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CASE REPORT

Successful treatment of chronic hepatitis C virus infection with crushed glecaprevir/pibrentasvir administered via a percutaneous endoscopic gastrostomy tube: case report and review of the literature

Yasuo Tanaka[1] · **Ryosuke Tateishi**[1] · **Kazuhiko Koike**[1]

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Abstract
Glecaprevir (GLE)/pibrentasvir (PIB) is a direct-acting antiviral regimen approved for patients infected with hepatitis C virus. No data are available on the safety and efficacy of this regimen when crushed and administered through a percutaneous endoscopic gastrostomy (PEG) tube. Here, we report a patient who successfully achieved a sustained viral response after treatment with GLE/PIB administered via a PEG tube. A 41-year-old female with chronic hepatitis C viral infection was referred to our department for treatment. She had a history of spina bifida and hydrocephalus, and she received a PEG tube for nutrition and medication due to an aftereffect of hydrocephalus. She received crushed GLE/PIB treatment through a PEG tube for 8 weeks and achieved a sustained viral response 12, without any treatment-related severe adverse events. This is the first documented case treated with GLE/PIB administered through a PEG tube. Based on this case report and a review of the literature, we discuss the safety and efficacy of direct-acting antiviral treatment via a PEG tube.

Keywords Hepatitis C virus · Direct acting antivirals · Glecaprevir/Pibrentasvir · Crushing · Percutaneous endoscopic gastrostomy tube

Introduction

Antiviral therapy for hepatitis C virus (HCV) has been improved considerably over the past few years. In addition, the approval of several interferon-free direct-acting antiviral (DAA) regimens has resulted in remarkably high sustained virologic response (SVR) rates with fewer side effects and a shorter duration of therapy compared with interferon-based regimens [1].

Glecaprevir (GLE, a nonstructural 3/4A protease inhibitor)/pibrentasvir (PIB, a nonstructural 5A inhibitor) is a fixed-dose combination tablet that was recently approved for use as a pangenotypic (genotype [GT] 1–6), once-daily, ribavirin-free treatment for chronic HCV infection [2]. Its use has resulted in high SVR rates, including in Japan in GT1-infected patients [3], GT2-infected patients [4], special populations (DAA-experienced patients, patients with severe renal impairment, GT3-infected patients, and patients after liver transplantation) [5, 6], and patients who failed to achieve a SVR with prior DAA regimens [7]. However, these data are based on studies in patients who can tolerate oral tablet administration, as DAAs are not available as injectable or oral suspension formulations. Individuals with neurological or oncological disorders may have difficulty swallowing whole tablets. However, crushing or splitting the tablets may affect the pharmacokinetic properties and relative bioavailability of the drug, which can result in decreased efficacy [8].

The safety and efficacy of ledipasvir (LDV)/sofosbuvir (SOF) [9] or elbasvir (EBR)/grazoprevir (GZR) [10] when the tablets are crushed and administered through a PEG tube (summarized in Table 1) have been reported; however, no data exist regarding GLE/PIB.

In this study, we describe a patient who successfully achieved a SVR after treatment with GLE/PIB administered through a PEG tube and review the literature to discuss the

✉ Yasuo Tanaka
yatanaka-gi@umin.ac.jp

[1] Department of Gastroenterology, Graduate School of Medicine, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan

Table 1 Reported cases who achieved SVR with DAA administered via a PEG tube

	First author	Age	Sex	Reason for dysphagia and PEG tube placement	HCV genotype, viral load	HCV-related liver disease	Previous treatment	Treatment regimen	Adverse events
1	Jindracek et al. [9]	61	Male	Benign pharyngeal ulceration	1, 5.8 log IU/mL	Compensated cirrhosis	Peg-interferon alpha-2b and ribavirin for 6 months	Ledipasvir 90 mg/Sofosbuvir 400 mg, 24 weeks	None
2	Yap et al. [10]	63	Male	Mucositis by radiation treatment of parotid cancer	1A, 6.3 log IU/mL	Chronic hepatitis	None	Elbasvir 50 mg/Grazoprevir 100 mg, 16 weeks	None
3	Our case	41	Female	Spina bifida and hydrocephalus	1B, 7.0 log IU/mL	HCV carrier with persistently normal ALT	None	Glecaprevir 300 mg/pibrentasvir 120 mg, 8 weeks	Constipation (mild)

possible safety and efficacy of DAA treatment using a PEG tube.

