

Crushing and Splitting Direct-Acting Antivirals for Hepatitis C Virus Treatment: A Case Series and Literature Review

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Limited data exist regarding the use of direct-acting antivirals (DAAs) for hepatitis C virus (HCV) in patients who are unable to swallow tablets. This case series describes HCV treatment in patients requiring tablet manipulation, providing evidence for safety and effectiveness of HCV DAA tablet manipulation.

Keywords. chronic; crushing; deglutition; direct-acting antiviral; hepatitis C; splitting; tablet.

KEY POINTS

This report comprises the largest and most comprehensive case series for hepatitis C virus (HCV) treatment with direct acting antiviral (DAA) tablet manipulation. The results suggest safety and effectiveness of HCV treatment requiring DAA tablet manipulation.

Chronic hepatitis C virus (HCV) affects >70 million people worldwide [1] and is an ongoing epidemic within the United States where approximately 2.4 million people are living with HCV [2]. Many benefits are observed among people treated for HCV who achieve a sustained virologic response (SVR), or virologic cure, such as reductions in liver-related morbidity and mortality, extrahepatic manifestations, and all-cause mortality [3–6]. The introduction of direct-acting antivirals (DAAs) has changed the HCV treatment landscape and offers safe and highly effective all-oral regimens over previous regimens

with extended durations and numerous adverse drug effects. The evolution in HCV pharmacotherapy is recognized by the American Association for the Study of Liver Diseases and the Infectious Diseases Society of America, which recommend treating almost all patients infected with HCV with oral DAAs and highlight SVR rates >90% for most patient populations [7]. Nonetheless, HCV treatment options for patients with difficulties swallowing whole tablets have largely remained unclear.

DAAs have been evaluated in many patient populations, yet limited data exist regarding use in patients unable to swallow whole tablets. Despite this paucity of data, clinical scenarios may require tablet manipulation (ie, crushing or splitting) due to dysphagia, physiological changes, concurrent medications, or disease states [8]. While it is often accepted that taking oral medications can be troublesome for children and adolescents due to medication taste and swallowing difficulties [9], adult populations also report a swallowing difficulty prevalence as high as 60% [8, 10].

With the increasing use of DAAs, including among niche populations such as pediatric patients and HCV-positive organ transplant recipients, and the potential impact splitting or crushing may have on tablet integrity [11], there is an unmet need for outcomes data in cases that require DAA tablet manipulation. The aim of this case series is to describe the safety and effectiveness of HCV treatment requiring DAA tablet manipulation in real-world scenarios. Additional literature is reviewed here to present an inclusive resource to practitioners.

CASE SERIES

We conducted a retrospective case series of patients prescribed DAA therapy requiring tablet manipulation from January 2013 to December 2019 at 3 academic tertiary medical centers in the United States. This study was approved by the institutional review board (IRB) at Vanderbilt University Medical Center as an exempt study. Review was not required by the IRB of Temple University or the University of South Carolina. Baseline demographics, comorbidities, HCV characteristics, reasons for and methods of DAA administration, DAA treatment information, and outcomes were collected (Table 1). Among 10 patients identified, most were male (60%), treatment naive (70%), with HCV genotype 1a infection (60%) and had a median age of 61 years (interquartile range [IQR], 56–68 years). Half were Black, and half were White. DAAs included sofosbuvir/velpatasvir (50%), ledipasvir/sofosbuvir (30%), and glecaprevir/pibrentasvir (20%). Patients either crushed (70%) or split (30%) tablets. Reasons for tablet manipulation included inability to swallow tablets due to history of cancer (60%); difficulty swallowing large tablets (10%); short gut syndrome requiring

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Table 1. Summary of Cases of Hepatitis C Treatment Requiring Direct-Acting Antiviral Tablet Manipulation

