This drug is well tolerated by most patients. Besides its activity in non-cirrhotic patients (either naïve or who failed prior treatment), dasabuvir has shown to be effective and safe in patients with compensated cirrhosis (Child-Pugh class A), liver transplant recipients and patients coinfecting with HIV-1.

5. Expert opinion

Dasabuvir is a non-nucleoside analog that binds the polymerase enzyme outside its active site. When compared to other DAAs, dasabuvir alone is only moderately effective in eradicating the virus. In combination as a triple therapy, dasabuvir potentiates the overall effect of other direct antiviral medications, achieving excellent rates of SVR in HCV genotype 1b. The addition of RBV results in optimal rates of SVR in genotype 1a.

Initially, dasabuvir was studied in non-cirrhotic, mostly healthy, primarily treatment-naïve patients with hepatitis C. Recent trials have amplified this study population, demonstrating excellent results in patients who failed prior antiviral therapy, patients with compensated cirrhosis, post-liver transplant patients and ultimately patients coinfecting with HIV-1.

One of the major limitations of dasabuvir is that its use is exclusive for genotype 1 patients.

In terms of its side effects and safety, dasabuvir is now licensed along with paritaprevir/r, ombitasvir and RBV. This combination of drugs is well tolerated with only minor to moderate side effects, not requiring discontinuation of treatment in the vast majority of patients. This improved safety profile is expected to boost patient adherence to treatment minimizing the development of viral resistance.

In conclusion, dasabuvir along with the other DAAs have revolutionized the treatment of HC genotype 1-infected patients. Its combination with paritaprevir/r, ombistavir and RBV seems to be highly effective and safe across different populations. Post-commercialization studies are warranted to further investigate its generalizability and safety.

Bibliography

Papers of special note have been highlighted as either of interest (.) or of considerable interest (..) to readers.

1. El-Serag HB. Epidemiology of viral hepatitis and hepatocellular carcinoma. *Gastroenterology* 2012;142(6):1264–73; e1 [PubMed: 22537432]
2. Lavanchy D. Evolving epidemiology of hepatitis C virus. *Clin Microbiol Infect* 2011;17(2):107–15 [PubMed: 21091831]
3. Mohd Hanafiah K, Groeger J, Flaxman AD, Wiersma ST. Global epidemiology of hepatitis C virus infection: new estimates of age-specific antibody to HCV seroprevalence. *Hepatology* 2013;57(4):1333–42 [PubMed: 23172780]
4. Negro F. Epidemiology of hepatitis C in Europe. *Dig Liver Dis* 2014;46S5:S158–S64
5. Kanwal F, Hoang T, Kramer JR, et al. Increasing prevalence of HCC and cirrhosis in patients with chronic hepatitis C virus infection. *Gastroenterology* 2011;140(4):1182–8; e1 [PubMed: 21184757]
6. Westbrook RH, Dusheiko G. Natural history of hepatitis C. *J Hepatol* 2014;61(1S):S58–68 [PubMed: 25443346]
7. Kiser JJ, Flexner C. Direct-acting antiviral agents for hepatitis C virus infection. *Annu Rev Pharmacol Toxicol* 2013;53:427–49 [PubMed: 23140245]
8. Rose L, Bias TE, Mathias CB, et al. Sofosbuvir: a nucleotide NS5B inhibitor for the treatment of chronic hepatitis C infection. *Ann Pharmacother* 2014;48(8):1019–29 [PubMed: 24811396]
9. Gaetano JN. Benefit-risk assessment of new and emerging treatments for hepatitis C: focus on simeprevir and sofosbuvir. *Drug Healthc Patient Saf* 2014;6:37–45 [PubMed: 24729731]
10. Lawitz E, Ghalib R, Rodriguez-Torres M, et al. COSMOS Study: SVR4 results of once-daily regimen of simeprevir (TMC435) plus sofosbuvir (GS-7977) with or without ribavirin in HCV genotype 1 null responders. 20th Conference on Retroviruses and Opportunistic Infections (CROI); 3 -- 6 March 2013; Atlanta, GA; Poster 34
11. Manns MP, von Hahn T. Novel therapies for hepatitis C - one pill fits all? *Nat Rev Drug Discov* 2013;12(8):595–610 [PubMed: 23807378] An excellent review article that summarizes new hepatitis C virus (HCV) therapies.
12. Gentile I, Buonomo AR, Borgia G. Dasabuvir: a non-nucleoside inhibitor of NS5B for the treatment of hepatitis C virus infection. *Rev Recent Clin Trials* 2014;9:115–23 [PubMed: 24882169]
13. Kwo PY, Vinayek R. The therapeutic approaches for hepatitis C virus: protease inhibitors and polymerase inhibitors. *Gut Liver* 2011;5(4):406–17 [PubMed: 22195237]
14. Menon R, Cohen D, Awni W, et al. Pharmacokinetics of the HCV polymerase inhibitor ABT-333 in US and Japanese Healthy Volunteers. *J Hepatol* 2010;52:S394–S94
15. Menon R, Cohen D, Nada A, et al. Pharmacokinetics, safety and tolerability of the HCV Polymerase Inhibitor ABT- 333 following multiple ascending doses and effect of co-administration of ketoconazole in healthy subjects. *J Hepatol* 2009;50:S348–S48
16. Maring C, Wagner D, Hutchinson D, et al. Preclinical potency, pharmacokinetic and ADME characterization of ABT-333, a novel non-nucleoside HCV polymerase inhibitor. *J Hepatol* 2009;50(1):S347
17. Rodriguez-Torres M, Lawitz E, Cohen D. Treatment-naïve, HCV genotype 1-infected subjects show significantly greater HCV RNA decreases when treated with 28 days of ABT-333 plus peginterferon and ribavirin compared to peginterferon and ribavirin alone. *Hepatology* 2009;50(Suppl 4):91A
18. Gaultier I, Cohen D, Dumas E, et al. 12-week efficacy and safety of ABT-072 or ABT-333 with pegylated interferon + ribavirin, following 3-day monotherapy in genotype 1 HCV- infected treatment-naïve subjects [abstract 1329]. 21st Conference of the Asian Pacific Association for the Study of the Liver (APASL); 17 -- 20 February 2011; Bangkok, Thailand
19. Pilot-Matias T, Koev G, Krishnan P, et al. In vitro combinatory effect of HCV NS3/4A protease inhibitor ABT-450, NS5A inhibitor ABT-267 and non- nucleoside NS5B polymerase inhibitor ABT-333. *J Hepatol* 2012;56:S338–S38

