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REVIEW

Grazoprevir/elbasvir for the treatment of adults with chronic hepatitis C: a short review on the clinical evidence and place in therapy

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Abstract: Chronic hepatitis C virus (HCV) infection impacts approximately 71 million people and approximately 400,000 deaths are attributed to HCV-related liver disease annually worldwide. Mainstay of treatment for over 25 years has been pegylated interferon until the advent of protease inhibitors, which has led to all-oral HCV treatment regimens that have changed the outlook of hepatitis C treatment. Grazoprevir/elbasvir provides high rates of efficacy and tolerability and is an all-oral once daily treatment option for HCV infection. Efficacy of grazoprevir/elbasvir has been proven in patients with cirrhosis, patients who have previously failed treatment with peginterferon and ribavirin (RBV), patients with end-stage renal disease and patients with HIV co-infection. Data have shown a high barrier to resistance despite the presence of resistance-associated substitutions. Grazoprevir/elbasvir represents a very promising regimen for treatment of HCV infection. This review provides a summary of pharmacology, efficacy, and safety of grazoprevir/elbasvir for the treatment of HCV infection.

Keywords: hepatitis C virus, grazoprevir, elbasvir, NS3, NS4, NS5A, protease inhibitors

Introduction

For more than 25 years, pegylated interferon and ribavirin (PR) have been the mainstay of treatment for hepatitis C virus (HCV) infection until the recent advent of protease inhibitors.[1–3] The emergence of protease inhibitor therapies in 2011 transformed the landscape of HCV treatment. However, there have been major limitations with initial direct-acting antiviral (DAA) agents including low genetic barrier to resistance, side effects, and significant drug-drug interactions.[4–6]

Grazoprevir is a second-generation NS3/4a protease inhibitor that demonstrates activity against resistance-associated substitutions (RAS) seen after failed therapy with first-generation protease inhibitors.[7–12] Elbasvir is a NS5A replication complex inhibitor. Grazoprevir-Elbasvir has been approved by Food and Drug Administration (FDA) since 2016 for the treatment of HCV genotype 1 and 4 and with ribavirin in select patient populations. It has also been studied in patients with advanced chronic kidney disease (CKD). The purpose of this review is to summarize pharmacology, efficacy, and safety of grazoprevir-elbasvir.

Pharmacology

Grazoprevir is a synthetically derived quinoline-based p2-p4 macrocyclic derivative that is a strong inhibitor of HCV NS3/4A protease.[13] NS3/4A protease is responsible for cleaving the long polyprotein produced from hepatitis C viral RNA template into

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single proteins. This is an essential process for HCV RNA replication, which is inhibited by grazoprevir. The HCV NS5A is a critical RNA binding protein associated with performing necessary functions for viral replication and virion assembly. Elbasvir directly inhibits the activity of NS5A protein within the HCV.

Pharmacokinetics and metabolism

Initial studies to evaluate pharmacokinetics of grazoprevir were performed in rats, dogs, and simian models.[14–16] Oral (5 mg/kg of body weight in rats and 1 mg/kg of body weight in dogs) and intravenous (bolus dose of 2 mg/kg of body weight in rats and 0.5 mg/kg of body weight in dogs) formulations were utilized in the studies.

The safety and pharmacokinetics of grazoprevir were evaluated by Brainard et al in healthy males after single-dose and multiple-dose administration.[17] An oral dose of 2–1,600 mg or placebo in fed or fasted state was administered to 24 healthy males in the single dose group. An oral dose of 100–1,000 mg or placebo once daily for 10 days was administered in 40 healthy males in the multiple-dose group. No serious adverse events occurred in the study, with one subject experiencing flu-like illness unrelated to the drug. Following single administration of an oral dose, the pharmacokinetic data revealed Tmax values of 2–5 hours and a terminal half-life of 15–34.4 hours. Pharmacokinetics was not affected by administration of the medication with a high-fat meal. Dose proportional increases in mean area under the curve (AUC), Cmax, and 24 hour concentration values were seen up to 200 mg. These values were much higher and did not increase in a dose proportional manner in doses greater than 200 mg. Steady state was obtained after six doses, and approximately three-fold increase in AUC and Cmax was noted for grazoprevir doses of 100–400 mg. Only 1.5-fold increase in AUC and Cmax was observed at doses higher than 400 mg.

