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Successful Treatment of Hepatitis C Virus-associated Oral Lichen Planus by Interferon-free Therapy with Direct-acting Antivirals

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OBJECTIVES: Oral lichen planus (OLP) is one of the extrahepatic manifestations of hepatitis C virus (HCV) infection. Presently developed interferon (IFN)-free direct-acting antivirals (DAAs) used to treat HCV infection have low side effect profiles and high efficacy. However, there are no studies examining the relationship between OLP and IFN-free DAAs. The aim of this study was to evaluate the disease course in patients with HCV-associated OLP, who received treatment with IFN-free DAAs.

METHODS: Seven patients with HCV-related OLP (including one with cutaneous LP), who received IFN-free treatment with daclatasvir (DCV)/asunaprevir (ASV) at our hospital in Japan from October, 2014 to February, 2015 were enrolled in the study. The subjects included four males and three females (average age, 73.9 years). We compared the symptoms of OLP in the patients before and at 24 weeks after the end of DAA therapy.

RESULTS: No worsening of symptoms was observed during treatment with the DAAs. The symptoms of OLP had subsided in all seven patients. Lesions of OLP and cutaneous LP disappeared in four, and improved in three of the seven patients after sustained virological response 24. No systemic clinical adverse events were observed in all patients.

CONCLUSIONS: Herein, we have reported the outcomes of HCV-associated OLP in patients who received successful treatment with IFN-free DAAs, using the DCV/ASV combination therapy.

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INTRODUCTION

Hepatitis C virus (HCV) infects >170 million people worldwide and causes chronic liver disease, liver cirrhosis, and hepatocellular carcinoma (HCC).[1] HCV infection is one of the most common infections affecting ~1.5–2 million people in Japan, where >30,000 deaths from HCC occur each year.[2] According to the World Health Organization survey involving 182 countries in 2008, the number of deaths from liver cancer in Japan ranked second in the world, after only China.[3,4]

Moreover, HCV induces extrahepatic manifestations including glomerular disease, hematologic diseases such as cryoglobulinemia and lymphoma, autoimmune disorders such as thyroiditis, and dermatologic conditions such as lichen planus (LP) and porphyria cutanea tarda.[5,6]

Until recently, the pegylated interferon (IFN) and ribavirin (RBV) regimen was the standard therapy for HCV chronic hepatitis. However, this combination therapy could achieve sustained virological response (SVR) rates of only 40–50% in patients with genotype 1, and is associated with significant gastrointestinal, hematological, and psychiatric side effects.[7,8] The currently developed IFN-free, direct-acting antivirals (DAAs) used to treat HCV infection have low side effect profiles and high efficacy.[9–11]

In July 2014, Japan approved the use of a combination therapy with daclatasvir (DCV; NS5A inhibitor) and asunaprevir (ASV; NS3 protease inhibitor), making it the first approved, all-oral, IFN-/RBV-free DAAs therapy. One year later, Japan's Ministry of Health, Labour and Welfare approved Harvoni, a combination of sofosbuvir (nucleotide polymerase inhibitor) and ledipasvir (NS5A inhibitor, as the first once-daily single tablet regimen for the treatment of genotype 1 chronic hepatitis C (CH-C)).

LP is a chronic, mucocutaneous disease that can affect the oral mucosa, skin, genital mucosa, scalp, and nails. LP is considered as one of the extrahepatic manifestations of HCV infection.[12,13] Oral LP (OLP) can develop, become exacerbated, and persist in patients receiving IFN treatment for hepatitis C.[14–17] In previous studies, we examined hepatitis C patients for oral lesions before, during, and after IFN treatment; OLP was seen in 11.7–16.7%.[14,17] Furthermore, in another study, we reported the case of a 65-year-old, Japanese, CH-C patient presenting with exacerbation of preexisting erosive OLP, and the appearance of cutaneous LP, and larynx leukoplakia following IFN and RBV therapy.[15] The larynx leukoplakia had developed into malignancy, subsequently.

Safety and efficacy of IFN-free DAAs in patients with OLP have not been proved yet. In this study, we examined the disease course in patients with HCV-associated OLP, who received treatment with IFN-free DAAs using the DCV/ASV combination therapy.

