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【 CASE REPORT 】

Severe Steroid-responsive Skin Disorders Related to Ledipasvir and Sofosbuvir for HCV

Tomoko Tadokoro, Asahiro Morishita, Koji Fujita, Kyoko Oura, Teppei Sakamoto, Takako Nomura, Joji Tani, Hirohito Yoneyama and Tsutomu Masaki

Abstract:
Combination therapy with ledipasvir and sofosbuvir (LDV/SOF), direct-acting antiviral agents, is highly effective against hepatitis C virus genotype 1 infection. Although LDV/SOF is safer than conventional treatment, reports have indicated that LDV/SOF was discontinued in certain cases due to severe skin disorders. A 68-year-old woman presented with a rash after starting LDV/SOF treatment. We interrupted LDV/SOF and began the oral administration of prednisolone (PSL). After the rash improved, we re-started LDV/SOF with PSL. After treatment, the rash clearly improved; we checked for a sustained virologic response 12 weeks after treatment. Steroids may therefore be an effective treatment option for controlling the side effects of LDV/SOF.

Key words: case reports, hepatitis C, ledipasvir and sofosbuvir, drug eruption, steroid

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Introduction

The number of new hepatitis C virus (HCV) infections has been decreasing for decades; however, the HCV-related morbidity and mortality are expected to continue rising for another 20 years (1). Several direct-acting antiviral agents (DAAs) have been designed and developed, including NS3/4A protease inhibitors, NS5B polymerase inhibitors and NS5A inhibitors (2). Ledipasvir (LDV), an NS5A inhibitor, and sofosbuvir (SOF), an NS5B polymerase inhibitor, have been associated with a high rate of sustained virologic response (SVR) among patients with HCV genotype 1 infection (3).

LDV/SOF for 12 weeks is a highly effective, well-tolerated interferon (IFN)- and ribavirin-free treatment for all patients with chronic HCV genotype 1 infection without cirrhosis or with compensated cirrhosis (4). Although this treatment has rapidly become widespread, fewer reports have addressed the side effects of LDV/SOF treatment than have addressed those of conventional treatment. Adverse events were mild to moderate in severity in 93% of the patients who experienced adverse events associated with LDV/SOF treatment. The most common adverse events were fatigue, headache, insomnia, and nausea (3). However, in a phase 3 clinical trial in Japan, the incidence of side effects was 21.7%: common side effects were fatigue, headache, nausea, diarrhea, and rash (4). Although many of these side effects are not serious, the discontinuation of LDV/SOF has been required in certain cases, and no consensus exists regarding the side effects of this drug treatment.

In this case report, we discuss how to continue LDV/SOF treatment despite its associated severe skin disorders.

Case Report

A 68-year-old Japanese woman presented with a bilateral eruption on her face and arms. She had a history of chronic hepatitis C without liver cirrhosis; her viral load was 6.5 log IU/mL, and her viral genotype was 1b. In addition, she exhibited the amino acid mutation Y93H in NS5A. Her medical history included type 2 diabetes mellitus without renal dysfunction but no allergic history. She had been treated with alogliptin for diabetes mellitus, although there were no contraindications for the co-administration of alogliptin with LDV/SOF. Therefore, given the situation, we started treat-

Department of Gastroenterology and Neurology, Kagawa University, Japan
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Correspondence to Dr. Tsutomu Masaki, tmasaki@med.kagawa-u.ac.jp

