Treatment of chronic hepatitis C virus infection with crushed ledipasvir/sofosbuvir administered through a percutaneous endoscopic gastrostomy tube in a patient with HIV coinfection

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Purpose. Ledipasvir/sofosbuvir is an oral combination therapy containing fixed doses of direct-acting antiviral agents indicated for the treatment of hepatitis C virus (HCV) infection. Currently there are limited data on the clinical efficacy of crushed ledipasvir/sofosbuvir administered via feeding tube.

Summary. This case report discusses the successful treatment of chronic HCV genotype 1b infection with crushed ledipasvir/sofosbuvir administered through a percutaneous endoscopic gastrostomy (PEG) tube in a patient with human immunodeficiency virus (HIV) coinfection and high-grade sarcoma who had severe swallowing difficulties. The patient received crushed ledipasvir/sofosbuvir daily for a total of 12 weeks. At 12 weeks the patient had achieved a sustained virologic response.

Conclusion. Currently, ledipasvir/sofosbuvir is available only as a tablet, with limited pharmacokinetic data available to guide clinicians on use of the fixed-dose combination medication in crushed form. This case report highlights our experience treating a patient with HCV/HIV coinfection through administration of crushed ledipasvir/sofosbuvir via PEG tube, which we found to be a safe and effective therapeutic option.

Keywords: crushing, direct-acting antivirals, hepatitis C virus, human immunodeficiency virus, ledipasvir, percutaneous endoscopic gastrostomy tube, sofosbuvir

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Hepatitis C virus (HCV) is a bloodborne virus transmitted through direct contact with blood from an infected host. It is estimated that 2.4 million people in the United States are HCV carriers. In 2017, there were an estimated 44,700 new US cases of acute HCV infection; an estimated 75% to 85% of affected patients will develop chronic infections, and 10% to 20% will develop cirrhosis, over 20 to 30 years.[1] In the United States, it is estimated that 5% of the adult population infected with HCV is coinfected with human immunodeficiency virus (HIV).[2] This coinfection leads to an accelerated progression of hepatic fibrosis such that cirrhosis can occur 12 years earlier than in patients with HCV monoinfection.[3] HCV accounts for approximately 80% of liver-related deaths in HIV/HCV-coinfected patients.[4]

HCV is a ribonucleic acid (RNA) virus of the Flaviviridae family of viruses. There are 6 major genotypes of HCV with subtypes. Genotype 1 (subtypes 1a, 1b, and 1c) is the most common in the United States, accounting for 75% of infections. Genotype 2 (subtypes 2a, 2b, and 2c) and genotype 3 (subtypes 3a and 3b) account for about 15% of infections in the United States. Worldwide the most common genotypes are 1 and 3. Genotypes 4, 5, 6, and 7 are rare in the United States, and originate in different areas of the world, including northern Africa, the Middle East, Southeast Asia, and the Democratic Republic

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of Congo. Newly infected HCV carriers are asymptomatic, with only 20% to 30% experiencing jaundice, loss of appetite, abdominal pain, and/or fatigue. Chronic HCV infection can also be asymptomatic or cause nonspecific symptoms.[1] As progression of the disease can lead to cirrhosis and liver cancer, treatment of these patients is a priority.[5]

Joint American Association for the Study of Liver Diseases and the Infectious Diseases Society of America (AASLD/IDSA) guidelines recommend treatment for all patients with chronic HCV infection except those with a short life expectancy or undergoing liver transplantation. Sustained virological response (SVR) has been a marker for HCV cure and is defined as undetectable HCV RNA at 12 weeks after treatment. Treatment options have included pegylated interferon, oral ribavirin, and direct-acting antiviral agents (DAAs), including HCV-specific protease inhibitors, NS5A replication complex inhibitors, and NS5B polymerase inhibitors. Factors influencing the choice of drug therapy include formulary availability, toxicities, drug cost, comorbidities, renal and/or hepatic impairment, and drug-drug interactions.[6] Pegylated interferon is no longer recommended. The use of ribavirin is limited by adverse effects including hemolytic anemia and teratogenicity.[7] Historically, for HIV/HCV-coinfected patients, peginterferon monotherapy or peginterferon in combination with ribavirin have resulted in low SVR rates and significant toxicities.[8-12] In 2011, the addition of telaprevir and boceprevir to peginterferon and ribavirin regimens led to an estimated 60% increase in SVR rates; however, the use of such regimens was limited due to drug interactions with antiretroviral therapy, significant pill burden, food restrictions, and adverse drug reactions.[13,14] The newer DAAs for the treatment of HCV are highly effective, more tolerable, and have fewer adverse effects and less monitoring requirements than traditional interferon- and ribavirin-based HCV treatment options.[15]