Mean AUC and Cmax increased in a greater than dose proportional manner at steady state in the multiple-dose group with median Tmax of 2.5–4 hours and half-life of 20 hours. The single-dose and multiple-dose groups demonstrated consistent pharmacokinetic data. Pharmacokinetic data were evaluated in six patients with HCV in another study, one with genotype 1 and five with genotype 3, which yielded higher drug exposure as compared to healthy controls (1.2–2.1 fold).[18]

A non-randomized, open-label Phase II study (C-SALT trial) assessed the efficacy, safety, and pharmacokinetics of grazoprevir plus elbasvir in patients with HCV genotype 1, 4, or 6 infection and Child-Pugh-B (CP-B) cirrhosis.[19] Pharmacokinetics of 30 patients with HCV genotype 1 infection and CP-B cirrhosis who received grazoprevir 50 mg and elbasvir 50 mg as separate entities was compared to that of 10 non-cirrhotic patients with HCV genotype 1 who received grazoprevir 100 mg/elbasvir 50 mg combination product. Plasma samples over 24 hours at treatment week 4 were collected in a subset of CP-B and non-cirrhotic patients. Results of the study demonstrated the exposure of elbasvir was similar in both groups but grazoprevir exposure was higher in CP-B cirrhotic patients compared to non-cirrhotic patients.

Clinical efficacy

In a randomized active-control trial, Manns et al evaluated the safety and efficacy of PR combined with either grazoprevir or boceprevir.[20] Treatment-naïve patients with genotype 1 infection and HCV RNA level $\geq 10^4$ IU/mL at screening were eligible. The study randomized 332 treatment-naïve genotype 1 patients (60% with genotype 1a) to receive either boceprevir + PR at standard doses (control) or grazoprevir 100, 200, 400, or 800 mg daily + PR for 12 weeks. Patients received an additional 12 weeks of PR alone if they achieved rapid virologic response (RVR), defined as HCV RNA not detected at week 4 of treatment, or 36 weeks of PR if RVR was not achieved. The study demonstrated higher sustained virologic response (SVR) rate at the 24-week follow-up (SVR_{24}) in the grazoprevir group (86%–93%) compared to the boceprevir group (61%).

Howe et al further explored the study to evaluate six patients with virologic failure.[21] The substitutions associated with clinical resistance to other protease inhibitors were present in 73 of 261 (28%) patients in the grazoprevir group at study enrollment. SVR_{24} was observed in 85% of these patients with genotype 1a and in 97% of the patients with genotype 1b despite the presence of variants. SVR_{24} was achieved in 59 of 66 patients (89%) in the 100 mg/day group.

Lagging and colleagues evaluated the efficacy of lower doses of grazoprevir in treatment naïve HCV genotype 1 patients with HCV RNA level ≥10,000 IU/mL.[22] Primary objective was SVR rate at 12 weeks after the end of treatment (SVR_{12}) for each group. Patients were randomized to receive grazoprevir 25 mg (n=29), 50 mg (n=28), or 100 mg (n=30) + PR for 12 weeks. Treatment with PR was extended by 12 weeks if HCV RNA was detectable at week 4. Of the 87 patients enrolled, 80% were genotype 1a and 18% were African American. SVR_{12} was achieved in 54.2%, 84%, and 88.5% of patients in grazoprevir 25 mg, 50 mg and 100 mg groups, respectively. Treatment failure occurred in 46%, 16%, and 15% of patients in grazoprevir 25 mg, 50 mg, and 100 mg groups, respectively. RAS were present in 38 of 87 patients (44%) at baseline, all of which were susceptible

to grazoprevir. Type and frequency of adverse events were similar in all three groups.

C-WORTHY was a randomized, multi-center, open-label, Phase II trial that evaluated safety and efficacy of 8 weeks versus 12 weeks of treatment with grazoprevir and elbasvir with or without ribavirin in HCV genotype 1 mono-infected and HIV/HCV co-infected patients.[23] Treatment-naïve patients with HCV RNA ≥10,000 IU/mL without cirrhosis were eligible to participate. HIV co-infected patients were required to be well controlled with raltegravir plus two nucleoside or nucleotide reverse transcriptase inhibitors for at least 8 weeks prior to enrollment and have undetectable HIV RNA for at least 24 weeks with CD4 count of 300 cells/mL or higher. Table 1 describes randomization of patients in eight study arms. Patients' bodyweight was utilized for ribavirin dosing (800–1,400 mg/day). The primary objective was to assess SVR_{12} for each group. The majority of the patients enrolled in the study were White (88%) males (59%) with median age of 52 years. Baseline HCV RNA was >2,000,000 IU/mL in 56% of the patients and 72% had HCV genotype 1a infection. In the co-infected patients, there were more males (80%) with younger age (mean 47 years) and higher baseline HCV RNA count. SVR_{12} was achieved in 93% with ribavirin and 98% without ribavirin treatment in the mono-infected patients treated for 12 weeks. In the co-infected patients, the SVR_{12} rate was 97% with ribavirin and 87% without ribavirin. No significant differences were noted in SVR_{12} rates for mono-infected and co-infected patients, for regimens with or without ribavirin, and dose of elbasvir. The SVR_{12} rates were lower in HCV genotype 1a patients receiving treatment for 8 weeks (80%) compared to 12 weeks (95%). Virologic failure occurred in 12 patients in the study, 10 patients with genotype 1a and two with genotype 1b.

