Safety of direct antiviral agents in the management of hepatitis C

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Safety of direct antiviral agents in the management of hepatitis C

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ABSTRACT

Introduction: Hepatitis C virus is a hepatotropic virus that generally leads to chronic hepatitis and various harmful sequelae. The lone standard of treatment has been pegylated interferon and ribavirin, which produces a modest response and many side effects. However, a new era of management was declared with the introduction of various directly acting antiviral agents.
**Areas covered:** Recent direct antiviral agents (DAAs) primarily target the non-structural proteins of the virus and affect its replication. These agents successfully achieve a sustained virologic response. However, some serious side effects were reported, which may or may not be drug-related effects. Important drug-drug interactions were also reported. The treating physician should be reasonably familiar with these effects. We review the safety profile of these agents in the management of HCV.

**Expert opinion:** Cautious concomitant drug intake is necessary for the new HCV therapies. Future HCV management will depend on interferon-free and likely ribavirin-free regimens. The co-administration of direct antiviral agents of different classes increases the probability of side effects and drug-drug interactions.

**Keywords:**
Direct antiviral agents - drug interactions - hepatitis C (HCV) - safety - side effects.

**1. INTRODUCTION**

Hepatitis C virus (HCV) is a common cause of chronic hepatitis that may detrimentally progress to liver cirrhosis, liver cell failure and hepatocellular carcinoma [1]. The genome of this RNA virus includes structural and non-structural proteins. The latter proteins are targets of a new generation of antiviral drugs, especially NS3/NS4A, NS5A and NS5B proteins [2].

The combination of pegylated interferon (peg-INF) and ribavirin were the only line of treatment before 2011. However, the nonspecific pathway, intolerable adverse events (AEs) and limited efficacy limited the use of this treatment regimen. The new era of
HCV treatments directly target viral replication, and these agents are named direct acting antivirals (DAAs) [3].

These agents were initially incorporated with peg-INF and ribavirin to enhance the sustained virologic response (SVR). Unfortunately, this regimen increased the incidence of AEs [3]. Therefore, the need for more effective and tolerable drugs resulted in the introduction of more DAAs to target structural and nonstructural proteins.

1.1. HCV resistance to DAAs
Patients who receive treatment for their HCV infection and exhibit treatment virological failure or relapse may have substitutions in their isolated and sequenced HCV. The most important factor that may allow or prevent the occurrence of these variant viral populations with resistance-associated substitutions (RASs) is the genetic barrier to resistance of DAAs, which is defined as the number and type of base pair mutation[s] that are required to cause amino acid substitution[s] that result in resistance. Other factors, such as drug exposure levels and viral replication power, may impact the development of RASs. Great differences are found in genetic barrier to resistance between different DAA classes and HCV genotypes [4]. Another factor that impacts treatment responses to DAAs is the occurrence of pretreatment viral polymorphisms, which are natural substitutions that vary according to genotype, and subtype [5].

1.2. Drug-drug interactions of DAAs
A new challenge for HCV management using the new DAAs is drug–drug interactions (DDIs). Some DAAs, such as proteases, are strong P450 CYP3A4 inhibitors. Other DAAs are inhibitors or substrates of the membrane transporter P-
glycoprotein (P-gp). Therefore, there is always a potential risk for DDIs with drugs that use the same metabolic pathways. Expected toxicity and adverse reactions may follow an increase in drug concentration. Decreased efficacy with treatment failure and development of resistant strains may result from reduced drug concentrations. The general outpatient use of DAAs increases the clinical significance and risk of DDIs [6,7].

2. **NS3/4A PROTEASE INHIBITORS**

2.1. First generation:

Boceprevir (BOC) and Telaprevir (TVR) were the first FDA approved therapeutic agents targeting HCV genotype 1 [8]. These agents are no longer recommended in treatment guidelines [9]. BOC and TVR were combined with peg-INF and ribavirin for relatively long durations (e.g., 24 weeks), which contributed to the cumulative high rates of AEs [9]. BOC and TVR are potent inhibitors of the CYP3A4 enzyme, which metabolizes numerous drugs. This inhibition explains the great tendency for drug-drug interactions and the undesirable clinical outcomes and AEs of the co-administered drugs. BOC and TVR exhibited considerable AEs. An increased incidence of anemia (15-49%) was definitely reported, which was primarily due to bone marrow suppression with the concomitant hemolytic effect of ribavirin [10]. Other AEs included fatigue (40-68%), nausea (23-48%), dysgeusia (6-45%) and diarrhea (14-32%). Dermatological AEs included rash, pruritus and anorectal itching [9-16]. Steven Johnson syndrome and toxic epidermal necrolysis were recorded as serious events [17]. These events was more obvious in patients with cirrhosis, in whom high rates of serious AEs (40.0%) were encountered, and death and severe
complications, such as severe sepsis and hepatic decompensation, occurred in 6.4% of patients. Low albumin levels and thrombocytopenia were important predictors for the occurrence of AEs in this group of patients [18].