KEY POINTS

- Direct-acting antiviral agents (DAAs) are highly effective in treating hepatitis C virus (HCV), but there is a lack of published data regarding administration of DAAs in crushed form through a percutaneous endoscopic gastrostomy (PEG) tube.
- This case report describes the successful treatment of a patient with multiple comorbidities and several swallowing difficulties with crushed ledipasvir/sofosbuvir, which was administered via PEG tube without major adverse events or drug interactions.
- Crushed ledipasvir/sofosbuvir may be a viable therapeutic option for patients with HCV infection who are unable to swallow and/or require PEG tube feeding.

According to the AASLD/IDSA guidelines, there are 4 comparable recommended treatment options for treatment-naive patients with HCV genotype 1b infection without cirrhosis: elbasvir/grazoprevir, glecaprevir/pibrentasvir, ledipasvir/sofosbuvir, and sofosbuvir/velpatasvir. There are limited data on the administration of crushed DAAs or administration of DAAs via percutaneous endoscopic gastrostomy (PEG) tube. Currently, 4 reported cases have demonstrated the efficacy of crushing DAAs for the treatment of HCV infection for patients unable to swallow or requiring a PEG tube.[16-19] Two case reports described treatment of a patient with crushed ledipasvir/sofosbuvir administered through a PEG tube[18,19]; in one of those case reports, Fulco et al[19] specifically described successfully treating a patient coinfected with HIV and HCV with ledipasvir/sofosbuvir. The 2 other case reports described treatment of a patient with crushed elbasvir/grazoprevir and glecaprevir/pibrentasvir.[16,17]

Ledipasvir/sofosbuvir (Harvoni, Gilead Sciences, Foster City, CA) is indicated for the treatment of chronic infection with HCV genotype 1, 4, 5, or 6 in patients with or without compensated cirrhosis. At the time of treating the patient described in this report, ledipasvir/sofosbuvir was available only as an oral tablet taken daily with or without food.[4] In August 2019, ledipasvir/sofosbuvir oral pellets were approved by the Food and Drug Administration (FDA). The oral pellets cannot be chewed; if sprinkled on food, the pellets must be mixed with nonacidic soft food and remain stable for 30 minutes after admixture.[20]

Our case report describes the success of treating an HIV/HCV-coinfected patient with active, high-grade soft tissue sarcoma of the throat with crushed ledipasvir/sofosbuvir administered through a PEG tube.

Case summary

After an infectious diseases consultation, a 57-year-old African American female patient with a newly diagnosed HCV genotype 1b infection was referred to an infectious diseases clinic for treatment. Her past medical history included a high-grade (stage III) soft tissue sarcoma of the throat, HIV infection, hypertension, deep vein thrombosis, right neck dissection, enucleation of the left eye, hysterectomy, and a negative hepatitis B test result. The patient's social history was positive for smoking tobacco, alcohol consumption, cocaine use, and marijuana use. She denied intravenous illegal drug use.

A PEG tube had been placed 2 years previously due to odynophagia associated with the sarcoma, a history of bilateral osteonecrosis of the jaw, and an abnormal barium swallow study indicating severe aspiration. The patient had been given olaratumab intravenously every 3 weeks for the past year as monotherapy for sarcoma.

