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New antiviral agents for the treatment of hepatitis C: ABT-450

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Abstract

Introduction: Hepatitis C virus (HCV) therapy continues to evolve rapidly. ABT-450 is a novel potent inhibitor of the non-structural 3/4A protease that has been studied in combination with several agents, allowing shorter duration of therapy and interferon-free/ribavirin-free all-oral regimens. Preliminary data from studies evaluating these new regimens are impressive with sustained virological response (SVR) rates of 88 – 100% after 12 weeks of therapy in patients with previously untreated HCV genotype 1 infection. SVR rates in treatment-experienced patients are also encouraging.

Areas covered: Efficacy and tolerability of antiviral regimens containing ABT-450 boosted with ritonavir (ABT-450/r). Results from published studies and abstracts from recent meetings are presented.

Expert opinion: Newer direct-acting antiviral agents such as ABT-450 promise effective and durable suppression of HCV with interferon/ribavirin-free all-oral regimens. This agent also allows for shorter duration of treatment and has tolerable side effects. Results of clinical trials including a broader spectrum of individuals with HCV infection are eagerly awaited.

Keywords

ABT-450; antiviral agents; hepatitis C; protease inhibitors; sustained virological response

1. Introduction

Hepatitis C virus (HCV) infection is responsible for approximately 40% of all chronic liver disease in the United States with an estimated prevalence of 1.6% of chronically infected individuals in the population as a whole, although this is probably an underestimate [1].

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Declaration of interest

AF Carrion and J Gutierrez have no conflict of interest.

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Worldwide, the estimated prevalence of HCV infection is 170 million people, with significant geographic variation [2].

Early detection of HCV infection allows for several interventions, including behavioral changes, counseling, early diagnosis of cirrhosis and screening/surveillance for gastroesophageal varices and hepatocellular carcinoma, and importantly, initiation of anti-HCV therapy. The importance of early diagnosis of HCV infection is emphasized in recent recommendations by the Centers for Disease Control and Prevention and the United States Preventive Services Taskforce to test all individuals born between 1945 and 1965, the so-called ‘baby boomers’, a cohort with high prevalence of infection [3].

HCV therapy continues to evolve rapidly with virological cure, that is sustained virological response (SVR), defined as undetectable HCV RNA in the serum 24 weeks after completion of treatment [4]. In recent trials however, the definition of SVR has been modified by diminishing the time after completion of therapy to 12 weeks (SVR12) to confirm viral eradication, and appears to be a comparable end point to the standard SVR definition allowing shorter follow-up during clinical trials [5]. During the American Association for the Study of Liver Disease (AASLD) Liver Meeting in November 2013, a high concordance between SVR rates at 24, 12 and 4 weeks post-treatment was demonstrated in clinical studies [6].

Appreciation of the HCV replicative cycle has facilitated identification of new antiviral targets, including the non-structural (NS)2/3 autoprotease, NS3/4A serine protease, NS3 RNA helicase, NS5A protein, NS5B RNA-dependent RNA polymerase and cyclophilins [7]. Other potential genomic targets for direct-acting antiviral agents (DAAs) include the nucleocapsid core protein and envelope glycoproteins E1 and E2 [7].

Introduction of telaprevir and boceprevir, first-generation DAAs, into clinical practice in 2011 heralded a new era in the treatment of HCV. Addition of either of these agents to pegylated interferon and ribavirin significantly improved SVR in individuals with untreated and previously treated HCV genotype 1 infection [8-11]. Telaprevir and boceprevir inhibit the NS3/4A serine protease, a critical enzymatic complex for HCV replication. Although clinically effective, their limitations include toxicity, frequent dosing (thrice daily), common drug--drug interaction (including calcineurin inhibitors used in solid-organ transplant recipients and anti-retroviral agents against HIV), and a low barrier to viral resistance [12,13].

Preliminary results of studies evaluating the efficacy of newer DAAs including sofosbuvir (NS5B inhibitor), simeprevir (NS3/4A inhibitor), daclatasvir (NS5A inhibitor) and asunaprevir (NS3/4A protease inhibitor) in interferon-free regimens are encouraging [14,15]. In addition, there are several other DAAs being studied in clinical trials. These newer generation DAAs have several advantages over boceprevir and telaprevir, including higher potency, more favorable pharmacokinetic profiles allowing for once-daily dosing and higher genetic barrier to resistance [16].

