



Promotion by Dentists of Treatment of Undiagnosed and Untreated HCV-Infected Patients



Yumiko Nagao^{1*}, Takeshi Sasaki², Tsukasa Kuzuyama³, Toru Takasato⁴, Shuei Yoshikawa⁵, Hidekazu Konishi⁶, Keiichi Oka⁷, Takahisa Yamaguchi⁸, Yasunari Konishi⁹, Hideo Hanada¹⁰, Hiroki Nishijima¹¹, Koichi Mishima¹² and Makoto Fujii¹³

¹Department of Organ System Interactions and Information, Saga University, Japan

²Sasaki Dental Clinic, Hohokuchokanda, Japan

³Kuzuyama Dental Clinic, Ushirodacho, Japan

⁴Takasato Dental Clinic, Ojikamimachi, Japan

⁵Yoshikawa Dental Clinic, Kamishinchicho, Japan

⁶Ouki Dental Clinic, Oukihonmachi, Japan

⁷Oka Dental Clinic, Kawanakayutakamachi, Japan

⁸Yamaguchi Dental Clinic, Toyouracho, Japan

⁹Konishi Dental Clinic, Choufukanayacho, Japan

¹⁰Hanada Dental Clinic, Kamishinchicho, Japan

¹¹Nishijima Dental Clinic, Yasuokaekimae, Japan

¹²Oral and Maxillofacial Surgery, Western Shimane Medical Center of Health and Welfare, Japan

¹³Fujii Dental Clinic, Takezakicho, Japan

Submission: May 12, 2018; **Published:** June 07, 2018

***Corresponding author:** Yumiko Nagao, Department of Organ System Interactions and Information, Faculty of Medicine, Saga University, 5-1-1 Nabeshima, Saga 849-8501, Japan, Tel: +81-952-34-2516; Fax: +81-952-34-2516; Email: nagaoyu@cc.saga-u.ac.jp

Abstract

Background: Hepatitis C virus (HCV) infection is common in Japan but may remain untreated. Oral lichen planus (OLP) is an extrahepatic manifestation of HCV infection. The aim of this study was to evaluate prospectively the frequency of referral, by dentists, of their patients to medical doctors for evaluation of untreated viral liver disease and OLP.

Materials and methods: Patients who visited 12 dental clinics in Japan from November 1, 2017 to January 31, 2018, were enrolled. The number of patients who visited a dentist, the number of HCV-infected patients, the number of HBV-infected patients, the number of OLP patients, the rate of HCV infection in OLP patients, the number referred to a family doctor for consultation regarding liver disease and the number of OLP patients referred for consultation were recorded.

Results: The total number of patients and the numbers of HCV-infected, HBV-infected, and OLP patients were 5,091, 40, 13, and 15, respectively. One patient was referred for consultation for untreated liver disease and was treated with DAAs. 73% (11/15) of OLP patients were encouraged to submit to examination for liver disease and hepatitis virus infection.

Conclusion: Patients who have complications of liver disease or oral extrahepatic manifestations may visit a dentist. Through cooperation between dentistry and medical care, undiagnosed and untreated hepatitis patients can be provided treatment. It is suggested that general dental clinics can introduce OLP patients relatively easily to medical clinics and hospital dentistry & oral-maxillofacial surgery centers can recommend treatment of untreated HCV-infected individuals.

Keywords: Oral lichen planus (OLP); Hepatitis C virus (HCV); Direct-acting antivirals (DAA); Dentist

Abbreviations: OLP: Oral Lichen Planus; HCV: Hepatitis C Virus; HBV: Hepatitis B Virus; CH-C: Chronic Hepatitis C; HCC: Hepatocellular Carcinoma; DAA: Direct-Acting Antivirals; SVR: Sustained Virological Response

