

Drug–Drug Interactions of Newly Approved Direct-Acting Antiviral Agents in Patients with Hepatitis C

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Lu-Hua Gao
Qing-He Nie
Xi-Tai Zhao 

Center of Infectious Diseases, Second
Affiliated Hospital, Air-Force Military
Medical University, Xi'an 710038,
People's Republic of China

Abstract: Hepatitis C is a major health problem worldwide, frequently resulting in cirrhosis and increasing the risk of hepatocellular carcinoma significantly. In recent years, the advent of direct-acting antivirals (DAAs) has dramatically improved the therapeutic outcomes in hepatitis C patients. In the last two years, several new DAA combinations have been approved for the treatment of the hepatitis C virus (HCV) infection, including elbasvir/grazoprevir, sofosbuvir/velpatasvir, sofosbuvir/velpatasvir/voxilaprevir, and glecaprevir/pibrentasvir. The newly approved DAA regimens may be prescribed with other drugs simultaneously, increasing the potential of pharmacokinetic interactions. Therefore, the knowledge and management of drug–drug interactions (DDIs) with DAAs should be considered a key issue in HCV therapy. This review summarizes researches of DDIs focusing on newly approved DAAs (elbasvir, grazoprevir, velpatasvir, voxilaprevir, glecaprevir, pibrentasvir) for patients undergoing HCV treatment to provide clinical consideration for comedication. With respect to DDIs, newly approved DAA regimens, including elbasvir/grazoprevir, sofosbuvir/velpatasvir, sofosbuvir/velpatasvir/voxilaprevir, and glecaprevir/pibrentasvir, are safely applicable.

Keywords: drug–drug interaction, direct-acting antiviral, chronic hepatitis C, pharmacokinetic, comedication

Introduction

The hepatitis C virus (HCV) has been a major health problem since its discovery in 1989, affecting over 184 million people globally, and remained mostly undetected.¹ About 25% chronic HCV patients develop Cirrhosis and account for a majority of HCV-related morbidity and mortality.¹ The conventional therapeutic strategy for an HCV infection is pegylated interferon plus ribavirin with sustained virologic response rates (SVR) of 70–80% for HCV 2 or 3 genotypes and SVR of 45–70% for HCV 1, 4, 5, and 6 genotypes.² However, the frequent use and severe adverse effects associated with interferon-based regimens give rise to numerous contraindications, resulting in an unsatisfactory overall efficacy of HCV treatment.

Since 2011, improved cure rates have been observed with the first generation of oral direct-acting antivirals (DAAs) combined with interferon and ribavirin.³ Because of fewer side effects, sustained virological response rate over 90%, and shortened treatment durations involved in DAA treatment, the US Food and Drug Administration (FDA) no longer suggests a combination of DAA oral regimens with interferon therapy after 2013.⁴ Recently, the DAAs have shown dramatic

Correspondence: Qing-He Nie
Center of Infectious Diseases, Second
Affiliated Hospital, Air-Force Military
Medical University, 569 Xinsi Road,
Baqiao District, Xi'an 710038, People's
Republic of China
Email nhqxn2020@163.com

advances in the therapeutic outcomes in hepatitis C patients owing to their high efficacy and favorable safety profile.⁵ Despite the high cost, all-oral regimens of DAAs are strongly recommended by several hepatitis C treatment guidelines and have been widely accepted by patients.^{6–8} Advancingly, DAA programs have been established to improve liver-related outcomes, such as reducing the risk of cirrhosis, hepatocellular carcinoma, decompensated liver disease, and all-cause mortality.^{9–12} Since December 2017, more than 10 types of DAAs have been approved for the treatment of hepatitis C. Although highly effective and well tolerable, DAAs can result in drug–drug interactions (DDIs) with multiple drugs as they participate in common metabolic pathways, such as cytochrome P450 (CYP450), organic anion transporting polypeptides (OATP), multidrug resistance protein (MRP), P-glycoprotein (P-gp), and breast cancer resistance protein (BCRP). Functioning as inducers, substrates, and/or inhibitors of metabolizing enzymes and transporters, DAAs can influence the plasma concentrations of coadministered drugs, augmenting toxicity or reducing effectiveness. As the use of comedications is frequent and diversified in chronic hepatitis C patients, a majority of patients are at the risk of DDIs induced lower efficacy or toxicity of DAAs or comedications.^{13,14} Therefore, none of the DAAs are completely free of DDIs, which can significantly alter drug exposure, and thus their efficacy and toxicity.

Considering a broad range of indications, the newly approved DAA regimens contained sofosbuvir/velpatasvir/voxilaprevir, elbasvir/grazoprevir, and glecaprevir/pibrentasvir, which may incur more interactions with comedications in the last two years. Appropriately, handling the pharmacokinetic interactions is imperative to improve the therapeutic effectiveness and safety in HCV-infected patients. Previous reviews summarized the relationship between DDIs and DAAs in different drug classes or specific drugs.^{15–19} This review summarizes the researches into newly approved DAAs (elbasvir, grazoprevir, velpatasvir, voxilaprevir, glecaprevir, pibrentasvir) associated DDIs, endeavoring to identify optimal treatment regiment for individual patients.

