Table II. Laboratory data of patient with hepatitis C virus infection at time of admission for Graves' ophthalmopathy.

Laboratory assay	Value	Unit	Standard value
RBC	376	x10⁴/mm³	430-570
Hb	11.9	g/dl	14.0-18.0
Ht	35.8	%	40.0-52.0
WBC	43	x10⁴/mm³	40-90
Plt	18.3	x10⁴/mm³	13.0-36.0
AST	12	U/l	13-33
ALT	9	U/l	8-42
LDH	122	U/l	119-229
ALP	233	U/l	115-359
γ-GTP	17	U/l	10-47
TP	7.47	g/dl	6.70-8.30
Alb	3.94	g/dl	4.00-5.00
ChE	135	IU/l	107-233
TC	117	mg/dl	128-256
TB	0.43	mg/dl	0.00-1.50
DB	0.06	mg/dl	0.00-0.60
BUN	13.1	mg/dl	8.0-22.0
Crea	0.69	mg/dl	0.60-1.10
Na	141	mEq/l	138-146
K	4.1	mEq/l	3.6-4.9
Cl	104	mEq/l	99-109
CRP	0.88	mg/dl	0.00-0.40
Glucose	107	mg/dl	80-109
HbA1c	4.4	%	4.3-5.8
CEA	1.1	ng/dl	0.0-5.0
SCC	LT1.0	ng/dl	0.0-1.5
FT_3	4.6	mg/dl	1.9-3.5
FT_4	1.58	ng/dl	0.88-1.56
TSH	0.007	μIU/ml	0.210-3.850
TgAb	8.5	IU/ml	0.0-9.0
TPOAb	92.2	IU/ml	0.0-5.0
TRAb	19.7	%	<15
TSAb	139	%	<180
hTRAb	7.0	IU/l	<1.0
RA	<15	IU/ml	0-30
ANA	Negative		
Anti-SS-A	Negative		
Anti-SS-B	Negative		
HCV RNA	Negative		

May 16, 2006.

antibodies (TgAb), 8.5 IU/ml (normal value <9). Anti-TSH receptor antibodies [TSH receptor antibody (TRAb), 19.7% (normal value <15); thyroid stimulating antibody (TSAb), 139% (normal value <180); human TSH receptor antibody (hTRAb), 7.0 IU/l (normal value <1.0)] were positive. He had bilateral ocular disorders of supraduction and abduction, with bilateral conjunctival injection and periorbital edema. There was no tachycardia or exophthalmos (right, 12 mm; left, 12 mm). The size of the thyroid was normal according to ultrasonography. He was diagnosed with Graves' disease with ophthalmopathy by an endocrinologist. Table II shows laboratory data upon admission for Graves' ophthalmopathy, which was classified as IIa, IVc using the American Thyroid Association classification system for orbital changes in Graves' ophthalmopathy (23), with a clinical activity score of 3 (24). MRI of the orbits showed conspicuous enlargement of the bilateral inferior rectus muscles (Fig. 1). As these manifestations were regarded as a severe adverse event of Peg-IFN plus RBV therapy, the combined therapy was discontinued on May 2, 2006.

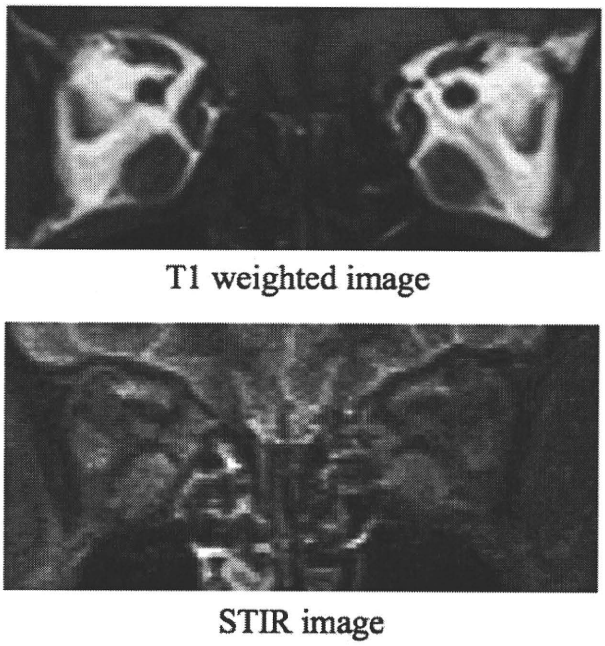
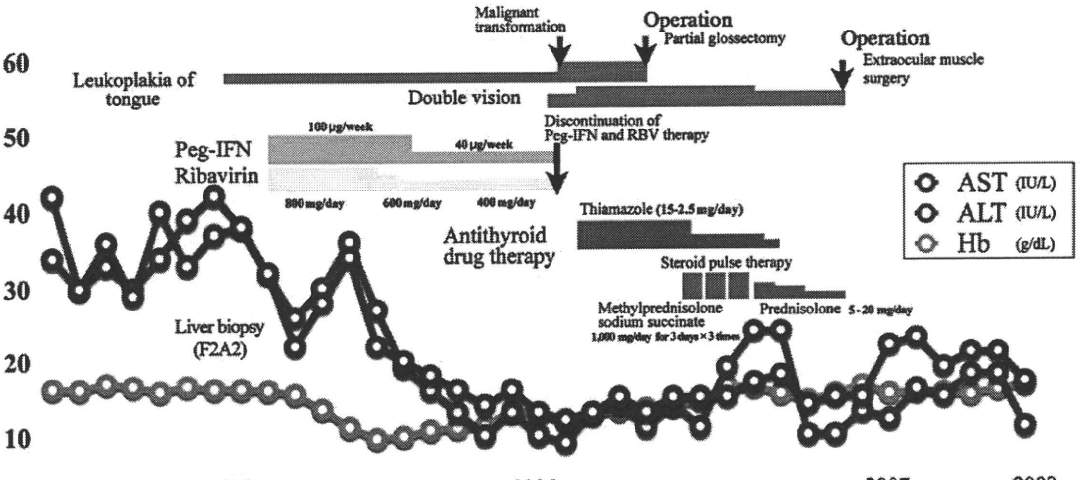


