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Name of Journal: *World Journal of Gastrointestinal Pharmacology and Therapeutics*

Manuscript NO: 74623

Manuscript Type: CASE REPORT

Hepatitis C virus treatment with glecaprevir and pibrentasvir in patients co-prescribed carbamazepine: Three case reports

Braude M *et al.* Glecaprevir-pibrentasvir with co-prescribed carbamazepine

Abstract

BACKGROUND

Highly effective and well-tolerated direct-acting antiviral (DAA) therapies have revolutionised the management of hepatitis C virus (HCV), however niche populations face treatment barriers. DAAs co-prescribed with several first-generation anti-epileptic drugs (AEDs) are contraindicated due to drug-drug interactions. A common example is carbamazepine whereby steady-state carbamazepine reduces the maximum concentration and area under the curve of velpatasvir, glecaprevir and pibrentasvir due to potent cytochrome P450 (CYP) 3A4 induction. Carbamazepine also induces P-glycoprotein which reduces glecaprevir and pibrentasvir's area under curve to infinite time. Sofosbuvir-velpatasvir and glecaprevir-pibrentasvir are contraindicated in patients who are co-prescribed carbamazepine due to risk of reduced DAA therapeutic effect and consequently, virological treatment failure. This presents a challenge for patients in whom carbamazepine substitution is medically unfeasible, impractical or unacceptable. However, the properties of current generation DAA therapies, including high-potency non-structural protein 5A inhibitory effect, may be sufficient to overcome reduced bioavailability arising from carbamazepine related CYP 3A4 and p-glycoprotein induction.

CASE SUMMARY

We present a case series of three patients with non-cirrhotic, treatment-naïve, genotype 1a, 1b, and 3a HCV who were treated with a 12 wk course of glecaprevir-pibrentasvir co-prescribed with carbamazepine for seizure disorders. Glecaprevir-pibrentasvir combination therapy was chosen due to potent *in vitro* activity and low barrier to pan-genotypic resistance associated variants. DAA therapy was dose-separated from carbamazepine and taken with meals to maximise time to peak concentration and improve absorption respectively. Sustained virological response at 12 wk was achieved in each patient with no adverse outcomes.

CONCLUSION

DAA therapies, including glecaprevir-pibrentasvir, warrant consideration as a therapeutic agent in people with HCV who are co-prescribed carbamazepine, particularly if AED substitution is not feasible.

Key Words: Antiepileptic drugs; Drug interactions; Hepatitis C virus; Sustained virological response; Health care access; Case report

Braude M, Ratnam DT, Marsh L, Abasszade JH, Dev AT. Hepatitis C virus treatment with glecaprevir and pibrentasvir in patients co-prescribed carbamazepine: Three case reports. *World J Gastrointest Pharmacol Ther* 2023; In press

Core Tip: Current hepatitis C virus (HCV) direct-acting antiviral (DAA) therapies are not recommended in patients who are co-prescribed carbamazepine. For glecaprevir-pibrentasvir, this is primarily due to carbamazepine's potent induction of cytochrome P450 3A4 and p-glycoprotein which reduces DAA plasma concentration and may therefore lead to virological failure. Despite theoretical reduction in DAA bioavailability, glecaprevir-pibrentasvir, prescribed over 12-wk, may be an effective treatment for non-cirrhotic patients with HCV who are co-prescribed carbamazepine. Glecaprevir-pibrentasvir should be considered for management of HCV in non-cirrhotic patients who are unable to substitute carbamazepine therapy. Further pharmacokinetic and potency data is required, in addition to further data in patients with cirrhosis.

INTRODUCTION

¹ Highly effective and well tolerated direct-acting antiviral (DAA) therapies have revolutionised the management of hepatitis C virus (HCV). Despite this, multiple barriers to HCV elimination exist, including niche drug-drug interactions. One such example pertains to carbamazepine. Carbamazepine is an anti-epileptic drug (AED) which is commonly prescribed for management of epilepsy, including stabilised and

difficult-to-manage cases. Carbamazepine may also be prescribed for management of bipolar affective disorder and neuropathic disorders^[1,2]. Neither sofosbuvir/velpatasvir or glecaprevir-pibrentasvir is recommended in patients treated with carbamazepine^[3]. This is reflected in the product information statements for sofosbuvir/velpatasvir and glecaprevir-pibrentasvir (last revised July 2021 and November 2021 respectively). The reason for this recommendation is based on evidence that carbamazepine induces both cytochrome P450 (CYP) 3A4 and intestinal P-glycoprotein (P-gp). Induction of these pathways can reduce DAA bioavailability, thereby increasing risk of HCV treatment failure. Importantly, neither sofosbuvir/velpatasvir or glecaprevir-pibrentasvir significantly impacts on bioavailability or efficacy of carbamazepine^[4].

