Title

Elbasvir/Grazoprevir: A New Direct Acting Antiviral Combination for Hepatitis C

Abstract

Purpose: The chemistry, pharmacology, pharmacodynamics, pharmacokinetics, efficacy, safety, dosage, administration, and role of elbasvir/grazoprevir in the treatment of hepatitis C are reviewed.

Summary: Elbasvir/grazoprevir (Zepatier™) was newly approved by the Food and Drug Administration for the treatment of chronic hepatitis C virus (HCV) genotypes 1 or 4 infections with or without ribavirin. Elbasvir/grazoprevir is recommended as monotherapy for treatment-naïve and treatment-experienced genotype 1a, 1b, and 4 HCV-infected patients with or without compensated cirrhosis; and with ribavirin for treatment-experienced genotypes 1a, 1b and 4 HCV-infected patients with or without compensated cirrhosis. Elbasvir/grazoprevir is a once-daily, fixed-dose combination tablet containing two direct-acting antiviral agents: the NS5A inhibitor elbasvir (50 mg) and the NS3/4A protease inhibitor grazoprevir (100 mg). It can be taken with or without food. Elbasvir exhibits antiviral activity against HCV genotypes 1a, 1b, 2a, 3a and 4 a; grazoprevir demonstrates sub-nanomolar to low-nanomolar median 50% effective concentration values against genotypes 1a, 1b, 2a. Elbasvir and grazoprevir undergo primarily fecal excretion, do not require dose adjustment in renal impairment, but are contraindicated in moderate and severe hepatic impairment. The adverse drug reactions most commonly reported for elbasvir/grazoprevir without ribavirin include fatigue, headache, and nausea, and those for elbasvir/grazoprevir with ribavirin include anemia and headache. In phase II and III clinical trials, elbasvir/grazoprevir administered orally at daily doses of 50/100 mg for 12 weeks was shown to achieve high sustained virologic response 12 weeks after the end of treatment.

Conclusion: Elbasvir/grazoprevir constitutes a new oral treatment option for patients with HCV genotypes 1 or 4 without requiring the use of interferon. Monitoring of liver function enzymes is warranted.

Keywords

Elbasvir, Grazoprevir, Hepatitis C, NS3/4A protease inhibitor, NS5A inhibitor

Introduction

Approximately 130 to 150 million people have chronic hepatitis C virus (HCV) infection and it is estimated that 500,000 deaths are attributed annually to HCV-related liver disease worldwide. Antiviral medications can cure approximately 90% of persons with HCV infection, thereby reducing the risk of death from liver cancer and cirrhosis, but access to HCV diagnosis and

treatment remains suboptimal.[1] In 2014, the Centers for Disease Control and Prevention reported 2,194 new acute cases of HCV, with estimated actual new cases of 30,500 (24,200 to 104,200). The estimated number of chronic cases of HCV in the United States is 2.7 to 3.9 million with 19,659 death certificates listing HCV as a cause of death.[2] As there is currently no vaccine for hepatitis C, the advent of direct-acting antiviral agents which allow the administration of interferon-free regimens is dramatically changing the management of hepatitis C. Elbasvir/grazoprevir (MK-8742/MK-5172, Zepatier™, Merck & Co., Inc. Kenilworth, New Jersey) is a once-daily, fixed-dose combination tablet containing the NS5A inhibitor elbasvir (50 mg) and the NS3/4A protease inhibitor grazoprevir (100 mg). Zepatier™ was approved by the Food and Drug Administration on January 28, 2016 for the treatment of chronic HCV genotypes 1 or 4 infections with or without ribavirin.[3] Elbasvir/grazoprevir is also approved in Canada for the treatment of HCV genotypes 1 and 4 infections with or without ribavirin and for HCV genotype 3 infection with sofosbuvir.[4] On May 26, 2016, the European Medicine Agency granted a marketing authorization for elbasvir/grazoprevir.[5] This article reviews the chemistry, pharmacology, pharmacodynamics, pharmacokinetics, clinical efficacy, safety, dosage, administration, and role of elbasvir/grazoprevir in the treatment of chronic hepatitis C.