Elbasvir/Grazoprevir

Elbasvir (ie, MK-8742) and grazoprevir (ie, MK-5172) are inhibitors of the HCV-specific NS5A protein and NS3/4A protease, respectively (Figure 1). Elbasvir (50 mg) and grazoprevir (100 mg) fixed-dose combination have been recommended for the treatment of HCV infection of genotypes 1 and 4. Elbasvir/grazoprevir is administered once a day, with or without the presence of food.²⁰ Given patients who have not been treated or have been treated with pegylated interferon combined with ribavirin, the recommended treatment duration is as follows: (1) In HCV genotype 1a patients without baseline NS5A polymorphisms, the treatment duration is 12 weeks; (2) In

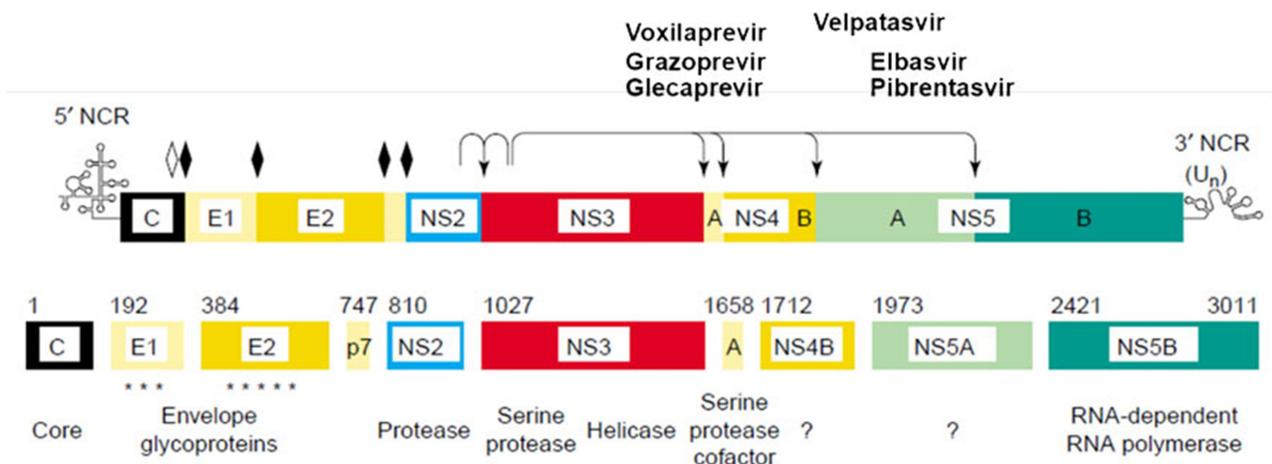


Figure 1 Mechanism of DAAs. Elbasvir, an inhibitor of NS5A; Grazoprevir, an inhibitor of the NS3/4A protease; Glecaprevir, an inhibitor of NS3/4A protease; Pibrentasvir, an inhibitor of NS5A; Velpatasvir, an inhibitor of the NS5A protein; Voxilaprevir, an inhibitor of the NS3/4A protease. Solid diamonds denote sites of the hepatitis C virus (HCV) polyprotein precursor cleaved by the endoplasmic reticulum signal peptidase. Amino acid positions are shown above each protein. The open diamond indicates further processing of the core protein by signal peptide peptidase. Arrows indicate sites cleaved by HCV NS2–3 and NS3 proteases. Asterisks in the E1 and E2 region indicate the glycosylation of the envelope proteins. Reproduced from Moradpour D, Brass V, Gosert R, Wölk B, Blum HE, Hepatitis C: molecular virology and antiviral targets, Trends in Molecular Medicine, 2002;8:476–482. Copyright (2002), with permission from Elsevier.⁸⁸

Abbreviation: NCR, noncoding region.

HCV genotype 1a and NS5A baseline polymorphism patients treatment is 16 weeks with ribavirin; (3) In HCV genotype 1b, treatment duration is 12 weeks. The approved course of treatment for HCV genotype 1a or 1b patients is 12 weeks prior to treatment with pegylated interferon and ribavirin plus protease inhibitors and ribavirin. The approved treatment period for the treatment-naïve HCV genotype 4 patients is 12 weeks. Finally, in the case of patients with HCV genotype 4, the previously approved treatment period for polyvinyl interferon combined with ribavirin is 16 weeks. These protocols are appropriate in patients with or without compensatory cirrhosis. Dosing of elbasvir/grazoprevir for any level of renal impairment, including hemodialysis, is not recommended based on gender or race/ethnicity. In patients with mild hepatic impairment (Child-Pugh A), elbasvir/grazoprevir can be safely used without dosage adjustment but is contraindicated in patients with moderate or severe hepatic impairment (Child-Pugh B or C) as grazoprevir exposure was significantly increased by 5- to 12-fold. Addition of ribavirin and a longer duration of 16 weeks are recommended in baseline NS5A resistance-associated polymorphism patients. Notably, no dose recommendations have been provided for children under 18 years old and elderly patients ([Supplementary Figure 1](#)).

The absolute bioavailabilities of elbasvir and grazoprevir are 32% and 27%, respectively.²¹ In the case of grazoprevir, a high-fat diet increases the area under the curve (AUC) by about 1.5-times and C_{max} by about 2.8-times. Slight decreases in AUC_{0-inf} and C_{max} have been observed with elbasvir and elbasvir/grazoprevir and may be administered without consideration of food (Co.). Elbasvir and grazoprevir are the substrates for CYP3A and P-gp and P-gp seems to have minimal negative effect on the absorption of the two drugs.²² Furthermore, grazoprevir may be transported by BCRP and it is a substrate for OATP1B1/3. Elbasvir is a CYP3A inhibitor in vitro, while grazoprevir is a weak CYP3A inhibitor in humans. Both elbasvir and grazoprevir are inhibitors of BCRP, but elbasvir is a weak inhibitor of P-gp, and grazoprevir is a weak inhibitor of CYP3A4.²³ Therefore, strong inducers of CYP3A4, including carbamazepine, phenytoin, rifampicin, and efavirenz are contraindicated and moderate inducers, such as nafcillin, etravirine, and modafinil, are not recommended. Furthermore, CYP3A4 inhibitors are not recommended to be applied combined with elbasvir and grazoprevir.²⁴ Additionally, OATP inhibitors including cyclosporine, atazanavir, lopinavir, darunavir, and tipranavir are

