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Single Case

A Hepatitis C Virus-Associated Chronic Hepatitis Patient Developing Various Adverse Events Including Severe Gingivitis, Gingival Bleeding, and Inflammation of Genital Vulva during the Course of Antiviral Therapy with Elbasvir/Grazoprevir

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Keywords
Hepatitis C virus-associated chronic hepatitis · Elbasvir/grazoprevir · Direct-acting antivirals · Gingival bleeding · Inflammation of vulva

Abstract
Oral direct-acting antivirals comprise the main therapy for hepatitis C virus (HCV)-associated liver disease in Japan. Daclatasvir/asunaprevir is the primary agent and sofosbuvir/ledipasvir is the secondary agent for HCV genotype 1b. Ombitasvir/paritaprevir/ritonavir was also recommended as a therapy for HCV genotype 1b. More recently, elbasvir (NS5A inhibitor)/grazoprevir (NS3/4A protease inhibitor) was also recommended as a potent therapy for HCV

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genotype 1b infection. This agent achieved an SVR_{12} as high as 96.5% for HCV virus-associated chronic hepatitis. We recently encountered a case treated with this agent and the female patient showed various adverse events, such as severe gingivitis, gingival bleeding, severe tonsillitis, inflammation of the genital vulva, and the sustained sensation of being hungry. In spite of the gingival bleeding, there was no depletion of the platelet count, nor elongation of the prothrombin time. She tolerated these adverse events and finally completed the therapy and achieved SVR_{12}.

Introduction

Antiviral therapy using oral direct-acting antivirals (DAAs) has recently become the main and most effective therapy for eradicating hepatitis C virus (HCV) in Japan. Daclatasvir/asunaprevir is the primary [1, 2] and sofosbuvir/ledipasvir is the secondary agent [3, 4]. Ombitasvir/paritaprevir/ritonavir is also used for eradicating HCV in HCV-associated chronic hepatitis and liver cirrhosis of Child stage A [5, 6].

More recently, elbasvir (NS5A inhibitor)/grazoprevir (NS3/4A protease inhibitor) is also recommended as a potent therapy for HCV genotype 1b infection. However, there are no detailed reports on the adverse events of this drug.

We recently encountered a HCV-associated chronic hepatitis patient who developed severe gingivitis, gingival bleeding, severe tonsillitis, inflammation of the genital vulva, and a sustained sensation of being hungry.

Case Report

A 61-year-old Japanese female (height: 163.0 cm; weight: 53.0 kg) with HCV-associated chronic hepatitis (genotype 1b) visited our clinic for treatment with oral DAAs. The patient had received acupuncture 28 years ago to treat persistent epigastralgia. Three weeks thereafter, her mother noticed slight icterus of her skin. One year later, when she was 35 years old, a test in another hospital revealed that her transaminases levels were rising. The peak of alanine transaminase (ALT) reached as high as about 280 IU/L. When she was 38 years old, her home doctor began to inject 60 mL of Stronger Neo-Minophagen C (it is usually used to lower serum transaminase) twice a week. This was continued for several years. However, her transaminases were unstable. She was told that HCV antibody was positive at that time. She did not receive IFN therapy (including PEG-IFN/ribavirin therapy). This was her first IFN-free DAA treatment, which is a standard therapy available in Japan for chronic HCV infection.

Table 1 shows the laboratory data at the beginning of the therapy and at the time of gingival bleeding (at the same time of inflammation of the genital vulva). The abnormal data at the beginning were as follows; serum alanine transaminase was 46 U/L, alkaline phosphatase was 389 U/L, total cholesterol was 114 mg/dL, and HCV-RNA was 3.6 logIU/mL of the viral load (real-time PCR). HCV was of the 1b type.

Abdominal ultrasonography and computed tomography revealed a normal-sized liver with a regular liver surface and no marked splenomegaly. Moreover, the architecture of the liver in ultrasonography was rough, suggesting chronic hepatitis.

As antiviral treatment, elbasvir (NS5A inhibitor, 50 mg/day) and grazoprevir (NS3/4A protease inhibitor, 100 mg/day) were administered from April 8, 2017 to June 30, 2017 (Fig. 1). Interestingly, she experienced the sensation of being hungry from the beginning of the therapy. She became hungry 2 h after each meal, and took 5 meals every day. Severe gingivitis and gingival bleeding occurred from 3 weeks after the beginning of the therapy and it lasted for about 10 days. She felt instability of the gingiva and pain on biting foods. At the same time, she felt severe burning of the throat. Simultaneously, she developed inflammation of the genital vulva (redness and edematous swelling) and also it lasted about 10 days. However, she tolerated the many adverse events, and finally completed the full regimen and achieved SVR_{12}.

Discussion

Oral DAAs are now the main therapy for HCV-associated liver disease in Japan. Daclatasvir/asunaprevir is the primary agent [1, 2], and sofosbuvir/ledipasvir is the secondary one [3, 4]. Ombitasvir/paritaprevir/ritonavir has also been recommended for HCV genotype 1b infection [5, 6]. More recently, elbasvir/grazoprevir was also recommended as a potent agent to eradicate HCV genotype 1b infection, and the DAA is being widely used because of a high SVR_{12} rate of 96.5%. However, there have been no precise reports of adverse events of the drug because it only recently started to be used.

Recently, we encountered a case involving various adverse events, such as severe gingivitis, gingival bleeding, severe tonsillitis, inflammation of the genital vulva, and the sustained sensation of being hungry. Gingival bleeding was thought to be the result of severe gingivitis because there was no depletion of platelet counts, nor elongation of the prothrombin time (Table 1).