The C-WORTHY part B study enrolled patients with genotype 1, treatment naïve, with cirrhosis (cohort 1) and patients who previously failed treatment with PR, with or without cirrhosis (cohort 2).[24] Patients were randomized to receive grazoprevir 100 mg/elbasvir 50 mg with or without ribavirin for 12 or 18 weeks. Patients were randomized in eight treatment groups as described in Table 2. Median age of the patients in the study was 56 years with most having cirrhosis (67%); 58% were males, and 92% were White. Patients in cohort 1 achieved SVR_{12} rates of 90%–97% with no significant benefit of extended treatment duration. One patient in cohort 1 had virologic breakthrough and five patients had virologic relapse. Patients in cohort 2 achieved SVR_{12} rates of 91%–100%, which was similar to treatment-naïve patients with cirrhosis. One patient had virologic breakthrough and three patients had virologic relapse. A subgroup analysis to assess the impact of ribavirin showed it did not contribute to additional efficacy in patients with cirrhosis, in patients who have previously failed PR therapy, and patients with high viral loads (>10,000,000 IU/mL).

C-WORTHY part D study compared the efficacy of grazoprevir 100 mg/elbasvir 50 mg with ribavirin therapy in HCV genotype 3 patients for 12 weeks versus 18 weeks.[25] This was an open-label study with patients randomized in 1:1 fashion with primary endpoint of SVR_{12}. A total of 21 patients were included in the 12-week (W12) group and 20 patients in the 18-week (W18) group. SVR_{12} rate of 45% was achieved in W12 group and 57.1% in W18 group. Breakthrough viremia occurred in six patients in W12 group and five patients in W18 group; none of the patients experienced relapse. There were 35 patients with baseline NS3 RAS and 18 (51%) achieved SVR_{12}. Seven out of 17 patients (41%) in W12 group and 11 out of 18 (61%) in W18 group achieved SVR_{12}. There were seven patients with baseline NS5A RAS and three (43%) achieved SVR_{12}. Two of five patients (40%) in W12 group and one of two patients (50%) in W18 group achieved SVR_{12}.

Table 1 C-WORTHY – study treatment groups

Treatment arm	Number of patients*	Infection	HCV genotype	Treatment	Duration	SVR_{12}
1	25	Mono-infected	1a + 1b	Grazoprevir 100 mg + elbasvir 20 mg + ribavirin	12 weeks	93%
2	27	Mono-infected	1a + 1b	Grazoprevir 100 mg + elbasvir 50 mg + ribavirin	12 weeks	93%
3	13	Mono-infected	1b	Grazoprevir 100 mg + elbasvir 50 mg	12 weeks	98%
4	30	Mono-infected	1a	Grazoprevir 100 mg + elbasvir 50 mg + ribavirin	8 weeks	80%
5	33	Mono-infected	1a + 1b	Grazoprevir 100 mg + elbasvir 50 mg + ribavirin	12 weeks	93%
6	31	Mono-infected	1a	Grazoprevir 100 mg + elbasvir 50 mg	12 weeks	98%
7	29	Co-infected	1a + 1b	Grazoprevir 100 mg + elbasvir 50 mg + ribavirin	12 weeks	97%
8	30	Co-infected	1a + 1b	Grazoprevir 100 mg + elbasvir 50 mg	12 weeks	87%

Notes: *Treatment-naïve and non-cirrhotic patients. Data from Sulkowski et al.[23]
Abbreviations: HCV, hepatitis C virus; SVR_{12}, sustained virologic response 12 weeks after treatment completion

Table 2 C-WORTHY – Part B study treatment groups

	Treatment arm	Number of patients	Treatment	Duration	SVR_{12}
Previously untreated; with cirrhosis	1	31	Grazoprevir 100 mg/elbasvir 50 mg + ribavirin	12 weeks	90%
	2	29	Grazoprevir 100 mg/elbasvir 50 mg	12 weeks	97%
	3	32	Grazoprevir 100 mg/elbasvir 50 mg + ribavirin	18 weeks	97%
	4	31	Grazoprevir 100 mg/elbasvir 50 mg	18 weeks	94%
PR-null, with or without cirrhosis	5	32	Grazoprevir 100 mg/elbasvir 50 mg + ribavirin	12 weeks	94%
	6	33	Grazoprevir 100 mg/elbasvir 50 mg	12 weeks	91%
	7	33	Grazoprevir 100 mg/elbasvir 50 mg + ribavirin	18 weeks	100%
	8	32	Grazoprevir 100 mg/elbasvir 50 mg	18 weeks	97%

Note: Data from Lawitz et al.[24]
Abbreviations: SVR_{12}, sustained virologic response 12 weeks after treatment completion; PR-null, previously untreated with Peg-interferon and Ribavirin.

