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Vedroprevir in the management of hepatitis C virus infection

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Abstract

Introduction: Hepatitis C Virus (HCV) is a chronic infection of the liver and the leading cause of liver failure and liver transplantation worldwide. While prior HCV therapies were prolonged and had variable success rates, the advent of direct-acting antivirals (DAAs) has dramatically improved HCV therapy with minimal side effects, shorter treatment durations, and higher cure rates.

Areas covered: In this paper, we review the literature discussing the use of Vedroprevir (GS-9451) in treatment of HCV in a variety of patient populations. Articles accessible on MEDLINE/PubMed were reviewed to provide context on chemistry, pharmacology, and efficacy of Vedroprevir in HCV treatment.

Expert opinion: Vedroprevir is highly effective in reducing treatment duration in combination with other DAAs without compromising treatment success rates. GS-9451 is insufficient as HCV monotherapy due to low threshold for development of high level of resistance and must be combined with other DAAs to achieve sustained virologic response (SVR).

Keywords

Hepatitis C virus; GS-9451; vedroprevir; direct-acting antivirals

1. Introduction

Hepatitis C virus (HCV) is a chronic infection of the liver and affects approximately 71 million people worldwide [1]. One of the leading causes of chronic liver disease, it causes about 400,000 global deaths annually and is the leading cause of liver transplantation [2,3]. Major risk factors of acquisition include use of contaminated needles or syringes, multiple sexual partners, patients on hemodialysis, and tattooing [4]. Chronic infection occurs in the majority of patients [5] and subsequent complications including cirrhosis and hepatocellular carcinoma account for significant patient morbidity and mortality [6–8].

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Declaration of interest

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The desired outcome in HCV treatment is achievement of sustained virologic response (SVR), defined as a maintained undetectable level of HCV RNA after completion of therapy. Patients who achieve SVR after treatment for their HCV are considered to be cured from the virus. Historically, achieving SVR was difficult, and the interferon (IFN)-based regimens used had long courses (over 24 weeks) and modest SVR rates [9]. There were also a number of toxicities associated with IFN-based regimens and in many cases the treatments were poorly tolerated by patients. Additionally, patients with advanced liver disease, HIV-coinfection, black race, and IL-28B non-CC haplotype were less likely to achieve SVR when treated with IFN-alfa based therapy [10].

The advent of oral direct-acting antivirals (DAAs) was a breakthrough in HCV treatment [11–16]. These medications began as first-generation protease inhibitors designed to target HCV replication as opposed to the host's immune response. Continued development of DAAs has resulted in very effective, IFN-free regimens, and treatment courses that are better tolerated with fewer side effects. Additionally, DAA IFN-free regimens have shorter duration and achieve higher SVR rates than IFN-based regimens [17]. In this article, we review the use of Gilead Sciences 9451 (GS-9451), or vedoprevir, as part of combination therapy with other DAAs in the treatment of HCV-infected patients (Table 1).

2. Clinical pharmacology

2.1. Overview of the market

While HCV therapy has dramatically improved, treatment remains challenging for patients with decompensated liver disease, end-stage kidney disease, pediatric patients, and rare concomitant disease states including hemophilia. Newer drug regimens will allow combination therapies possible to individualize treatment similar to what transformed antiretroviral therapy for HIV infection. Treatment for all patients living with HCV remains the current goal [13].

Currently, there are several HCV serine protease inhibitors approved by the US Food and Drug Administration and available for combination therapy in the market. These include boceprevir, telaprevir (no longer available), simeprevir, paritaprevir/ritonavir, grazoprevir, glecaprevir, and voxilaprevir. Vedoprevir adds to the list and voids a huge gap in the need for more potent antivirals to treat over 71 million HCV-infected patients worldwide.

2.2. Introduction to the compound

Vedoprevir, or GS-9451, is a potent inhibitor of the HCV NS3 protease (Box 1). NS3 is a serine protease that cleaves the HCV polyprotein and helps generate the viral replication complex. Through binding NS3, vedoprevir halts the assembly of the viral replication complex, thus interfering with the assembly and release of viral particles.

2.3. Chemistry and pharmacodynamics

Vedoprevir was discovered among a new class of carboxylic acid HCV NS3 protease inhibitors, and was noted for its high antiviral activity, bioavailability, selectivity, and low toxicity [18]. In biochemical assays, vedoprevir showed minimal inhibitory effect on other

mammalian proteases when compared to the genotype 1b NS3 protease [18]. Vedoprevir did not have high activity across non-genotype 1 HCV and significantly higher concentrations were required to provide the same inhibitory effect [19].

2.4. Pharmacokinetics and metabolism

Preclinical studies of vedoprevir showed high oral bioavailability in rats, dogs, and monkeys. Vedoprevir rapidly distributes to the liver and remains there for at least 12 h, with liver concentrations being 40-fold higher than in plasma [19]. In humans, maximal concentrations are achieved after 3–5 h, regardless of dose [20]. The median plasma half-life is 14–17 h, consistent with a once-daily dosing schedule. Vedoprevir is minimally metabolized, and excreted by the gastrointestinal (GI) tract largely in its parent drug form.