We surveyed postmarketing surveillance reports of daclatasvir/asunaprevir [7], sofosbuvir/ledipasvir [8], ombitasvir/paritaprevir/ritonavir [9], and elbasvir/grazoprevir (this drug) [10]. However, no report described similar adverse events to our adverse events. So, the present report is thought to be the first to describe the adverse events of severe gingivitis, gingival bleeding, and inflammation of the genital vulva on treatment with DAAs. Why the sustained sensation of being hungry appeared in this case was not elucidated. Hypoglycemia was not present in this case.

Conclusions

In the postmarketing surveillance reports of the previously used DAAs, namely, daclatasvir/asunaprevir, sofosbuvir/ledipasvir, or ombitasvir/paritaprevir/ritonavir, there is no description of the adverse events of severe gingivitis, gingival bleeding, or inflammation of the genital vulva. This is the first report of these adverse effects on treatment with DAAs.

Statement of Ethics

The authors have no ethical conflicts to disclose. Informed consent was obtained from the patient to be included in this report. This study was approved by the Medical Ethics Committee on Human Research of St. Marianna University, Yokohama City Seibu Hospital.

Disclosure Statement

The authors have no conflicts of interest to declare.

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10 Postmarketing surveillance of elbasvir/grazoprevir in Japan. Page 3 (from November 18, 2016 to May 17, 2017).

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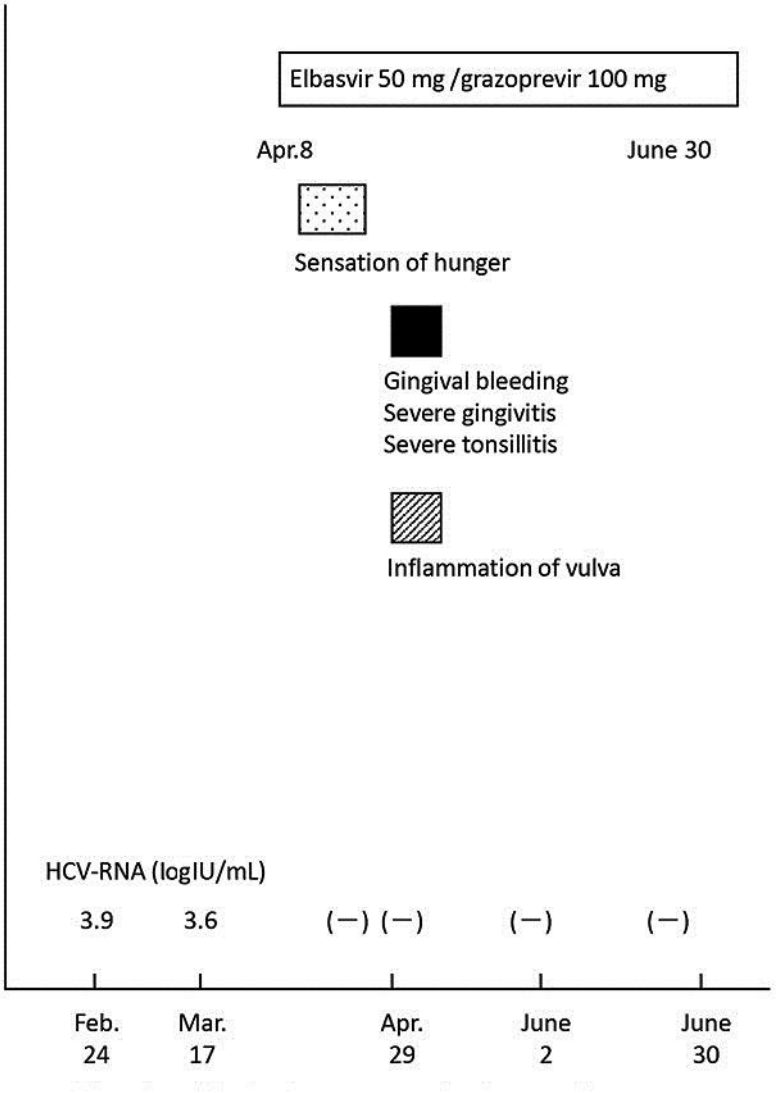

Fig. 1. Clinical course of the patient.

Table 1. Laboratory data at the beginning of the therapy and on the development of gingival bleeding and inflammation of the vulva

	At the beginning of therapy	At the time of gingival bleeding
Peripheral blood		
WBC	3,250	5,080
RBC, $\times 10^4$	432	428
Hg, g/dL	14.5	14.0
Ht, %	43.0	41.5
PLT, $\times 10^4$	12.0	12.8
Coagulation		
PT, %	90.7	91.5
PT-INR	1.10	1.04
Blood chemistry		
TP, g/dL	7.1	7.0
Alb, g/dL	3.8	3.6
T-Bil, mg/dL	0.6	0.6
AST, U/L	41	25
ALT, U/L	46	24
LDH, U/L	198	183
ALP, U/L	389	383
γ-GTP, U/L	29	23
Cr, mg/dL	0.61	0.66
T-cho, mg/dL	114	110
Glu, mg/dL	164	224
Viral markers		
HBs-antigen	(–)	/
HCV-Ab	(+)	(+)
HCV-RNA, log10 IU/mL	3.6	(–)
HCV genotype	Ib	/
Tumor marker		
AFP, ng/mL	3.9	2.8