20. Poordad F, Lawitz E, Kowdley KV, et al. Exploratory study of oral combination antiviral therapy for hepatitis C. *N Engl J Med* 2013;368(1):45–53 [PubMed: 23281975]
21. Kowdley KV, Lawitz E, Poordad F, et al. Phase 2b trial of interferon-free therapy for hepatitis C Virus genotype 1. *N Engl J Med* 2014;370(3):222–32 [PubMed: 24428468] A very interesting pivotal trial that evaluates different combinations of direct-acting antivirals in the management of HCV.
22. Feld JJ, Kowdley KV, Coakley E, et al. Treatment of HCV with ABT-450/r-ombitasvir and dasabuvir with ribavirin. *N Engl J Med* 2014;370(17):1594–603 [PubMed: 24720703]
23. Zeuzem S, Jacobson IM, Baykal T, et al. Retreatment of HCV with ABT-450/r-ombitasvir and dasabuvir with ribavirin. *N Engl J Med* 2014;370(17):1604–14 [PubMed: 24720679]
24. Ferenci P, Nyberg A, Enayati P, et al. PEARL III: 12 weeks of ABT-450/R/267 + ABT-333 achieved SVR in >99% of 419 treatment-naïve HCV genotype 1B-infected adults with or without ribavirin. *J Hepatol* 2014;60(1):S527
25. Maieron A, Puoti M, Enejosa J, et al. SVR12 of 99% achieved with a ribavirin- free regimen of ABT-450/r/ombitasvir and dasabuvir in HCV genotype 1b infected patients. ACG Annual Scientific Meeting; 17 -- 21 October 2014; Philadelphia, PA; Oral Paper 4
26. Poordad F, Hezode C, Trinh R, et al. ABT-450/r-ombitasvir and dasabuvir with ribavirin for hepatitis C with cirrhosis. *N Engl J Med* 2014;370(21):1973–82 [PubMed: 24725237] A clinical trial that highlights the efficacy of a dasabuvir containing regimen in patients with compensated cirrhosis.
27. Everson G, Lee S, Zeuzem S, et al. Normalization of liver-related laboratory parameters in HCV genotype 1-infected patients with cirrhosis after treatment with ABT-450/R/ombitasvir, dasabuvir and ribavirin ACG Annual Scientific Meeting. 17 -- 21 October 2014; Philadelphia, PA; Oral Paper 5
28. Kwo PY, Mantry PS, Coakley E, et al. An interferon-free antiviral regimen for HCV after liver transplantation. *N Engl J Med* 2014;371:2375–82 [PubMed: 25386767] Interesting trial that explores the efficacy of a dasabuvir containing regimens in liver transplant recipient patients.
29. Eron JJ, Lalezari J, Slim J, et al. Safety and efficacy of ombitasvir - 450/r and dasabuvir and ribavirin in HCV/HIV-1 co-infected patients receiving atazanavir or raltegravir ART regimens. *J Int AIDS Soc* 2014;17(4 Suppl 3):19500 [PubMed: 25394009] A recent study that demonstrated the efficacy of a dasabuvir containing regimen in patients coinfectd with HIV-1.
30. Cohen D, Xie W, Larsen L, et al. Safety of ribavirin-containing regimens of ABT- 450/r, ABT-333, and ABT-267 for the treatment of HCV zenotype 1 infection and efficacy in subjects with ribavirin dose reductions. *Hepatology* 2013;S1:140A
31. Rodriguez-Torres M, Nunes F, Cohen D, et al. Interferon-free regimens of ABT-450/r, ABT-267, ABT-333, and ribavirin achieve high sustained virologic response 4 weeks post-treatment rates in patients with chronic HCV genotype 1 regardless of race, ethnicity, or other baseline characteristics [abstract 514]. DDW; 18 -- 21 May 2013; Orlando, FL
32. Ferenci P, Bernstein D, Lalezari J, et al. ABT-450/r-ombitasvir and dasabuvir with or without ribavirin for HCV. *N Engl J Med* 2014;370(21):1983–92 [PubMed: 24795200]
33. Zhou S Drugs behave as substrates, inhibitors and inducers of human cytochrome P450 3A4. *Curr Drug Metab* 2008;9(4):310–22 [PubMed: 18473749]
34. Zhou S, Xue C, Yu X, et al. Clinically important drug interactions potentially involving mechanism-based inhibition of cytochrome P450 3A4 and the role of therapeutic drug monitoring. *Ther Drug Monit* 2007;29(6):687–710 [PubMed: 18043468]
35. Koev G, Mondal R, Beyer J, et al. Characterization of resistant mutations selected in vitro by the non-nucleoside HCV polymerase inhibitors ABT-333 and ABT-072. *J Hepatol* 2009;50:S346–S47
36. Middleton T, He Y, Beyer J, et al. Resistance profile of ABT-333 and relationship to viral load decrease in patients treated in combination with peg- interferon and ribavirin for 28 days. *J Hepatol* 2010;52:S296–S97
37. Pilot-Matias T, Tripathi RL, Koev G, et al. Characterization of resistant variants in NS3 and NS5B detected in subjects treated with ABT-450/r, ribavirin, and either ABT-072 or ABT-333 in the pilot and co-pilot studies who experienced virologic breakthrough or relapse. *Hepatology* 2012;56:569A–70A

