

# Sofosbuvir Induced Steven Johnson Syndrome in a Patient With Hepatitis C Virus-Related Cirrhosis

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Sofosbuvir is an imperative drug used in treatment regimens for hepatitis C virus (HCV). It is considered relatively safe with fewer adverse effects than other treatments. Here, we report a rare and potentially serious, dermatologic, adverse effect following the use of sofosbuvir. A 35-year-old man with genotype 3-related HCV cirrhosis presented with decompensated ascites and jaundice following 7 weeks of therapy with peginterferon alpha-2a and oral ribavirin. After peginterferon withdrawal and stabilization, oral sofosbuvir and ribavirin were started; 10 days later, he developed itching over the trunk and legs, followed by multiple papules and vesicles over an erythematous base. Over the next 15 days, the rash progressed with the formation of blisters and peeling skin. Simultaneously, the oral mucosa and lips developed crusting and painful erosions. Considering drug-induced Steven John Syndrome (SJS), sofosbuvir and ribavirin were withdrawn and the patient was treated with topical emollients, steroids, and supportive care. The lesions improved over the next 4 weeks, with some residual hyperpigmentation. Rechallenge with sofosbuvir alone at one eighth the dose resulted in similar skin and mucosal lesions after 2 months; these lesions also improved after sofosbuvir withdrawal. The Algorithm of Drug Causality for Epidermal Necrolysis score was 7, which suggested sofosbuvir as the very probable drug resulting in SJS in our patient. *Conclusion:* The appearance of SJS following sofosbuvir use is an important and potentially fatal complication from a drug that serves as the backbone of several HCV treatment regimens. Treating physicians must use sofosbuvir with caution and consider withholding or discontinuing this drug in patients with such severe dermatologic manifestations. (*Hepatology Communications* 2018;2:16-20)

## Introduction

Sofosbuvir is an imperative drug used for the treatment of hepatitis C virus infection (HCV). It is relatively safe with fewer adverse effects than other treatments.<sup>(1)</sup> In this paper, we report a rare and potentially serious, dermatologic, adverse effect following the use of sofosbuvir.

## Case Summary

A 35-year-old male presented with a 3-year history of easily becoming fatigued; he was diagnosed as compensated HCV-related cirrhosis of the liver with a Child-Turcotte-Pugh score of 6 and model for end stage liver disease (MELD) score of 11. He was treated with peginterferon (PEG-IFN) alpha-2a (180

*Abbreviations:* BSA, body surface area; DAA, direct-acting antiviral; HCV, hepatitis C virus; IFN, interferon; MELD, model for end stage liver disease; PEG-IFN, peginterferon; SJS, Steven Johnson syndrome.

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**FIG. 1.** Patient with decompensated HCV cirrhosis treated with sofosbuvir and ribavirin. (A) Diffuse erythematous exfoliating rash over the abdomen after 10 days of sofosbuvir. (B) Crusted erosions over the lips with erythematous rash over the face after 25 days of sofosbuvir.

$\mu\text{g}/\text{week}$ ) and ribavirin (1,200 mg/day) for 7 weeks, after which he presented to our hospital with decompensated jaundice and ascites. Evaluation showed a Child-Turcotte-Pugh score of 10 and MELD score of 17. His HCV genotype was 3 with a viral load of 4,300 IU/mL. There were small esophageal varices on endoscopic evaluation. He had anemia (hemoglobin, 11.8 g/dL), thrombocytopenia (platelet count,  $70 \times 10^9 /\mu\text{L}$ ), and deranged liver function tests (total bilirubin, 3.5 mg/dL; conjugated bilirubin, 1.6 mg/dL; aspartate aminotransferase, 85 U/L; alanine aminotransferase, 66 U/L; alkaline phosphatase, 110 U/L), and hypoalbuminemia (protein/albumin, 6.5/2.5 mg/dL). His total leucocyte count, serum electrolytes levels, renal function tests, thyroid function tests, and autoimmune marker levels were normal, and hepatitis B and human immunodeficiency virus markers were all

negative. There was no history of atopy, drug allergy, radiation exposure, chemicals, upper respiratory tract infection, or any autoimmune diseases. His chronic medications included oral propranolol, folate, furosemide, spironolactone, calcium citrate, and multivitamins. He was started on oral sofosbuvir (400 mg/day) and ribavirin (1,200 mg/day) for the treatment of the HCV infection. Ten days after the treatment, he developed itching over his trunk and over the next 15 days gradually developed multiple papules and vesicles over an erythematous base (Fig. 1A). The possibility of viral exanthems or erythema multiforme or drug rash was considered, and the patient was treated with topical emollients, oral antihistamines, and empirical antibiotics. However, the rashes progressed to involve the legs, whole of the abdomen, and extensor surfaces of arms with involvement of palms and soles. The vesicles