Data Selection

Available *in vitro* and preclinical studies, as well as Phase I, II, and III clinical studies published in English were evaluated to summarize the chemistry, pharmacology, efficacy, and safety of elbasvir/grazoprevir in the treatment of chronic hepatitis C.

Chemistry and Pharmacology

Elbasvir has a molecular formula of $C_{49}H_{55}N_9O_7$ and a molecular weight of 882.02 [3] Grazoprevir has a molecular formula of $C_{38}H_{50}N_6O_9S$ and a molecular weight of 766.8).[3] Elbasvir/grazoprevir is a combination of two direct-acting antiviral agents with two distinct mechanisms of action and non-overlapping resistance profiles to target HCV at multiple stages of the viral lifecycle. Elbasvir is an inhibitor of HCV NS5A, which is necessary for viral RNA replication and virion assembly.[3] Grazoprevir is a selective inhibitor of HCV NS3/4A protease, an enzyme involved in the proteolytic cleavage of the HCV encoded polyprotein (into mature forms of the NS3, NS4A, NS4B, NS5A and NS5B proteins) and viral replication.[6]

Pharmacokinetics

Studies in non-HCV-infected adult subjects and in HCV-infected adult subjects showed that elbasvir pharmacokinetics were similar and were approximately dose-proportional over the range of 5-100 mg once daily. In HCV-infected subjects, grazoprevir pharmacokinetics increased in a greater than dose-proportional manner over the range of 10-800 mg once daily. Grazoprevir oral exposures were approximately 2-fold greater in HCV-infected subjects compared to healthy subjects. Administration of ribavirin or sofosbuvir did not significantly alter plasma area under the concentration-time curve (AUC) and maximum concentration ($C_{max)}$ of elbasvir and grazoprevir were observed with as compared to administration of elbasvir/grazoprevir alone. Steady-state pharmacokinetics were reached within approximately 6 days following once daily administration of elbasvir/grazoprevir 50/100 mg to HCV-infected subjects (Table 1).[3] Following administration of elbasvir/grazoprevir to HCV-infected subjects, peak plasma concentrations of elbasvir and grazoprevir occurred at a median time to C_{max} ($T_{max)}$ of 3 hours (range of 3 to 6 hours) and 2 hours (range of 30 minutes to 3 hours) respectively. Following administration of a single dose of elbasvir/grazoprevir with a high-fat (900 kcal, 500 kcal from fat) meal to healthy

subjects, the AUC from time zero to infinity ($AUC_{0\text{-}inf)}$ and C_{max} increased for grazoprevir approximately 1.5- and 2.8-fold, respectively, and decreased for elbasvir approximately 11% and 15%, respectively.[3] Given that those differences are not clinically relevant, elbasvir/grazoprevir may be taken without regard to food. The geometric mean at steady state $AUC_{0\text{-}24h}$ is 2180 (nM•hr) and 1860 (nM•hr) and the geometric mean C_{max} is 137 (nM) and 220 (nM) for elbasvir and grazoprevir respectively.

The geometric mean apparent terminal half-lives for elbasvir (50 mg) and grazoprevir (100 mg) are approximately 24 and 31 hours respectively in HCV-infected subjects; the estimated apparent volumes of distribution of elbasvir and grazoprevir are 608 L and 1250 L respectively. Both elbasvir and grazoprevir are highly bound (> 99.9% and 98.8% respectively) to human plasma proteins: albumin and alpha-1 acid glycoprotein. Renal and hepatic impairment have minimal impact on plasma protein binding. In preclinical distribution studies, elbasvir distributed into most tissues including the liver and grazoprevir distributed predominantly to the liver. Elbasvir/grazoprevir undergo partial elimination by oxidative metabolism, primarily by CYP3A. No circulating metabolites of either elbasvir or grazoprevir were detected in human plasma. Elbasvir and grazoprevir are substrates of CYP3A4, P-glycoprotein and the organic anion-transporting polypeptide OATP1B1/3.[7] Following administration of a radiolabeled dose, elbasvir and grazoprevir undergo primarily fecal excretion (> 90%) while less than 1% is excreted in the urine. As such, elbasvir/grazoprevir does not require any dose adjustment in patients with renal impairment, including patients on hemodialysis.[7,8,9] In non-HCV subjects with mild, moderate or severe hepatic impairment, the grazoprevir AUC values were 1.7-, 5-, and 12 fold higher respectively however, the elbasvir AUC values were not significantly altered. Accordingly,

elbasvir/grazoprevir is contraindicated in moderate to severe hepatic impairment, and no dosage adjustment is recommended in patients with mild hepatic impairment.[7]