Introduction

An estimated 1.5 to 2 million people are infected with hepatitis C virus (HCV) in Japan and about 30,000 deaths occur

from hepatocellular carcinoma (HCC) each year [1,2]. Treatment of chronic viral hepatitis C has advanced dramatically in the past

decade with the introduction of direct-acting antivirals (DAAs) [3-5]. However, 800 thousand to one million of these HCV-infected individuals do not know they are infected or remain untreated [6]. HCV infection also is known to cause extrahepatic manifestations in the oral cavity, such as oral lichen planus (OLP) [7,8]. OLP is a chronic inflammatory, mucocutaneous disease, mostly affecting middle-aged females [9]. The rates of HCV infection in patients with OLP are high in Japan, ranging from 62% to 67.8% [10,11]. OLP in HCV-infected individuals was reported to be improved by treatment with DAAs [12-14]. We reported previously a retrospective study showing it is possible to encourage the treatment of patients with viral hepatitis through dentistry [15]. In this study, we examined prospectively the frequency of encouragement of consultation for HCV and hepatitis B virus (HBV)-infection, by dentists, among patients who visited dental clinics.

Materials and Methods

The twelve medical institutions participating in the study were eleven dental clinics which belong to the Shimonoseki-City Dental Association in Yamaguchi prefecture and an oral

and maxillofacial surgery center, Western Shimane Medical Center of Health and Welfare in Shimane prefecture. These medical institutions are located in the west of Japan (Figure 1). Parameters examined during the three months from November 1, 2017 to January 31, 2018 are: the number of patients who visited the dental offices, the number of HCV-infected patients, the number of HBV-infected patients, the number of OLP patients, the rate of HCV infection in OLP patients, the number recommended to consultation a family doctor regarding liver disease, and the number of OLP patients recommended to obtain advice regarding liver disease. The dentists interviewed each patient to determine their clinical history and systemic diseases, including liver disease, and offered testing for HCV and HBV infection and referral to a primary physician. They obtained this information in cooperation with a medical institution. Anti-HCV and serum HCV RNA was measured using a chemiluminescent enzyme immunoassay (CLEIA) kit and a quantitative polymerase chain reaction (PCR) assay, respectively. Hepatitis B surface antigen (HBsAg) was measured using a chemiluminescent immunoassay (CLIA) kit.

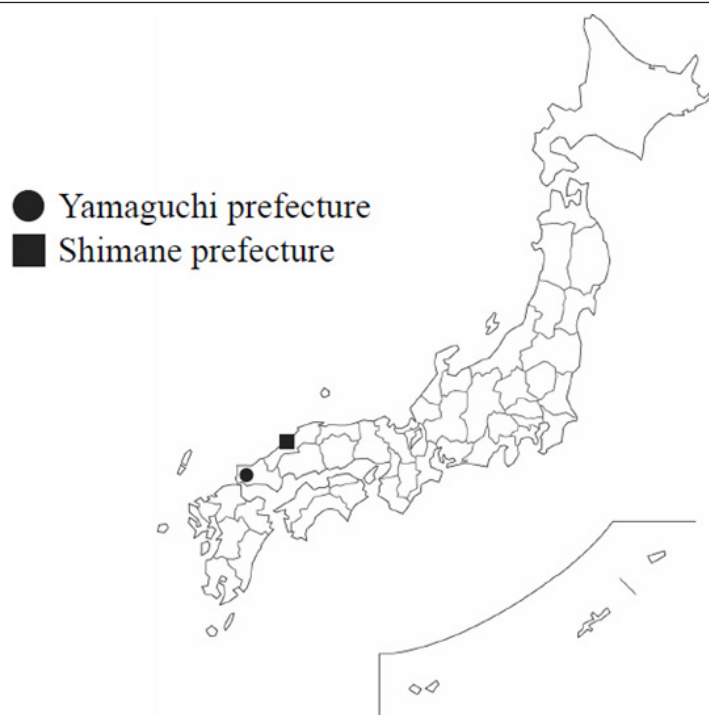


Figure 1: The locations of the 12 medical institutions in western Japan. The black circle indicates Yamaguchi prefecture and the black square indicates Shimane prefecture.

Ethical considerations

The study was approved by the Ethics Committee of Saga University (reference number: 29-15 and 29-56) in accordance with the Declaration of Helsinki. The study received ethical approval for the use of an opt-out methodology, based on unbiased information.