2.2. Newer generations of protease inhibitors:

The serious AEs of first generation drugs and their interactions with some drug classes, such as human immunodeficiency virus infection (HIV), immunosuppression and antihyperlipidemics, limited their clinical use [19]. These limitations were reduced in the second wave of first generation proteases, such as simeprevir, which was FDA approved in 2013 [20]. Protease inhibitors (PIs) are not a favorable clinical choice for the treatment of HCV genotype 3 because of their limited in vitro and in vivo activity [21,22]. The polymorphism Q80K is frequently present (up to 50%) in genotype 1a patients, and this mutation is associated with resistance to simeprevir-containing therapies [23]. Proteases were approved for the management of HCV genotypes 1 and 4 with/without ribavirin and peg-INF because of their proven preclinical and clinical efficacy in these genotypes [24]. Many studies to detect the efficacy of this treatment in combination with sofosbuvir are ongoing [25].

2.2.1. Safety:

Better patient adherence and fewer AEs are achieved with simeprevir. Adverse events, such as fatigue, headache and nausea, were only graded 1-2 by most patients. Rash (17%) and pruritus (11%) were graded 1-2, but these grades increased when simeprevir was combined with ribavirin. Rash severity occasionally increased to grade 3. Notably, treatment termination because of these AEs was not reported [25].
Grade 2-3 photosensitivity was reported without the need to terminate therapy [26]. Other infrequent AEs included visual impairment, retinal tear and cholelithiasis [26]. Laboratory abnormalities included anemia (14%), neutropenia (1%), and elevated serum amylase, with no clinical pancreatitis or hyperglycemia (up to grade 3). Hyperbilirubinemia (7%) was transient and resolved by the end of treatment [23,26].

3. NS5B INHIBITORS: SOFOSBUVIR

NS5B polymerase inhibitors are categorized into two groups: nucleoside polymerase inhibitors (NIs) and non-nucleoside polymerase inhibitors (NNIs). NIs interact with the catalytic site for NS5B to targets viral RNA synthesis. A high barrier of resistance characterizes this group. NNIs bind to different allosteric sites on the NS5B protein and prevent proper viral RNA synthesis. This group exhibits a lower barrier of resistance [24].

Sofosbuvir was FDA approved in December 2013 and introduced a new era of oral nucleotide polymerase inhibitors that may be combined with other DAAs to create interferon-free regimens [27].

Sofosbuvir (formerly known as GS-7977) (400 mg, once daily tablet) is a pangenotypic DAA that undergoes hepatic phosphorylation to the active triphosphate nucleotide, which terminates viral replication by targeting the active site on NS5B polymerase. Sofosbuvir remarkably reduced HCV RNA and achieved SVR12 [28]. However, sofosbuvir cannot be used as a monotherapy and must be administered in combination with interferon, ribavirin and/or other DAAs [29].
3.1. Safety:

The efficacy and safety of sofosbuvir were evaluated in many phase 2 and 3 studies (tables 1 and 2) [29-32]. The FISSION study randomized patients to receive a 12-week course of sofosbuvir plus ribavirin or 24 weeks of the standard peg-INF alpha-2a plus ribavirin. The results revealed good safety profiles with treatment discontinuation of 1% in the 12 weeks group compared to 11% in the 24 weeks group. The most common adverse effects in both groups were fatigue (36% and 55%, respectively), headache (25% and 44%, respectively), insomnia (12% and 26%, respectively) and myalgia (8% and 16%, respectively). Anemia was more frequently reported in the 24 weeks group than the 12 weeks group (12% compared to 8%, respectively). Hemoglobin reduction below 8.5 g/dl was reported in 2% of the 24 weeks group and less than 1% in the 12 weeks group. Thrombocytopenia (<50,000/mm³) was also reported in 7% of the 24 weeks group compared to zero cases in the 12 weeks group. Neutropenia (white blood cells: 1000 to 1500/mm³) was 4% in the 24 weeks group only [33].

The addition of peg-INF increased the incidence of many AEs. The NEUTRINO trial used sofosbuvir in combination with peg-IFN and ribavirin for 12 weeks, and the results clarified the effect of interferon. The incidence of anemia increased to 21%, hemoglobin reduction below 8.5 was 2%, neutropenia increased to 6%, and nausea occurred in 25% of cases [33].

The FUSION trial used sofosbuvir and ribavirin for 16 weeks compared to 12 weeks. No discontinuation of treatment was reported in the 16 weeks group compared to 1%
in the 12 weeks group. Common AEs included fatigue, nausea and headache. Hemoglobin dropped to less than 8.5 g/dl in 2% of patients in the 12-week arm only [27]. The POSITRON trial recruited patients with no other treatment options to receive sofosbuvir and ribavirin for 12 weeks, and the most common AEs were fatigue and insomnia in the treatment group compared to placebo. Anemia was only reported in 1% of the active group [27].