Pharmacodynamics and Resistance

Elbasvir had median 50% effective concentration (EC_{50}) values against full-length chimeric replicons containing NS5A from clinical isolates of genotypes 1a, 1b, 4a, 4b, 4d, 4f, 4g, 4m, 4o and 4q of 5, 9, 0.2, 3600, 0.45, 1.9, 36.3, 0.6, 2.2 and 0.5 pmol/L respectively.[3,6] Grazoprevir had median EC_{50} values against full-length chimeric replicons containing NS3/4A from clinical isolates of genotypes 1a, 1b, 4a, 4b and 4g of 0.8, 0.3, 0.3, 0.16, 0.24 pmol/L respectively. The combination of elbasvir and grazoprevir showed no antagonistic effect in reducing HCV RNA levels in replicon cells.[3] In cell culture, the single NS5A substitutions M28A/G/T, Q30D/E/H/K/R, L31M/V, H58D and Y93C/H/N in HCV genotype 1a replicons reduced the antiviral activity of elbasvir 1.5- to 2000-fold, the single NS5A substitutions L28M, L31F and Y93H in HCV genotype 1b replicons reduced elbasvir antiviral activity 2- to 17-fold, and the single NS5A substitutions L30S, M31V and Y93H in HCV genotype 4 replicons reduced elbasvir antiviral activity 3- to 23-fold.[3] In cell culture, the single NS3 substitutions Y56H, R155K, A156G/T/V and D168A/E/G/N/S/V/Y in HCV genotype 1a replicons reduced antiviral activity of grazoprevir 2- to 81-fold, the single NS3 substitutions F43S, Y56F, V107I, A156S/T/V and D168A/G/V in HCV genotype 1b replicons reduced grazoprevir antiviral activity 1.5- to 375-fold, and the single NS3 substitutions D168A/V in HCV genotype 4 replicons reduced grazoprevir antiviral activity 110- to 320-fold. The single substitution V36L/M, Q80K/R or V107I had no impact on grazoprevir antiviral activity.[3] In general, in HCV genotype 1a, 1b, or 4 replicons, combinations of elbasvir resistance-associated substitutions further reduced elbasvir/grazoprevir antiviral activity. In phase II or III clinical trials, among

patients receiving elbasvir/grazoprevir (with or without ribavirin) who experienced virologic failure, NS5A substitutions that emerged during treatment included M28A/G/T, Q30H/K/R/Y, L31F/M/V, H58D and Y93H/N/S in HCV genotype 1a, L28M, L31F/V and Y93H in HCV genotype 1b, and L28S/T, M31I/V, P58D and Y93H in HCV genotype 4, and NS3 substitutions that emerged during treatment included V36L/M, Y56H, V107I, R155I/K, A156G/T/V, V158A and D168A/G/N/V/Y in HCV genotype 1a, Y56F, V107I and A156T in HCV genotype 1b, and A156M/T/V, D168A/G and V170I in HCV genotype 4.[3,6] Therefore, testing for NS5A polymorphisms in patients with HCV genotype 1a is recommended prior to treatment with elbasvir/grazoprevir.[3]

In randomized, single-dose placebo- and active-controlled (moxifloxacin 400 mg) 3-period cross-over studies on healthy subjects, supratherapeutic doses of elbasvir (700 mg) and grazoprevir (1600 mg and 4000 mg) did not prolong the corrected QT interval to a clinically-significant extent.[3]