CYP 3A4 induction reduces the maximum concentration of glecaprevir, pibrentasvir and velpatasvir by approximately two-thirds and the area under the curve by one-half^[5]. Induction of P-gp by carbamazepine additionally effects glecaprevir and pibrentasvir metabolism. In a phase one, healthy human study, Kosloski *et al*^[4] attributed carbamazepine P-gp induction to a 66% and 51% reduction in area under curve to infinite time of glecaprevir and pibrentasvir. Furthermore, sofosbuvir's intestinal absorption (but not the active metabolite, GS-331007)^[6] may be halved by induction of intestinal P-gp^[7]. This does not appear to be significant at carbamazepine doses of less than or equal to 400 mg/d^[7], however, patients on higher doses of carbamazepine have been successfully treated for HCV without sofosbuvir dose adjustment^[8].

There are emerging clinical data which demonstrate successful HCV treatment using DAAs in patients co-prescribed carbamazepine. van Seyen *et al*^[8] described four carbamazepine-treated patients with HCV who achieved sustained viral response after 12 wk of treatment (SVR12) with sofosbuvir (400 mg daily) plus dose-escalated daclatasvir (90 mg daily, 60 mg twice daily, or 60 mg three times daily) ± ribavirin. Three of the patients, one of whom was cirrhotic, were managed with a daily carbamazepine dose of greater than or equal to 1000 mg. A retrospective audit by Natali *et al*^[9] has described a non-cirrhotic patient with genotype 1a HCV on carbamazepine

who was successfully treated with an 8 wk course of glecaprevir-pibrentasvir. Data pertaining to DAAs in patients co-prescribed with carbamazepine analogues is also emerging. Sofusbuvir together with dose-escalated daclatasvir has been shown to successfully treat a patient co-prescribed oxcarbazepine^[6]. Recently, Marcos-Fosch *et al*^[10], reported a case series which included four patients with non-cirrhotic HCV who were successfully treated with DAAs whilst co-prescribed oxcarbazepine and eslicarbazepine. Two of the patients were treated with an 8 wk course of glecaprevir-pibrentasvir (genotypes 1b and 3), another with sofosbuvir-ledipasvir (genotype 1b), and the fourth with 12 wk of sofosbuvir-velpatasvir.

In this case series, we report glecaprevir-pibrentasvir HCV treatment in three patients with non-cirrhotic, treatment-naïve HCV, in whom AED substitution was either not tolerated or accepted. This case series adds to the relative paucity of literature supporting the use of DAA therapies in people with co-prescribed carbamazepine.

CASE PRESENTATION

Chief complaints

Case 1: A 43-year-old lady with genotype 1b, non-cirrhotic HCV required antiviral therapy. However, she was on carbamazepine which is contraindicated with DAA therapy.

Case 2: A 72-year-old man with long-standing genotype 1a, non-cirrhotic HCV required antiviral therapy. He was on carbamazepine which is contraindicated with DAA therapy.

Case 3: A 52-year-old lady presented to her general practitioner for management of treatment-naïve, non-cirrhotic genotype 3a HCV. She was on carbamazepine which is contraindicated with DAA therapies.

History of present illness

Case 1: The patient had medically acquired, treatment-naive, non-cirrhotic genotype 1b HCV. She was a long-term patient in our hepatology clinic.

Case 2: The patient had been monitored in our hepatology clinic for 10-years, but had not been treated due to limited treatment options and stable, non-cirrhotic liver disease.

Case 3: The patient, who had been diagnosed with HCV, lived in a regional area, 250 kilometres from the nearest tertiary medical centre, and received all medical care from her primary care practitioner.