Age, y	Sex	GT	Fibrosis Stage	Baseline Viral Load, IU/mL	DAA	Previous HCV Treatment	Method of Administration	Pertinent Medical History	Management of Potential Drug Interactions With DAA	Patient-Reported Adherence	SVR ₁₂ Achieved
67	Male	1a	FIB-4 1.35 ^a	>25 million	GLE/PIB	Naive	Crushed and taken by PEG tube	NAT ⁺ heart/kidney transplant, HTN, HLD, DM, GI bleeding	Atorvastatin, changed to pravastatin; quetiapine, monitored; tacrolimus, dosed simultaneously with GLE/PIB	No missed doses	Yes
68	Female	1a	FIB-4 1.71 ^a	1 483 153	GLE/PIB	Naive	Crushed and taken by PEG tube	NAT ⁺ heart/kidney transplant, TTR amyloidosis, ESRD	Pantoprazole, dosed simultaneously with GLE/PIB; oxycodone, monitored; tacrolimus, monitored	2 missed doses	Yes
71	Male	1a	F2-F3 (cirrhotic changes on imaging)	447 762	LDV/SOF	Naive	Split in half and taken by mouth	Short gut syndrome, ischemic colitis requiring colectomy	NA	No missed doses	Yes
61	Male	1a	F0	2 257 722	LDV/SOF	Experienced (IFN)	Crushed and taken with a small amount of orange juice	h/o squamous cell carcinoma of larynx, HTN, DM, HLD	Magnesium, separated from LDV/SOF by 4 h	No missed doses	LTFU (undetectable at EOT)
54	Male	1a	F0-F1	>25 million	LDV/SOF	Naive	Crushed and taken by mouth	h/o laryngeal cancer	NA	Several missed doses	LTFU (undetectable at EOT)
60	Male	3	F2-F3 (cirrhotic changes on imaging)	686 71	SOF/VEL	Naive	Crushed and taken by PEG tube	h/o carcinoma of tonsil, HCC, GERD, HTN	NA	1 missed dose	Yes
73	Male	3	F2	8560	SOF/VEL	Naive	Crushed and taken by mouth	h/o malignant neoplasm of supraglottis	NA	No missed doses	Yes
41	Female	3	F0	268 231	SOF/VEL	Naive	Split in half and taken on gelatin	Scoliosis with Harrington rod, BMI 17.8 kg/m ²	NA	No missed doses	Yes
60	Female	1a	F0	3 746 315	SOF/VEL	Experienced (SMV + SOF)	Crushed and taken sprinkled on applesauce	h/o squamous cell carcinoma of larynx, GERD, HTN, CAD	NA	31 missed doses	Yes
50	Female	3	F4	30 784	SOF/VEL + RBV	Experienced (IFN)	Split in quarters and taken by mouth	Decompensated cirrhosis, h/o submandibular malignant mass	Calcium carbonate, separated from SOF/VEL by 4 h; ranitidine, held while on SOF/VEL	4 missed doses	LTFU (undetectable at EOT)

Abbreviations: BMI, body mass index; CAD, coronary artery disease; DAA, direct-acting antiviral; DM, diabetes mellitus; EOT, end of treatment; ESRD, end-stage renal disease; FIB-4, Fibrosis-4 Index for Liver Fibrosis; GERD, gastroesophageal reflux disease; GI, gastrointestinal; GLE, glecaprevir; GT, genotype; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HLD, hyperlipidemia; h/o, history of; HTN, hypertension; IFN, interferon; LDV, ledipasvir; LTFU, lost to follow-up; NA, not applicable; NAT⁺, nucleic acid test positive; PEG, percutaneous endoscopic gastrostomy; PIB, pibrentasvir; RBV, ribavirin; SMV, simeprevir; SOF, sofosbuvir; SVR₁₂, sustained virologic response at 12 weeks; TTR, transthyretin; VEL, velpatasvir.

^aFIB-4 is provided when other staging data not available.

enteral feeding (10%); and inpatient intubation after multiorgan transplant (20%). All patients were prescribed 12 weeks of DAA therapy and had undetectable HCV viral loads by day 56 on treatment. The median time to on-treatment viral load assessment was 33 days (IQR, 27–44 days). All patients with available data ($n = 7$) achieved SVR at 12 weeks (SVR₁₂). Three patients achieved undetectable viral loads at end of treatment but were lost to follow-up prior to SVR₁₂ assessments. No patients experienced severe adverse events, but unpleasant taste was reported ($n = 4$). Eight patients (80%) completed treatment with ≤ 4 missed doses. One patient reported missing “several” doses; another completed treatment 31 days after the anticipated end of treatment date and still achieved SVR₁₂.