Box 1.**Drug summary.**

Drug Name	Dasabuvir (ABT-333)
Phase (for indication under discussion)	Pre-registration phase
Indication (specific to discussion)	Hepatitis C virus infection (HCV)
Pharmacology description/mechanism of action	HCV-NS5B polymerase inhibitor
Route of administration	Oral
Chemical structure	Inhibitor of the non-structural (NS)5B polymerase
Pivotal trial(s)	[21–24,26,28,29]

Table 1.

Virologic response to dasabuvir-containing regimens in main clinical trials.

Trial	Arm	Treatment time (weeks)	Sustained virologic response (%)
AVIATOR [21] n = 438 Genotype 1 (non-cirrhotic, previously untreated patients)	Paritaprevir/r (150 mg) + ombitavir + dasabuvir (400 mg b.i.d) + RBV	8	87.5
	Paritaprevir/r (150 mg) + dasabuvir (400 mg b.i.d) + RBV	12	82.9
	Paritaprevir/r (100 mg) + ombistavir (400 mg b.i.d) + RBV	12	84.6
	Paritaprevir/r (200 mg) + ombistavir (400 mg b.i.d) + RBV		92.5
	Paritaprevir/r (150 mg) + ombitasvir + dasabuvir (400 mg b.i.d)	12	88.6
	Paritaprevir/r (100 mg) + ombistavir + dasabuvir (400 mg b.i.d) + RBV	12	97.4
	Paritaprevir/r (150 mg) + ombistavir + dasabuvir (400 mg b.i.d) + RBV		95
	Paritaprevir/r (100 mg) + ombistavir + dasabuvir (400 mg b.i.d) + RBV	24	92.5
	Paritaprevir/r (150 mg) + ombistavir + dasabuvir (400 mg b.i.d) + RBV		90
	Paritaprevir/r (200 mg) + ombitasvir + RBV	12	88.9
AVIATOR [21] n = 133 Genotype 1 (non-cirrhotic patients without a response to prior therapy)	Paritaprevir/r (100 mg) + ombitasvir + dasabuvir (400 b.i.d) + RBV	12	91.3
	Paritaprevir/r (150 mg) + ombitasvir + dasabuvir (400 b.i.d) + RBV		95.5
	Paritaprevir/r (100 mg) + ombitavir + dasabuvir (400 b.i.d) + RBV	24	91.3
	Paritaprevir/r (150 mg) + ombitavir + dasabuvir (400 b.i.d) + RBV		100
	Paritaprevir/r (150 mg) + ombitavir + dasabuvir + RBV	12	96.2
SAPHIRE I [22] n = 631 Genotype 1 (naïve to treatment non-cirrhotic patients)			
SAPHIRE II [23] n = 394 Genotype 1 (non-cirrhotic patients without a response to prior therapy)	Paritaprevir/r (150 mg) + ombitavir + dasabuvir + RBV	12	96.3
TURQUOISE-I [29] n = 63 Genotype 1	Paritaprevir/r (150 mg) + ombistavir + dasabuvir + RBV + atazanavir or raltegravir	12	93.5