Results

In the 12 medical institutions, the total number of patients, the number of HCV-infected patients, the number of HBV-infected patients, and the number of OLP patients were 5,091, 40, 13 and 15, respectively (Table 1). The 40 HCV-infected patients were 17 men and 23 women with an average age of 73.8 years. The 13 HBV-infected patients were 5 men and 8 women

with an average age of 63.8 years. The 15 OLP patients were 3 men and 12 women with an average age of 67.6 years. The diagnoses of the 53 infected patients were: chronic hepatitis C (CH-C) (26 patients), during treatment of CH-C (1 patient), CH-C with sustained virological response (SVR) (13 patients), chronic hepatitis B (9 patients), and HBV asymptomatic carrier (4 patients). Consultation for untreated CH-C was recommended

for one patient, a 72-year-old female, who was then treated with DAAs. Eleven of the 15 (73%) patients with OLP were advised to seek examinations for liver disease and testing for HBV and HCV infection. The diagnoses of these 11 patients were: CH-C with SVR (1 patient) and normal liver (10 patients). The prevalence of HCV infection in the OLP patients was 6.7% [1-15].

Table 1: Characteristics of the 5, 091 patients.

No.	1	2	3	4	5	6	7	8	9	10	11	12	Total (n) %		
Institutions	Dental clinic	Dental clinic	Dental clinic	Dental clinic	Dental clinic	Dental clinic	Dental clinic	Dental clinic	Dental clinic	Dental clinic	Dental clinic	Hospital dentistry			
Number of patients (n)	245	777	342	130	487	461	489	540	86	486	492	556	5,091		
HCV infected patients	Number of patients (n) %	0 (0%)	5 (0.6%)	1 (0.3%)	2 (1.5%)	0 (0%)	2 (0.4%)	5 (1.0%)	4 (0.7%)	1 (1.2%)	7 (1.4%)	5 (1.0%)	8 (1.4%)	40 (0.8%)	
	Sex (M/F)	0/0	3/2	0/1	0/2	0/0	2/0	2/3	2/2	1/0	3/4	3/2	1/7	17/23	
	Average age (yr)	-	72.6	78	68.5	-	82	71.2	70	83	76	68	68.6	73.8	
	Number encouraged to undergo a medical examination (n) %	-	0 (0%)	0 (0%)	0 (0%)	-	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (13%)	1 (2.5%)	
	Liver diagnosis (40 patients)	CH-C	-	4	0	1	-	0	4	2	1	7	2	5	26
		During treatment of CH-C	-	0	0	0	-	0	0	1	0	0	0	0	1
CH-C SVR		-	1	1	1	-	2	1	1	0	0	3	3	13	
HBV infected patients	Number of patients (n) %	0 (0%)	1 (0.1%)	0 (0%)	1 (0.8%)	3 (0.6%)	2 (0.4%)	0 (0%)	2 (0.4%)	0 (0%)	1 (0.2%)	0 (0%)	3 (0.5%)	13 (0.3%)	
	Sex (M/F)	0/0	1/0	0/0	0/1	1/2	1/1	0/0	0/2	0/0	0/1	0/0	2/1	5/8	
	Average age (yr)	-	76	-	53.9	77	43	-	65	-	72	-	60	63.8	
	Number encouraged to undergo a medical examination (n) %	-	0 (0%)	-	0 (0%)	0 (0%)	0 (0%)	-	0 (0%)	-	0 (0%)	-	0 (0%)	0 (0%)	
	Liver diagnosis (13 patients)	CH-B	-	1	-	1	3	2	0	1	-	1	-	0	9
		HBV asymptomatic carrier	-	0	-	0	0	0	0	1	-	0	-	3	4