DISCUSSION

The need to manipulate HCV DAAs reflects a real-world clinical challenge in delivering HCV care. Although pellets of commonly prescribed HCV DAAs are now approved for pediatric use, these are unlikely to be used in the real-world adult population as multiple packets (ranging from 2 to 6) would be needed to constitute an adult dose, which may exceed the costs of standard tablets and prove a barrier during the insurance authorization process. Current DAA tablet formulations are not enteric-coated or sustained-release, so tablets can be split or crushed without concerns for degrading the drug release mechanism. However, stability and pharmacokinetic data of crushed or split tablets are not readily available. Reports of DAA tablet manipulation are limited to 2 small phase 1 pharmacokinetic studies [12, 13] and case reports (Table 2) [14–23]. Pijnenburg et al [12] conducted a phase 1, single-dose trial evaluating pharmacokinetic data of elbasvir/grazoprevir in 11 healthy adult volunteers. Pharmacokinetic similarities were demonstrated between crushed and suspended elbasvir/grazoprevir tablets compared with whole tablets; thus, crushed tablets can be an administration option for patients with swallowing disorders. Oberoi et al [13] evaluated pharmacokinetic data for a single dose of glecaprevir/pibrentasvir in 25 healthy adults. Among 5 different administration mode groups evaluated (ie, whole tablets, halved tablets, crushed tablets, tablets ground into a powder, and ground powder mixed in Jell-O), all manipulation strategies had clinically significant impact on drug exposure except halving tablets, which did not affect exposure levels. These data comprise all publicly available pharmacokinetic results on this issue.

To date, 11 individual case reports of DAA tablet manipulation have been published (Table 2) [14–24]. Five cases describe treatment with sofosbuvir/velpatasvir in patients with HCV genotypes 1a, 1b, 2b, and 4 [19–23]. In these cases, patients crushed tablets and either administered by mouth [19, 22, 23] or via percutaneous endoscopic gastrostomy (PEG) tube [20, 21]. SVR₁₂ was achieved in 4 patients [19, 20, 22, 23] and was not reported

in the remaining case [21]. The addition of the case series described here doubles the number of sofosbuvir/velpatasvir reported tablet manipulation cases and expands to previously unreported patient populations treated with sofosbuvir/velpatasvir. These newly reported patients include 4 with HCV genotype 3 infection, 1 patient with decompensated cirrhosis, and 2 patients who split tablets. Ledipasvir/sofosbuvir tablet manipulation was previously reported in 3 cases, all achieving SVR₁₂ [16–18]. All patients had HCV genotype 1, and tablets were crushed, dissolved, and administered by PEG tube [16, 17] or gastrostomy button [18]. Three additional cases of treatment with ledipasvir/sofosbuvir in HCV genotype 1 patients with oral administration after crushing and splitting tablets are newly reported here. Additional published case reports include 2 patients with genotype 1a HCV treated with elbasvir/grazoprevir [14, 24] and a genotype 1b patient treated with glecaprevir/pibrentasvir [15]; all patients achieved SVR₁₂ [14, 15, 24].

Recently Waldman et al described treatment of 25 patients with glecaprevir/pibrentasvir after receiving heart or heart/kidney transplants from HCV nucleic acid test–positive (NAT⁺) donors, 8 of whom crushed GLE/PIB a median of 6 days during the course of HCV treatment [25]. There was no difference in SVR rates between the 2 groups. Our data add to this report and include 2 additional cases of crushed glecaprevir/pibrentasvir following organ transplant from HCV NAT⁺ donors who received crushed tablets through the entire course of DAA treatment and achieved SVR₁₂.

These data comprise the largest and most comprehensive case series of safety and efficacy data for HCV DAA tablet manipulation and fill important data gaps related to DAA tablet manipulation. This series describes the first cases of tablet manipulation in patients with genotype 3 infection and a patient with decompensated cirrhosis. The definition of tablet manipulation in this case series expands on previous literature to include splitting in addition to crushing, thus reflecting a wider variety of real-world practice. These data additionally build on previous reports of HCV NAT⁺ donor organ transplants with longer duration of tablet manipulation during treatment. The presence of patients lost to follow-up reflect the real-world challenges of HCV treatment despite high efficacy. As there were no severe adverse effects reported in this series or in any of the cases from the literature, these data suggest safety of DAA manipulation.