No AEs led to the discontinuation of treatment in an Egyptian study that compared 12 versus 24 weeks of treatment using sofosbuvir and weight-based ribavirin. Fatigue, headache, anemia and insomnia were the most common AEs. Two patients reported serious AEs (dyspnea and cerebral ischemia) in the study population of 103 patients [34].

Many trials investigated the probability of developing resistance in patients who failed to achieve SVR. No resistance-associated variants (RAV) were identified. The only subject documented with resistance variant S282T (relapsed in week 4) was later undetectable 12 weeks after treatment. This patient received sofosbuvir as a monotherapy in the ELECTRON study, which suggests that sofosbuvir must be used in combination with other DAAs as an option for the treatment of future relapse patients without fear of resistance development [35].

Pharmacokinetic studies of sofosbuvir and its predominant active metabolite GS-331007 demonstrated that sofosbuvir was a substrate of drug transporter p-glycoprotein and breast cancer resistance protein (BCRP), but its metabolite was not a substrate. The non-CYP450 metabolic pathway suggests a lower level of drug interactions, and potent P-gp inducers (e.g., carbamazepine, oxcarbazepine and rifampin) are not recommended with sofosbuvir to prevent the loss of virological response secondary to accelerated metabolism. Co-administration of p-gp inhibitors
increases sofosbuvir levels without increasing the active metabolite. Sofosbuvir may be safely co-administered with p-gp inhibitors substrates. Notably, post-marketing reports of sofosbuvir include cases of serious adverse drug events, such as severe symptomatic bradycardia, with the co-administration of sofosbuvir and amiodarone via an unclear mechanism [36]. Sofosbuvir must not be prescribed for patients with severe renal impairment (i.e., estimated glomerular filtration (eGFR) rate less than 30 ml/min) or end-stage renal disease because preclinical animal trials suggest hepatobiliary and cardiac toxicity in these patients [37].

4. NS5A INHIBITORS:

4.1. NS5A INHIBITORS: DACLATASVIR

Daclatasvir (DCV) was FDA approved for the treatment of HCV genotype 3 in combination with sofosbuvir in July 2015. Ally-1, Ally-2 and Ally-3 are clinical trials that evaluated the efficacy of the daclatasvir/sofosbuvir combination for the treatment of HCV genotypes 1–6 in cirrhotic and post-liver transplant patients in combination with ribavirin, HIV patients co-infected with HCV genotypes 1-6, and treatment-naïve and treatment-experienced patients with HCV genotype 3 [38].

4.1.1. Safety:

The therapeutic dose of DCV is 60 mg taken once daily, which may be modified if used in combination with other CYP450 substrates. Therapeutic efficacy is lost when DCV is combined with strong CYP3A4 inducers, but dose adjustment is necessary in combination with CYP3A4 inhibitors. Therefore, the dose may be reduced to 30 mg
when taken with strong inhibitors and increased to 90 mg when co-administered with moderate inducers of the same enzyme (table 3) [39].

DDIs are not restricted to the CYP450 pathway. DCV is a substrate and inhibitor of p-glycoproteins, OATP1B1, BCRP and organic cation transporter-1. These metabolic pathways explain the basis of the use of DDIs with various drugs, such as dabigatran etexilate (P-glycoprotein/ABCB1 substrate), which requires dose adjustments when administered with daclatsvir-containing regimens [40].

Evaluations of daclatasvir/sofosbuvir regimens for HCV-HIV co-infected patients (ALLY-2 trial) revealed SVR in 97% of patients at week 12. The most common side effects were headache, fatigue and nausea. Four patients stopped treatment due to severe adverse effects not related to anti-HCV therapy. Elevated bilirubin (graded 3-4) levels and an elevated lipase level without clinical pancreatitis were reported in patients receiving ritonavir-atazanavir-based antiretroviral therapy. No treatment discontinuation was reported due to AEs [41].

The ALLY-3 trial evaluated the SVR of daclatasvir/sofosbuvir for the treatment of cirrhotic and non-cirrhotic HCV genotype 3-infected patients. Twelve-week treatment revealed SVRs of 90% and 86% in treatment-naïve and treatment-experienced patients, respectively. The SVR results were 63% and 96% in cirrhotic and non-cirrhotic patients, respectively. Treatment was generally tolerable. Common AEs were fatigue, headache, nausea, insomnia, abdominal pain and arthralgia. Notably, no reports of treatment discontinuation occurred because of AEs. Grades 3-4 laboratory
abnormalities included a transient elevation of international normalized ratio (INR), thrombocytopenia and elevated serum lipase levels [38].

However, other studies reported an occurrence of AEs that were quite severe and led to treatment discontinuation (e.g., one case developed fibromyalgia and another case developed stroke). Other studies reported significant AEs, including elevated blood sugar levels, reduced phosphorus, hypokalemia, psoriasis exacerbation, gastroenteritis and colitis [42].

5. FIXED-DOSE COMBINATIONS:

Some fixed-dose combinations are approved for the management of HCV, and the presence of these combinations in treatment guidelines is increasing.