contraindicated with the elbasvir/grazoprevir regimen. The elimination of elbasvir and grazoprevir mainly occurs in the liver, with an average time of 24 h and 31 h, respectively.²⁵ As Elbasvir and grazoprevir are affected by oxidative metabolism, the combination of mainly CYP3A, whether CYP3A substrate or strong CYP3A inducer, with elbasvir/grazoprevir is forbidden as they can significantly reduce the plasma concentrations of elbasvir and grazoprevir to decrease the therapeutic effect. Whereas with few accurate clinical data, elbasvir/grazoprevir combined with a moderate dose of CYP3A inducer is still not recommended.⁵ Furthermore, as both drugs are metabolized by the liver, they are prohibited in patients with moderate and severe liver injury (Child-Pugh B or C).²⁶ The peak plasma concentration is attained in 3 h for elbasvir and 2 h for grazoprevir. Elbasvir binds to plasma proteins at a rate of 99.9% and grazoprevir binds to plasma proteins at a rate of 98.8%.²⁷ They are mainly eliminated by feces (>90%) and minimally excreted by urine (<1%), indicating that dosage adjustment is unnecessary in patients with renal impairment (Co.). The C-SURFER study demonstrated that elbasvir/grazoprevir can be safely used in hemodialysis patients with advanced chronic kidney disease.²⁸ Several real-world studies had confirmed the efficacy and safety of elbasvir/grazoprevir in severe chronic kidney disease patients, including those that have renal replacement therapy.²⁹⁻³²

The pharmacokinetics of elbasvir/grazoprevir or comedications may be influenced by potential common metabolic pathways, resulting in reduced efficacy and other adverse events. Studies in healthy subjects evaluated the potential pharmacokinetic interactions of grazoprevir when coadministered with inducers or inhibitors of CYP3A, BCRP, OATP, and P-gp. The results indicated that grazoprevir (as a CYP3A/BCRP inhibitor) caused 3-fold, 34%, and 43% increase in AUC of atorvastatin, midazolam, and atazanavir, respectively. The AUC of grazoprevir decreased by 84% when coadministered with efavirenz, and the AUC increased by 10.58, 12.86, 7.5, 12.61, and 8.35 fold, respectively, when coadministered with efavirenz, atazanavir, ritonavir, or pantoprazole based on the pharmacokinetic parameters of fixed-dose combination of lopinavir/ritonavir, darunavir/ritonavir, and a single intravenous or oral dose of rifampin.^{22,33,34} Given that the solubility of elbasvir and grazoprevir is pH-dependent, Feng et al³⁵ performed pharmacokinetic studies in 16 healthy subjects to evaluate the efficacy of famotidine, elbasvir, and grazoprevir demonstrated that famotidine

and pantoprazole had no clinically relevant effects on the pharmacokinetics of the elbasvir/grazoprevir coadministration. It could be speculated that acid-reducing agents including H₂-receptor antagonists, proton-pump inhibitors, and antacids, with pharmacokinetic properties which is similar to famotidine or pantoprazole, may be administered with elbasvir and grazoprevir without dose adjustment. When elbasvir/grazoprevir regimen was combined with ketoconazole, the AUC and C_{max} value for elbasvir were increased by 80% and 29%, respectively, while the AUC and C_{max} value for grazoprevir increased by 202% and 13%, respectively.⁵

Coinfection with HCV is extremely common in patients with HIV infection (10%–30%). In HIV-infected patients who received injectable treatment (90%), HCV treatment faced a therapeutic challenge due to the complex interactions between antiretroviral agents and DAAs.³⁶ A pharmacokinetic study had assessed the potential interactions between grazoprevir and ritonavir-boosted HIV protease inhibitors, indicating that the atazanavir AUC₀₋₂₄ was modestly increased by 43% with co-administrated grazoprevir, while atazanavir AUC₀₋₂₄ was not impacted by lopinavir and darunavir. Additionally, the grazoprevir AUC₀₋₂₄ was significantly increased by atazanavir/ritonavir, lopinavir/lopinavir, and darunavir/ritonavir by 10.58-fold, 12.86-fold, and 7.5-fold, respectively.³⁴ It is clear that ritonavir-boosted HIV protease inhibitors are not eligible for coadministration combined with fixed-dose elbasvir/grazoprevir. However, other antiretroviral agents such as tenofovir, abacavir, emtricitabine, lamivudine, raltegravir, dolutegravir, and rilpivirine can be safely administered with elbasvir/grazoprevir without adverse effects during the HCV or HIV therapy confirmed in the C-EDGE CO-INFECTION and C-WORTHY studies.^{37,38}

Frequent HIV/HCV coinfection and opioid agonist therapy lead to poor patients compliance and complicated DDIs, chronic hepatitis C therapy remains a huge challenge in subjects who used injectable drugs. In addition, no clinically meaningful pharmacokinetic interactions have been observed among elbasvir, grazoprevir, buprenorphine, and naloxone.^{39,40} Results from a placebo-controlled, randomized, and double-blind trial documented that the fixed-dose combination of elbasvir (50 mg) and grazoprevir (100 mg) was effective in the treatment of HCV infection in patients receiving opioid agonist therapy and with ongoing drug use, including amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, opioids, phencyclidine, and propoxyphene.⁴¹ Moreover, DDIs

between DAAs and immunosuppressant agents remain a major concern for HCV infection therapy in solid organ transplantation recipients. Previously, a study conducted in healthy subjects indicated that elbasvir/grazoprevir resulted in a 43% increase in the tacrolimus AUC, while cyclosporine was not recommended for concomitant use with elbasvir/grazoprevir owing to the 15.2-fold increase of grazoprevir AUC. Notably, mycophenolate mofetil and prednisone did not incur any DDIs with elbasvir/grazoprevir.⁴² Clinical trials have demonstrated that coadministration of elbasvir/grazoprevir and recommended immunosuppressants is a safe and effective treatment for HCV infection in post-liver or renal transplantation patients with careful monitoring and appropriate dose adjustment.^{43,44} Elbasvir/grazoprevir and oral contraceptives ethinyl estradiol and levonorgestrel were found to lack pharmacokinetic interactions indicate that elbasvir/grazoprevir could be concomitantly administered to female HCV patients with childbearing potential to prevent pregnancy.⁴⁵