C-EDGE-TN was a Phase III study that evaluated the efficacy and safety of grazoprevir/elbasvir fixed-dose combination regimen without interferon or ribavirin in treatment-naïve patients mono-infected with HCV genotypes 1, 4, or 6 with or without cirrhosis.[26] Patients received a fixed-dose combination of grazoprevir 100 mg/elbasvir 50 mg at the start of the study (immediate-treatment group) or placebo (deferred treatment group) for 16 weeks following which they received treatment in an open-label manner. The study aimed to enroll 20% of patients with cirrhosis and 15% with genotype 4 or genotype 6 infection. A total of 421 patients were enrolled, of whom 54% were male, 63% White, 6% with genotype 4, 3% with genotype 6, and 91% genotype 1, and 22% of the patients had cirrhosis. The SVR_{12} rates were 92% in patients with genotype 1 infection, 100% in genotype 4 infection, and 80% in genotype 6 infection. SVR_{12} rates between cirrhotic and non-cirrhotic patients were similar; 97% vs 94% respectively. Virologic failure was seen in 13 patients (11 with genotype 1 and two with genotype 6 infection).

The C-EDGE Co-Infection study was a Phase II study evaluating 218 patients with hepatitis C genotype 1, 4, or 6 and HIV.[27] Patients were treated with a combination therapy of grazoprevir 100 mg/elbasvir 50 mg once daily for 12 weeks. Patients were eligible to enroll if they were on antiretroviral therapy for at least 8 weeks with an undetectable HIV RNA level, and CD4 count greater than 200 cells/mm^3 or HIV treatment-naïve patients with CD4 count greater than 500 cells/mm^3 and an HIV RNA level less than 50,000 copies/mL. SVR_{12} was attained in 210 patients (96%) and all 35 patients with cirrhosis achieved SVR_{12}.

C-SALVAGE was a Phase II study that evaluated the safety and efficacy of 12 weeks of grazoprevir 100 mg/elbasvir 50 mg daily in patients with prior treatment failure with a regimen containing a protease inhibitor such as boceprevir, telaprevir, or simeprevir.[28] The study included patients with or without cirrhosis. SVR_{24} rates were high at 96.2% in spite of prior exposure and presence of NS3 substitutions. Ninety two percent (33/36) of patients with baseline NS3 or NS5A resistance and 94% (32/34) of patients with cirrhosis achieved $SVR_{24.}$

The C-SURFER was a randomized, parallel-group, placebo-controlled study that evaluated efficacy and safety of grazoprevir 100 mg/elbasvir 50 mg in patients with advanced (stage 4–5) CKD infected with HCV genotype 1.[29] This study included patients who had failed pegylated interferon therapy and treatment-naïve patients with or without cirrhosis. Of the 122 patients who received treatment in the immediate group, 80% were treatment naïve, 6% had cirrhosis, and 52% were genotype 1a. The study comprised 18% of patients with stage 4 and 82% of patients with stage 5 CKD, with 76% on hemodialysis. SVR_{12} was 99% in the immediate group and 98% in the deferred treatment group. SVR_{12} was achieved by 11 (84·6%) of 13 patients with detectable baseline NS5A RAS and 100% of patients with genotype 1a infection.

The C-SALT trial was a non-randomized, open-label Phase II study that assessed the efficacy, safety, and pharmacokinetics of grazoprevir plus elbasvir in patients with HCV genotype 1, 4, or 6 infection and CP-B cirrhosis.[19] The study enrolled 30 patients with HCV genotype 1 infection and CP-B cirrhosis who received grazoprevir 50 mg/elbasvir 50 mg and 10 non-cirrhotic patients with HCV genotype 1 who received grazoprevir 100 mg/elbasvir 50 mg in the pharmacokinetics analyses group. All patients received treatment for 12 weeks. SVR_{12} was achieved in 90% of patients with CP-B cirrhosis and in 100% of non-cirrhotic patients. Relapse occurred in two patients in the CP-B cirrhosis arm and one patient died due to progression of liver disease versus none in the non-cirrhotic arm. At the 12-week follow-up, Child-Pugh score decreased in 18 patients and increased in four patients in the CP-B cirrhosis group.