OLP patients	Number of patients (n) %	0	4	1	0	1	1	0	0	0	0	1	7	15
	Sex (M/F)	0/0	0/4	0/1	0/0	1/0	0/1	0/0	0/0	0/0	0/0	1/0	1/6	3/12
	Average age (yr)	-	58.5	78	-	74	55	-	-	-	-	75	65.3	67.6
	Number encouraged to undergo a medical examination (n) %	-	1 (25%)	1 (100%)	-	1 (100%)	0 (0%)	-	-	-	-	1 (100%)	7 (100%)	11 (73.3%)
	Anti-HCV (positive) (n) %	-	0 (0%)	1 (100%)	-	0 (0%)	0 (0%)	-	-	-	-	0 (0%)	0 (0%)	1 (6.7%)
	Anti-HCV (negative) (n) %	-	1 (25%)	0 (0%)	-	1 (100%)	0 (0%)	-	-	-	-	1 (100%)	7 (100%)	10 (66.7%)
	Anti-HCV (unknown) (n) %	-	3 (75%)	0 (0%)	-	0 (0%)	1 (100%)	-	-	-	-	0 (0%)	0 (0%)	4 (26.7%)
	Liver diagnosis in OLP patients (15 patients)													
CH-C SVR (n) %	-	0 (0%)	1 (100%)	-	0 (0%)	0 (0%)	-	-	-	-	0 (0%)	0 (0%)	1 (6.7%)	
Normal liver (n) %	-	1 (25%)	0 (0%)	-	1 (100%)	0 (0%)	-	-	-	-	1 (100%)	7 (100%)	10 (66.7%)	
Unknown (n) %	-	3 (75%)	0 (0%)	-	0 (0%)	1 (100%)	-	-	-	-	0 (0%)	0 (0%)	4 (26.7%)	

HCV: Hepatitis C Virus; HBV: Hepatitis B Virus; SVR: Sustained Virological Response; OLP: Oral Lichen Planus; CH-C: Chronic Hepatitis C; CH-B: Chronic Hepatitis B; M: Male; F: Female

Discussion

Yamaguchi prefecture and Shimane prefecture are always highly ranked in our country in terms of deaths due to liver cancer. The domestic ranking of mortality rate was 3rd in Yamaguchi prefecture in 2015 and 3rd in Shimane prefecture in 2016. Patients who have complications of liver disease or extrahepatic manifestations may visit a dentist. Through cooperation between dentistry and medical care, patients with undiagnosed or untreated hepatitis can be provided treatment.

In this study, there was no case of recommendation from the general dental clinic to a family medical doctor for untreated chronic hepatitis C. The most common reason was "Because patients with CH-C already attend their family doctor". A general dentist may have difficulty grasping accurately the ramifications of liver disease and providing appropriate advice to patients with HCV or HBV liver disease. One oral surgeon working in a hospital setting referred an untreated HCV-infected patient to a liver specialist. Eventually, this patient was treated with DAAs, involving a 12-week course of ledipasvir (LDV) 90mg and sofosbuvir (SOF) 400mg (Harvoni®; Gilead Sciences Inc., Foster City, CA, USA).

Meanwhile, the proportion OLP patients recommended for screening for liver disease was high (73%). It is suggested that general dentists can refer patients with OLP relatively easily to a family doctor. In our retrospective survey, we reported that

the rate of referral and examining HCV infection was 57% and the rate of HCV infection was 29% at an observation period of 1 year and 10 months [15]. We recommended treatment to 80% of HCV-infected patients. As a result, 60% of untreated patients commenced or completed antiviral therapy and all achieved SVR. In the present study, the low referral rate from dentists to family physicians for liver disease patients may be related to the short duration of the study (3 months). Therefore, if this study is continued for a long time, it may be possible to raise the rate of identifying untreated hepatitis patients via a general dentist. In the future, it is desirable to push promote this survey in multiple dental clinics.

Conclusion

In this study, we examined prospectively the rate of recommendation for consultation by a family doctor or liver specialist regarding liver disease and the relationship between OLP, HCV, and HBV infection in 5,091 patients who consulted general dental clinics and a hospital dentistry. It is suggested that general dental clinics could introduce OLP patients relatively easily to the medical clinics, and hospital dentistry & oral-maxillofacial surgery centers could recommend treatment of untreated, HCV-infected individuals by a liver specialist.

Acknowledgement

We thank the Shimonoseki-City Dental Association for support of this study and Dr. Yutaka Horie (Shimaneken Saiseikai

Gotsu General Hospital) for treatment of chronic hepatitis C. This study was supported in part by a Grant-in-Aid for Scientific Research (C) (No.17K12012) from the Ministry of Education, Culture, Sports, Science and Technology of Japan.