A large number of studies have demonstrated that the dosage of atorvastatin should not exceed 20 mg/day and the dose of rosuvastatin should not exceed 10 mg/day when used in combination with elbasvir/grazoprevir. The maximum recommended dosage of fluvastatin, lovastatin, and simvastatin should not exceed 80 mg/day.⁴⁶ In order to prevent elbasvir/grazoprevir from increasing the concentration of statins, close monitoring the reduction of the amiodarone dose is necessary to assist the treatment to proceed safely.⁴⁷ According to relevant research, when the elbasvir/grazoprevir regimen is coadministered with phenytoin, carbamazepine, rifampin, cyclosporine, and other drugs, significant interactions occur.⁴⁶ In summary, cyclosporine, rosuvastatin, atorvastatin are not recommended for combination with elbasvir/grazoprevir.⁴⁷ Table 1 summarizes the available evidence and clinical recommendations for the concomitant administration of elbasvir/grazoprevir and other drugs.

Sofosbuvir/Velpatasvir/Voxilaprevir

Sofosbuvir is a nucleotide-like inhibitor of HCV NS5B polymerase and a prodrug. The active metabolite of sofosbuvir is metabolized to GS-461203 and the inactive metabolite of sofosbuvir is dephosphorylated to GS-331007. Velpatasvir (ie, GS-5816) and voxilaprevir (ie, GS-9857) are pangenotypic HCV NS5A and NS3/4A protease inhibitors, respectively (Figure 1). The sofosbuvir and velpatasvir fixed-dose combination was approved for the

Table 1 Drug–Drug Interactions Associated with Elbasvir and Grazoprevir[#]

Concomitant Drugs	EBR's Effects on AUC*	GZR's Effects on AUC*	EBR/GZR's Effects on AUC*	Subjects	Comments ⁹
Famotidine ²⁰			GZR 1.10↑, EBR 1.05↑	Healthy	No dose adjustments are needed.
Pantoprazole ²⁰			GZR 1.12↑, EBR 1.05↑	Healthy	No dose adjustments are needed.
Ethinyl estradiol ³⁰	Ethinyl estradiol 1.01↑	Ethinyl estradiol 1.10↑		Healthy	No dose adjustments are needed.
Levonorgestrel ³⁰	Levonorgestrel 1.14↑	Levonorgestrel 1.23↑		Healthy	No dose adjustments are needed.
Buprenorphine/naloxone ²⁵	EBR 1.22↑, buprenorphine 0.98↓, norbuprenorphine 0.97↓, naloxone 0.88↓			Healthy	No dose adjustments are needed.
Atazanavir/ritonavir ¹⁹		Atazanavir 1.43↑, GZR 10.58↑		Healthy	Co-use of atazanavir/ritonavir with EBR/GZR is contraindicated.
Darunavir/ritonavir ¹⁹		Darunavir 1.11↑, GZR 7.50↑		Healthy	Co-use of darunavir/ritonavir with EBR/GZR is contraindicated.
Lopinavir/ritonavir ¹⁹		Lopinavir 1.03↑, GZR 12.86↑		Healthy	Co-use of lopinavir/ritonavir with EBR/GZR is contraindicated.
Efavirenz ¹⁸		GZR 0.16↓, efavirenz unaffected		Healthy	Co-use of efavirenz with EBR/GZR is contraindicated.
Atorvastatin ¹⁰		Atorvastatin 3.00↑		Healthy	Dose adjustments may be needed.
Pitavastatin ¹⁰		Pitavastatin 1.11↑		Healthy	No dose adjustments are needed.
Midazolam ¹⁰		Midazolam 1.34↑		Healthy	
Rifampin ^{†11}		GZR 12.61↑, 8.35↑, 0.93↓		Healthy	Co-use of rifampin with EBR/GZR is contraindicated.
Tacrolimus ²⁷			Tacrolimus 1.43↑, EBR/GZR almost unaffected	Healthy	Frequent monitoring of tacrolimus is required.
Cyclosporine ²⁷			EBR 1.98↑, GZR 15.21↑, cyclosporine almost unaffected	Healthy	Co-use of cyclosporine with EBR/GZR is contraindicated.
Mycophenolate mofetil ²⁷			Mycophenolic acid 0.95↓, EBR 1.07↑, GZR 0.74↓	Healthy	No dose adjustments are needed.
Prednisone ²⁷			Prednisone 1.08↑, prednisolone 1.08↑, EBR 1.17↑, GZR 1.09↑	Healthy	No dose adjustments are needed.

Notes: [#]This table is not all inclusive; *, [†]Increase; [‡]Decrease; The value refers to a ratio of AUCs of a tested drug with or without co-administered drugs; AUCs include AUC₀₋₁₂, AUC₀₋₂₄ (area under the concentration-time curve from time 0 to 12 or 24 hours), and AUC_{0-∞} (that from time 0 to infinity); [†]Co-administration with a single intravenous, oral, or multiple oral dose of 600mg rifampin.