5.1. LEDIPASVIR/SOFOSBUVIR fixed-dose combination

Ledipasvir is a newly discovered oral NS5A inhibitor that may be safely combined with sofosbuvir without fear of DDI or the need for dose reduction [43]. Ledipasvir exhibited a >3 log viral load reduction when first tested as monotherapy for patients infected with HCV GT1a [43]. Ledipasvir is also active against the sofosbuvir-resistant variant (S282T mutation) [43,44].

Two phase 2 trials (LONESTAR and NIAID ERADICATE) examined the efficiency of a once daily fixed-dose combination of sofosbuvir/ledipasvir (SOF/LDV). These
trials were followed by several different trials (ION–I, ION–II, ION–III and ION–IV) (table 4) [44-51].

5.1.1 Safety:

Phase 2 and 3 trials revealed good responses to the SOF/LDV fixed-dose combination for the treatment of HCV GT1 patients. SVR12 ranged from 93% to 100%. No treatment discontinuation due to adverse drug events was reported in the LONESTAR trial. Common AEs were nausea, anemia, headache and respiratory tract infection. The incidence of AEs was higher in patients receiving ribavirin. Four patients reported serious events: one patient experienced delirium, one patient had peptic ulcer exacerbation, one patient had a spinal compression fracture, and one patient experienced treatment-related events, including anemia and suicidal ideation. Patients who received ribavirin exhibited grade 3-4 hematological abnormalities and mild bilirubin elevation [44].

In the ION-I study, 1.1% (10 cases) of patients discontinued treatment due to AEs, and 3.8% (33 cases) had serious AEs (cellulitis, chest pain, gastroenteritis, pneumonia and hand fracture). Common AEs were more prominent in the ribavirin-receiving groups (fatigue, insomnia, headache and nausea). Hemoglobin reduction was similarly reported in this group (22-25%). Anemia was not reported in patients who did not have ribavirin in their regimen [48].

No cases of permanent treatment discontinuation were reported in the ION-II study. The most common AEs were headache, fatigue, insomnia and upper respiratory tract
infection, which were more prominent in patients receiving ribavirin. All cases with anemia occurred in the group receiving ribavirin [49]. Similar patterns of AEs were noted in the ION-III study, but only 3 cases discontinued treatment (road accident, lung cancer and severe arthralgia). Cases of anemia were reported in the LDV/SOF/RBV group and were less frequent in the LDV/SOF only group [50].

No treatment discontinuation due to AEs occurred in the ION-IV trial, which treated patients with HIV co-infection, but serious AEs were reported: 2 patients developed hepatocellular carcinoma, 2 patients had portal vein thrombosis (these 4 patients were originally cirrhotic) and 3 patients suffered severe infections (sepsis and spontaneous bacterial peritonitis). Grades 3-4 elevation in serum lipase and creatine kinase were reported with no episodes of pancreatitis. Hyperglycemia was reported in 5 patients who were diabetic or had abnormal baseline HbA1C. No HIV virologic failure was reported. All patients received an antiretroviral regimen of tenofovir and emtricitabine with efavirenz, rilpivirine or raltegravir [51].

SOF/LDV combination was used in patients with more advanced liver disease in the SOLAR 1 and SOLAR 2 studies, which included 2 cohorts: Cohort A (cirrhotic patients with moderate or severe hepatic impairment) and cohort B (post-liver transplantation patients). The study population was randomly assigned to receive either 12 or 24 weeks of SOF/LDV/Ribavirin [52,53]. Both studies achieved good SVRs, but 13 of the 337 patients (4%) in the SOLAR 1 study discontinued treatment because of AEs, and there were 10 deaths primarily because of complications related to liver decompensation [52]. Seven (2%) of the 333 patients who received treatment in SOLAR 2 study prematurely discontinued therapy due to adverse effects, and there were 17 deaths, primarily from complications of liver failure [53].
Ledipasvir is an inhibitor of p-glycoprotein and BCRP, and the combination of ledipasvir with potent p-gp potent inducers (carbamazepine, oxcarbazepine, phenytoin, phenobarbital, and rifampicin) is not recommended to avoid a loss of therapeutic response due to accelerated metabolism. Antacid administration must be separated by 4 hours. The dose of the H2 receptor blocker famotidine must not exceed 40 mg twice daily or equivalent, and administration must be separated by 12 hours. Proton pump inhibitors should be dosed as 20 mg or equivalent and may be administered simultaneously under fasting conditions. Co-administration of PPIs, especially rosuvastatin, may be associated with an increased risk of myopathies and rhabdomyolysis. Severe asymptomatic bradycardia of unknown mechanism may accompany LDV/SOF when used with amiodarone [54].