Conflict of Interest

YN (the corresponding author) is a member of a donation-funded Department, funded by Okuda Internal Medicine, Circulatory Medicine and Naniwamarukaiji Inc.. The remaining authors disclose no conflicts.

References

1. Matsuda A, Matsuda T, Shibata A, Katanoda K, Sobue T, et al. (2013) Cancer incidence and incidence rates in Japan in 2007: a study of 21 population-based cancer registries for the Monitoring of Cancer Incidence in Japan (MCIJ) project. *Jpn J Clin Oncol* 43: 328-336.
2. Uemura M, Sasaki Y, Yamada T, Gotoh K, Eguchi H, et al. (2014) Serum antibody titers against hepatitis C virus and postoperative intrahepatic recurrence of hepatocellular carcinoma. *Ann Surg Oncol* 21: 1719-1725.
3. Kumada H, Suzuki Y, Ikeda K, Toyota J, Karino Y, et al. (2014) Daclatasvir plus asunaprevir for chronic HCV genotype 1b infection. *Hepatology* 59: 2083-2091.
4. Omata M, Nishiguchi S, Ueno Y, Mochizuki H, Izumi N, et al. (2014) Sofosbuvir plus ribavirin in Japanese patients with chronic genotype 2 HCV infection: an open-label, phase 3 trial. *J Viral Hepat* 21: 762-768.
5. Mizokami M, Yokosuka O, Takehara T, Sakamoto N, Korenaga M, et al. (2015) 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* 15: 645-653.
6. Tanaka J, Koyama T, Mizui M, Uchida S, Katayama K, et al. (2011) Total numbers of undiagnosed carriers of hepatitis C and B viruses in Japan estimated by age- and area-specific prevalence on the national scale. *Intervirology* 54: 185-195.
7. Zignego AL, Ferri C, Pileri SA, Caini P, Bianchi FB (2007) Extrahepatic manifestations of hepatitis C virus infection: a general overview and guidelines for a clinical approach. *Dig Liver Dis* 39: 2-17.
8. Negro F, Forton D, Craxi A, Sulkowski MS, Feld JJ, et al. (2015) Extrahepatic morbidity and mortality of chronic hepatitis C. *Gastroenterology* 149: 1345-1360.
9. Scully C, Beyli M, Ferreiro MC, Ficarra G, Gill Y, et al. (1998) Update on oral lichen planus: etiopathogenesis and management. *Crit Rev Oral Biol Med* 9: 86-122.
10. Nagao Y, Sata M, Tanikawa K, Itoh K, Kameyama T (1995) Lichen planus and hepatitis C virus in the northern Kyushu region of Japan. *Eur J Clin Invest* 25: 910-914.
11. Nagao Y, Sata M (2012) A retrospective case-control study of hepatitis C virus infection and oral lichen planus in Japan: association study with mutations in the core and NS5A region of hepatitis C virus. *BMC Gastroenterol* 12: 31.
12. Nagao Y, Kimura K, Kawahigashi Y, Sata M (2016) Successful treatment of hepatitis C virus-associated oral lichen planus by interferon-free therapy with direct-acting antivirals. *Clin Transl Gastroenterol* 7: e179.
13. Misaka K, Kishimoto T, Kawahigashi Y, Sata M, Nagao Y (2016) Use of direct-acting antivirals for the treatment of hepatitis C virus-associated oral lichen planus: A case report. *Case Rep Gastroenterol* 10: 617-622.
14. Yoshikawa A, Terashita K, Morikawa K, Matsuda S, Yamamura T, et al. (2017) Interferon-free therapy with sofosbuvir plus ribavirin for successful treatment of genotype 2 hepatitis C virus with lichen planus: a case report. *Clin J Gastroenterol* 10: 270-273.
15. Nagao Y, Tsuji M (2017) The discovery through dentistry of potentially HCV-infected Japanese patients and intervention with treatment. *Adv Res Gastroentero Hepatol* 7: 1-7.



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DOI: [10.19080/ARGH.2018.09.555773](https://doi.org/10.19080/ARGH.2018.09.555773)

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