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METHODS

Patients. Seven patients with clinically and/or histopathologically confirmed HCV-related OLP who received IFN-free treatment with DCV/ASV at the Kurume University Hospital in Japan from October, 2014 to February, 2015 were enrolled in the study (**Table 1**). The subjects included four males and three females (average age; 73.9), of whom five suffered from CH-C, one from CH-C with post-HCC treatment, and one from HCV-related liver cirrhosis (LC-C), Child-Pugh Class A with post-HCC treatment. One of the subjects (patient number 6) presented with cutaneous LP. Five of the seven patients were treated with the IFN and RBV regimen therapy at the Kurume University Hospital in the past. Hepatologists and an oral surgeon examined all patients. All patients with HCV genotype 1 received both DCV 60 mg once daily and ASV 100 mg twice daily for 24 weeks.

Outcome for OLP before and after treatment with DAAs. The OLP lesions were clinically examined in all patients before, during, and at 24 weeks after the end of the DCV/ASV combination therapy.

Serological assays. All subjects were tested for red blood cell count, white blood cell count, platelet count, hemoglobin, and the following liver function tests: serum alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, alpha-fetoprotein, total bilirubin, direct bilirubin, total cholesterol, total protein, and albumin.

Evaluation of liver diseases. Anti-HCV was measured using a chemiluminescent enzyme immunoassay kit (Lumipulse II HCV, Fujirebio; Tokyo, Japan). HCV RNA levels were analyzed in serum by quantitative polymerase chain reaction assay (COBAS AMPLICOR HCV MONITOR v 2.0 Test, COBAS AmpliPrep/COBAS Taq-Man HCV Test, Roche Molecular Systems; Branchburg, NJ, USA).[18,19] HCV genotype was determined by polymerase chain reaction assay using a mixture of primers for the subtype, as reported previously.[20] Ultrasonographic examination was performed on all patients to investigate the shape of the liver and to identify lesions within the liver. Computed tomography was also performed on some patients. We used other possible predictors of progression of LC, including serum albumin, total bilirubin, prothrombin time, and platelet. Liver biopsy was performed in some patients.

Ethical considerations. This investigation was undertaken with the understanding and consent of each participating subject, and was conducted in full accordance with the ethical principles of the World Medical Association Declaration of Helsinki. The study protocol was approved by the Ethics Committee of Saga Medical School (reference number: 27–36) in accordance with the Declaration of Helsinki. Written informed consent for participation in the study was obtained from each patient.

Statistical analysis. All data were expressed as mean ± s.e. Differences between baseline and SVR24 were analyzed using Wilcoxon signed-rank test. Differences were significant at $P<0.05$ (two-tailed). All statistical analyses were

Table 1 The characteristics of seven patients with OLP

No.	1	2	3	4	5	6	7
Sex	F	M	M	F	M	F	M
Age	72	59	76	72	84	77	77
Liver disease	CH-C	CH-C	CH-C	CH-C	CH-C, post HCC	LC-C, post HCC	CH-C
HCV genotype/ level of HCV RNA	Ib/high	Ib/high	Ib/high	Ib/high	Ib/high	Ib/high	Ib/high
IL28B gene (rs8099917) TT/non-TT	Non-TT	Non-TT	Non-TT	Non-TT	TT	Non-TT	Non-TT
History of treatment of IFN	Yes	Yes	No	Yes	No	Yes	Yes
Exacerbation of OLP at past IFN therapy	Yes	Yes	—	Yes	—	Yes	Yes
Systemic disease except the liver disease	No	Hypertension, diabetes mellitus, and ventricular extrasystole	Asthma, reflux esophagitis, and gallbladder polyp	Postoperative coxarthrosis	Hypertension and arrhythmia	Hypothyroidism and osteoporosis	Hypertension and post larynx cancer
Presence or absence of smoking	Never smoker	Ever smoker	Smoking cessation	Never smoker	Never smoker	Never smoker	Smoking cessation
Effect of DAAs therapy	SVR24	SVR24	SVR24	SVR24	SVR24	SVR24	SVR24
Type of OLP before DAA therapy	Erosive	Erosive	Reticular	Reticular	Reticular	Erosive	Erosive and reticular
Sites of OLP before DAA therapy	Bilateral buccal mucosa	Bilateral buccal mucosa, tongue, and lower lip	Bilateral buccal mucosa	Bilateral buccal mucosa	Bilateral buccal mucosa	Bilateral buccal mucosa and bilateral calves skin	Bilateral buccal mucosa and lower lip
Topical steroids to OLP before DAA therapy	Not received	Received	Not received	Not received	Not received	Received	Received
Findings of OLP after SVR24	All disappearance	Lesions at buccal mucosa: disappearance. Lesions at tongue and lower lip: reduction of erosion	All disappearance	Lesion became unclear, but a slight white spot remained	All disappearance	All disappearance	Lesions at buccal mucosa: disappearance. Lesions at lower lip: disappearance of erosion, but a slight white spot remained
Turning point of OLP after SVR24	Disappearance	Improvement	Disappearance	Improvement	Disappearance	Disappearance	Improvement
Topical steroids to OLP after DAA therapy	Not received	Received	Not received	Not received	Not received	Not received	Not received