Clinical Trials

Elbasvir/grazoprevir have been studied in both treatment-naïve and treatment-experienced patients with chronic HCV infection primarily genotypes 1 and 4 (Table 1). It was studied in patients with or without compensated cirrhosis, in patients with HIV/HCV co-infection, and in patients with chronic kidney disease. It was administered with or without ribavirin. Sustained virologic response (SVR), meaning undetectable viral load, was used as the clinical endpoint in HCV clinical trials as a surrogate marker for cure, mostly at week 12 after treatment (SVR_{12}), but also at week 24 after treatment (SVR_{24}).[10-16] Table 1 is a summary of all published phase II and

III studies. Elbasvir was given at the dose of 50 mg (but 20 mg was also used), grazoprevir was always given at the dose of 100 mg daily, and ribavirin was dosed according to body weight.[10-16]

Phase II Trials

C-WORHTY (12 weeks vs 18 weeks)[10] was a randomized open-label study of elbasvir/grazoprevir in treatment-naïve with cirrhosis and treatment-experienced with or without well compensated cirrhosis (Child Pugh A). Eligible patients were adults with genotype 1 and with HCV RNA levels >10,000 IU/mL. Patients with a history of chronic hepatitis not caused by HCV, co-infection with HIV, evidence of hepatocellular carcinoma, decompensated liver disease, previous receipt of any HCV direct-acting antivirals, renal impairment as defined by a creatinine clearance less than 50 mL/minute, neutropenia, and thrombocytopenia were excluded. In cohort 1 of the study which included treatment-naïve patients with cirrhosis, patients were given elbasvir 50 mg plus grazoprevir 100 mg with or without ribavirin for either 12 or 18 weeks. In cohort 2 of the study which included treatment-experienced patients with peginterferon and ribavirin, with or without cirrhosis, patients were given elbasvir 50 mg plus grazoprevir 100 mg with or without ribavirin for either 12 or 18 weeks. Primary endpoints were SVR_{12} rates. Among all participants, 92% were white and 67% had cirrhosis. In cohort 1, SVR_{12} rates were between 90 and 97%. In cohort 2, SVR_{12} rates were between 91 and 100%. SVR_{12} rates for treatment-experienced patients with cirrhosis were 94% (95% CI, 80 to 99) with genotype 1a and 100% (95% CI, 78 to 100) with genotype 1b. This trial in genotype 1 showed that elbasvir 50 mg plus grazoprevir 100 mg for 12 to 18 weeks resulted in high SVR_{12} in treatment-naïve patients with cirrhosis and in treatment-experienced patients with or without cirrhosis regardless of the

addition of ribavirin. Limitations include the small sample size in each treatment arm and the lack of power to determine the precise contribution of ribavirin or extended treatment duration.

C WORTHY (8 weeks vs 12 weeks)[11] was a randomized open-label study of elbasvir/grazoprevir in treatment-naïve noncirrhotic patients with or without HIV/HCV co-infection. Eligible patients were adults with genotype 1, with HCV RNA levels >10,000 IU/mL, and with a body weight of at least 50 Kg. Patients with a history of hepatitis not caused by HCV, evidence of hepatocellular carcinoma, decompensated liver disease, and previous HCV therapy were excluded. Patients with HIV must be well-controlled with raltegravir plus two nucleoside or nucleotide reverse transcriptase inhibitors for at least 8 weeks before enrollment, must have undetectable HIV RNA for at least 24 weeks, and must have a CD4 count of at least 300 cells/mcL. In part A of the study which included patients mono-infected, patients were given elbasvir 20 or 50 mg plus grazoprevir 100 mg with or without ribavirin for 12 weeks. In part B of the study which included patients mono-infected and co-infected with HIV/HCV, patients were given elbasvir 50 mg plus grazoprevir 100 mg with or without ribavirin for either 8 or 12 weeks. Patients with HIV/HCV coinfection received treatment for 12 weeks. Primary endpoints were SVR_{12} rates. Among all participants, 88% were white, 73% were mono-infected and 27% were co-infected with HIV. SVR_{12} rates were 92% with genotype 1a and 95% with genotype 1b. SVR_{12} rates for mono-infected patients were between 93 and 98%. SVR_{12} rates for HIV/HCV co-infected patients were between 87 and 97%. SVR_{12} rates in mono-infected treated for 12 weeks without ribavirin were 98% (95% CI, 88 to 100) and with ribavirin were 93% (95% CI 85 to 97). This trial showed that elbasvir 50 mg plus grazoprevir 100 mg with or without ribavirin for 12 weeks resulted in high SVR_{12} in treatment-naïve noncirrhotic patients with genotype 1

regardless of whether they are mono-infected or co-infected with HIV. Limitations include the lack of active-comparator control, the small sample size in each arm, and the small number of patients co-infected with HIV.