2. ABT-450

ABT-450 (Box 1) is a novel potent inhibitor of the NS3/4A protease that rapidly and consistently suppresses HCV [17]. This agent has been studied in combination with interferon and ribavirin as well as in interferon-free regimens along with other new generation DAAs. ABT-450 is metabolized by the Cytochrome P450 isoform 3A (CYP3A); therefore, ritonavir is used concurrently (ABT-450/r) to increase plasma concentrations and to prolong the half-life of this agent allowing for once-daily dosing [17]. Several antiviral regimens combining ABT-450 with other agents have shown impressive results, tolerable side effects, and importantly, provided support of 'all-oral' interferon-free regimens against HCV.

2.1 ABT-450/r, pegylated interferon and ribavirin

Varying doses of ABT-450/r (50/100, 100/100 and 200/100 mg orally daily) alone for 3 days, followed by combination with pegylated interferon *a*-2a (180 μ/week) and weight-based ribavirin (1000 -- 1200 mg) for 12 weeks were compared in a randomized trial [18]. Thirty-five treatment näıve patients with HCV genotype 1 infection (28 with subtype 1a and 7 with subtype 1b) and no histologic evidence of cirrhosis were treated with this regimen. SVR12 was observed in 63, 75 and 88% of patients treated with ABT-450/r at doses of 50/100, 100/100 and 200/100 mg, respectively. Adverse events were similar in the pegylated interferon/ribavirin plus ABT-450/r and pegylated interferon/ribavirin groups.

2.2 ABT-450/r, ABT-267, ABT-333 and ribavirin

Results from a Phase IIb trial (M11-652 AVIATOR) evaluating ABT-450/r in combination with the NS5A inhibitor ABT-267, the NS5B non-nucleoside polymerase inhibitor ABT-333 and weight-based ribavirin were presented at the 2013 European Association for the Study of the Liver Annual Meeting [19]. This randomized, multicenter, open-label trial included 247 previously untreated as well as prior null responders with HCV genotype 1 infection (163 patients with subtype 1a and 84 patients with subtype 1b) without cirrhosis (37% with F2--F3 scores). Treatment duration was for 8, 12 or 24 weeks. Preliminary results for the 8 and 12 weeks treatment arms revealed SVR12 in 87.5 and 97.5% of previously untreated individuals, respectively. The efficacy of this combination regimen was also evaluated in patients with HCV genotype 1 infection who had previously failed treatment with pegylated interferon and ribavirin (49% null responders) in a Phase III randomized, multicenter, double-blind, placebo-controlled trial (M13-098 SAPHIRE-II), including 394 treatment-experienced patients with HCV genotype 1 infection (49% were previous null responders to pegylated interferon and ribavirin). SVR12 was achieved in 96% of patients after 12 weeks of therapy with no difference in response by HCV genotype 1 subtypes, 1a or 1b [20]. Discontinuation of treatment due to medication-related adverse events occurred in 1%, most commonly being fatigue or headache.

2.3 ABT-450/r, ABT-333 and ribavirin

The safety and efficacy of ABT-450/r combined with ABT-333 and ribavirin were evaluated in a non-randomized (patients were sequentially enrolled into three different treatment groups), multicenter, open-label Phase IIa trial involving 50 patients with HCV genotype 1

infection (44 patients with subtype 1a and 6 patients with subtype 1b) [21]. Previously untreated (33 patients) and null or partial responders to prior therapy (17 patients) with HCV genotype 1 infection and no histologic evidence of cirrhosis received this novel all-oral regimen (ABT-450/r, ABT-333 and ribavirin) for 12 weeks and were followed for 48 weeks after treatment. Previously untreated patients received ABT-450 at doses of 250 mg (group 1) and 150 mg (group 2) orally daily. Patients who had a null or partial response to prior treatment with pegylated interferon and ribavirin received 150 mg orally daily of ABT-450 (group 3). All three groups received 100 mg orally daily of ritonavir, 400 mg orally twice daily of ABT-333 and weight-based ribavirin (1000 mg for < 75 kg and 1200 mg for ≠75 kg) divided into two doses. SVR12 was 95 and 93% of previously untreated patients in groups 1 and 2, respectively, and 47% in previously treated patients (null or partial responders). The most common adverse events were fatigue, headache, insomnia and nausea. Only one patient discontinued therapy due to asymptomatic elevation of aminotransferases. No serious adverse events were reported.