CH-C, chronic hepatitis C; DAAs, direct-acting antivirals; F, female; IFN, interferon; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; LC-C, liver cirrhosis type C; M, male; non-TT, minor allele; OLP, oral lichen planus; SVR, sustained virological response; TT, major allele.

Table 2 Comparison of the biochemical data in baseline and SVR24

		Baseline	SVR24	*P* value
BMI	Mean ± s.d.	19.1 ± 8.3	23.1 ± 4.1	0.0469
AST (U/l)	Mean ± s.d.	57.1 ± 29.1	28.9 ± 9.4	0.0313
ALT (U/l)	Mean ± s.d.	52.9 ± 31.1	18.4 ± 4.7	NS
ALP (U/l)	Mean ± s.d.	357.1 ± 140.9	303.9 ± 110.0	NS
γGTP (U/l)	Mean ± s.d.	36.6 ± 20.7	25.4 ± 13.1	NS
T.pro (g/dl)	Mean ± s.d.	7.40 ± 0.4	7.67 ± 0.4	NS
Alb (g/dl)	Mean ± s.d.	3.83 ± 0.6	4.19 ± 0.3	NS
BUN (mg/dl)	Mean ± s.d.	15.1 ± 2.5	17.0 ± 3.1	0.0469
AFP (ng/dl)	Mean ± s.d.	40.5 ± 65.0	5.9 ± 4.2	NS
PIVKAII (mAU/ml)	Mean ± s.d.	18.8 ± 5.8	25.2 ± 6.0	0.0313
RBC ($\times 10^4$/μl)	Mean ± s.d.	431 ± 36.9	438.6 ± 25.4	NS
Hb (g/dl)	Mean ± s.d.	14.0 ± 1.5	13.9 ± 1.1	NS
WBC (μl)	Mean ± s.d.	46.0 ± 12.7	52.0 ± 20.8	NS
Plt ($\times 10^4$/μl)	Mean ± s.d.	13.6 ± 4.2	13.8 ± 4.6	NS

AFP, alpha-fetoprotein; Alb, albumin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; BUN, blood urea nitrogen; γGTP, γ-glutamyl transpeptidase; Hb, hemoglobin; NS, not significant; PIVKAII, protein induced by vitamin K absence or antagonists II; Plt, platelet; RBC, red blood cell; T.pro, total protein; WBC, white blood cell.

conducted using JMP Version 11.1.1 software (SAS Institute, Cary, NC, USA). The level of statistical significance was defined as $P<0.05$.

RESULTS

Treatment outcomes for liver disease. All subjects presented with undetectable HCV RNA levels at 8 weeks after DAAs treatment. Furthermore, all subjects achieved SVR 12 weeks (SVR12) and 24 weeks (SVR24) after the end of treatment. A comparison of the biochemical data at baseline and SVR24 is shown in **Table 2**. Serum aspartate aminotransferase and alanine aminotransferase levels, and alpha-fetoprotein were decreased, whereas albumin levels were increased. No systemic clinical adverse events were observed in the patients.

Outcomes for OLP. No deterioration of symptoms was observed in the patients during DAAs treatment. The symptoms of OLP/cutaneous LP had subsided in all patients; the lesions had disappeared in four, and improved in three of the seven patients after SVR24 (**Table 1**; **Figures 1** and **2**). Disappearance of OLP lesions on the buccal mucosa, bilaterally, and decrease in erosive lesions on the tongue and lower lip were observed in a 59-year-old Japanese male patient (**Table 1**). Similar findings were observed in another 77-year-old male patient. In one of the patients, a 72-year-old Japanese female, the OLP lesions appeared to fade away until a slight white spot remained. We conducted an extended follow-up for OLP. Although OLP lesions did not completely disappear about three patients, the symptom and the discomfort of two patients (number 4 after SVR40 and number 7 after SVR52 in **Table 1**) disappeared, and the lesion of one patient (number 2 in **Table 1**) reduced after SVR52.