Abbreviations: EBR, elbasvir; GZR, grazoprevir; AUC, area under concentration-time curve; ORT, opioid replacement therapy; DDI, drug–drug interaction.

treatment of HCV infection of all six genotypes consisting of 400 mg sofosbuvir and 100 mg velpatasvir. Sofosbuvir and velpatasvir are administered once a day, irrespective of food.³³ As for sofosbuvir/velpatasvir regimens, a fixed-dose combination of sofosbuvir, velpatasvir, and voxilaprevir (400/100/100 mg, once daily) is available for the treatment of HCV-infected patients who are untreated or previously treated with a regimen containing sofosbuvir and/or an NS5A inhibitor.^{34,48} Sofosbuvir/velpatasvir/voxilaprevir is suitable for chronic hepatitis C adult patients, with or without compensatory cirrhosis. These patients were (1) genotype 1 to 6, who had received an NS5A inhibitor treatment or (2) genotype 1a or 3 who had been administered sofosbuvir without an NS5A inhibitor. For patients with mild or moderate renal impairment or mild liver impairment (Child-Pugh A), it is unnecessary to adjust the dose of sofosbuvir/velpatasvir/voxilaprevir. The sofosbuvir/velpatasvir/voxilaprevir regimen is not recommended in patients with severe renal injury, severe liver injury, or end-stage renal disease (Child-Pugh B or C). No dosage adjustment for the sofosbuvir/velpatasvir/voxilaprevir regimen is warranted in geriatric patients, while its use in pediatric patients remains unclear ([Supplementary Figure 2](#)). Sofosbuvir has been well studied and is prescribed for chronic HCV infection patients for over 4 years, so it will not be discussed further in this review.

As the perpetrators of DDIs, velpatasvir and voxilaprevir inhibit drug transporters, including OATP1B1, P-gp, BCRP, and OATP1B3. Specifically, velpatasvir is an inhibitor of OATP2B1 and a substrate of P-gp and BCRP in vivo, and in vitro, which is slowly metabolized by CYP2B6, CYP2C8, and CYP3A4. Velpatasvir administration resulted in increased pravastatin, rosuvastatin, and digoxin exposure by 35%, 160–170%, and 34%, respectively.^{48,49} As the substrate of OATP, P-gp, and CYP, the AUC of velpatasvir increased by 47%, 103%, and 70% when coadministered a single dose of rifampin, cyclosporine, or ketoconazole, respectively, but decreased by 82% following multiple doses of rifampin.⁵⁰ Food slightly altered the velpatasvir AUC and significantly increased the voxilaprevir AUC.^{34,51} Velpatasvir was demonstrated to have higher aqueous solubility in acidic conditions, indicating that the coadministration of acid-reducing agents should be handled cautiously.⁵¹ Famotidine (40 mg twice daily) does not impact the velpatasvir AUC, while omeprazole (20 mg or 40 mg) can reduce the velpatasvir AUC by 37–56%.^{49,50} Voxilaprevir is a substrate of P-gp, BCRP, OATP1B1, and OATP1B3

in vivo, and in vitro, and slowly metabolized in the liver by CYP1A2, CYP2C8, and CYP3A4.^{34,52} Meanwhile, voxilaprevir is an inhibitor of drug transporters P-gp, BCRP, OATP1B1, and OATP1B3, demonstrating a biliary elimination with a $t_{1/2}$ of approximately 33 h.⁶ Voxilaprevir helps to increase the AUC of pravastatin, rosuvastatin, and dabigatran by 116%, 639%, and 161%, respectively, while the pharmacokinetics of bicittegravir, cobicistat, darunavir, elvitegravir, emtricitabine, rilpivirine, tenofovir alafenamide, tenofovir, ethinyl estradiol, and norgestrel remain unaltered.⁵³ The voxilaprevir AUC was increased by 84%, 691%, 839%, 331% and 143–171%, or decreased by 73%, when coadministered with voriconazole, single-dose rifampin, cyclosporine A, a single dose of atazanavir/r, boosted antiretroviral regimens, or multiple-dose rifampin, respectively, but remained unaltered by unboosted antiretroviral regimens.⁵³

Velpatasvir and voxilaprevir are primarily eliminated through biliary excretion and merely excreted in the urine. Thus, it was unnecessary to adjust the dose when velpatasvir and voxilaprevir are administered to patients with mild to severe renal impairment.^{54,55} It was demonstrated that liver injury has no significant effect on the clinical exposure of velpatasvir. Contrarily, voxilaprevir is not approved in patients with moderate or severe liver function injury (Child-Pugh B or C) since the exposure level in patients was significantly increased compared to healthy subjects.^{54,57,58} Healthy or HCV/HIV co-infected subjects participated in Phase 1 studies, evaluating DDIs between sofosbuvir/velpatasvir and HIV antiretroviral agents, demonstrated the absence of clinically relevant changes in darunavir/ritonavir, emtricitabine, lopinavir/ritonavir, atazanavir/ritonavir (r), raltegravir, efavirenz, elvitegravir, dolutegravir, cobicistat, or tenofovir alafenamide pharmacokinetics. Rilpivirine and tenofovir (as tenofovir disoproxil fumarate, but not as tenofovir alafenamide) exposure was increased to 40–81% when coadministered with sofosbuvir/velpatasvir. Furthermore, velpatasvir exposure was decreased to 53% and increased to 142% by efavirenz and atazanavir/r, respectively.⁴⁹ Velpatasvir does not interfere with the efficacy of norgestimate/ethinyl estradiol.⁵⁸ A post-analysis of the three ASTRAL studies indicated that the efficacy and safety of sofosbuvir/velpatasvir was not affected by methadone or buprenorphine in HCV-infected patients receiving 12-week-opioid replacement treatment.⁵⁹ No clinically relevant interactions were observed with combination of velpatasvir and cyclosporine.⁴⁹ Rindone et al⁶⁰ reported an apparent interaction between sofosbuvir/velpatasvir and

warfarin that resulted in a subtarget International Normalized Ratio (INR) and subsequent thrombosis. It is unsuggestive that drugs including St. John's wort (*Hypericum perforatum*), carbamazepine, oxcarbazepine, phenobarbitone, phenytoin, rifabutin, rifapentine, atazanavir, lopinavir, efavirenz, tipranavir/ritonavir, amiodarone, cyclosporin, rosuvastatin, ethinyl oestradiol, pitavastatin to be combined with sofosbuvir/velpatasvir/voxilaprevir.⁶¹ In addition, the coadministration of rifampicin/darunavir with sofosbuvir/velpatasvir/voxilaprevir is contraindicated.⁶¹ In a French study, mainly including the failure of sofosbuvir + NS5 inhibitors, 43 patients were treated with sofosbuvir/velpatasvir/voxilaprevir + ribavirin for 8 (n=34) or 12 weeks (n = 9), and the initial detection rate of SVR12 was about 95%.⁶² Statins, including atorvastatin, lovastatin, simvastatin, and fluvastatin, are recommended to be combined with sofosbuvir/velpatasvir/voxilaprevir with the lowest dose.⁶¹ Based on the reported side-effects, such as symptomatic bradycardia and heart block, amiodarone is not recommended in combination with sofosbuvir/velpatasvir/voxilaprevir. Velpatasvir and voxilaprevir related DDIs have been confirmed by clinical studies summarized in Table 2.