C-SALVAGE[12] was a randomized open-label study of elbasvir/grazoprevir in patients with or without cirrhosis after failure of combination therapy containing one of the following direct-acting antivirals: boceprevir, telaprevir, or simeprevir. Eligible patients were treatment-experienced adults with genotype 1 and with HCV RNA levels >10,000 IU/mL. Patients with decompensated liver disease, hepatocellular carcinoma, thrombocytopenia, and HIV or HBV co-infection were excluded. Patients were given elbasvir 50 mg plus grazoprevir 100 mg plus ribavirin for 12 weeks. Primary endpoints were SVR_{12} rates. Among all the participants, 83.5% had a history of virologic failure on a regimen containing a NS3/4A protease inhibitor, 15.2% discontinued prior treatment because of adverse events, and 43.3% harbored NS3 Resistance-Associated Variants (RAV). SVR_{12} rate was 93.3% (95% CI 77.9 to 99.2) with genotype 1a and 98.0% (95% CI 89.1 to 99.9) with genotype 1b. SVR_{12} rate was 94.1% (95% CI 80.3 to 99.3) in patients with cirrhosis and 97.8% (95% CI 88.2 to 99.9) in patients without cirrhosis. SVR_{12} rate was 95.5% (95% CI 87.3 to 99.1) among patients with prior virologic failure and 100% (95% CI 75.3 to 100.0) among patients with prior non-virologic failure. This trial showed that elbasvir 50 mg plus grazoprevir 100 mg plus ribavirin for 12 weeks resulted in high SVR_{12} in treatment-experienced patients with or without cirrhosis. Limitations include the lack of active-comparator control, the small sample size in each arm, and the absence of sofosbuvir-experienced patients. Buti et al[13] conducted an evaluation of these patients 24 weeks after cessation of study therapy

and demonstrated that SVR_{24} rate remained 96.2% and all 3 relapses occurred by posttherapy week 8.

Phase III Trials

C-EDGE[14] was a randomized blinded study of elbasvir/grazoprevir in treatment-naïve patients with or without cirrhosis. Eligible patients were adults with genotype 1, 4, or 6, and with HCV RNA levels >10,000 IU/mL. Patients with decompensated liver disease, hepatocellular carcinoma, thrombocytopenia, uncontrolled diabetes mellitus, and HIV or HBV co-infection were excluded. Patients were randomized to receive either immediate or deferred elbasvir 50 mg plus grazoprevir 100 mg for 12 weeks. The deferred group received initially matching placebo. Primary endpoints were SVR_{12} rates. Among all the participants, 46% were women, 37% were nonwhite, 91% had genotype 1, and 22% had cirrhosis. SVR_{12} rates were 92% (95% CI, 86 to 97) with genotype 1a, 99% (95% CI, 95 to 100) with genotype 1b, 100% (95% CI, 82 to 100) with genotype 4, and 80% (95% CI, 44 to 98) with genotype 6. SVR_{12} rates were 97% (95% CI, 90 to 100) in patients with cirrhosis and 94% (95% CI, 90 to 97) in patients without cirrhosis. This trial showed that elbasvir 50 mg plus grazoprevir 100 mg for 12 weeks resulted in high SVR_{12} in treatment-naïve patients with genotype 1, 4, or 6 with or without cirrhosis. Limitations include the lack of active-comparator control and the limited number of patients with genotypes 4 and 6.