Three patients received topical steroid therapy for the erosion of OLP before DAAs treatment, and only one received steroid therapy after treatment.

DISCUSSION

The elimination of HCV reduces not only the development of HCC, but also the onset of conditions such as malignant lymphoma, Type 2 diabetes, and chronic kidney disease.[21–23] Furthermore, the elimination of a virus has been shown to reduce bone fracture, osteoporosis, and the development of hemorrhagic stroke.[24,25] In a previous study, we have reported that the disappearance of HCV RNA and improvements in liver function over a period of >3 years appears to resolve OLP lesions.[26] Thus, the elimination of HCV inhibits the onset of various extrahepatic manifestations.

In 2014, a 24-week treatment with DCV/ASV provided a highly effective option for patients who had no effective treatment options available (ineligible for, or intolerant to IFN-based therapy) and for those who did not achieve SVR following prior treatment.[9] SVR24 was achieved by 87.4% of the IFN-ineligible/-intolerant patients and 80.5% of the nonresponders (null and partial patients); rates were similar in cirrhosis (90.9%) and noncirrhosis (84.0%) patients, and in patients with *IL28B* (rs12979869) CC (84.5%) or non-CC (84.8%) genotypes.

In the present study, all subjects (*IL28B* (rs8099917) non-TT; six patients, TT; one patient) achieved SVR12 and SVR24. This result was comparable with the phase 3 study of DCV/ASV therapy in Japan.[9]

Recently, Garcovich *et al.*[27] reported that it is possible, but not proven that more effective and rapid antiviral responses observed with IFN-free antiviral regimens will improve outcomes in clinical settings, especially when HCV infection is burdened by extrahepatic manifestations. Makara *et al.*[28] reported a successful case of HCV-associated mixed cryoglobulinemia effectively treated with an IFN-free combination of newly approved DAAs and RBV. However, there are no reports about IFN-free DAA treatment for HCV-associated OLP. The safety and efficacy of IFN-free DAA therapy in patients with OLP has not been proven yet. In the present study, we have reported the outcomes of HCV-associated OLP in patients who received successful treatment with IFN-free DAAs, using the DCV/ASV combination therapy. We consider that OLP lesions may completely disappear by long follow-up in patients after the extermination of HCV.

In this study, the lesions of OLP in three of the seven patients did not completely disappear after IFN-free DAAs therapy.

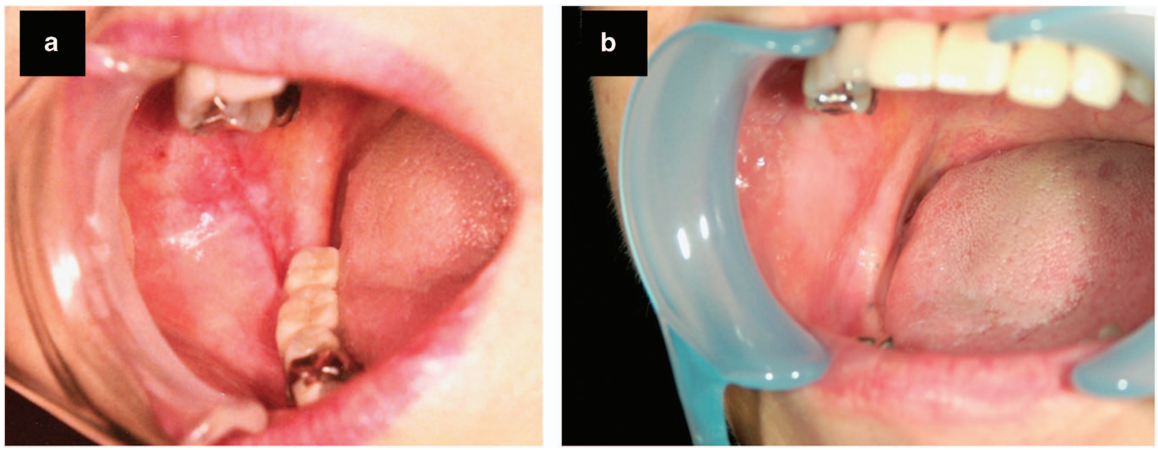

Figure 1 Clinical photographs showing disappearance of OLP lesions from the buccal mucosa of the patient. (**a**) OLP lesions affecting the buccal mucosa on both sides of the mouth. (**b**) Disappearance of OLP 13 months later, following the treatment with DAAs. DAAs, direct-acting antivirals; OLP, oral lichen planus.