Glecaprevir/Pibrentasvir

Glecaprevir (ie, ABT-493) is an HCV NS3/4A protease inhibitor and pibrentasvir (ie, ABT-530) is an NS5A inhibitor (Figure 1). A fixed-dose combination of glecaprevir and pibrentasvir (300/120 mg, once daily) is available for the treatment of patients with all 6 genotypes of chronic HCV infection, without cirrhosis or with compensated cirrhosis (Child-Pugh A).⁶³ The approved dose is 3 tablets once daily. For the HCV genotype 2, 4, 5, or 6 infection patients, no ribavirin treatment was recommended with shorter than 12 weeks of treatment duration. Only patients with genotype 1 infection can be treated for 8 weeks, but this limitation highlighted the need for an 8-week pan-genotype treatment for other HCV genotype-infected patients is requisite.⁶⁴ Most patients with genotype 2, 4, or 6 have baseline polymorphisms in NS5A, but with none in NS3.⁶⁵ No dosage adjustment is recommended for compensated cirrhosis (Child-Pugh A), any degree of renal impairment including patients receiving dialysis, or geriatric patients. Glecaprevir/pibrentasvir has not been approved for moderate liver damage patients (Child-Pugh B) and is forbidden for patients with severe liver damage (Child-Pugh C). The safety and effectiveness of

glecaprevir/pibrentasvir in children under the age of 18 have not been illuminated (Supplementary Figure 3).

In healthy subjects, glecaprevir and pibrentasvir exposures are minimally affected by food.^{66,67} Glecaprevir and pibrentasvir are weakly inhibited by CYP3A, CYP1A2, and uridine glucuronosyltransferase 1A1.⁶⁸ Both drugs are substrates of P-gp and BCRP transporters, and glecaprevir is additionally a substrate of OATP1B1/3. Furthermore, these drugs are inhibitors of P-gp, OATP1B1/3, BCRP, and weak inhibitors of CYP3A4 and UGT1A1.^{32,69} The biliary-fecal pathway is the major excretion route of glecaprevir/pibrentasvir, and the mean $t_{1/2}$ of glecaprevir/pibrentasvir are 7.5 h and 26 h, respectively.^{69,70} No dosage adjustment is required in patients with renal function impairment. The AUC in patients with moderate liver dysfunction was 100% higher than those observed in patients with severe liver dysfunction. Similarly, the pibrentasvir AUC in patients with moderate and severe liver dysfunction increased by 26% and 115%, respectively. Therefore, glecaprevir/pibrentasvir is not recommended in patients with moderate or severe liver function impairment.⁷¹ No dosage adjustment for glecaprevir and pibrentasvir is necessary in subjects with mild to severe renal impairment or end-stage renal disease, with or without hemodialysis.⁷²

The safety and efficacy of fixed-dose glecaprevir/pibrentasvir were confirmed in Phase 3 trials, EXPEDITION-4 and CERTAIN-1, which enrolled HCV-infected patients with stage 4/5 chronic kidney disease, or dialysis-dependent end-stage renal disease.^{73,74} The phase 1 studies demonstrated a weak effect of ritonavir on glecaprevir and pibrentasvir pharmacokinetics. Furthermore, raltegravir, dolutegravir, or rilpivirine anchor antiretroviral regimens were safe when coadministered with glecaprevir/pibrentasvir in an ongoing phase 3 trial EXPEDITION-2.^{63,75-77} Hence, substrates of CYP including caffeine, dextromethorphan hydrobromide, midazolam, omeprazole, and tolbutamide were not affected by coadministered glecaprevir/pibrentasvir.^{78,79} Continued monitoring and reduction of digoxin dose or dosing frequency are needed when used concomitantly with glecaprevir/pibrentasvir.⁸⁰ Glecaprevir and pibrentasvir exposures are not affected by losartan or valsartan, while losartan and valsartan AUCs increased by 151% and 36%, respectively. Nevertheless, according to losartan and valsartan label recommendations, no dosage adjustments are required.⁸⁰ Cyclosporine does not induce significant DDIs when coadministered with glecaprevir/pibrentasvir, while tacrolimus dosage adjustment may be necessary due to increased exposure by 45% when coadministered with

Table 2 Drug–Drug Interactions Associated with Velpatasvir and Voxilaprevir[#]