2.5. Clinical efficacy

Preclinical studies of vedoprevir demonstrated potent NS3 inhibition using laboratory strains as well as patient-derived NS3 protease gene isolates [19]. In a phase I, randomized trial of vedoprevir monotherapy, doses of 200 and 400 mg/day yielded median maximal HCV RNA reductions of $-3.2 \log_{10}$ in genotype 1a patients and $-3.5 \log_{10}$ in genotype 1b patients. Significantly less activity was seen against genotype 2a HCV when compared to genotype 1. Of note, a dose of 60 mg/day resulted in minimal or no reduction of HCV RNA levels [20].

In the TRILOGY-2 study [21], investigators sought to determine whether addition of vedoprevir in the treatment regimen of genotype-1 HCV-infected patients could reduce treatment duration or eliminate the need for ribavirin. While 12-week-based regimens were shown to achieve high SVR12 rates [22], the efficacy of shorter treatment durations was unknown. Forty-six previously treated cirrhotic patients received 8 weeks of either ledipasvir/sofosbuvir (LDV/SOF) + vedoprevir $\pm$ ribavirin. The observed SVR12 rates were comparable in the group with ribavirin (88%) and without ribavirin (95%). The maintained high SVR12 rate corroborated a phase IIa proof-of-concept study which showed 95% SVR12 rate in non-cirrhotic genotype-1 HCV-infected patients receiving 6 weeks of LDV/SOF plus either GS-9669 or vedoprevir [14]. A 6-week regimen of LDV/SOF + vedoprevir was tested in treatment-naïve and treatment-experienced genotype-1 HCV-infected cirrhotic patients and showed a moderate SVR12 rate of 76%. There was no statistically significant difference in SVR12 rate between treatment-naïve and treatment-experienced patients, although cirrhosis was an impediment in achieving SVR with short-course DAA therapy [23].

Further reduction of treatment duration to a 4-week DAA regimen was explored in a phase 2a trial. Fifty treatment-naïve genotype-1 HCV-infected non-cirrhotic patients were assigned to receive LDV/SOF + vedoprevir $\pm$ GS-9669. Only 40% of the three-drug group and 20% of the four-drug group achieved SVR12 [24]. Despite the large number of treatment failures, the majority of patients were successfully retreated with 12 weeks of LDV/SOF [25].

2.6. Safety and tolerability

In patients treated with vedroprevir as part of a three- or four-drug regimen, the most common adverse events were fatigue, diarrhea, and headache [14,24]. Two serious events (vertigo and angioedema) in the four-drug group were reported, but deemed to be unrelated to the study drug. In a phase I ascending-dose study of vedroprevir monotherapy, 36 adverse events were reported among the 41 patients in the safety analysis, the most common being headache and dyspepsia. A serious adverse event was reported in one patient (heroin overdose) resulting in the patient's death. This event occurred several days after dosing of the study drug was completed and was thought to be unrelated to the study drug [20]. Across multiple phase 2 studies, vedroprevir was well tolerated in combination with other DAAs and rarely discontinued [14,23,24].

2.7. Regulatory affairs

Vedroprevir is currently being used in combination therapy with SOF and LDV in early phase studies. The current status of development of this drug is not known.

3. Conclusion

DAAs have resulted in significant improvements in HCV treatment and cure. Vedroprevir has been shown to be effective when combined with LDV/SOF in patients with genotype 1 HCV. In particular, high SVR12 rates were demonstrated in 12-week and 8-week regimens, and modest to high rates were shown in 6-week regimens. A 4-week regimen was shown to be insufficient to achieve SVR in the majority of patients. Cirrhosis remains an impediment to successful treatment. Prior treatment experience did not seem to significantly affect probability of cure. Voxilaprevir, a second-generation serine protease inhibitor derived from vedroprevir, has been approved in combination with SOF and velpatasvir for patients with DAA failure.

4. Expert opinion

4.1. Treatment duration

The TRILOGY-2 study demonstrated efficacy of treatment with vedroprevir with LDV/SOF for 8 weeks with SVR12 rates approaching 95%. Efficacy of vedroprevir with at least two other potent DAAs was again demonstrated in a proof-of-concept study where treatment duration was 6 weeks and patients achieved similar SVR12 rates; however, this study was performed only in non-cirrhotic patients. When a 6-week combination DAA regimen with vedroprevir was tested in cirrhotic patients, the SVR12 rate dropped to 76%. Four-week combination regimens proved to be insufficient with unacceptably low SVR12 rates of 20% and 40%.

4.2. Special populations

Studies of vedroprevir in special populations including HIV/ HCV-coinfected patients, cirrhotic patients, and treatment-experienced patients are limited. A 6-week combination regimen with GS-9451 in cirrhotic patients showed a modest SVR12 rate of 76% when compared to 88% and 95% rates achieved in non-cirrhotic patients. There are no studies that

have evaluated effects of HIV coinfection as compared to HCV mono-infection. A 6-week regimen of LDV/SOF + vedroprevir showed no statistically significant difference in SVR12 between treatment-naïve and treatment-experienced patients.