Case report

A 41-year-old female with HCV infection (GT1B) was referred to our department for HCV treatment. She was born with spina bifida and developed hydrocephalus at 3 months old, at which time a ventriculoperitoneal (VP) shunt was placed. When she was 17 years old, she was diagnosed with chronic HCV infection. At the age of 31 years, she developed VP shunt dysfunction, and a VP shunt revision was performed. However, she suffered from dysphagia as an aftereffect of the VP shunt dysfunction, and a PEG tube was placed to deliver food and medications. For administration of her medications, her guardians crushed the tablets and injected them with water. The patient had a platelet count of 33.8×10^4/μL, hemoglobin level of 14.1 g/dL, ALT level of 21 IU/L, and HCV RNA level of 7.0 log IU/mL. No continuous elevation in the ALT level was observed after birth, and she was considered an HCV carrier with persistently normal ALT. Her albumin level (2.9 g/dl) may have been depressed due to nutritional deficiencies, whereas her total bilirubin (0.2 mg/dl) and prothrombin time (100%) showed that liver function was not impaired. She had no history of previous HCV treatment or HBV infection. Her FIB-4 index was 0.58, and liver stiffness measured by transient elastography was 6.0 kPa, showing no evidence of cirrhosis. Her medications were levetiracetam and clonazepam for epilepsy, which was an aftereffect of the VP dysfunction, lansoprazole for reflux esophagitis, L-carbocisteine as a mucoregulatory drug, bifidobacteria (LAC-B Granular Powder®) and sodium picosulfate hydrate for chronic constipation, and RACOL®-NF liquid for enteral use for nutrition.

This case was treatment naïve, and we recommended GLE (300 mg/day)/PIB (120 mg/day) therapy for 8 weeks; the patient and her guardians agreed to this treatment plan. No potential drug interaction was observed with GLE/PIB. She received GLE/PIB daily through a PEG tube at the same time as her other crushed medications. Immediately prior to administration, GLE/PIB was crushed into powder with a food mill and resuspended in water. During treatment, she complained of worsened constipation after 1 week of therapy; however, the degree was mild, and we prescribed magnesium oxide laxatives to relieve the symptoms. She received the full dose of GLE/PIB for 8 weeks without any other complaints. During the treatment course, no liver or kidney dysfunction was observed.

Her HCV viral load was 1.3 log IU/ml at 2 weeks of therapy, and serum HCV RNA was undetectable at 5 weeks of therapy; she achieved a SVR lasting at least 12 weeks after treatment.

Discussion

Patients with dysphagia due to neurological or oncological disorders may have difficulty swallowing whole tablets, and some of them receive a PEG tube for nutrition and medication. As reported previously (Table 1), dysphagia due to benign pharyngeal ulceration or mucositis after radiation treatment for parotid cancer may require placement of a PEG tube. Our case was born with spina bifida, which is a birth defect with incomplete closing of the backbone and membranes around the spinal cord. Spina bifida is often associated with hydrocephalus, necessitating placement of a VP shunt to relieve pressure on the brain. Our patient received a PEG tube due as an aftereffect. However, the data regarding the safety and efficacy of administering crushed DAA via a

PEG tube are not available; therefore, a treatment protocol for patients with a PEG tube needs to be established.

No pharmacokinetic data are available on the effect of crushing or splitting LDV/SOF or EBR/GZR, whereas data on GLE/PIB from a phase 1 study were available [8]. In a pharmacokinetic study, cutting GLE/PIB tablets in half had minimal impact on GLE/PIB exposure (≤ 15% difference in C_{max} and AUC_{inf}) compared with whole GLE/PIB tablets; however, crushing or grinding the tablets resulted in lower GLE exposure (47–50% and 27–36% differences in C_{max} and AUC_{inf}, respectively) and higher PIB exposure (21–75% and 33–83% differences in C_{max} and AUC_{inf}, respectively). The increased bioavailability of crushed PIB may be attributed to the increased absorption efficiency caused by decreased particle size, and to the increase in effective surface area available for dissolution. The reason for the decreased bioavailability of GLE is not certain; however, it might be due to differences in disintegration and dissolution compared with intact tablets, caused by the pH of the medium, pKa of GLE and PIB, and location of absorption [8]. Although GLE exposure was expected to be low with crushing, we achieved a SVR 12 without extending the treatment period. One possible explanation for successful SVR12 is that the patient was underweight (approximately 36 kg) due to nutritional deficiencies only via PEG, and the plasma GLE concentration might, therefore, have reached the therapeutically effective range in spite of lower GLE exposure. The other possibility is that higher PIB exposure compensated for the effect of lower GLE exposure. Both of these theories require further verification.

The patient described in this manuscript complained of mild constipation. The most common adverse reactions with GLE/PIB are itching (4.8%), headache (4.2%), fatigue (3.0%), and bilirubin elevation (2.4%); however, constipation is rare (0.6%) in Japan [11]. Constipation is one of the major gastrointestinal tract issues seen in patients fed home enteral nutrition [12]. Our patient already used sodium picosulfate hydrate for chronic constipation, and worsened constipation was managed with magnesium oxide laxatives; however, we need to be cautious of worsening the present condition with DAA treatment.

In Japan, LDV/SOF is approved for patients with HCV GT1 or GT2 without severe renal impairment, and EBR/GZR is approved for GT1. GLE/PIB can be used for patients of all GTs and results in a shorter treatment duration for naïve and non-cirrhotic patients with HCV. Although previous studies and the current report do not validate the safety and efficacy of these regimens using a PEG tube, they potentially provide a guide for choosing better treatment regimens suitable for patients of certain populations.

In conclusion, we present the first documented clinical case of a patient with HCV who was successfully treated with crushed GLE/PIB tablets administered through a PEG tube, without any severe adverse events. In this DAA era, GLE/PIB is a possible treatment choice for patients with HCV who have a PEG tube.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Human rights All procedures followed have been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Informed consent Informed consent was obtained from all patients for being included in the study.

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