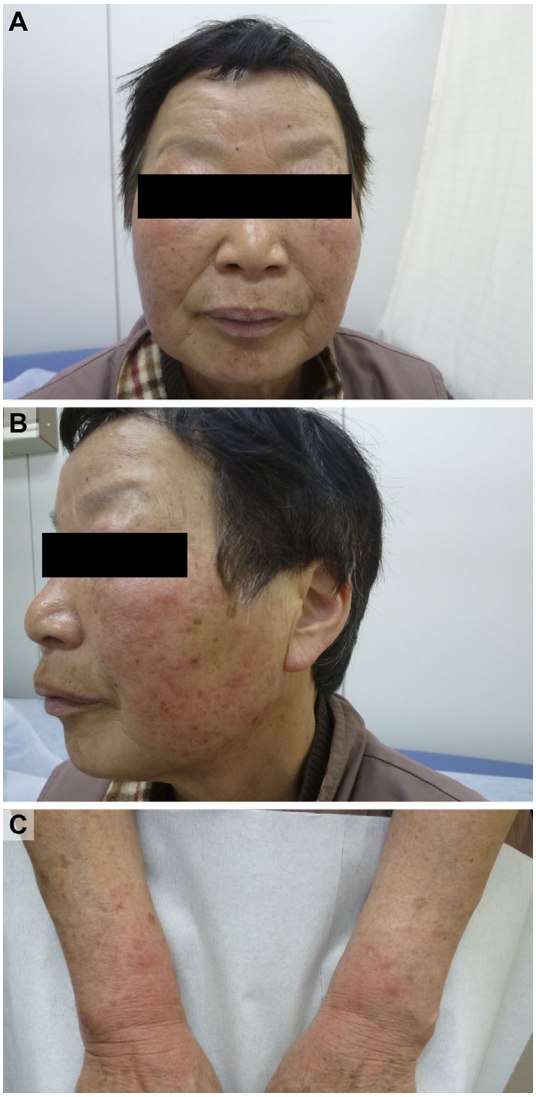

Figure 1. **Maculopapular rash in a patient on LDV/SOF. The patient developed a diffuse erythematous maculopapular rash on her face (A and B) and both upper extremities (C). There was no evidence of mucosal abnormalities, including in her eyes.**

Table. **Laboratory Data for the Patient on the Date of Consultation, Immediately after the Onset. The Laboratory Data Revealed No Abnormalities in White Blood Cell Counts or Liver Enzymes. An LTT with LDV/SOF was Positive with a Stimulation Index of 2.48.**

Metric	Value	Unit	Reference
CRP	0.01	mg/dL	0-0.2
TP	7.1	g/dL	6.5-8.2
Alb	4.2	g/dL	3.5-5.5
A/G	1.45		1-1.8
BUN	20.8	mg/dL	7-20
Cr	0.58	mg/dL	0.5-1
T-bil	0.6	mg/dL	0.1-1.2
D-bil	0.1	mg/dL	0.1-0.6
AST	25	U/L	10-35
ALT	19	U/L	5-40
ALP	267	U/L	100-340
LDH	225	U/L	110-220
γ-GTP	16	U/L	0-30
ChE	372	U/L	200-452
T-chol	211	mg/dL	130-219
TG	62	mg/dL	30-149
FBS	113	mg/dL	70-110
Na	139	mmol/L	135-146
K	4	mmol/L	3.5-4.6
Cl	105	mmol/L	96-110
WBC	6,020	/μL	4,700-8,700
RBC	429×10^4	/μL	370-490
Hb	12.3	g/dL	11-15
Ht	38.4	%	35-45
Plt	23.6×10^4	/μL	15-35
Neut	67.7	%	38-71.9
Eos	0.8	%	0.2-6.8
Baso	1	%	0-1
Lym	25.4	%	26-46.6
Mono	5.1	%	2.3-7.7
PT	132	%	80-100
Type IV collagen 7s	3.8	ng/mL	0-6
M2BPGi	2.52		0-1
FIB-4index	1.68		
LTT index	2.48		≤1.8

ment with LDV/SOF for chronic hepatitis C. LDV/SOF was administered as a 90/400 mg combination tablet once daily for 12 weeks.

Nine days after commencing LDV/SOF treatment, the patient developed a rash on her face (Fig. 1A and B) and on both upper extremities (Fig. 1C). The rash gradually worsened, and the patient visited us 12 days after beginning LDV/SOF treatment. According to a physical examination, her vital signs and cardiovascular findings were normal, and her lungs were clear to auscultation. She had developed a diffuse erythematous maculopapular rash on her face and both upper extremities. There was no evidence of mucosal abnormalities, including in her eyes. Laboratory examinations after the onset of the rash revealed that the patient's white blood cell counts (including eosinophils) and liver enzyme levels were all within the normal ranges (Table), and there was no significant change during the course of treatment. With respect to the severity of the telaprevir-associated rash (5), the patient's rash was regarded as Grade 2. In addition, based on the Common Terminology Criteria for Adverse Events (CTCAE), version 4.0, this case was regarded as Grade 3. The rash expanded within a few days; therefore, LDV/SOF was discontinued immediately. She was injected with 100 mg of hydrocortisone and monoammonium glycyrrhizinate, and oral administration of 10 mg of prednisolone (PSL) and antihistamines was initiated. The rash improved promptly post-treatment. Although virus volumes had been dropping well until the discontinuation of LDV/SOF, they had not become negative. We carefully educated the patient on the risk of re-administration of suspect medicine in order to ensure informed consent, but the patient did not want to interrupt her treatment. We therefore