History of past illness

Case 1: The patient was managed with 300 mg twice daily immediate-release carbamazepine for secondary seizure disorder following a childhood intracranial haemorrhage in the setting of congenital factor VIII deficiency.

Case 2: The patient had been managed with immediate-release carbamazepine, 200 mg twice daily for nocturnal seizures. He had been seizure-free for 20 years. Substitution to an alternative AED had been discussed with the patient. However, AED substitution would have required a 12-wk driving moratorium. The patient declined this as he was the primary carer for his partner, and given their remote geographic living situation, required his car to attend medical appointments and other care responsibilities.

Case 3: The patient was managed with 400 mg/600 mg twice daily carbamazepine for generalised seizure disorder. She had been seizure-free for many years and did not wish to trial AED substitution to facilitate DAA therapy.

Personal and family history

Case 1: She had no additional person or relevant family history.

Case 2: He had a history of dyslipidaemia, hypertension, and depression. Other medications included rosuvastatin and fluoxetine. There was no relevant family history.

Case 3: She had no additional relevant person or family history.

Physical examination

Case 1: The patient had no signs or features of chronic liver disease, nor any extrahepatic manifestations of HCV.

Case 2: The patient had no signs or features of chronic liver disease, nor any extrahepatic manifestations of HCV.

Case 3: The patient had no signs or features of chronic liver disease, nor any extrahepatic manifestations of HCV.

Laboratory examinations

Case 1: The patient's pre-treatment viral load was \log_{10} 5.21 IU/mL.

Case 2: The patient's pre-treatment viral load was \log_{10} 6.81 IU/mL. His pre-treatment alanine aminotransferase was 31 U/L (< 35).

Case 3: The patient's pre-treatment viral load was \log_{10} 6.1 IU/mL. The aspartate aminotransferase to platelet ratio index was 0.21, indicating a high negative predictive value for ruling out cirrhosis.

Imaging examinations

Case 1: The patient was non-cirrhotic based on ultrasonography. The liver stiffness was 2.3 kPa on Fibroscan, which confers a high negative predictive value for ruling out cirrhosis.

Case 2: The patient had no sonographic features of cirrhosis. The liver stiffness was 5.9 kPa on Fibroscan, with a high negative predictive value for ruling out cirrhosis.

Case 3: The patient was non-cirrhotic based on ultrasonography.

MULTIDISCIPLINARY EXPERT CONSULTATION

Case 1: When DAA therapies became available a decision was made to substitute carbamazepine to levetiracetam to facilitate HCV treatment. Levetiracetam 500 mg twice a day was commenced with a plan to wean carbamazepine by 200 mg per week. However, the patient experienced seizure recurrence within two weeks of carbamazepine withdrawal. Alternative AED substitution strategies were declined by the patient. A discussion between the hepatology, pharmacy and neurology teams was coordinated. Recommendation was to consider co-prescribed glecaprevir-pibrentasvir without adjusting the patient's carbamazepine therapy.

Case 2: Careful consideration was given to this case, and given the patient's situation, recommendation was made to trial co-prescribed glecaprevir-pibrentasvir without changing the patient's carbamazepine therapy. This followed a discussion between our hepatology and pharmacy teams, as well as a risk *vs* benefit discussion with the patient.

Case 3: The medical practitioner prescribed glecaprevir-pibrentasvir treatment together with co-prescribed Carbamazepine following a risk *vs* benefit discussion with the patient. The case was subsequently discussed with a tertiary health centre given our experience with previous similar cases. Based on further discussion, glecaprevir-pibrentasvir treatment was extended to a 12 wk course and was dose-separated from carbamazepine.

FINAL DIAGNOSIS

Case 1: HCV with reduced treatment options due to contraindication of carbamazepine with co-prescribed DAA therapies, and seizure recurrence with AED substitution therapy.

Case 2: HCV with reduced treatment options due to contraindication of carbamazepine with co-prescribed DAA therapies, and inability to substitute AED therapy due to extenuating social factors.

Case 3: HCV with reduced treatment options due to contraindication of carbamazepine with co-prescribed DAA therapies, and patient preference to avoid AED substitution.