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**FIG. 2.** Patient with decompensated HCV cirrhosis treated with sofosbuvir and ribavirin. (A) Resolution of rash with some residual hyperpigmentation over the trunk after 4 weeks of sofosbuvir withdrawal. (B) Complete healing of erosions over the lips after 4 weeks of sofosbuvir withdrawal.

coalesced to form blisters at multiple places, which led to progressive skin desquamation that left raw erosions over the next week. Simultaneously, painful erosions and hemorrhagic crusting appeared over the mucosal surfaces of the lips and buccal mucosa, causing odynophagia (Fig. 1B). These were associated with anorexia, generalized weakness, and worsening fatigue. Considering the diagnosis of Steven Johnson syndrome (SJS), sofosbuvir and ribavirin were stopped. The patient was hospitalized and managed with hydration, topical emollients, steroids,

and nutritional support. Within the next 4 weeks, the oral and skin lesions improved (Fig. 2).

There was a need to complete the treatment for HCV infection in our patient. Because sofosbuvir was the most essential drug needed for his treatment, it was pertinent to exclude it as an implicating drug for SJS before re-initiating treatment. Ribavirin is known to cause dermatologic reactions, including SJS. Therefore, after weighing the risk–benefit ratio, rechallenge after 8 weeks with sofosbuvir alone at one eighth the

**TABLE 1. ALGORITHM OF DRUG CAUSALITY FOR EPIDERMAL NECROLYSIS SCORE**

No.	Criteria	Values	Rules to Apply	Score
1.	Delay from initial drug component intake to onset of reaction (index day)	Suggestive	5-28 days	+3
2.	Drug present in the body on index day	Definite	Drug continued up to index day or stopped at a time point <5 times the elimination half-life* before the index day	+0
3.	Prechallenge/rechallenge	Positive; specific for disease and drug	SJS/TEN after use of the same drug	+4
4.	Dechallenge	Neutral	Drug stopped	+0
5.	Type of drug (notoriety)	Unknown	All other drugs, including newly released ones with no previous reports	+0
6.	Other cause	Not possible	Rank all drugs from highest to lowest intermediate score	+0
	Total		Very probable	7

\*Drug's (or active metabolite's) elimination half-life from serum and/or tissues, taking into account kidney function for drugs predominantly cleared by kidney and liver function for those with high hepatic clearance (Sofosbuvir: 0.4 hours and GS-331007: 27 hours). Abbreviations: TEN, toxic epidermal necrolysis.

original dose was attempted under close observation in the hospital and after obtaining informed consent from relatives. It resulted in the development of similar painful papulovesicular rashes over the legs and erosions over the upper lip in the next 3 days. Sofosbuvir was withdrawn, and the patient was treated with topical emollients, following which the rash resolved over the next 2 weeks. The Algorithm of Drug Causality for Epidermal Necrolysis score<sup>(2)</sup> was 7, which suggested sofosbuvir as the very probable drug resulting in SJS in our case (Table 1).

## Discussion

According to the World Health Organization's 2017 global hepatitis report,<sup>(3)</sup> HCV infection has a global incidence of 23.7 per 100,000; the estimated number of persons newly infected (1.75 million) exceeds the estimated number of persons dying from end-stage HCV infection (399,000) and being cured (843,000). Therefore, its eradication continues to be an unmet challenge. With the advent of new direct-acting antivirals (DAAs), there has been a significant improvement in the cure rates of HCV infection. However, there is a potential barrier to their widespread use due to associated adverse effects.