At the time of the patient's presentation to the clinic, a fixed-dose combination of abacavir 600 mg, dolutegravir 50 mg, and lamivudine 300 mg was being administered daily via the PEG tube for the treatment of HIV infection. Her other medications at the time of presentation were aspirin 81 mg daily, hydroxyzine 10 mg daily, oxycodone IR 30 mg every 4 hours as needed, oxycodone/acetaminophen (10 mg/325 mg) every 6 hours as needed, and Nutren (Nestle HealthCare Nutrition) 1.5 kcal/mL every 6 hours, all of which were administered via the PEG tube (Table 1).

The following were the patient's laboratory values at the time of initial assessment: aspartate aminotransferase (AST), 38 U/L; alanine aminotransferase (ALT), 37 U/L; albumin, 3.3 g/dL; total protein, 8.9 g/dL; International Normalized Ratio, 1.0; total bilirubin, 0.4 mg/dL; lactate dehydrogenase, 223 U/L; and serum creatinine, 0.56 mg/dL. The patient had an HIV RNA load of <40 copies/mL and a CD4 T-lymphocyte count of 602 cells/mm^3; the HCV RNA load was 1.29×10^6 copies/mL (Table 2). Her liver fibrosis was graded as stage F1-F2.

The patient was initiated on a 12-week regimen of ledipasvir/sofosbuvir for treatment of HCV infection at the outpatient infectious diseases clinic. She was instructed to crush and dissolve 1 tablet of ledipasvir/sofosbuvir in water and administer it via the PEG tube in the morning each day for 12 weeks. The PEG tube was to be flushed with water before and after each administration. The patient was directed to wait 30 minutes to administer her nutrition formula or other medications to avoid any potential for decreased ledipasvir/sofosbuvir absorption.[8,9] The patient reported fatigue, which did not differ in degree from that experienced prior to initiation of treatment. The patient's HCV RNA load was less than 12 IU/mL (lower limit of quantification, <12 IU/mL) at the end of 12 weeks of treatment, with SVR achieved while maintaining HIV viral load at an undetectable level.

Discussion

This case report describes our initial experience with crushable ledipasvir/sofosbuvir tablets in the treatment of an HIV/HCV coinfected patient with high-grade soft tissue sarcoma of the throat who was unable to swallow tablets. Crushable ledipasvir/sofosbuvir tablets provide a viable option to successfully achieve SVR when PEG tube administration is the only option.

The use of the fixed-dose combination ledipasvir/sofosbuvir tablet in patients infected with HCV genotype 1, 4, 5, or 6 has been well established.[15] However, there are practice challenges when patients suffer difficulties with swallowing, as ledipasvir/sofosbuvir is usually taken orally in solid tablet form. Guidelines for the administration of ledipasvir/sofosbuvir by feeding tubes for treatment of HCV infection are not available. Ledipasvir/sofosbuvir was recently approved as a pellet form, but at the time of the events described here that formulation was not available. Additionally, the pellet form is FDA approved only for administration by mouth.[20]

Prior to this report, a few case reports described treatment of HCV infection through administration of a crushed DAA, with elbasvir/grazoprevir, glecaprevir/pibrentasvir, and ledipasvir/sofosbuvir (all used as monotherapy) each producing a virologic response,[16-19] although no pharmacokinetic information for any of these agents was available.

Yap et al[16] reported that SVR was achieved with crushed elbasvir/grazoprevir administered for 16 weeks in a patient with HCV genotype 1a infection and a high-grade mucoepidermoid carcinoma. Tanaka et al[7] described successfully achieving an SVR in a patient with HCV genotype 1b infection, spina bifida, and hydrocephalus with use of glecaprevir/pibrentasvir for 12 weeks. Jindracek et al[18] reported

Table 1. Patient's Maintenance Medications

Medication	Dosing	Indication
Abacavir/dolutegravir/lamivudine	600 mg/50 mg/300 mg by PEG tube daily	HIV infection
Olaratumab	600 mg (per 250 mL of 0.9% sodium chloride injection) infused IV over 60 min	Soft tissue sarcoma of the throat
Aspirin	81 mg by PEG tube daily	Prevention of cardiovascular disease
Oxycodone/acetaminophen	10 mg/325 mg by PEG tube every 6 hours as needed for pain	Chronic cancer pain
Oxycodone IR	30 mg by PEG tube every 4 hours as needed for pain	Chronic cancer pain
Hydroxyzine	10 mg/5 mL by PEG tube at bedtime	Itching
Famotidine	40 mg IV as single dose	Premedication before olaratumab infusion
Nutren (Nestle Healthcare) formula	0.07 g (1.5 kcal/mL) by PEG tube 6 times daily	Nutrition

Abbreviations: IR, immediate release; PEG, percutaneous endoscopic gastrostomy; IV, intravenously.