5.2. OMBITASVIR/PARITAPREVIR/RITONAVIR fixed-dose combination

Another interferon–free regimen in a single tablet containing multiple active ingredients was produced to improve patient adherence. A fixed-dose combination (FDC) of an ombitasvir (12.5 mg), paritaprevir (75 mg), and ritonavir (50 mg) (HCV NS5A inhibitor; an HCV NS3/4A protease inhibitor; and a CYP3A inhibitor, respectively) tablet co-packaged with a dasabuvir tablet was FDA approved for the treatment of HCV GT1 with or without ribavirin in December 2014. Ritonavir is an HCV inactive drug, but the addition of ritonavir to the combination enhanced the pharmacokinetic characteristics of ombitasvir [55].

The efficacy and safety of ombitasvir/paritaprevir/ritonavir FDC plus dasabuvir with ribavirin was evaluated in different multicenter phase 3 clinical trials. These trials
included chronic HCV GT1-infected patients with or without cirrhosis who were treatment naïve or treatment experienced. The results of these trials demonstrated appealing SVR12 results of 86.7-100% (table 5) [56-60].

5.2.1 Safety:

Overall, the reported AEs were mild to moderate. Headache, fatigue, insomnia, diarrhea, asthenia and pruritus were the most common AES (figure 1). Three patients in the SAPHIRE-I trial discontinued treatment due to adverse drug reactions, but one of these patients achieved SVR12 post-treatment. Recorded serious AEs included grade 3-4 hyperbilirubinemia (13 of 469 patients), grade 3-4 elevation of alanine aminotransferase level (0.9%) that returned to normal or reduced to grade 1 while continuing treatment, and grade 3-4 reduced hemoglobin levels. A total of 47.5% of patients had grade 1 reductions in hemoglobin level, and 5.8% had reduced hemoglobin levels to grade 2. Management of anemia necessitated the modification of ribavirin dose in 5.5% of patients, and a single patient required erythropoietin. No cases required blood transfusion [56].

Three patients (1%) in the SAPPHIRE-II study discontinued treatment due to serious AEs. One patient stopped treatment for unrelated causes (acute renal failure unrelated to DAA therapy), and the other 2 patients had a grade 3 elevation of ALT and diarrhea. Grade 3-4 elevation of bilirubin (2.4%), grade 3-4 elevation of ALT (1.7%) and grade 3-4 reduction of hemoglobin (0.3%) were also reported. Hemoglobin reductions were otherwise grades 1 and 2 (52% and 4.7%, respectively), and no treatment discontinuation was needed due to anemia [57].

The results of the PEARL-II study demonstrated that 2 patients (1.1%) discontinued treatment due to AEs: one patient had pancreatitis that was unrelated to treatment
(elevated amylase level at baseline), and the other patient had anxiety, tachycardia and dyspnea. Anemia occurred in 42\% of patients who received ribavirin compared to 5.5\% without ribavirin intake. Hyperbilirubinemia was more frequent with ribavirin co-administration [58]. The elevation of alanine aminotransferase exceeded 3-5 times the upper level of normal in 3 patients, but all levels returned to normal by the 12th week of treatment [58]. Patients who received ribavirin in the PEARL-III and PEARL-IV studies had a higher incidence of serious AEs and treatment discontinuation than the comparison group [59].

AEs were higher in incidence in the 24-week treatment group than 12-week group in the TURQUOISE study. Treatment discontinuation because of AEs was reported in 1.9\% and 2.3\% in the 12- and 24-weeks groups, respectively. Hyperbilirubinemia that returned to normal by end of treatment was documented in 1.6\% of patients who reported clinical jaundice and 9.7\% of patients who recorded grade 3-4 high bilirubin levels [59]. Otherwise, 52.6\% of patients showed grade 1 hemoglobin reduction. Grade 2 hemoglobin reduction was higher in the 24 weeks than 12 weeks groups (10.5\% compared to 5.8\%). Grade 3 anemia occurred in 0.8\% of patients (higher in the 12 week group 1\% compared to 0.6\%). One patient suffered from grade 4 anemia. One patient exhibited advanced cirrhosis and developed metformin-induced lactic acidosis with subsequent liver injury that required liver transplantation. This patient died out from complications, including multi-organ failure and septic shock, 80 days after the last dose of the study drug [59]. This combination is not recommended for patients with Child B and C cirrhosis.

5.2.2 Contraindications and precautions:

The ombitasvir/paritaprevir/ritonavir plus dasabuvir combination is contraindicated in patients with Child score B and C due to the potential hepatic decompensation or fatal
outcome that may require liver transplantation. The presence of four active ingredients requires increased attention to the co-administration of any drugs for the risk of possible DDI [61].

Many drugs are being studied for DDIs based on metabolism mechanisms (table 6a and 6b). The combination of potent CYP3A inducers (carbamazepine, oxcarbazepine, phenytoin and phenobarbital) are contraindicated due to the significant reduction of blood levels of DAAs. Additional risk of a clinically significant elevation of ALT occurs if an FDC is co-administered with ethinylestradiol contraception [61,62].