Figure 1. MRI of the orbits shows conspicuous enlargement of the bilateral inferior rectus muscles before steroid pulse therapy (coronal view).

Thiamazole (Mercazole®; Chugai Pharmaceutical Co., Ltd., Tokyo, Japan) (15 mg/day), an anti-thyroid drug, was administered as of May 19, 2006. After 4 weeks, the thyroid functions of the patient had normalized, but his ocular symptoms persisted. Consequently, methylprednisolone sodium succinate (Solu-Medrol®; Pfizer Inc., Tokyo, Japan) (1000 mg/day for 3 successive days, 3 courses) was started on July 11, 2006 as a steroid pulse therapy. Thiamazole dosage was reduced and terminated on August 12, 2006. The treatment was followed by oral prednisolone (Predonine®; Shionogi & Co., Ltd., Osaka, Japan) (20 mg daily) as of August 4, which was discontinued on October 15, 2006. Thyroid function improved and orbital edema and conjunctival injection were no longer apparent, but the double vision remained. The patient underwent extraocular muscle surgery on November 25, 2006. Fig. 2 illustrates the clinical course of the patient.



	7.30	11.22	12.15	5.20	6.14	6.21	6.28	7.15	8.2	9.6	10.7	10.18	11.5	2.10	5.16	5.29	6.12	6.19	6.30	7.19	7.25	8.1	8.22	8.26	10.2	10.31	12.26	1.12	2.5	4.6	7.6	10.5	12.25	1.18
HCV RNA level (KIU/mL)	MT 500	1590	MT 500	1900	2400	78	6	LTS	LTS	LTS	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
HCV RNA	-	-	-	-	-	-	-	-	-	-	neg.	neg.	neg.	neg.	neg.	-	-	-	-	-	neg.	-	neg.	neg.	neg.	neg.	neg.	-	-	-	neg.	-	neg.	-
FT3 (pg/mL)	-	-	-	-	-	-	-	-	-	-	-	-	-	4.1	4.6	3.7	2.2	2.2	-	1.1	-	2.3	3.3	3.3	-	3.1	3.0	-	3.5	2.9	2.9	3.1	3.3	3.3
FT4 (ng/dL)	-	-	-	1.29	1.34	-	-	-	-	-	-	-	-	1.58	1.26	0.8	0.64	-	0.42	-	0.66	1.42	1.24	-	1.12	1.15	-	1.13	1.17	1.20	1.34	1.22	1.34
TSH (μIU/mL)	-	-	-	2.30	2.37	-	-	-	-	-	-	-	-	0.016	0.007	0.028	0.147	3.450	-	9.000	-	44.17	3.700	3.150	-	1.460	3.160	-	2.050	3.220	4.250	1.500	5.070	3.910
TgAb (IU/mL)	-	-	-	-	-	-	-	-	-	-	-	-	-	7.5	8.5	-	-	-	-	-	-	-	3.9	-	9.1	-	-	-	-	-	-	-	-	-
TPOAb (IU/mL)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	92.2	-	-	-	-	-	-	58.5	-	-	13.6	-	-	-	-	-	-	-	-	-
TRAb (%)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	19.7	-	-	-	23.1	-	-	16.4	-	11.2	-	-	-	-	12.9	-	-	-	7.3	-	0.3
TSAb (%)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	139	-	-	-	199	-	-	378	-	326	-	-	-	-	119	-	-	-	128	-	184
hTRAb (IU/L)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	7.0	-	-	-	6.8	-	-	5.0	-	1.9	-	-	-	-	1.6	-	-	-	1.3	-	<1.0

Figure 2. Clinical course of the patient.