C-EDGE CO-STAR was a Phase III study evaluating the efficacy and safety of grazoprevir and elbasvir in

treatment-naïve, HCV genotype 1, 4, or 6 infected patients receiving opioid agonist therapy for at least 3 months.[30] This was a double blind, placebo-controlled, parallel-group study in which patients were randomized in a 2:1 fashion to an immediate treatment group (ITG) or a deferred treatment group (DTG). The ITG group received grazoprevir/elbasvir for 12 weeks and the DTG group received placebo for 12 weeks, followed by 12 weeks of open-label grazoprevir/elbasvir. Patients were allowed to use non-prescribed drugs, which were monitored by urine drug screens. Of the 301 patients randomized, 76% had genotype 1a, 15% had genotype 1b, 6% had genotype 4, 5% had genotype 6, 20% had cirrhosis, and 7% had HIV. At baseline, 79% were receiving methadone and 21% were receiving buprenorphine. A positive urine drug screen was present in 59% of patients for at least one of the following eight drug classes: amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, opiates, phencyclidine, and propoxyphene. Cocaine positivity was present in 10% of the patients, and opiate positivity was present in 25% of the patients. The modified data showed an SVR_{12} rate of 95% overall. Five patients were successfully treated but had virologic failure with a different genotype, subtype, or viral strain.

Asselah et al evaluated 103 HCV genotype 4 infected patients.[31] They analyzed 66 treatment-naïve (TN) patients and 37 treatment-experienced (TE) patients, including 17 cirrhotic patients. Overall, 97% of the TN (6/6 cirrhotic patients) and 86% of the TE genotype 4 patients achieved SVR_{12}. Among TE patients, 9/9 prior relapsers and 23/28 prior on treatment failures achieved SVR_{12}. Among TE cirrhotic patients, 77%, including 3/3 prior relapsers and 4/4 treated with grazoprevir/elbasvir and ribavirin for 16 weeks, achieved SVR_{12}. Longer duration of treatment and use of ribavirin increased the response rate in patients with prior on therapy failure.

Additional pertinent studies evaluating the use of grazoprevir/elbasvir therapy in various patient populations are described in Table 3.[32–35]

Safety and tolerability

Various studies have demonstrated favorable safety and tolerability profile for grazoprevir. Transient and mild adverse events were reported in an initial phase I study utilizing grazoprevir doses from 50 mg to 800 mg daily for a week in 84 HCV genotype 1 and three non-cirrhotic patients.[18] In a randomized, active-controlled trial, Manns et al evaluated the safety and efficacy of PR combined with either grazoprevir or boceprevir.[20] Patients received grazoprevir 100 mg, 200 mg, 400 mg, or 800 mg daily with standard dose PR, or boceprevir with PR at standard doses. Safety was evaluated in 332 patients and the rate of serious adverse events was

Table 3 Additional studies evaluating use of grazoprevir/elbasvir for treatment of HCV

Study	Study design	Treatment	Genotype	Patient population	SVR
Brown et al[32]	Randomized, open-label, Phase II	Genotype 2: GZR 100 mg + RBV ± EBR 50 mg for 12 weeks; genotype 4, 5 or 6: randomized to GZR/EBR ± RBV for 12 weeks.	2, 4, 5, or 6	Treatment naïve, non-cirrhotic patients	Genotype 2: SVR_{12} of 80% in GZR/EBR + RBV and 73% in GZR + RBV. Genotype 4: SVR_{12} of 90% in GZR/EBR and 100% in GZR/EBR + RBV. Genotype 5: SVR_{12} of 25% in GZR/EBR vs 100% in GZR/EBR + RBV. Genotype 6: SVR_{12} of 75% in both groups
Hezode et al[33]	Randomized, placebo-controlled, Phase III study	12 weeks of GZR/EBR 100 mg/50 mg in ITG vs DTG	1, 4, or 6	159 patients with HCV and sickle cell anemia, thalassemia, or hemophilia A/B or von Willebrand disease	SVR_{12} of 93.5% in the ITG. SVR_{12} was achieved in 94.7%, 97.6%, and 89.4% of patients with sickle cell disease, b-thalassemia, and hemophilia A/B or von Willebrand disease, respectively
Kwo et al[34]	Randomized, open-label, Phase III study	12 vs 16 weeks of treatment with GZR/EBR 100 mg/50 mg ± RBV	1,4, or 6	420 patients included: 35% with cirrhosis, 64% with null or partial response to PR treatment.	12 weeks of treatment: SVR_{12} of 92% in GZR/EBR vs SVR_{12} of 94% in GZR/EBR + RBV 16 weeks of treatment: SVR_{12} of 92% in GZR/EBR vs 98% in GZR/EBR + RBV
Sperl et al[35]	Randomized, open-label, Phase III study	12 weeks of GZR/EBR 100 mg/50 mg (n=129) vs sofosbuvir 400 mg + PR (n=128)	1 or 4	83% non-cirrhotic, 75% treatment naïve, 82% genotype 1b	SVR_{12} of 99% in GZR/EBR group and 90% in sofosbuvir/PR group