Concomitant Drugs	VEL's Effects on AUC*	VOX's Effects on AUC*	SOF/VEL's Effects on AUC*	SOF/VEL/VOX's Effects on AUC*	Subjects	Comments ^{31,32}
Pravastatin ^{34,44}	Pravastatin 1.35↑			Pravastatin 2.16↑	Healthy	Pravastatin may be administered with SOF/VEL/VOX at an adequate dose but does not incur clinically relevant DDIs with SOF/VEL.
Rosuvastatin ^{34,44}	Rosuvastatin 2.70↑			Rosuvastatin 7.39↑	Healthy	Rosuvastatin may be administered with SOF/VLE at an adequate dose and is not recommended for co-use with SOF/VEL/VOX.
Digoxin ³⁴	Digoxin 1.34↑				Healthy	Therapeutic concentration monitoring of digoxin is recommended when co-administered with SOF/VEL or SOF/VEL/VOX.
Rifampin ^{†34,44}	VEL 1.47↑, 0.18↓	VOX 7.91↑, 0.27↓			Healthy	Rifampin is not recommended for co-use with SOF/VEL and contraindicated with SOF/VEL/VOX.
Cyclosporine ^{34,44}	VEL 2.03↑	VOX 9.39↑			Healthy	Cyclosporine may be co-administered with SOF/VEL without restriction but is not recommended for co-use with SOF/VEL/VOX.
Ketoconazole ³⁴	VEL 1.70↑				Healthy	No dose adjustments are needed.
Famotidine ³⁹			VEL almost unaffected		Healthy	Dose adjustments of famotidine may be required.
Omeprazole ^{†39}			VLE 0.44–0.63↓, 0.62–0.74↓, 0.47↓		Healthy	Omeprazole may be co-administered with SOF/VEL or SOF/VEL/VOX at an adequate dose and should be taken 4 hours later.
Atazanavir/ritonavir ^{40,44}			Atazanavir almost unaffected, VEL 2.42↑	VOX 4.31↑	Healthy	Atazanavir can be administered with SOF/VEL but is not recommended for co-use with SOF/VEL/VOX.
Darunavir/ritonavir ^{40,44}			No clinically relevant changes	Darunavir not affected	Healthy	No dose adjustments are needed.
Lopinavir/ritonavir ⁴⁰			No clinically relevant changes		Healthy	Lopinavir can be administered with SOF/VEL but is not recommended for co-use with SOF/VEL/VOX.
Cobicistat ^{40,44}			No clinically relevant changes	Cobicistat not affected	Healthy	No dose adjustments are needed.
Dolutegravir ⁴⁰			No clinically relevant changes		Healthy	No dose adjustments are needed.
Efavirenz ^{40,44}			Efavirenz almost unaffected, VEL 0.47↓	VEL 0.47↓	Healthy	Co-administration of efavirenz with SOF/VEL or SOF/VEL/VOX is not recommended.

(Continued)

Table 2 (Continued).

Concomitant Drugs	VEL's Effects on AUC*	VOX's Effects on AUC*	SOF/VEL's Effects on AUC*	SOF/VEL/VOX's Effects on AUC*	Subjects	Comments ^{31,32}
Elvitegravir ^{40,44}			No clinically relevant changes	Elvitegravir not affected	Healthy	No dose adjustments are needed.
Emtricitabine ^{40,44}			No clinically relevant changes	Emtricitabine not affected	Healthy	No dose adjustments are needed.
Raltegravir ⁴⁰			No clinically relevant changes		Healthy	No dose adjustments are needed.
Rilpivirine ^{40,44}			No clinically relevant changes	Rilpivirine not affected	Healthy	No dose adjustments are needed.
Tenofovir alafenamide ^{40,44}			No clinically relevant changes	Tenofovir not affected	Healthy	No dose adjustments are needed.
Tenofovir disoproxil fumarate ^{40,44}			Tenofovir 1.40–1.81↑	Tenofovir not affected	Healthy	No dose adjustments are needed.
Bictegravir ⁴⁴				Bictegravir not affected	Healthy	
Dabigatran etexilate ⁴⁴				Dabigatran 2.61↑	Healthy	Clinical monitoring of dabigatran is needed.
Ethinyl estradiol ^{41,44}	Ethinyl estradiol 1.06↑			No changes	Healthy	No dose adjustments are needed.
Norgestimate ^{41,44}	Norelgestromin 0.89↓, norgestrel 0.91↓			No changes	Healthy	No dose adjustments are needed.
Voriconazole ⁴⁴				VOX 1.84↑	Healthy	No dose adjustments are needed.

Notes: #This table is not all inclusive; *, †Increase; ‡Decrease; The value refers to a ratio of AUCs of a tested drug with or without co-administered drugs; AUCs include AUC₀₋₂₄ (area under the concentration-time curve from time 0 to 24 hours) and AUC_{0-∞} (that from time 0 to infinity); †Co-administration with a single dose and multiple-dose of rifampin; ‡Co-administration with 20mg omeprazole under fasted or fed conditions, or with 40mg omeprazole under fed conditions.

Abbreviations: VEL, velpatasvir; AUC, area under the concentration-time curve; VOX, voxilaprevir; SOF, sofosbuvir; DDI, drug–drug interaction.

glecaprevir/pibrentasvir.⁸¹ A phase 1 study conducted in healthy subjects revealed that no clinically significant pharmacokinetic interactions were observed between glecaprevir/pibrentasvir and felodipine or amlodipine.⁸² In the EU, the combination of glecaprevir/pibrentasvir with formulations containing atazanavir, atorvastatin, simvastatin, dabigatran ester, estradiol alkyne, and strong P-gp and CYP3A inducers (such as rifampin, carbamazepine, St. John's wort, phenobarbital, phenytoin sodium, and primidone) is prohibited.⁶⁸ In the according study, the SVR12 was 100% (n/N = 9/9) after simeprevir, daclatasvir, and sofosbuvir were administered for 8 weeks in a small number of genotype 1 HCV-infected patients with compensated cirrhosis.⁸³ Glecaprevir/

pibrentasvir with ombitasvir/paritaprevir/ritonavir and dasabuvir were coadministered to three patients who had failed to respond in their last treatment regimen within 9 months.⁸⁴ The combination of dabigatran, atazanavir, simvastatin, atorvastatin, ethinyl estradiol containing contraceptives, and rifampicin could induce multiple drug interactions.⁸⁵ Furthermore, methadone or buprenorphine/naloxone combined with glecaprevir/pibrentasvir demonstrated good safety. In addition, in a comprehensive analysis of a glecaprevir/pibrentasvir phase 3 trial, subjects receiving opioid substitution therapy achieved the same high virological cure rates as those not receiving opioid substitution treatment.⁸⁶ Additionally, drugs including St. John's wort

(*Hypericum perforatum*), carbamazepine, darunavir, lopinavir, efavirenz, ritonavir, ethinyl estradiol, atorvastatin, lovastatin, simvastatin should not be combined with glecaprevir/pibrentasvir.⁶¹ Coadministration of rifampicin and atazanavir with glecaprevir/pibrentasvir is contraindicated. Pitavastatin and fluvastatin are recommended in the lowest dose when combined with glecaprevir/pibrentasvir.⁶¹ Drugs, including oxcarbazepine, phenobarbitone, phenytoin, rifabutin, and rifapentine, should be avoided in combination with glecaprevir/pibrentasvir.⁶¹ Detailed DDIs with glecaprevir and pibrentasvir are presented in Table 3.