TREATMENT

Case 1: Several years after the initial attempt at AED substitution, decision was made to prescribe a 12 wk course of glecaprevir-pibrentasvir without changing the patient's carbamazepine therapy. DAA therapy was administered with food and was taken between morning (0700) and evening (1900) carbamazepine doses.

Case 2: The patient accepted and completed treatment with 12-wk of glecaprevir-pibrentasvir, dose-separated from carbamazepine.

Case 3: The patient accepted and completed treatment with 12-wk of glecaprevir-pibrentasvir, dose-separated from carbamazepine.

OUTCOME AND FOLLOW-UP

Case 1: The patient's HCV viral load was log 1.61 IU/mL by week four of DAA therapy. The HCV viral load was undetectable at end of treatment (EOT), and remained undetectable 12-wk following the EOT, with SVR12 was achieved. No treatment adverse effects were reported. The carbamazepine level remained unchanged at 28

micromol/L (range 17-51 micromol/L) at the EOT. The patient was subsequently discharged back to her primary care practitioner (Table 1).

Case 2: HCV viral load was undetectable at four weeks, eight weeks, EOT, and at 12 wk post treatment. There were no adverse drug reactions and the patient was discharged from hepatology follow-up (Table 1).

Case 3: DAA treatment was well-tolerated and HCV viral load was undetectable at the EOT and at 12 wk post treatment (Table 1).

DISCUSSION

Drug-drug interactions remain an issue in the management of HCV^[11], particularly in circumstances where substitution therapy or drug holidays are not feasible, practical or acceptable. However, current DAA therapies are highly potent and evidence is accumulating that SVR12 can be achieved despite carbamazepine induced reduction in DAA bioavailability^[6,8-10].

We report HCV SVR12 with glecaprevir-pibrentasvir in three non-cirrhotic patients who were managed with carbamazepine for seizure disorders. We chose pibrentasvir over a velpatasvir-containing regimen due to its potent *in vitro* activity against pan-genotypic resistance associated variants, including Y93H, which may confer resistance to other non-structural protein 5A inhibitors^[12,13]. We acknowledge that sofosbuvir-based regimens may also be beneficial given the limited metabolism of GS-331007 by carbamazepine^[6].

Our treatment strategy relied on a triad of: (1) Dose-separating glecaprevir-pibrentasvir from carbamazepine; (2) Administering glecaprevir-pibrentasvir with food; and (3) Treatment extension of glecaprevir-pibrentasvir to 12 wk. To outline each of these in turn, dose separation was hypothesised to optimise first pass bioavailability of glecaprevir and pibrentasvir. This is because glecaprevir and pibrentasvir each has a time to peak concentration of five hours, which is like that of immediate-release

carbamazepine. Dose-separation of carbamazepine and DAA therapy may result in greater peak DAA bioavailability. The absolute benefit of this is not known given that the area under the curve for minimum effective concentration of carbamazepine is in the order of 12-17 h and would therefore overlap with dose separated DAA therapy. In addition to dose separation, we recommended co-administration of DAA therapy with food to enhance glecaprevir-pibrentasvir absorption. Finally, we recommended DAA treatment extension to bolster suppression of HCV viral replication.

A limitation of this study is the small sample size. Our findings are however, mirrored by other small case series, as outlined previously. Another limitation is that we did not monitor drug levels during treatment. Decision against on-treatment drug monitoring was made due to: (1) The excellent *in vivo* potency of glecaprevir-pibrentasvir^[14]; (2) The availability of salvage therapies; and (3) The minimal effect of glecaprevir-pibrentasvir on carbamazepine metabolism^[4]. We suggest that on-treatment DAA levels and viral titres may not be requisite in treatment-naïve, non-cirrhotic patients, though should be considered in people with previous treatment failure and/or compensated cirrhosis until further data is available.

CONCLUSION

Glecaprevir-pibrentasvir over a 12 wk course administered with food appears to overcome reduced DAA plasma concentrations resulting from carbamazepine related CYP 3A4 and P-gp induction. This treatment regimen should be considered in non-cirrhotic HCV in whom carbamazepine substitution, or a drug holiday is not possible, particularly given the potency of pibrentasvir and low likelihood of pan-genotypic resistance associated variants. Further pharmacokinetic and controlled studies are required to bolster this contention. Until further research, close on-treatment monitoring should be provided with specialist involvement.

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