Table 2. Patient's HCV and HIV Viral Loads Throughout Course of Treatment

	At Initial ID Consult	At Treatment Initiation[a]	After 4 Weeks of Treatment	After 8 Weeks of Treatment	At End of 12 Weeks of Treatment	12 Weeks After Treatment Completion
HCV RNA, IU/mL	600,797	128,610	<12	<12	<12	<12
HIV RNA, copies × 10^6/mL	235	<40	<40	<40	<40	<40

Abbreviations: HCV, hepatitis C virus; HIV, human immunodeficiency virus.
[a]At initiation of ledipasvir/sofosbuvir (90 mg/400 mg by PEG tube daily).

their experience with use of crushed ledipasvir/sofosbuvir in a treatment-experienced patient with HCV genotype 1 infection and benign pharyngeal ulcerations; after 12 weeks SVR was achieved. Fulco et al[19] reported successfully treating a patient coinfected with HCV genotype 1a and HIV with crushed ledipasvir/sofosbuvir. They recommended that crushed ledipasvir/sofosbuvir be administered via the gastrostomy button once daily in the morning for 12 weeks. Fulco et al specifically discussed administering the patient's ranitidine every evening to avoid any potential for decreased ledipasvir/sofosbuvir absorption. In each of these case reports, patients were counseled to crush and dissolve the DAA in water before administering it via a PEG tube.[16-19]

In the case reported here, the patient was initiated on ledipasvir/sofosbuvir and received the medication for a total of 12 weeks. The time interval of 30 minutes between administration of ledipasvir/sofosbuvir, antiretrovirals, and the other aforementioned medications via the PEG tube was found to be safe and to allow adequate ledipasvir/sofosbuvir absorption. The desired suppression of both HCV and HIV was achieved, with no treatment-related severe adverse events noted. These findings are in agreement with data in the literature showing the safety and efficacy of the combination of dolutegravir, abacavir, and lamivudine with sofosbuvir-based DAA therapy.[21-23]

At the time of writing, our patient completed ledipasvir/sofosbuvir therapy without any treatment-related severe adverse events. Commonly reported adverse reactions to ledipasvir/sofosbuvir include headaches, fatigue, asthenia, nausea, diarrhea, and increased serum lipase.[20]

Drug-drug interactions remain a common cause of adverse drug reactions and can reduce the clinical effectiveness of medication regimens. Providers should be aware of such interactions and take careful consideration to avoid medication errors. There were no significant drug-drug interactions, besides ledipasvir 90 mg and famotidine 40 mg IV which was administered as pretreatment for immunotherapy. Famotidine can potentially cause ledipasvir to be less effective due to decrease absorption. According to the package insert, ledipasvir/sofosbuvir may be administered simultaneously with histamine H_2 receptor antagonists given at dosages less than or comparable to famotidine 40 mg twice a day.[20] Pharmacokinetic data may reveal the differences of the crushed ledipasvir/sofosbuvir tablets administered via a PEG tube and the relationship with H_2 receptor antagonism in these individuals. Here we report only the clinical outcome of treatment with crushed ledipasvir/sofosbuvir; no pharmacokinetic data were collected for this case report.

Conclusion

We describe a HIV/HCV coinfected patient with high-grade postresection sarcoma of the throat who responded well to crushed ledipasvir/sofosbuvir administered via a PEG tube. SVR was achieved at the end of 12 weeks of treatment. This case report provides further evidence that certain DAAs can be administered through an alternative route to patients with dysphagia or similar complications.

Disclosures

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