Discussion

Given the advent of new drugs and targeted screening campaigns, hepatitis C could be eliminated in the near future. Multiple interferon-free and oral DAA regimens are available for the treatment of all patients with cirrhosis, HIV-coinfection, and other disease populations historically

considered difficult to cure.⁸⁷ Owing to the favorable efficacy, safety profile, and relatively short duration (typically 12 weeks), DAA regimens can be used to treat more patients than interferon-based regimens. However, frequent and multiple comorbidities and complications associated with chronic hepatitis C can significantly affect the safety and effectiveness of therapeutics. Therefore, the simultaneous use of several drugs in HCV-infected patients, with concomitant chronic diseases, is markedly prevalent. Moreover, this favorable efficacy and safety profile of DAA regimens has been accelerating the widespread use of DAAs in HCV-infected patients. The DDIs between DAAs and other drugs should be particularly concerning as they may directly influence the therapeutic effects and increase the frequency and severity of adverse events, potentially leading to treatment failure of the HCV infection or disturbances in comorbidity therapy. The present review summarized the research related to DDIs in newly approved DAAs.

Table 3 Drug–Drug Interactions Between Glecaprevir/Pibrentasvir and Co-Administered Drugs[#]

Concomitant Drugs	GLE/PIB's Effects on AUC*	Subjects	Comments ⁴⁵
Ritonavir ^{†46,47}	GLE 2.01↑, PIB 1.89↑	Healthy	Co-use is not recommended.
Methadone ⁵⁸	Methadone almost unaffected	On ORT	No dose adjustment is required.
Buprenorphine/ Naloxone ⁵⁸	Buprenorphine 1.17↑, norbuprenorphine 1.30↑, Naloxone almost unaffected	On ORT	No dose adjustment is required.
Caffeine ⁵⁴	Caffeine 1.35↑	Healthy	No dose adjustment is required.
Midazolam ⁵⁴	Midazolam 1.27↑	Healthy	No dose adjustment is required.
Omeprazole ⁵⁴	Omeprazole almost unaffected	Healthy	No dose adjustment is required.
Tolbutamide ⁵⁴	Tolbutamide almost unaffected	Healthy	No dose adjustment is required.
Dextromethorphan ⁵⁴	Dextromethorphan 0.75↓	Healthy	No dose adjustment is required.
Digoxin ⁵⁵	Digoxin 1.48↑, GLE/PIB almost unaffected	Healthy	Monitoring and dose adjustments of digoxin are needed.
Losartan ⁵⁶	Losartan 1.56↑, GLE/PIB almost unaffected	Healthy	No dose adjustment is required
Valsartan ⁵⁶	Valsartan 1.31↑, GLE/PIB almost unaffected	Healthy	No dose adjustment is required
Felodipine ⁵⁹	Felodipine 1.31↑, GLE/PIB almost unaffected	Healthy	No dose adjustment is required
Amlodipine ⁵⁹	Amlodipine 1.21↑, GLE/PIB almost unaffected	Healthy	No dose adjustment is required
Cyclosporine ⁵⁷	Cyclosporine almost unaffected, GLE 1.37↑, PIB 1.22↑	Healthy	Co-use is not recommended.
Tacrolimus ⁵⁷	Tacrolimus 1.45↑, GLE/PIB almost unaffected	Healthy	No dose adjustment is required

Notes: [#]This table is not all inclusive; *, [†]Increase; [‡]Decrease; The value refers to a ratio of AUCs of a tested drug with or without co-administered drugs. AUCs include AUC₀₋₂₄ (area under the concentration-time curve from time 0 to 24 hours) and AUC_{0-∞} (that from time 0 to infinity); [†]Ritonavir is co-administered with GLE or PIB, respectively in two phase-I trials.

Abbreviations: VEL, velpatasvir; VOX, voxilaprevir; AUC, area under the curve; ORT, opioid replacement therapy; DDI, drug–drug interaction.

Classical DAAs (including simeprevir, daclatasvir, ledipasvir, sofosbuvir, paritaprevir, ombitasvir, and dasabuvir) have been extensively used in clinical applications and their DDIs with commonly prescribed medications have been evaluated by physicians.¹⁹ The evaluation of DDIs is crucial in the research and development of drugs from preclinical studies to post-market clinical observations. However, unknown DDIs with DAAs are almost inevitable due to the complexity of clinical medications, with continuous monitoring and evaluation required for further evidence. The possibility of DDIs must be considered in determining the best treatment for individual patients. Furthermore, access to a drug interaction database is recommended during the treatment process. In addition, whether DDIs should be used for HCV treatment as indicated following the American Association for the Study of Liver Diseases and the Infectious Diseases Society of America (AASLD-IDSA) guideline was carefully checked by consulting the Liverpool HEP drug interactions checker. Importantly, the patient's medication chart needs to be carefully examined, including self-medication, which is time-consuming and requires sufficient interaction with pharmaceutical companies.

Conclusions

In conclusion, newly approved DAA regimens including elbasvir/grazoprevir, sofosbuvir/velpatasvir, sofosbuvir/velpatasvir/voxilaprevir, and glecaprevir/pibrentasvir are safe to take with other drugs, in the respect of DDIs. This review will provide useful information for the treatment of HCV infection.

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