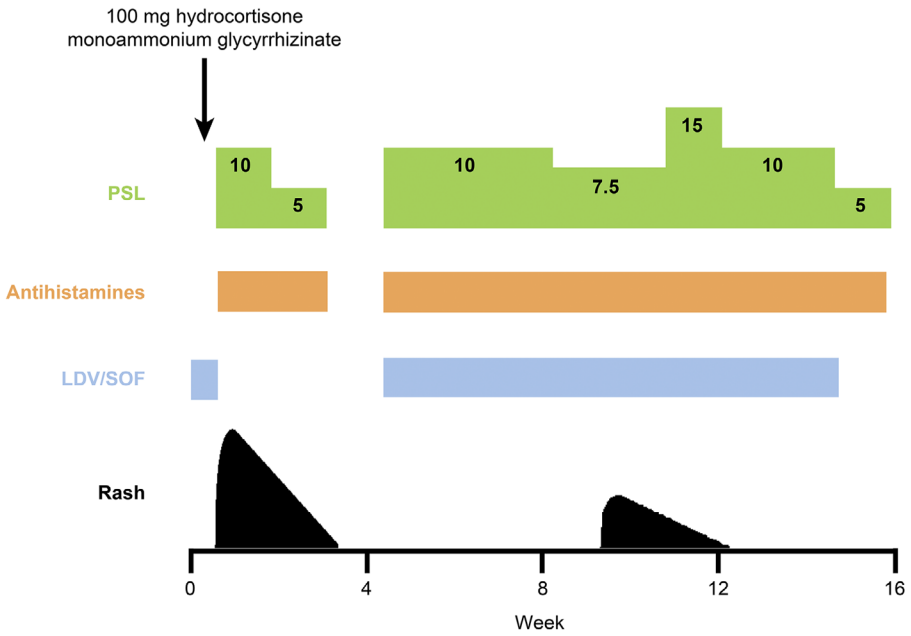

Figure 2. **Clinical course of the patient. Nine days after beginning LDV/SOF treatment, the patient had developed a rash. We stopped LDV/SOF immediately, injected 100 mg of hydrocortisone and monoammonium glycyrrhizinate and began the oral administration of 10 mg of PSL and antihistamines. After her rash had completely healed, we re-administered LDV/SOF with 10 mg of PSL and antihistamines. After the dosage of PSL was reduced to 7.5 mg, the rash relapsed; therefore, we transiently administered 15 mg of PSL and subsequently continued with 10 mg of PSL until the end of LDV/SOF treatment. After 12 weeks of LDV/SOF, the rash had clearly improved, and we gradually reduced the PSL dose.**

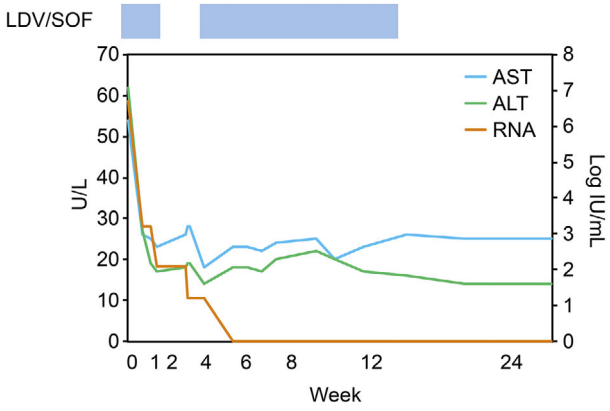

Figure 3. **The course of HCV. The patient had a history of chronic hepatitis C, and her viral load was 6.5 log IU/mL. Before treatment, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were slightly elevated; however, these metrics returned to normal immediately after LDV/SOF treatment commenced. In addition, virus antibody titers continued to decrease until LDV/SOF was discontinued, but they did not become negative. After LDV/SOF treatment had been suspended for approximately 20 days, we re-administered LDV/SOF for a total of 12 weeks. The patient achieved SVR at 12 weeks after LDV/SOF treatment.**