Trial	Arm	Treatment time (weeks)	Sustained virologic response (%)
Patients with hepatitis C virus (naïve or previously treated) and HIV-1 coinfection			
TURQUOISE-II [26] n = 380 Genotype 1 (cirrhotic patients, naïve to treatment or nonresponders)	Paritaprevir/r (150 mg) + ombitavir + dasabuvir + RBV	12	91.8
		24	95.9
Liver transplant recipients [28] n = 34 Genotype 1 (patients with no or mild fibrosis)	Paritaprevir/r (150 mg) + ombitavir + dasabuvir + RBV	12	97
		24	97

b.i.d: Twice daily.

Table 2.

Adverse events associated to dasabuvir-containing regimens.

	Dasabuvir + PEG-INF + ribavirin [18] (n = 16)	3D + RBV in treatment- naïve patients [22] (SAPHIRE-I) (n = 473)	3D + RBV in treatment- experienced patients [23] (SAPHIRE-II) (n = 297)	3D + RBV in patients coinfectd with hepatitis C virus and HIV-1 [29] (TURQUOISE I) (n = 63)	3D + RBV in patients with compensated cirrhosis [26] (TURQUOISE II) (n = 380)	3D + RBV in liver transplant patients with no or mild fibrosis [28] (n = 34)
Headache	6 (38)	156 (33.0)	108 (36.4)	10 (15.8)	111 (29.2)	15 (44)
Fatigue	6 (38)	164 (34.7)	99 (33.3)	30 (47.6)	148 (38.9)	17 (50)
Nausea	3 (19)	60 (20.2)	112 (23.7)	11 (17.4)	72 (18.9)	8 (24)
Pruritus	--	80 (16.9)	41 (13.8)	8 (12.6)	71 (71)	--
Insomnia	--	66 (14.0)	42 (14.1)	12 (19.0)	63 (16.6)	9 (26)
Asthenia	--	47 (15.8)	57 (12.1)	--	51 (13.4)	8 (24)
Diarrhea	5 (31)	39 (13.1)	65 (13.7)	5 (7.9)	59 (15.5)	9 (26)
Rash	--	26 (8.8)	51 (10.8)	--	48 (12.6)	7 (21)
Myalgia	1 (6)	--	--	-	--	--
Dizziness	2 (13)					
Cough	--	--	--	7 (11.1)	--	11 (32)
Anemia	--	--	--	-	34 (8.9)	10 (29)
Peripheral edema	--	--	--	-	--	6 (18)
Back pain	0 (0)	--	--	-	--	6 (18)
Upper respiratory infection		--	--	9 (14.2)	--	--

Table 3.

FDA-approved dasabuvir-containing regimen for HCV genotype 1 treatment.

HCV genotype	Presence of cirrhosis	FDA-approved regimen	Dosage administration	Duration of treatment (weeks)
1a	Non-cirrhotic	Ombistavir	Once daily	12
		Paritaprevir		
		Ritonavir		
		+Ribavirin		
		+Dasabuvir		
	Cirrhotic	Ombistavir	Once daily	24
		Paritaprevir		
		Ritonavir		
		+Ribavirin		
		+Dasabuvir		
1b	NonCirrhotic	Ombistavir	Once daily	12
		Paritaprevir		
		Ritonavir		
		+Dasabuvir		
	Cirrhotic	Ombistavir	Once daily	12
		Paritaprevir		
		Ritonavir		
		+Ribavirin		
		+Dasabuvir	Twice daily	

HCV: Hepatitis C virus.