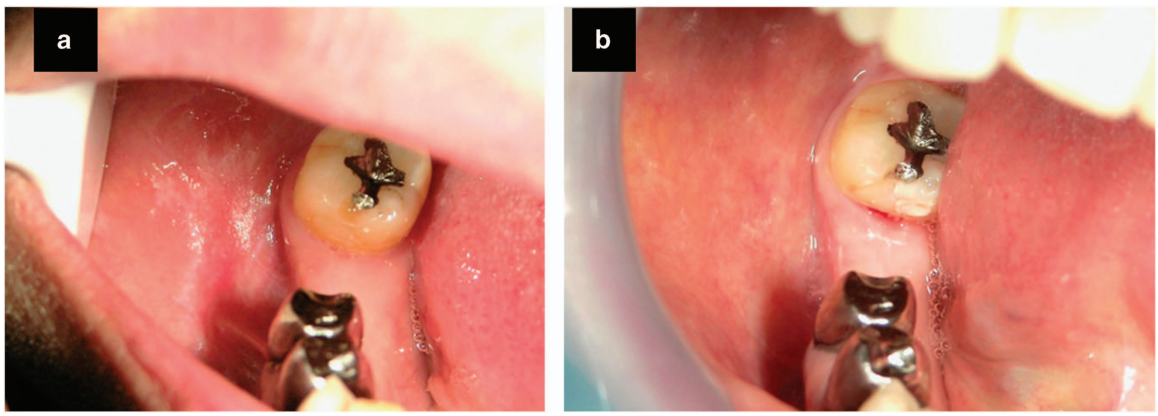

Figure 2 Clinical photograph showing the disappearance of OLP lesions from the buccal mucosa of another patient. (**a**) OLP lesions affecting the buccal mucosa on both sides of the mouth. (**b**) Disappearance of OLP 13 months later, following the treatment with DAAs. DAAs, direct-acting antivirals; OLP, oral lichen planus.

Presence of smoking and diabetes were considered as one of the reason why OLP lesions did not disappear.

Tobacco use was reported to be a risk factor that develops cancer in OLP.[29] Klosek *et al.*[30] reported smoking in OLP patients correlated with both microvessel density and c-Met-positive staining. The authors showed the c-Met expression with smoking habit was statistically significant within the OLP group ($P<10^{-6}$). c-MET is the receptor for hepatocyte growth factor, tyrosine kinase with downstream targets involved in a variety of cellular signaling pathways including proliferation, motility, migration, and invasion.[31] c-Met receptor is expressed selectively in several normal human epithelial tissues as well as in carcinoma.

Diabetes has been also supposed to have a role in the OLP pathogenesis.[32] Baykal *et al.*[33] revealed the prevalence of metabolic syndrome in LP patients. Among the metabolic syndrome criteria, mean fasting blood glucose and diastolic blood pressure were also significantly higher in LP patients than in controls ($P=0.012$ and $P=0.021$, respectively). We previously reported an association OLP and insulin resistance induced by HCV infection.[34,35]

Conventionally, there were problems such as inability to complete IFN therapy due to worsening of OLP lesions following IFN therapy. IFN therapy has led to the development of oral mucosal lesions, resulting in oral candidiasis and inhibited salivary secretion.[36] Treatment of HCV infection using IFN-free therapeutic methods may help improve the associated extrahepatic manifestations seen in the patients. Awareness of extrahepatic manifestations is necessary not only for the hepatologist, but also for the non-hepatologist. Guidelines on DAA therapy for the treatment of HCV-associated extrahepatic manifestations in Japan are expected to come into effect immediately.

Our study showed that patients with HCV-associated OLP were treated safely and effectively with IFN-free DAA therapy. We intend to conduct further studies involving larger samples in future.

CONFLICT OF INTEREST

Guarantor of the article: Yumiko Nagao, DDS, MD, PhD.
Specific author contributions: Data collection, design of the work, and drafting the work: Yumiko Nagao; analysis and

interpretation of data: Kanae Kimura and Yuji Kawahigashi; design of the work and interpretation of data: Michio Sata; approved the final version of the submitted work: all the authors.