Other drugs that may cause serious events in combined treatment include inhaled fluticasone, pravastatin, rosuvastatin and quetiapine. These drugs should be replaced with alternatives if possible. Strict monitoring is a must with certain drugs, such as amiodarone, tacrolimus and cyclosporine. Patients with ritonavir hypersensitivity should be monitored for the risk of development of toxic epidermal necrolysis and Stevens-Johnson syndrome [61,62].

6. CONCLUSION

Direct antiviral agents are a great milestone in the management of hepatitis C virus. These agents exhibited excellent results in sustained virologic response, but they are not free of potential mild and serious side effects. These agents also have numerous drug-drug interactions that must be considered.

7. EXPERT OPINION

DAAs were developed in a step-wise manner. The first primary aim was a successful drug to reliably achieve viral eradication. This goal was successfully met with the
appearance of the backbone drug sofosbuvir. However, studies and clinical practice revealed that this drug cannot be used as a monotherapy, and other direct antiviral agents from different classes must be developed.

Several points should be considered in treatment decisions: pangenotypic coverage, which simply means more unification for treatment guidelines; high barriers to avoid resistance; drug-drug interactions; side effects; and cost. Special considerations should be given to unique patients populations, such as renal impairment/dialysis, post-liver/kidney transplantation with immunosuppressant intake, and patients on necessary and unavoidable drugs, such as antiepileptic agents. Antiviral therapies in these groups require cautious selection to avoid possible harm from drug-drug interactions or a lower antiviral response. No single agent can achieve these missions together, and there is a need to combine drugs. Gilead and Abbvie companies provide multi-class drugs in fixed-dose combinations. Studies otherwise depended on the use of sofosbuvir with different drugs.

Side effects occurred within acceptable limits. Most serious events were unrelated to drug administration. Proper history taking, examinations and assessments before treatment and strict adherence to guidelines may alleviate the development of side effects. The removal of ribavirin in future treatment regimens may also greatly reduce AEs.

The expected next steps should focus on the use of shorter (may be ultrashort) durations of treatment while retaining high efficacy. This short-term therapy may also reduce the occurrence of AEs. Treatment durations of 24 weeks have been reduced to 6-8 weeks, but shorter durations, including one-day treatments, may be achieved with more potent drugs.
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Declaration of Interest
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** of considerable interest


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Table 1: Sofosbuvir clinical trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Blinding</th>
<th>Study arms</th>
<th>Patients selected</th>
<th>Treatment duration</th>
<th>Efficacy</th>
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<tr>
<td>FISSION</td>
<td>Open-label</td>
<td>Sofosbuvir plus ribavirin for 12 weeks (256 patients) or peginterferon alfa-2a plus ribavirin for 24 weeks (243)</td>
<td>GT2,3 treatment naïve patients</td>
<td>12 and 24 weeks</td>
<td>SVR12 total :67%</td>
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<td>SOF+RBV (12 &amp;24 weeks subgroups) :</td>
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<td>INF+RBV group (active control group):</td>
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<td>• GT3:63%</td>
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<td>POSTERON</td>
<td>blinded</td>
<td>Sofosbuvir and ribavirin (207 patients) or matching placebo (71)</td>
<td>Patient for whom INF is not an option</td>
<td>12 weeks</td>
<td>SVR12 was 78% in SOF+RBV while 0% in placebo group</td>
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<td>• GT3 SVR: 61%</td>
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<td>FUSION</td>
<td>blinded</td>
<td>Sofosbuvir and ribavirin for 12 weeks (103 patients) or 16 weeks (98)</td>
<td>Patients failed INF-regimen</td>
<td>12-16 weeks</td>
<td>SVR in 12 week group : 71%</td>
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<td>SVR in 16 week group : 50%</td>
</tr>
<tr>
<td>NEUTRINO</td>
<td>open-label</td>
<td>a single open-label study, (327 patients), 12 weeks Sofosbuvir plus peginterferon alfa-2a and ribavirin</td>
<td>GT1-6, treatment naïve patients</td>
<td>12 week</td>
<td>• SVR is 90%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Historical control SVR 60%</td>
</tr>
<tr>
<td>VALENCE</td>
<td>unblinded</td>
<td>Sofosbuvir and ribavirin or placebo for 12 weeks (or 24 weeks for genotype 3 patients in active treatment arm)</td>
<td>GT2,3 treatment naïve and patients failed to achieve SVR on INF-containing regimen</td>
<td>12 or 24 weeks</td>
<td>No difference in patients reported outcomes between the 2 arms of the study</td>
</tr>
<tr>
<td>PHOTON 1 and 2</td>
<td>Open-label, non-randomized,</td>
<td>Sofosbuvir plus ribavirin</td>
<td>HCV-HIV co-infected patients.</td>
<td>12 -24 week</td>
<td>SVR12  &quot;PHOTON2&quot;</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>GT1,4 were treatment naïve, GT2,3 were treatment experienced</td>
<td></td>
<td>• GT1:85%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• GT2: 88%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• GT3:89%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• GT4: 84%</td>
</tr>
</tbody>
</table>
Table 2: Percentage of common AEs experienced by patients in clinical trials for sofosbuvir and ribavirin with or without interferon