C-SURFER[15] was a double-blind study comprising a randomized study of safety and an observational study of efficacy of elbasvir/grazoprevir in treatment-naïve and treatment-

experienced patients with or without cirrhosis but with chronic kidney disease stages 4 and 5 including patients on hemodialysis. Eligible patients were adults with genotype 1 and with HCV RNA levels >10,000 IU/mL. Patients with decompensated liver disease, hepatocellular carcinoma, thrombocytopenia, uncontrolled diabetes mellitus, and HIV or HBV co-infection were excluded. Patients were randomized to receive either immediate or deferred elbasvir 50 mg plus grazoprevir 100 mg for 12 weeks. The deferred group received initially matching placebo. An additional small cohort of patients received the same regimen and underwent intensive pharmacokinetic sampling. Primary endpoints were SVR_{12} rates. Among all the participants, 46% were African American, 76% were on hemodialysis, 80% were treatment-naive, and 6% had cirrhosis. In the full analysis set, SVR_{12} rates were 94.3% (95% CI, 88.5 to 97.7) in the immediate treatment group and pharmacokinetic population. SVR_{12} rates were 100% (95% CI, 94.1 to 100.0) with genotype 1a and 98.2% (95% CI, 90.3 to 100.0) with genotype 1b. SVR_{12} rates were 99.1% (95% CI, 95.0 to 100.0) in patients without cirrhosis and 100.0% (95% CI, 54.1 to 100.0) in patients with cirrhosis. SVR_{12} rates were 100.0% (95% CI, 84.6 to 100.0) in patients with chronic kidney disease stage 4, 98.9% (95% CI, 94.2 to 100.0) in patients with chronic kidney disease stage 5, and 98.9% (95% CI, 93.8 to 100.0) in patients on hemodialysis. This trial showed that elbasvir 50 mg plus grazoprevir 100 mg for 12 weeks resulted in very high SVR_{12} in mostly treatment-naïve patients with genotype 1 and chronic kidney disease. Limitations include the lack of active-comparator control, the limited number of patients with cirrhosis, and the exclusion of patients receiving peritoneal dialysis.

C-EDGE CO-INFECTION[16] was a non-randomized open-label study of elbasvir/grazoprevir in treatment-naïve patients with or without well compensated cirrhosis (Child Pugh A) but co-

infected with HIV/HCV. Eligible patients were adults with genotype 1, 4, or 6, and with HCV RNA levels >10,000 IU/mL. All patients must be co-infected with HIV and either naïve to antiretroviral therapy or receiving tenofovir or abacavir plus emtricitabine or lamivudine plus raltegravir, dolutegravir, or riplivirine for at least 8 weeks before enrolment. Patients naïve to antiretroviral therapy must have a CD4 count of more than 500 cells/mcL and patients receiving antiretrovirals must have a CD4 count of more than 200 cells/mcL. Patients with decompensated liver disease or with a Child Pugh score more than 6 points, hepatocellular carcinoma, or HBV co-infection were excluded. All patients received elbasvir 50 mg plus grazoprevir 100 mg for 12 weeks. Primary endpoints were SVR_{12} rates. Among all participants, 77% were white and 16% had cirrhosis. SVR_{12} rates were 96.5% (95% CI, 92.1 to 98.9) with genotype 1a, 95.5% (95% CI, 84.5 to 99.4) with genotype 1b, and 96.4% (95% CI, 81.7 to 99.9). The two patients with genotype 6 who were included in the study achieved SVR_{12}. SVR_{12} rates were 100.0% (95% CI, 90.0 to 100.0) in patients with cirrhosis and 95.6% (95% CI, 91.6 to 98.1) in patients without cirrhosis. This trial showed that elbasvir 50 mg plus grazoprevir 100 mg for 12 weeks resulted in very high SVR_{12} in treatment-naïve HIV/HCV co-infected patients with genotype 1, 4, and 6 with or without cirrhosis. Limitations include the lack of active-comparator control and the limited number of patients with cirrhosis and those with genotypes 4 and 6.