Abbreviations: DTG, deferred treatment group; EBR, elbasvir; GZR, grazoprevir; HCV, hepatitis C virus; ITG, immediate treatment group; RBV, ribavirin; SVR_{12}, sustained virologic response 12 weeks after treatment completion; PR, Peg-interferon + ribavirin.

similar in both groups (9% in grazoprevir group and 8% boceprevir group). The rate of adverse events leading to discontinuation of therapy was 7% in the grazoprevir group and 14% in the boceprevir group. Transaminase levels were increased significantly in patients receiving 400 mg and 800 mg doses of grazoprevir. The grazoprevir dose in these patients was decreased to 100 mg and transaminase levels normalized by week 16.

Safety of grazoprevir was evaluated in 87 treatment-naïve, non-cirrhotic, genotype one patients by Lagging et al.[22] Adverse events were similar in all the three groups. One patient in this study experienced myositis with transaminase levels >3× the upper limit of normal (ULN), total bilirubin >2× ULN, and CPK level of 1,032 U/L after 7 days of grazoprevir 100 mg. The patient required discontinuation of therapy leading to normalization of laboratory values.

The C-WORTHY study conducted by Sulkowski et al reported common adverse events to be mild to moderate fatigue, headache, nausea, and diarrhea.[23] Overall, adverse events occurred in 56% of the patients with three patients reporting serious adverse events. Serious adverse events consisted of one case of nausea, one of asthenia related to the study drug, and one of staphylococcal infection, which was determined to be unrelated to the study drug. Ribavirin containing regimens had higher rates of adverse events, bilirubin elevation, or hemoglobin decrease. Transaminase elevations were not seen after 4 weeks of therapy.

Lawitz et al reported common adverse events of fatigue, headache, and asthenia of mild to moderate intensity.[24] Serious adverse events were reported in seven patients, but only one patient had abdominal pain which was thought to be due to the study medication. One patient experienced transaminase increase, which resolved without interruption of therapy. Once again the rate of adverse events, bilirubin elevation, and hemoglobin decrease was higher in groups receiving ribavirin.

Most common adverse events reported in the C-WORTHY part D study included headache, upper respiratory tract infection, and nausea.[25] One patient discontinued therapy due to experiencing dyspnea, fatigue, and asthenia 2–3 days after starting treatment in the W18 group. C-EDGE-TN study also reported common adverse events of headache, fatigue, and nausea.[26] There were nine serious adverse events reported, none of which were attributed to the study drug. Two patients discontinued study medication due to elevated aminotransferase levels and one patient due to palpitations and anxiety. In the C-EDGE Co-Infection study, the most common side effects were fatigue (13%), headache (12%), and nausea (9%) with no discontinuation due to adverse events.[27] Two patients had transient HIV viremia.

Both groups in the C-SALT study experienced common adverse events of fatigue, arthralgia, nausea, and headache.[19] Four serious adverse events were reported in the CP-B cirrhosis group, none of which were attributed to the study drug. Transient bilirubin elevation without AST/ALT elevation was noted in four patients and one patient died due to progression of liver disease in the CP-B cirrhosis group.

In the C-EDGE CO-STAR study, occurrence of adverse events reported was similar in both groups with most common adverse events being fatigue, headache, nausea, and diarrhea.[30] Serious adverse events were reported in 7% of the ITG and 4% of the DTG. One death occurred in the DTG group while on placebo.

Dusheiko et al conducted a safety analysis of grazoprevir/elbasvir from the results of studies published in which the therapy was given for 8, 12, 16, or 18 weeks.[36] Adverse events and laboratory abnormalities reported on therapy or within 14 days of end of treatment were evaluated. A total of 1,795 patients were included in the evaluation: 1,033 received grazoprevir/elbasvir without ribavirin, 657 received grazoprevir/elbasvir with ribavirin, and 105 received placebo. Of the patients enrolled, 61% were male, 13% were Black, 27% had compensated cirrhosis, and 18% were HIV/HCV co-infected. The safety profile of grazoprevir/elbasvir without ribavirin was similar to placebo but the addition of ribavirin was associated with more adverse events. The most commonly reported adverse events were headache and fatigue in the patients receiving grazoprevir/elbasvir with or without ribavirin. There were three deaths among patients receiving grazoprevir/elbasvir that were unrelated to the study medication, while no patients in the placebo group died. Sex, age, presence of cirrhosis, and HIV/HCV co-infection were not associated with adverse events. ALT elevations of >5× the ULN at or after treatment week 8 occurred in 0.8% of the patients with normal ALT values at baseline. The ALT elevations were asymptomatic and the values normalized in the majority of the cases without any intervention.