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Study Highlights

WHAT IS CURRENT KNOWLEDGE

- ✓ Oral lichen planus (OLP) is one of the extrahepatic manifestations of hepatitis C virus (HCV) infection.
- ✓ Recent studies show that all-oral, interferon (IFN)-free and direct-acting antivirals (DAAs) can cure most chronically infected HCV patients, and can achieve high sustained virological response rates.
- ✓ The impact of the relationship between OLP and IFN-free DAAs is unknown.

WHAT IS NEW HERE

- ✓ We evaluated the disease course in seven patients with HCV-associated OLP who received treatment with IFN-free DAAs.
- ✓ The symptoms of OLP had subsided in all patients.
- ✓ Lesions of OLP and cutaneous LP disappeared in four, and improved in three of the seven patients.
- ✓ The availability of DAAs enables the successful treatment of HCV-infected OLP patients.

1. Global Burden Of Hepatitis C Working Group. Global burden of disease (GBD) for hepatitis C. *J Clin Pharmacol* 2004; **44**: 20–29.
2. Uemura M, Sasaki Y, Yamada T *et al.* Serum antibody titers against hepatitis C virus and postoperative intrahepatic recurrence of hepatocellular carcinoma. *Ann Surg Oncol* 2014; **21**: 1719–1725.
3. Ferlay J, Shin HR, Bray F *et al.* Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int J Cancer* 2010; **127**: 2893–2917.
4. Ikeda M, Mitsunaga S, Shimizu S *et al.* Current status of hepatocellular carcinoma in Japan. *Chin Clin Oncol* 2013; **2**: 40.
5. Gumber SC, Chopra S. Hepatitis C: a multifaceted disease. Review of extrahepatic manifestations. *Ann Intern Med* 1995; **123**: 615–620.
6. Cacoub P, Gragnani L, Comarmond C *et al.* Extrahepatic manifestations of chronic hepatitis C virus infection. *Dig Liver Dis* 2014; **46** (Suppl 5): S165–S173.
7. Manns MP, McHutchison JG, Gordon SC *et al.* Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. *Lancet* 2001; **358**: 958–965.
8. Fried MW, Shiffman ML, Reddy KR *et al.* Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. *N Engl J Med* 2002; **347**: 975–982.
9. Kumada H, Suzuki Y, Ikeda K *et al.* Daclatasvir plus asunaprevir for chronic HCV genotype 1b infection. *Hepatology* 2014; **59**: 2083–2091.
10. Omata M, Nishiguchi S, Ueno Y *et al.* Sofosbuvir plus ribavirin in Japanese patients with chronic genotype 2 HCV infection: an open-label, phase 3 trial. *J Viral Hepat* 2014; **21**: 762–768.
11. Mizokami M, Yokosuka O, Takehara T *et al.* Ledipasvir and sofosbuvir fixed-dose combination with and without ribavirin for 12 weeks in treatment-naive and previously treated Japanese patients with genotype 1 hepatitis C: an open-label, randomised, phase 3 trial. *Lancet Infect Dis* 2015; **15**: 645–653.
12. Nagao Y, Sata M, Tanikawa K *et al.* Lichen planus and hepatitis C virus in the northern Kyushu region of Japan. *Eur J Clin Invest* 1995; **25**: 910–914.
13. Carrozzo M, Gandolfo S, Carbone M *et al.* Hepatitis C virus infection in Italian patients with oral lichen planus: a prospective case-control study. *J Oral Pathol Med* 1996; **25**: 527–533.
14. Nagao Y, Sata M, Ide T *et al.* Development and exacerbation of oral lichen planus during and after interferon therapy for hepatitis C. *Eur J Clin Invest* 1996; **26**: 1171–1174.
15. Nagao Y, Kawaguchi T, Ide T *et al.* Exacerbation of oral erosive lichen planus by combination of interferon and ribavirin therapy for chronic hepatitis C. *Int J Mol Med* 2005; **15**: 237–241.
16. Grossmann Sde M, Teixeira R, de Aguiar MC *et al.* Exacerbation of oral lichen planus lesions during treatment of chronic hepatitis C with pegylated interferon and ribavirin. *Eur J Gastroenterol Hepatol* 2008; **20**: 702–706.