suggested the re-administration of LDV/SOF in conjunction with a steroid and antihistamines to protect against skin disorders in the hospital. After LDV/SOF had been suspended for approximately 20 days, we re-administered LDV/SOF with 10 mg of PSL and antihistamines in the hospital. There were no side effects, including rash; therefore, we reduced the dosage of PSL to 7.5 mg. However, following this reduction, the rash relapsed. To address this issue, we increased PSL to 15 mg temporarily and then continued with 10 mg of PSL until the end of the LDV/SOF treatment. After LDV/SOF had been administered for a total of 12 weeks, the rash had clearly improved, and we gradually reduced the dosage of PSL. No related problems were observed post-treatment, and we re-evaluated the patient for SVR at 12 weeks post-treatment (Fig. 2, 3). A lymphocyte transformation test (LTT) with LDV/SOF was positive, with a stimulation index of 2.48. Based on these results, we concluded that the maculopapular rash had been due to LDV/SOF and had been cured by steroid treatment.

Discussion

This case report provides two important clinical suggestions regarding the treatment of skin disorders produced by LDV/SOF therapy for patients with chronic hepatitis C. Steroids may be useful for treating drug eruptions due to LDV/SOF, and the temporary interruption of LDV/SOF due to side effects may be permissible.

First, steroids may be useful for treating drug eruptions

caused by LDV/SOF. To date, 73.0% of patients treated with telaprevir in combination with pegylated IFN alpha-2b and ribavirin, the first approved DAA in Japan, achieved SVR (6). However, these medications produce several adverse effects, such as cutaneous eruption, anemia and anal pruritus, among others (7). Fortunately, countermeasures exist for skin disorders induced by the aforementioned combination therapy. Steroids are effective for drug eruptions caused by this therapy (8). In a randomized controlled phase 3 trial in Japan, 3% of patients receiving LDV/SOF for chronic hepatitis C developed a rash (4). Furthermore, a post-marketing survey in Japan reported that 0.03% of patients developed a severe rash (https://www.harvoni.jp/~/media/files/gilead/harvoni/proper/hvn_post_marketing_surveillance_final_report.pdf?la=ja-jp). However, no definitive conclusions indicating that this rash was due to LDV/SOF were drawn. In the present case, the LTT result was positive. The LTT was performed to assess T-cell proliferation as an indicator of drug sensitization. This patient's rash seemed to be a maculopapular drug eruption because it consisted of small bilateral red spots, some of which were slightly raised and flowed into one another. In the maculopapular type, the positive rate of the LTT is over 50% (8). Although the basic treatment for drug eruption is discontinuation of the suspect medicine, LDV/SOF was effective for the patient in this case, and she did not want to undergo alternative treatment with IFNs. Furthermore, her virus had the amino acid mutation Y93H in NS5A. In the HCV genome, resistance-associated substitutions present at specific sites confer resistance to some DAAs; Y93H is the major resistance mutation (9, 10). At the time when this patient was treated, there were other DAAs available, including daclatasvir/asunaprevir and ombitasvir/paritaprevir/ritonavir, but they were not useful for Y93H in NS5A. Therefore, we had no choice but to use LDV/SOF. In the case described here, an oral steroid was effective for LDV/SOF-induced skin disorders. Furthermore, the rash relapsed when the PSL dose was reduced to 7.5 mg; therefore, a dose of at least 10 mg of PSL was needed in this case.

Second, temporary interruption of LDV/SOF is permissible for some patients. While temporary interruption of LDV/SOF has not been reported, LDV/SOF treatment for only 8 weeks can result in a high rate of SVR (11). Consequently, consecutive treatment with LDV/SOF for 8 or more weeks may be effective, despite earlier interruption in the treatment.

LDV/SOF is one of the most effective treatments for hepatitis C and is therefore generally too beneficial to discontinue. If LDV/SOF is discontinued due to a side effect, such as a skin disorder, SVR for chronic hepatitis C might not be achieved. Therefore, oral steroids are useful for treating drug-induced skin disorders caused by LDV/SOF. Although LDV/SOF has been discontinued due to severe skin disorders in certain cases, if the situation permits, the re-administration of LDV/SOF in combination with a steroid and strict monitoring may be a potential treatment option.

The authors state that they have no Conflict of Interest (COI).

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