2.4 ABT-450/r, ABT-072 and ribavirin

The efficacy of another all-oral antiviral regimen with ABT-450/r, ABT-072 (NS5B polymerase inhibitor) and ribavirin was evaluated in a Phase IIa, multicenter, open-label, single-arm trial, including 11 previously untreated patients with HCV genotype 1 infection (eight patients with subtype 1a and three patients with subtype 1b) [22]. ABT-450 was administered at a dose of 150 mg orally daily. Ritonavir 100 mg orally daily, ABT-072 400 mg orally daily and weight-based ribavirin 1000 – 1200 mg orally daily divided in two doses were also administered for 12 weeks. All 11 patients achieved end-of-treatment response (undetectable HCV RNA at the end of therapy). SVR rates at 12, 24 and 48 weeks were 91, 91 and 73%, respectively. Viral sequencing of the sole patient who developed relapse after 24 weeks post-treatment demonstrated variants in the NS5B conferring resistance to ABT-072. The most common adverse events were headache, fatigue, xerosis, nausea, gastroesophageal reflux and skin rash. No severe adverse events were reported.

2.5 ABT-450/r and ABT-267

Preliminary data from the PEARL-I study, a randomized, multicenter, open-label trial evaluating a simplified interferon-free/ribavirin-free antiviral regimen with two oral agents (ABT-450/r and ABT-267) in patients with HCV genotype 1b infection and no histologic evidence of cirrhosis was presented at the 2013 AASLD Annual Meeting [23]. Non-cirrhotic patients with genotype 1b infection received ABT-450/r (150/100 mg orally daily) and ABT-267 (25 mg orally daily) for 12 weeks. SVR at 4 weeks post-treatment was achieved in all 42 previously untreated patients (32% with *IL28B* CC genotype) and in 88% of null responders to previous treatment with pegylated interferon/ribavirin (5% with *IL28B* CC genotype). Reported adverse events include headache, nausea, xerosis, fatigue, pruritus and diarrhea. Only one patient interrupted therapy due to elevation of aminotransferases and bilirubin.

2.6 Adverse events associated with ABT-450

Although a variety of adverse events have been reported in trials evaluating antiviral regimens containing ABT-450, most have been mild and did not require treatment

interruption. The most common adverse events reported are presented in Table 1. Interferon-free regimens with other new generation DAAs such as sofosbuvir (in combination with ribavirin) have also been associated with generally mild adverse reactions such as fatigue and irritability (10 – 40%), nausea (18%) and anemia (9%) [24]. Anemia is typically a dose-limiting toxicity of ribavirin when used in combination with pegylated interferon, resulting in dose modification in 20 – 30% of patients [25]. When used in combination with pegylated interferon and ribavirin, boceprevir and telaprevir further increase the incidence of anemia up to 40% [9,11]. Therefore, anemia has remained a potential concern with newer combination regimens that include ribavirin. Data presented at the 2013 AASLD Annual Meeting are reassuring in that anemia occurred in only 6.5% of patients treated with ABT-450/r, ABT-267, ABT-333 and weight-based ribavirin for 12 -- 24 weeks. Although these patients required ribavirin dose reductions, this intervention did not diminish SVR [26].

3. Conclusions

New antiviral regimens containing ABT-450 have yielded impressive results in treatment of non-cirrhotic patients with HCV genotype 1 infection (Table 2) and have been well tolerated. Concurrent use of ritonavir as a booster for ABT-450 requires careful pre-treatment assessment and on-treatment monitoring for drug--drug interactions. The efficacy of this novel antiviral agent extends to previously treated patients. ABT-450 containing regimens also facilitate shorter duration of therapy (12 weeks) and interferon-free/ribavirin-free all-oral antiviral treatment.

4. Expert opinion

Treatment of HCV infection has dramatically changed over the past few years with licensure of potent DAAs such as boceprevir, telaprevir, and more recently simeprevir and sofosbuvir. Additionally, emerging data support the efficacy of interferon-free all-oral regimens, which represent a major breakthrough in treatment of HCV infection. The use of ribavirin remains a concern, mainly because of hematologic toxicity frequently requiring erythroid-stimulating agents such as erythropoietin or darbepoetin *a* and/or dose reductions. Results from the PEARL-I study evaluating the efficacy of a ribavirin-free regimen (ABT-450 and ABT-267) show comparable efficacy to other regimens containing ribavirin in treatment näıve and previously treated patients with HCV genotype 1 infection and no histologic evidence of cirrhosis. This study however, only included patients with HCV genotype 1b infection, which is more responsive to antiviral therapy than 1a. Final results from the AVIATOR study (66% of patients with subtype 1a) comparing the efficacy of ABT-450/r, ABT-267 and ABT-333 with and without ribavirin will help to further clarify the role of ribavirin in this new era of DAAs. The use of co-formulated tablets (i.e., ABT-450/r and ABT-267) is being investigated in a Phase III clinical trial and will simplify antiviral therapy. Newer DAAs also permit shorter duration of therapy and available data support the efficacy of 12 weeks of therapy with regimens containing ABT-450 for treatment of HCV genotype 1 infection, irrespective of previous exposure to antiviral agents.