Resistance-associated substitution

Development of RAS occurs due to the combination of high replication rate (10^{12} virions/day) of HCV and viral replication prone to errors. RAS testing is generally performed at baseline and at the time of virologic failure. *NS3* and *NS5A* genes are amplified with a reverse transcription polymerase chain reaction and population sequencing.[28] Response to suppression of these sequences is compared to wild-type

HCV sequencing for reference and categorized as low- or high-level resistance. Decreased efficacy of antiviral drugs is attributed to the continuous production of the RAS. Known variants associated with resistance to protease inhibitors include Q41R, F43S, R155K, V36M, T54S/A, and D168. Grazoprevir and elbasvir in vitro studies have shown no cross-resistance among them as these agents are active against one another's RAS.[37] Manns et al obtained baseline RAS in 261 of 264 patients.[20] They identified 73 patients (28%) who had the presence of RAS to at least one other protease inhibitor. Of the 73 patients, 96% achieved SVR_{24} and six patients experienced virologic treatment failure. Howe et al further analyzed virologic resistance among the six patients.[21] To assess genotypic variation at baseline or at virologic failure, the *NS3/4A* gene was amplified from samples with RNA levels ≥1,000 IU/mL using reverse transcription polymerase chain reaction followed by population and selective clonal sequences. Resultant amino acid sequences were compared to wild-type HCV1a or 1b reference sequences. A single NS3A protease amino acid substitution was considered clinically relevant. Five of the six patients with virologic treatment failure were in the 100 mg/day group. Four of the five patients were found to have low or undetectable trough plasma levels compared to the median levels in the pharmacokinetic substudy. One patient who experienced virologic treatment failure in the 200 mg/day group was infected with genotype 1b at the initiation of treatment, but had reinfection with genotype 3a after completion of treatment.

Sulkowski et al assessed the presence of RAS in patients receiving grazoprevir/elbasvir treatment.[23] Seventy-five patients out of 216 (35%) had the presence of NS3 RAS at baseline; 68 patients (91%) achieved SVR_{12}. At baseline, 25 patients (12%) had the presence of NS5A RAS known to have more than five-fold resistance to elbasvir or other NS5A inhibitors. Seventeen of the 25 patients (68%) achieved SVR_{12}.

Lawitz et al assessed the presence of RAS at baseline and at treatment failure.[24] At baseline, NS3 RAS were present in 79 of 248 patients (32%) and SVR_{12} was achieved in 73 of 79 patients (92%). NS5A RAS were present in 34 of 243 patients (14%) at baseline, of whom 28 achieved SVR_{12} (82%). Ten patients had virologic treatment failure. Eight of 10 patients had detectable NS3 or NS5A RAS present. Common RAS detected in these patients included NS3:Y56H, A156T/G/V, D168A/Y, NS5A:M28T, Q30L/R, L31M, and Y93H/N. Based on the results of these studies, cross-resistance of many RAS, selected by other protease inhibitors, to grazoprevir/elbasvir, seems to be absent. In patients with prior exposure to protease inhibitors, C-SALVAGE demonstrated rare potential for transient NS3 RAS as well as rare NS5A RAS persisting over the 24-week follow-up.[28] Due to concerns with RAS leading to virologic failures, baseline polymorphism testing should be done prior to initiation of grazoprevir/elbasvir and duration of therapy should be adjusted accordingly.[38]

Drug interactions

Both grazoprevir and elbasvir are substrates of CYP3A4 and P-glycoprotein. Grazoprevir is also a substrate of the organic anion-transporting polypeptide (OATP). Co-administration of grazoprevir/elbasvir with OATP1B1/3 is contraindicated. Use of strong inducers of CYP3A4 is contraindicated while on grazoprevir/elbasvir, and use of moderate CYP3A4 inducers or inhibitors is not recommended while on grazoprevir/elbasvir therapy. Grazoprevir/elbasvir use in combination with statins should be used cautiously as exposure to statins is increased. Drug-drug interactions with grazoprevir and elbasvir are summarized in Tables 4 and 5.[38]