<table>
<thead>
<tr>
<th></th>
<th>NEUTRINO</th>
<th>FISSION</th>
<th>POSITRON</th>
<th>FUSION</th>
<th>VALENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>59</td>
<td>36</td>
<td>44</td>
<td>45</td>
<td>23</td>
</tr>
<tr>
<td>Headache</td>
<td>36</td>
<td>25</td>
<td>21</td>
<td>25</td>
<td>29</td>
</tr>
<tr>
<td>Insomnia</td>
<td>25</td>
<td>12</td>
<td>19</td>
<td>20</td>
<td>11</td>
</tr>
<tr>
<td>Nausea</td>
<td>34</td>
<td>46</td>
<td>22</td>
<td>21</td>
<td>31</td>
</tr>
<tr>
<td>Itching</td>
<td>17</td>
<td>7</td>
<td>11</td>
<td>12</td>
<td>24</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>12</td>
<td>9</td>
<td>9</td>
<td>15</td>
<td>5</td>
</tr>
<tr>
<td>Anemia (Hb &lt;10)</td>
<td>29</td>
<td>10</td>
<td>8</td>
<td>12</td>
<td>7</td>
</tr>
</tbody>
</table>

Table 3: Dose modification of daclatasvir

<table>
<thead>
<tr>
<th>Dose modification</th>
<th>Co-medication</th>
<th>cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contraindicated</td>
<td>CYP3A4 strong inducer:</td>
<td>Loss of virologic response</td>
</tr>
<tr>
<td>combination</td>
<td>Carbamazepine, oxcarbazepine, phenytoin, phenobarbital, Rifampicin, St. John’s wort</td>
<td></td>
</tr>
<tr>
<td>90 mg dose-adjusted</td>
<td>Moderate CYP3A4 inducers:</td>
<td>Combination decrease blood level of DCT</td>
</tr>
<tr>
<td>combinations</td>
<td>Dexamethasone, nafcillin, bosentan and efavirenz</td>
<td></td>
</tr>
<tr>
<td>30 mg dose-adjusted</td>
<td>Moderate CYP3A4 inhibitors:</td>
<td>Combination decrease blood level of DCT</td>
</tr>
<tr>
<td>combination</td>
<td>diltiazem , verapamil, fluconazole and ciprofloxacin</td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Blinding</td>
<td>Study design</td>
</tr>
<tr>
<td>-------</td>
<td>-----------</td>
<td>--------------</td>
</tr>
<tr>
<td></td>
<td>Open - label</td>
<td>Randomized, phase 2</td>
</tr>
<tr>
<td>LONESTAR</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Open - label</td>
<td>Phase 2</td>
</tr>
<tr>
<td>NIAID ERADICATE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ION III</td>
<td>Open-label, randomized</td>
<td>Phase 3</td>
</tr>
<tr>
<td>ION IV</td>
<td>Open label</td>
<td>Phase 3</td>
</tr>
<tr>
<td>Study</td>
<td>Blinding</td>
<td>Study design</td>
</tr>
<tr>
<td>-------</td>
<td>----------</td>
<td>--------------</td>
</tr>
</tbody>
</table>
| SAPPHIRE-I | Double-blind | Placebo controlled | HCV GT1 (1a , 1b) chronic infected untreated patients | 12 weeks of active ombitasvir/paritaprevir/ritonavir + RBV | The primary end point is to assess the non-inferiority and superiority to historical control (Telparvir, INF and ribavirin):  
GT 1a:  
• non inferior SVR12 72%  
• superior SVR12 95.3%  
GT1b:  
• non inferior SVR12 80%  
• superior SVR 12 98%  
(compared with historical control, to be non-inferior must exceed 70%, to be superior must exceed 80%) |
| SAPPHIRE-II | Double-blind | Placebo controlled | HCV GT1, non-cirrhotic relapse on INF/RBV | 12 weeks of active ombitasvir/paritaprevir/ritonavir + RBV | Primary end point is SVR at 12 week post treatment:  
HCV GT1a: 96%  
HCV GT 1b: 96.7%  
Total: 96.3% |
| PEARL-II | Open-label | Randomized, parallel | HCV GT1 infected patients, without cirrhosis, previously treated with INF/RBV | 12 week of Ombitasvir/paritaprevir/Ritonavir + dasabuvir  
• With RBV – group 1  
• Without RBV – group 2 | SVR 12 week after treatment  
Group 1: 96.6%  
Group 2: 100%  
Both group were non inferior to the historical SVR rate (telprevir/ RBV) and also were found to be superior |
| PEARL-III | Double-blind | Randomized, parallel | HCV GT1b infected patients, without cirrhosis, treatment naïve | 12 week of Ombitasvir/paritaprevir/Ritonavir + dasabuvir with or without weight based dose RBV | SVR 12 week after treatment  
• RBV group: 99.5%  
• With no RBV group: 99% |
| PEARL-IV | Double-blind | Randomized, parallel | HCV GT1a infected patients, without cirrhosis, treatment naïve | 12 week of Ombitasvir/paritaprevir/Ritonavir + dasabuvir with or without weight based dose RBV | SVR 12 week after treatment  
• RBV group: 97%  
• With no RBV group: 90.2% |
| TURQUOISE-II | Open-label | Parallel – randomized | HCV GT1( 1a and 1b), child pugh class A cirrhotic treatment naïve and treatment experienced patients | Ombitasvir/paritaprevir/Ritonavir + dasabuvir with or weight based dose RBV for 12 or 24 week | SVR 12 week after treatment  
12 week group  
• GT 1a: 88.6% |
Table 6: Mechanism of DDIs with ombitasvir / paritaprevir / ritonavir:

6a: Metabolism of ombitasvir / paritaprevir / ritonavir

<table>
<thead>
<tr>
<th>Pharmacologic class</th>
<th>Metabolism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ombitasvir</td>
<td>NS5A inhibitor</td>
</tr>
<tr>
<td>Paritaprevir</td>
<td>NS/4A inhibitor</td>
</tr>
<tr>
<td>Ritonavir</td>
<td>CYP3A inhibitor</td>
</tr>
<tr>
<td>dasabuvir</td>
<td>Non-nucleoside NS5B balm polymerase inhibitor</td>
</tr>
</tbody>
</table>

6b: DDI with ombitasvir / paritaprevir / ritonavir

<table>
<thead>
<tr>
<th>Drug</th>
<th>Outcome</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alfuzosin</td>
<td>Increased risk of hypotension</td>
<td>CYP3A4 inhibition by 3D combination</td>
</tr>
<tr>
<td>Tamsulosin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Silodosin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Loss of therapeutic response of Ombitasvir/paritaprevir/ritonavir</td>
<td>CYP3A4 and CYP2C8 potent inducer combination are contraindicaded due to accelerated metabolism</td>
</tr>
<tr>
<td>Eslicarbazepine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phenytoin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fosphenytoin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug</td>
<td>Interaction Description</td>
<td>CYP Enzyme Involvement</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>---------------------------------------------</td>
<td>---------------------------------------------</td>
</tr>
<tr>
<td>Rifabutin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rifampin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rifapentine</td>
<td></td>
<td></td>
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<tr>
<td>Bosentan</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nafcillin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nevirapine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>St. John's wort</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>Increased risk of QT prolongation</td>
<td>CYP2C8 inhibitor may increase blood level of</td>
</tr>
<tr>
<td>gemfibrozil</td>
<td></td>
<td>dasabuvir</td>
</tr>
<tr>
<td>Colchicine</td>
<td>Serious renal &amp;/or hepatic impairment</td>
<td>CYP3A4 inhibition by 3D combination increase colchicine blood level</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>Reduced efficacy of 3D combination</td>
<td>CYP3A4 induction by dexamethasone</td>
</tr>
<tr>
<td>Dihydroergotamine and ergotamine</td>
<td>Ergot toxicity</td>
<td>CYP3A4 inhibition by Ombitasvir/paritaprevir/ritonavir</td>
</tr>
<tr>
<td>efavirenz</td>
<td>Intolerable liver enzyme elevation</td>
<td>Unclear mechanism</td>
</tr>
<tr>
<td>ethinylestradiol</td>
<td>Potential ALT elevation and possible contraceptive failure</td>
<td>Unspecified mechanism and possible inhibition by protease inhibitor (ritonavir)</td>
</tr>
<tr>
<td>lovastatin</td>
<td>Increased risk of myopathies</td>
<td>CYP3A4 inhibition by Ombitasvir/paritaprevir/ritonavir increase level of lovastatin</td>
</tr>
<tr>
<td>simvastatin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>sildenafil</td>
<td>Increased risk of ADEs: visual impairment, hypotension and priapism</td>
<td></td>
</tr>
<tr>
<td>midazolam</td>
<td>Increased risk of prolonged sedation and respiratory depression</td>
<td>CYP3A4 inhibition by Ombitasvir/paritaprevir/ritonavir increase level of CYP3A4 dependent benzodiazepines</td>
</tr>
<tr>
<td>triazolam</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Figure 1: Common adverse events of ombitasvir/paritaprevir/ritonavir in different clinical trials:

Article highlights

- HCV direct antiviral agents targeting the viral replication achieved a great success in terms of viral eradication.
- Despite this great achievement, there were some reported side effects for these agents as well as important drug-drug interactions.
- Cautious concomitant drug intake is a must while taking the new HCV therapies.
- Different DAAs classes have shown marked variations in their safety and drug-drug interactions profile.
- Future HCV management depending mainly on DAAs combination regimens will raise more attention to the higher probabilities for side effects and drug-drug interactions.