Antiviral regimens containing ABT-450 are highly effective in both treatment näıve and previously treated non-cirrhotic patients with HCV genotype 1a and 1b. However, the efficacy of these regimens in patients with advanced fibrosis or cirrhosis, one of the most challenging treatment populations, remains unclear with only one study (M11-652 AVIATOR) including patients with bridging fibrosis (F3 stage). The efficacy of ABT-450/r, ABT-267, ABT-333 and ribavirin was similar in treatment näıve and null responders to previous treatment with pegylated interferon and ribavirin with F2–F3 fibrosis compared to those with F0--F1 scores (95.7 – 97.8% vs 95.1 – 97.3%, respectively). Data from ongoing clinical trials evaluating the efficacy and safety of ABT-450 containing regimens in patients with HCV genotype 1 infection and compensated cirrhosis are eagerly awaited (TURQUOISE-II trial, ClinicalTrials.gov identifier ; and ClinicalTrials.gov identifier).

An additional potential advantage of ABT-450-containing regimens includes pan-genotypic antiviral activity (against genotypes 2 and 3), which is being evaluated in an ongoing clinical trial (ClinicalTrials.gov identifier). The efficacy of ABT-450/r and ABT-267 with and without ribavirin is also being studied in patients with HCV genotype 1 and HIV co-infection (TURQUOISE-I trial, ClinicalTrials.gov identifier).

Drug--drug interactions are anticipated with regimens containing ABT-450/r (ritonavir boosted). Ritonavir is a potent inhibitor of CYP3A, responsible for the metabolism of approximately 50% of pharmacologic agents used in current practice, including immunosuppressants (cyclosporine, tacrolimus and sirolimus), macrolide antibiotics, tricyclic antidepressants, selective serotonin reuptake inhibitors (citalopram, sertraline, norfluoxetine), antipsychotics (haloperidol, risperidone, ziprasidone, quetiapine, aripiprazole), opioid analgesics (codeine, fentanyl, methadone, tramadol), benzo-diazepines (alprazolam, midazolam, diazepam), sedative hypnotics (zopiclone, zolpidem, zaleplon), statins (atorvastatin, lovastatin, simvastatin, cerivastatin), antiarrhythmics (amiodarone, dronedarone), calcium channel blockers, phosphodiesterase inhibitors (sildenafil, tadalafil), warfarin, clopidogrel and several others [27,28].

In summary, newer DAAs such as ABT-450 promise effective and durable suppression of HCV with interferon-free/ribavirin-free all-oral once-daily regimens for 12 weeks and tolerable side effects. The results of clinical trials including a broader spectrum of individuals with HCV infection and longer follow-up are eagerly awaited; in the interim, the landscape of HCV treatment continues to rapidly change.

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Box 1.

Drug summary.

Drug name	ABT-450
Phase	III
Indication	Hepatitis C virus infection
Pharmacology description	Protease inhibitor
Route of administration	Oral
Chemical structure	Inhibitor of the non-structural (NS)3/4A protease
Pivotal trial(s)	[18-23]

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Table 1.

Adverse events associated with ABT-450 [29].

Adverse event	Frequency
Fatigue	35 – 47%
Nausea	21 – 24%
Headache	14 – 26%
Dizziness	5 – 29%
Insomnia	Up to 26%
Skin rash	6 – 21%
Vomiting	Up to 21%
Pruritus	Up to 21%
Anemia	6.5%

Table 2.

Efficacy of anti-HCV regimens containing ABT-450 in patients with HCV genotype 1 infection and no histologic evidence of cirrhosis.

Antiviral regimen	SVR* (treatment naïve)	SVR* (previously treated)	HCV genotype/subtype	Duration of therapy
ABT-450/r, pegylated interferon, and ribavirin	88%	NA	1a (80%) 1b (20%)	12 weeks
ABT-450/r, ABT-267, ABT-333, and ribavirin	97.5%	96%	1a (66%) 1b (34%)	12 weeks
ABT-450/r, ABT-333, and ribavirin	93 -- 95%	47%	1a (88%) 1b (12%)	12 weeks
ABT-450/r, ABT-072, and ribavirin	91%	NA	1a (78%) 1b (22%)	12 weeks
ABT-450/r and ABT-267	100%	88%	1b (100%)	12 weeks

*SVR rates are presented as SVR12 for all regimens except ‘ABT-450/r and ABT-267’, which is SVR4.

SVR: Sustained virological response; HCV: Hepatitis C virus; NA: Not applicable.