4.3. Resistance-associated substitutions

The most common NS3 protease amino acid substitutions occur at positions R155, A156, and D168. Each of these mutations is often missed by standard population sequencing, but detectable with deep-sequencing technology [26]. The majority of protease inhibitor-resistant mutations occur early and often with vedroprevir monotherapy (not with combination therapy). In a study of 33 patients, only 2 had detectable changes at positions 155, 156, or 168 at baseline, whereas 70% and 100% of patients had mutations at these positions on days 2 and 4 of monotherapy, respectively. R155K was the most commonly observed drug-resistant mutation among genotype 1a patients [26], and genotype 1b patients had mutations at position D168 (D168E/G/V). Each of these mutations conferred a high level of resistance to vedroprevir, supporting the use of combination therapy for HCV treatment [27].

Optimal treatment of resistance-associated substitutions of HCV remains unclear, although recent evidence shows that retreatment can be successful. In a recent study, patients who failed 4–6 weeks of LDV/SOF with GS-9669 and/or vedroprevir were retreated with LDV/SOF for 12 weeks. Eighty-five percent of the patients had NS5A-resistant substitutions of genotype-1 HCV prior to re-treatment. The SVR12 rate was 91% after re-treatment, with one relapse [25].

Studies of resistance-associated substitutions have been conclusive in that resistance to GS-9451 monotherapy occurs early in treatment, and almost universally across all patients by the fourth day of treatment. Combination of GS-9451 with other DAAs is necessary for HCV treatment, and monotherapy is insufficient to achieve cure.

4.4. DAA failures

While treatment of genotype 1 HCV with 6-week and 8-week combination regimens including vedroprevir have been very effective, some treatment failures do occur. Advanced liver fibrosis has been shown to be an impediment which decreases efficacy of DAA treatment. Patients who failed to achieve SVR12 after a 4-week combination regimen with vedroprevir were able to be successfully retreated with LDV/SOF for 12 weeks and achieve SVR.

4.5. Cost

Cost of treatment for HCV continues to be in flux. While it was originally a barrier in effectively treating patients with HCV infection, the most recent therapy was released at a significant discount. Historically, the high costs established by the pharmaceutical companies that develop HCV therapeutics have caused insurance companies to be selective in which patients they will cover treatment costs for, although this is starting to change. If patients do not have advanced liver disease or abstain from substance use, they are often precluded from HCV treatment [28–30]. HIV coinfection can also predispose patients to

being denied coverage by their insurance companies, despite Infectious Diseases Society of America / American Association for the Study of Liver Diseases (IDSA/AASLD) guidelines which prioritize treatment for this population [31]. Cost of vedoprevir is not applicable at this time due to its early stage in development.

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Box 1.**Drug summary**

Drug name	GS-9451
Phase (for indication under discussion)	II
Indication (specific to discussion)	Treatment of chronic hepatitis C virus
Pharmacology description/ mechanism	Inhibitor of hepatitis C virus NS3 protease inhibitor
Route of administration	Oral
Chemical structure	$C_{45}H_{60}ClN_7O_9S$
Pivotal trials	[14,23]

Table 1.
Clinical trials in various patient populations using vedroprevir alone or in combination with other DAAs.

Author/trial	Population	Regimen	Outcome (SVR12)
TRILGY-2 (2014, NCT02226549)	n = 46, treatment-experience, cirrhotic	8 wks LDV/SOF + VDV ± RBV	95% – three-drug group 88% – four-drug group
Kohli et al. [14] <i>Ann Intern Med.</i>	n = 50, treatment-naïve, GT-1	4 wks LDV/SOF + VDV ± GS-9669	40% – three-drug group 20% – four-drug group
Kattakuzhy et al. [23] <i>CID</i>	n = 50, GT-1	6 wks LDV/SOF + VDV	76% – total 72% – treatment-naïve 80% – treatment-experienced
Petersen et al. <i>Hepatology</i>	n = 60, GT-1, treatment-naïve	12 wks LDV/SOF OR 6 wks LDV/SOF + GS-9669 OR 6 wks LDV/SOF + VDV	100% – LDV/SOF 95% – LDV/SOF + GS-9669 95% – LDV/SOF + VDV
Wyles et al. <i>Hepatology</i>	n = 140, GT-1, non-cirrhotic	12–24 wks VDV + TGV + RBV + (LDV 30 mg OR LDV 90 mg)	48% – 12 wks, low-dose LDV 68% – 12wks, high-dose LDV 81% – 24wks, high-dose LDV
Lawitz et al. [20] <i>Antiviral Therapy</i>	n = 33, GT-1, treatment-naïve	3 days placebo OR VDV 60 mg OR VDV 200 mg OR VDV 400 mg	Not assessed (phase I study)

DAA: direct-acting antiviral; GT: genotype; LDV: ledipasvir; RBV: Ribavirin; SOF: sofosbuvir; TGV: tegobuvir; VDV: vedroprevir; wks: weeks.