Safety

Adverse Events

Elbasvir/grazoprevir was studied alone and in combination with ribavirin for the treatment of HCV infection.[10-16] Its safety was assessed in clinical trials when used alone and in combination

with ribavirin.[3] In clinical trials, elbasvir/grazoprevir was well tolerated and adverse events were described as mild to moderate.[10-16] In phase II trials, the most commonly reported adverse events were fatigue (13%-26%), headache (12%-23%), nausea 9% and asthenia 14%.[10,11] Similar adverse events were also observed in phase III trials such as headache (17%), fatigue (16%), and nausea (9%).[14,16] In addition, an integrated analysis of the safety and efficacy of elbasvir/grazoprevir was conducted and found that fatigue and headache were most seen in patients receiving treatment with ribavirin.[12] The incidence of fatigue was 12% in the elbasvir/grazoprevir group compared to 24.7% in the ribavirin group, and the incidence of headache was 11.5% in the elbasvir/grazoprevir group compared to 16.3% in the ribavirin group. The incidence of nausea, insomnia, and anemia were 12.6%, 8.8% and 9.1% respectively in the ribavirin group.[17,18] Other reported adverse events in the ribavirin group were asthenia (9.3%), pruritus (8.8%), rash (6.8%), and dyspnea (6.4%).[3,17] Elbasvir/grazoprevir was also well tolerated in patients with chronic kidney disease and in patients with HIV co-infection.[3,11,15,16] Moreover, its tolerability profile in patients with cirrhosis appeared to be similar to those without cirrhosis.[3,10,14] In clinical trials, an increase in alanine aminotransferase (ALT) has been observed 8 weeks into the treatment course in patients on elbasvir/grazoprevir with or without ribavirin.[3,18] However, this has been associated with an increase in serum plasma concentration of grazoprevir but was not related to the treatment duration. Most of ALT elevations were resolved during treatment or after completion of therapy.[3,18] Also, an elevation in bilirubin levels at greater than 2.5 times normal limits were more observed in the ribavirin group (6%) compared to the elbasvir/grazoprevir group (1%), regardless of treatment duration. The increase in bilirubin was not associated with the elevation in ALT levels.[3,18]

Drug Interactions

Elbasvir and grazoprevir are substrates of CYP3A4 and P-glycoprotein. The drug absorption is minimally affected by intestinal P-glycoprotein; however, its blood concentration and therapeutic effect may be affected by co-administration with CYP3A4 inducers or inhibitors.[3] As a result, elbasvir/grazoprevir is contraindicated with strong CYP3A4 inducers such as carbamazepine, phenytoin, rifampin, St. John's Wort, and with efavirenz, where the co-administration with efavirenz leads to more than 80% decrease in exposure to grazoprevir.[3,22] Also, co-administration with moderate CYP3A4 inducers such as nafcillin, bosentan, etravirine and modafinil, or with strong CYP3A4 inhibitors such as ketoconazole and ritonavir is not recommended due to potential increase in elbasvir and grazeprovir concentrations leading to increased risk of hepatotoxicity.[3] Elbasvir/grazoprevir is a substrate of organic anion transporting polypeptides 1 B1/3 (OAPT1B1/3), hence co-administration with OAPT1B1/3 inhibitors such as HIV medications including atazanavir, darunavir, lopinavir, saquinavir, tipranavir and cyclosporine is contraindicated.[3,22] HMG-CoA reductase inhibitors such as atorvastatin, rosuvastatin, fluvastatin, lovastatin and simvastatin require close monitoring for adverse events such as myopathy when co-administered with elbasvir/grazoprevir, and the lowest necessary dose should be used for fluvastatin, lovastatin and simvastatin.[3,17] The maximum recommended dose for atorvastatin and rosuvastatin is 20 mg and 10 mg respectively when co-administered with elbasvir/grazoprevir.[3]

Special Populations

The safety and efficacy of elbasvir/grazoprevir has not been established in the pediatric population.[3] It has been studied in geriatric patients where an increase in ALT levels has been