Dermatologic adverse effects in HCV infection may result from the infection *per se* or may relate to the medications given. Among the currently used DAAs, the incidence of rash has been reported up to 8%-9% with sofosbuvir plus ribavirin; up to 3.9% with sofosbuvir plus ledipasvir; up to 14% with sofosbuvir, ledipasvir, plus ribavirin; up to 8% with sofosbuvir plus daclatasvir; and up to 18%-20% with a PEG-IFN and ribavirin combination.<sup>(1,4-6)</sup> Addition of sofosbuvir to the PEG-IFN and ribavirin combination did not seem to increase the incidence of rash (20%),<sup>(4)</sup> which implies that rash due to sofosbuvir alone is rare. Moreover, the literature on the incidence of rash due to sofosbuvir alone is limited. A real-world experience with sofosbuvir-based DAA regimens reported rash in up to 2.6% (n = 344) of patients: 6% with sofosbuvir, PEG-IFN, plus ribavirin; 0% with sofosbuvir plus ribavirin; and 0% with sofosbuvir and daclatasvir/ledipasvir with or without ribavirin.<sup>(7)</sup> Two other real-world studies did not report any rash related to sofosbuvir-based regimens.<sup>(8,9)</sup> Interestingly, these studies failed to provide the morphologic description of the rash associated with the DAAs. However, recently there have been reports of seborrheic

dermatitis and erythema multiforme with the use of sofosbuvir and daclatasvir,<sup>(10,11)</sup> lichenoid eruptions with sofosbuvir and simeprevir,<sup>(12)</sup> and erythrodermic pityriasis rubra pilaris eruptions with sofosbuvir.<sup>(13)</sup> In all these cases, onset of rash led to drug discontinuation.

Drug rashes may be graded into mild, moderate, severe, and life threatening, depending on the extent of involvement and associated complications and mortality.<sup>(14)</sup> Life-threatening reactions include SJS, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms, erythema multiforme, acute generalized exanthematous pustulosis, and any rash that requires therapy with systemic corticosteroids. While mild and moderate cases improve with topical medications and supportive treatment, the severe and life-threatening cases also require permanent discontinuation of therapy.

Rashes reported in the literature due to sofosbuvir-containing regimens were mild or moderate and improved with topical medications. However, to the best of our knowledge, there are no reports of SJS related to the use of sofosbuvir. Our patient developed SJS, possibly due to the continued use of the drug after the first appearance of skin eruptions.

Classically, SJS presents with a prodrome of malaise, fatigue, arthralgia, or headache. It is followed by painful or pruritic papules, vesicles, blisters or necrosis of skin, and peeling of <10% of the body surface area (BSA).<sup>(15)</sup> It predominantly involves torso, extensor surfaces, and mucocutaneous areas and is attended with a mortality rate of 5%.<sup>(15)</sup> Our patient had characteristic and rapidly progressing painful, pruritic, papulovesicular lesions with desquamation of <10% BSA and involvement of mucosal surfaces consistent with SJS. Toxic epidermal necrolysis, which classically involves >30% BSA, and exfoliative erythroderma that presents with predominant erythema, scaling, and induration without any blisters or mucosal involvement were excluded at the outset. Erythema multiforme and viral exanthems were unlikely as our patient had excessive skin sloughing and pain. Staphylococcal scalded skin syndrome and drug reaction with eosinophilia and systemic symptoms were excluded as there was lack of fever, toxic features, eosinophilia, and lymphadenopathy. Bullous drug eruptions were ruled out due to the presence of mucosal involvement and the absence of abrupt presentation within hours. Mixed cryoglobulinemia and porphyria cutanea tarda related to HCV were excluded based on the absence of purpura, skin ulcers, arthralgias, and neurologic or renal involvement for the former and the lack of vesiculobullous eruptions limited to sun-exposed areas or face for the latter.<sup>(14)</sup>

The complete reversal of rash 4 weeks after the withdrawal of sofosbuvir and the reappearance of a similar rash after its rechallenge along with an Algorithm of Drug Causality for Epidermal Necrolysis score of 7 implied that sofosbuvir is the likely culprit drug.

The pathogenesis of SJS is not clear, and a possible hypothesis includes Fas-mediated apoptosis or cytotoxic T-cell-mediated lysis of keratinocytes and immune-mediated injury in a genetically predisposed individual.<sup>(15)</sup> Further studies are warranted to demonstrate the exact mechanisms behind sofosbuvir-related SJS.