Conclusion

The grazoprevir/elbasvir regimen has significant advantages over first-generation direct-acting agents. It has a favorable pharmacokinetic profile with high liver concentration that allows for once-daily dosing with a single tablet. Grazoprevir/elbasvir demonstrates a high barrier to resistance with activity against substitutions known to have resistance to first-generation protease inhibitors.[37] It demonstrates high SVR rates among HCV genotype 1 and 4 treatment-naïve and treatment-experienced patients, including compensated cirrhotics, without necessity of interferon injection. In addition, it presents an option for therapy without the need for

Table 4 Use of medications contraindicated with grazoprevir/elbasvir[38]

Contraindicated medications that cause decreases in grazoprevir and elbasvir plasma concentrations due to CYP3A induction, leading to loss of virologic response:
• Phenytoin
• Carbamazepine
• Rifampin
• St. John's Wort (*Hypericum perforatum*)
• Efavirenz
Contraindicated medications that cause significant increase in grazoprevir plasma concentrations due to OATP1B1/3 inhibition which may lead to ALT elevations:
• Atazanavir
• Darunavir
• Lopinavir
• Saquinavir
• Tipranavir
• Cyclosporine

Table 5 Drug-drug interactions of grazoprevir and elbasvir

Medication	Effect on concentration	Comment
Nafcillin	Decreases grazoprevir and elbasvir concentrations	Co-administration not recommended
Ketoconazole	Increases grazoprevir and elbasvir concentrations	
Bosentan	Decreases grazoprevir and elbasvir concentrations	
Etravirine	Decreases grazoprevir and elbasvir concentrations	
Elvitegravir/ cobicistat/ emtricitabine/ tenofovir (disoproxil fumarate or alafenamide)	Increases grazoprevir and elbasvir concentrations	
Modafinil	Decreases grazoprevir and elbasvir concentrations	
Tacrolimus	Increased tacrolimus concentrations	Frequent monitoring of tacrolimus whole blood concentrations, renal function, and adverse events upon initiation of co-administration is recommended
Atorvastatin	Increases concentrations of statins	Do not exceed atorvastatin 20 mg daily dose while on grazoprevir/elbasvir
Fluvastatin Lovastatin Simvastatin		Use lowest necessary statin dose and monitor closely for myopathy while on grazoprevir/elbasvir
Rosuvastatin		Do not exceed rosuvastatin 10 mg daily dose while on grazoprevir/elbasvir

Note: Data from Zepatier™ (elbasvir/grazoprevir) [package insert].[38]

ribavirin in genotype 1 patients. Further data are needed on the potential for use of this medication in patients with decompensated cirrhosis.

Grazoprevir/elbasvir has also demonstrated efficacy among HCV/HIV co-infected patients with SVR_{12} rates greater than 95% in HCV genotype 1, 4, and 6 patients.[27] These data suggest that the efficacy of grazoprevir/elbasvir is similar in mono-infected and co-infected patients. Since grazoprevir is a mild CYP3A4 inhibitor, there are clinically important drug-drug interactions that should be thoroughly evaluated when it is utilized concomitantly with anti-retroviral therapy. Grazoprevir/elbasvir does not have an interaction with pantoprazole or famotidine, thus making this regimen more attractive for patients who take these agents, as other HCV DAA regimens require separation of acid reducing agents.

There has been an unmet medical need to treat HCV infection in patients with CKD and those on hemodialysis. Clinical trials with grazoprevir/elbasvir in CKD demonstrate extremely promising efficacy and tolerability.[29] With an aging HCV population and expected increased incidence of renal impairment in this cohort, the grazoprevir/elbasvir regimen seems particularly attractive, representing the first oral ribavirin-free regimen to be evaluated in this patient population.

Current data demonstrate the combination of grazoprevir/elbasvir to be a very efficacious regimen representing a strong protease inhibitor/NS5A inhibitor oral, single-tablet regimen for treatment of HCV infection in patients with compensated cirrhosis, HCV/HIV co-infection and with CKD. Additionally, it represents a medication that maintains safety and efficacy regardless of the severity of fibrosis. A high degree of all-oral efficacy was maintained even among patients with prior exposure to earlier generation protease inhibitors.[28] This regimen is safe and effective and is well tolerated among HCV patients with narcotic and opioid dependence including methadone and cocaine.[30] The robust data among the general genotype 1 and 4 population provide another option for a field in need of a viable competitive market, for which cost of therapy is the limiting factor. These data include patients with cirrhosis, treatment experience, HIV co-infection, exposure to protease inhibitors and those on dialysis – potentially expanding the utility of this regimen in a broad arena of patients.

Disclosure

The authors report no conflicts of interest in this work.

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