17. Nagao Y, Sata M. Analysis of the factors motivating HCV-infected patients to accept interferon therapy. *BMC Res Notes* 2012; **5**: 470.
18. Lee SC, Antony A, Lee N *et al.* Improved version 2.0 qualitative and quantitative AMPLICOR reverse transcription-PCR tests for hepatitis C virus RNA: calibration to international units, enhanced genotype reactivity, and performance characteristics. *J Clin Microbiol* 2000; **38**: 4171–4179.
19. Sizmann D, Boeck C, Boelter J *et al.* Fully automated quantification of hepatitis C virus (HCV) RNA in human plasma and human serum by the COBAS AmpliPrep/COBAS TaqMan system. *J Clin Virol* 2007; **38**: 326–333.
20. Dusheiko G, Schmilovitz-Weiss H, Brown D *et al.* Hepatitis C virus genotypes: an investigation of type-specific differences in geographic origin and disease. *Hepatology* 1994; **19**: 13–18.
21. Kawamura Y, Ikeda K, Arase Y *et al.* Viral elimination reduces incidence of malignant lymphoma in patients with hepatitis C. *Am J Med* 2007; **120**: 1034–1041.
22. Arase Y, Suzuki F, Suzuki Y *et al.* Sustained virological response reduces incidence of onset of type 2 diabetes in chronic hepatitis C. *Hepatology* 2009; **49**: 739–744.
23. Arase Y, Suzuki F, Kawamura Y *et al.* Development rate of chronic kidney disease in hepatitis C virus patients with advanced fibrosis after interferon therapy. *Hepatol Res* 2011; **41**: 946–954.
24. Arase Y, Suzuki F, Suzuki Y *et al.* Virus clearance reduces bone fracture in postmenopausal women with osteoporosis and chronic liver disease caused by hepatitis C virus. *J Med Virol* 2010; **82**: 390–395.
25. Arase Y, Kobayashi M, Kawamura Y *et al.* Impact of virus clearance for the development of hemorrhagic stroke in chronic hepatitis C. *J Med Virol* 2014; **86**: 169–175.
26. Nagao Y, Sata M, Suzuki H *et al.* Histological improvement of oral lichen planus in patients with chronic hepatitis C treated with interferon. *Gastroenterology* 1999; **117**: 283–284.
27. Garcovich S, Garcovich M, Capizzi R *et al.* Cutaneous manifestations of hepatitis C in the era of new antiviral agents. *World J Hepatol* 2015; **7**: 2740–2748.
28. Makara M, Sulyok M, Csacsovszki O *et al.* Successful treatment of HCV-associated cryoglobulinemia with ombitasvir/paritaprevir/ritonavir, dasabuvir and ribavirin: a case report. *J Clin Virol* 2015; **72**: 66–68.
29. Gonzalez-Moles MA, Scully C, Gil-Montoya JA. Oral lichen planus: controversies surrounding malignant transformation. *Oral Dis* 2008; **14**: 229–243.
30. Klosek SK, Sporny S, Stasikowska-Kanicka O *et al.* Cigarette smoking induces overexpression of c-Met receptor in microvessels of oral lichen planus. *Arch Med Sci* 2011; **7**: 706–712.
31. Organ SL, Tsao MS. An overview of the c-MET signaling pathway. *Ther Adv Med Oncol* 2011; **3**: S7–S19.
32. Albrecht M, Banoczy J, Dinya E *et al.* Occurrence of oral leukoplakia and lichen planus in diabetes mellitus. *J Oral Pathol Med* 1992; **21**: 364–366.
33. Baykal L, Arica DA, Yayli S *et al.* Prevalence of metabolic syndrome in patients with mucosal lichen planus: a case-control study. *Am J Clin Dermatol* 2015; **16**: 439–445.
34. Nagao Y, Kawasaki K, Sata M. Insulin resistance and lichen planus in patients with HCV-infectious liver diseases. *J Gastroenterol Hepatol* 2008; **23**: 580–585.
35. Nagao Y, Sata M. Oral verrucous carcinoma arising from lichen planus and esophageal squamous cell carcinoma in a patient with hepatitis C virus-related liver cirrhosis-hyperinsulinemia and malignant transformation: a case report. *Biomed Rep* 2013; **1**: 53–56.
36. Nagao Y, Hashimoto K, Sata M. Candidiasis and other oral mucosal lesions during and after interferon therapy for HCV-related chronic liver diseases. *BMC Gastroenterol* 2012; **12**: 155.