The safety and efficacy of HCV treatment despite DAA tablet manipulation seen in our case series align with existing literature to support use of tablet manipulation of HCV DAAs when needed; however, further study remains warranted to examine tablet stability and effects on pharmacokinetic and safety profiles. In summary, this real-world case series of 10 cases of HCV DAA manipulation and review of the published literature demonstrate the safety and efficacy of tablet manipulation and provide a resource for clinicians treating HCV amid challenging clinical circumstances.

Table 2. Literature Review Summary of Hepatitis C Treatment Cases Requiring Tablet Manipulation

First Author	Age, y	Sex	GT	Fibrosis Stage	DAA	Previous HCV Treatment	Method of Administration	Reason for Tablet Manipulation	SVR ₁₂ Achieved	Adverse Events
Yap [14]	63	Male	1a	Noncirrhotic	EBV/GRZ	Naive	Crushed, dissolved, PEG	Dysphagia due to head and neck cancer	Yes	NR
Shah [24]	64	Female	1a	Noncirrhotic	EBV/GRZ	Experienced (PEG-IFN/RBV)	Crushed, dissolved, PEG	Esophageal dysmotility disorder	Yes	None
Tanaka [15]	41	Female	1b	Noncirrhotic	GLE/PIB	Naive	Crushed, dissolved, PEG	Dysphagia with spina bifida and hydrocephalus	Yes	Constipation
Huffman [16]	57	Female	1b	Noncirrhotic	LDV/SOF	Naive	Crushed, dissolved, PEG	Odynophagia with h/o head and neck cancer	Yes	Fatigue
Jindracek [17]	61	Male	1	Compensated cirrhosis	LDV/SOF	Experienced (PEG-IFN/RBV)	Crushed, dissolved, PEG	Dysphagia due to pharyngeal ulcer, h/o head and neck cancer	Yes	None
Fulco [18]	19	Female	1a	Noncirrhotic	LDV/SOF	Naive	Crushed, dissolved, gastrostomy button	Gastrostomy button for historical failure to thrive	Yes	NR
Lalanne [19]	70	Female	1b	Hepatocellular carcinoma, noncirrhotic F3	SOF/VEL	Naive	Crushed and taken with food and an acidic beverage	Dysphagia due to previous oropharyngectomy, h/o head and neck cancer	Yes	None
Van Seyen [20]	54	Male	2b	Normal liver enzymes	SOF/VEL	Not reported	Crushed, dissolved, PEG	Left-sided hemiparesis following stroke	Yes	None
Caceres-Velasco [21]	53	NR	1a	Advanced fibrosis and thrombo-cytopenia	SOF/VEL	Naive	Crushed, dissolved, PEG	h/o head and neck cancer with subtotal maxillectomy, PEG for nutritional feedings	NR	None
Puebla Villalacusa [22]	65	Male	4	Noncirrhotic	SOF/VEL	Not reported	Crushed, dissolved in water, and taken by mouth	Dysphagia with h/o head and neck cancer	Yes	Bitter taste
Mogul [23]	62	Female	4	Noncirrhotic	SOF/VEL	Naive	Crushed and taken on soft food	Dysphagia	Yes	Headache and fatigue

Abbreviations: DAA, direct-acting antiviral; EBV, elbasvir; GLE, glecaprevir; GRZ, grazoprevir; GT, genotype; HCV, hepatitis C virus; h/o, history of; LDV, ledipasvir; NR, not reported; PEG, percutaneous epigastric gastrostomy; PEG-IFN, pegylated interferon; PIB, pibrentasvir; RBV, ribavirin; SOF, sofosbuvir; SVR₁₂, sustained virologic response at 12 weeks; VEL, velpatasvir.

Notes

Potential conflicts of interest. D. E. K. is an independent consultant for AbbVie and has participated on an advisory panel for Gilead Sciences. All other authors report no potential conflicts of interest.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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