observed, however, no dosage adjustment is recommended in geriatrics.[3] A higher plasma concentration of elbasvir/grazoprevir has been detected in females than in males, however no dosage adjustment is recommended.[3] It is not known whether elbasvir/grazoprevir is excreted in human breast milk, therefore its use in nursing mothers should weigh the benefits of the drug to the mother and any potential risk on the breastfed child.[3] Even though high plasma concentrations of elbasvir and grazoprevir have been observed in Asians compared to Caucasians in clinical trials, no dose adjustment is recommended in this population.[3] Elbasvir/grazoprevir is contraindicated in patients with Child-Pugh B due to lack of clinical safety and efficacy data and in patients with Child-Pugh C due to a 12-fold increase in grazoprevir concentration. No dosage adjustment is necessary in patients with mild hepatic impairment or Child Pugh A.[3] The tolerability profile of elbasvir/grazoprevir is similar in cirrhotic and non-cirrhotic patients.[3,10,14] Elbasvir/grazoprevir is recommended to be used in patients with creatinine clearance less than 30 mL/min with HCV infection due to genotype 1a,1b and 4 without any dose adjustment.[3,22] It is well-tolerated in patients with chronic kidney disease stages 4 and 5 and in patients on hemodialysis.[3,15] In patients with HIV coinfection, elbasvir/grazoprevir is recommended for use with antiretroviral medications with no clinically significant drug-drug interactions such as abacavir, emtricitabine, enfuvirtide, lamivudine, raltegravir, dolutegravir, rilpivirine, and tenofovir.[22] In terms of safety, Elbasvir/grazoprevir is well tolerated in patients with HIV/HCV co-infection.[3,11,16]

Dosage and Administration

Elbasvir/grazoprevir is supplied in tablets of 50 mg elbasvir and 100 mg grazoprevir.[3] The recommended dose for its current approved indication for the treatment of adults with chronic

HCV genotype 1 and 4 infection is one tablet daily with or without food.[3] The recommended treatment duration for patients with genotype 1 is 12 weeks. This includes genotype 1 a and 1 b patients without cirrhosis or with compensated cirrhosis and PEG-IFN/RBV treatment experienced with or without cirrhosis. However, for genotype 1a and 1b nonstructural protein 3 protease inhibitor plus PEG-IFN/RBV treatment experienced patients with or without cirrhosis, the recommended treatment is elbasvir/grazoprevir plus ribavirin for 12 weeks as well. Patients with genotype 1a who have a baseline high fold-change NS5A RAV for elbasvir and failed nonstructural protein 3 protease inhibitor plus PEG-IFN/RBV are recommended to receive elbasvir/grazoprevir plus ribavirin for 16 weeks. On the other hand, genotype 4 patients with or without cirrhosis are recommended to receive elbasvir/grazoprevir for 12 weeks except PEG-INF/RBVtreatment experienced patients without cirrhosis or with compensated cirrhosis should be treated for 16 weeks..[3]Hence, in order to determine treatment duration, patients with genotype 1a should be tested for the virus NS5A resistance associated polymorphism before initiating treatment; also, a liver function test is recommended for all patients before starting treatment.[3]

Place in Therapy

The Infectious Diseases Society of America (IDSA) and the American Association for the Study of Liver Diseases (AASLD), in collaboration with the International Antiviral Society – USA (IAS-USA) maintain a living guidance for testing, managing, and treating hepatitis C.[22] According to these guidelines, elbasvir/grazoprevir is recommended as monotherapy for treatment-naïve and treatment-experienced (pegylated interferon plus ribavirin) genotype 1a, 1b, and 4 HCV-infected patients with or without compensated cirrhosis.[22] Elbasvir/grazoprevir is recommended with ribavirin for treatment-experienced (telaprevir, boceprevir, or simeprevir)

genotypes 1a, 1b and 4 HCV-infected patients with or without compensated cirrhosis.[22] Table 2 illustrates the recommended elbasvir/grazoprevir regimens for patients with HCV. The approximate cost of elbasvir/grazoprevir is $54,600 for a 12-week treatment course and $72,800 for a 16-week treatment course, which is less expensive than other available combination direct-acting antivirals for the treatment of HCV infection.[23,24]

Summary

Elbasvir/grazoprevir achieves a high cure rate in the treatment of patients with chronic HCV with a once-daily oral regimen and without serious adverse effects, however it requires close monitoring of liver function enzymes. It is an effective option for patients with HCV genotype 1a, 1b, or 4 with and without compensated cirrhosis, and is a particularly attractive option in patients with chronic kidney disease including dialysis and in patients with HIV co-infection.

Declaration of Conflicting Interests

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