Management of SJS relies on the withdrawal of the offending drug in addition to hydration, nutrition, antibiotics, and supportive care. Oral corticosteroids or intravenous immunoglobulins may be given in a select group of patients. Our patient improved with sofosbuvir withdrawal, topical emollients, steroids, and supportive care without any residual complications.

The appearance of SJS following sofosbuvir use is an important and potentially fatal complication from a drug that serves as the backbone of several HCV treatment regimens. Treating physicians must use sofosbuvir with caution and consider withholding or discontinuing this drug in patients with such a severe dermatologic manifestation.

## REFERENCES

- 1) Mangia A, Piazzolla V. Overall efficacy and safety results of sofosbuvir-based therapies in phase II and III studies. *Dig Liver Dis* 2014;46(Suppl. 5):S179-S185.
- 2) Sassolas B, Haddad C, Mockenhaupt M, Dunant A, Liss Y, Bork K, et al. ALDEN, an algorithm for assessment of drug causality in Stevens-Johnson Syndrome and toxic epidermal necrolysis: comparison with case-control analysis. *Clin Pharmacol Ther* 2010;88:60-68.

- 3) World Health Organization. Global hepatitis report, 2017. Geneva, Switzerland: WHO;2017.
- 4) Patel P, Malik K, Krishnamurthy K. Cutaneous adverse events in chronic hepatitis c patients treated with new direct-acting antivirals: a systematic review and meta-analysis. *J Cutan Med Surg* 2016;20:58-66.
- 5) Banerjee D, Reddy KR. Review article: safety and tolerability of direct-acting anti-viral agents in the new era of hepatitis C therapy. *Aliment Pharmacol Ther* 2016;43:674-696.
- 6) Poordad F, Schiff ER, Vierling JM, Landis C, Fontana RJ, Yang R, et al. Daclatasvir with sofosbuvir and ribavirin for hepatitis C virus infection with advanced cirrhosis or post-liver transplantation recurrence. *Hepatology* 2016;63:1493-1505.
- 7) Hlaing NKT, Mitrani RA, Aung ST, Phyo WW, Serper M, Kyaw AMM, et al. Safety and efficacy of sofosbuvir-based direct-acting antiviral regimens for hepatitis C virus genotypes 1-4 and 6 in Myanmar: real-world experience. *J Viral Hepat* 2017;24:927-935.
- 8) Juanbeltz R, Goni Esarte S, Uriz-Otano JI, Martinez Echeverria A, Elizalde I, Zozaya JM, et al. Safety of oral direct acting antiviral regimens for chronic hepatitis C in real life conditions. *Postgrad Med* 2017;129:476-483.
- 9) Chen JH, Zeng Z, Zhang XX, Zhang Y, Zhang RW, Wang S, et al. Efficacy and safety of combined directly acting antivirals for treatment of Chinese chronic hepatitis C patients in a real-world setting. *World J Gastroenterol* 2017;23:4072-4079.
- 10) Wang Y, Liu P. A case of erythema multiforme drug eruption associated with erythrodermic psoriasis induced by sofosbuvir and daclatasvir. *J Clin Pharm Ther* 2017;42:108-110.
- 11) Welzel TM, Petersen J, Herzer K, Ferenci P, Gschwantler M, Wedemeyer H, et al. Daclatasvir plus sofosbuvir, with or without ribavirin, achieved high sustained virological response rates in patients with HCV infection and advanced liver disease in a real-world cohort. *Gut* 2016;65:1861-1870.
- 12) Simpson CL, McCausland D, Chu EY. Photo-distributed lichenoid eruption secondary to direct anti-viral therapy for hepatitis C. *J Cutan Pathol* 2015;42:769-773.
- 13) Cheung EJ, Jedrych JJ, English JC 3rd. Sofosbuvir-induced erythrodermic pityriasis rubra pilaris-like drug eruption. *J Drugs Dermatol* 2015;14:1161-1162.
- 14) Cacoub P, Bourliere M, Lubbe J, Dupin N, Buggisch P, Dusheiko G, et al. Dermatological side effects of hepatitis C and its treatment: patient management in the era of direct-acting antivirals. *J Hepatol* 2012;56:455-463.
- 15) Hazin R, Ibrahim OA, Hazin MI, Kimyai-Asadi A. Stevens-Johnson syndrome: pathogenesis, diagnosis, and management. *Ann Med* 2008;40:129-138.