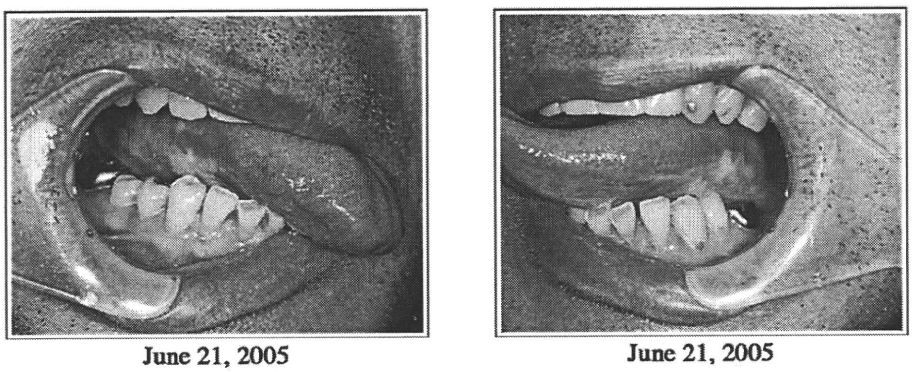


Figure 3. Bilateral oral leukoplakia of the tongue.

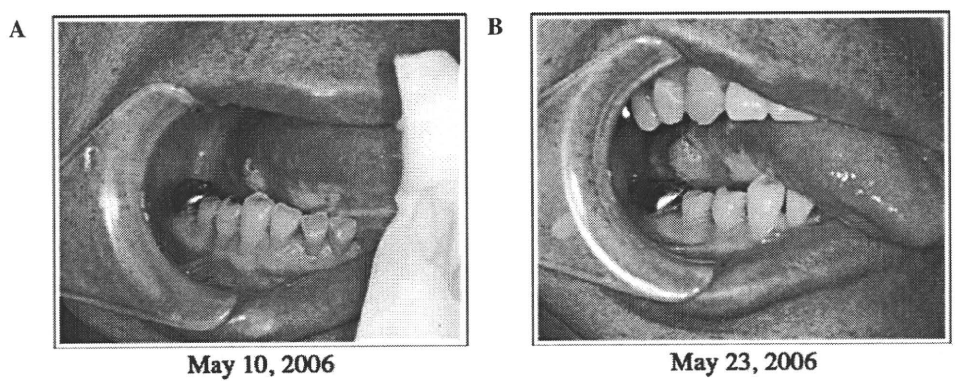


Figure 4. (A) Squamous cell carcinoma on the right lateral surface transformed from leukoplakia. (B) The mass exhibited a tendency for enhancement.

Table III. Cases of Graves' ophthalmopathy associated with IFN treatment for hepatitis C.

Year	Language	Refs.	Patient	Course
2000	French	33	62/man	Development of ophthalmopathy after IFN-α treatment
2002	English	34	47/man	Development of ophthalmopathy after treatment with a 6 month course of IFN-α and RBV
2002	French	35	49/woman	Development of ophthalmopathy after IFN-α treatment
2005	English	36	47/woman	Development of ophthalmopathy after IFN-α and RBV treatment
2007	English	37	50/woman	Exacerbation of ophthalmopathy during treatment with peg-IFN-α and RBV
2008	English	Our case	69/man	Development of ophthalmopathy during treatment with peg-IFN-α and RBV

The patient had symmetrically-located pre-cancerous leukoplakia on both lateral surfaces of the tongue before combination therapy with Peg-IFN α-2b plus RBV (Fig. 3). Cytodiagnosis of the tongue showed no evidence of malignancy, and the patient did not notice the lingual leukoplakia until they were discovered by us. The leukoplakia lesions remained unaltered during the combination therapy and for 20 weeks after it srarted. The patient did not have regular checkups after November 15, 2005 but, in April 2006, became aware of a mass at the right base of the tongue. Upon examination on May 9, 2006, the presence of a superficial mass on the right lateral surface of the tongue was confirmed. The mass measured 7 mm x 8 mm, had a granular surface and a hard-ened area, and was without pain (Fig. 4A). The Peg-IFN plus RBV therapy, which had been administered for 47 weeks, was stopped on May 2, 2006. The mass exhibited a tendency for enhancement (Fig. 4B), and there was no induration of the tumoral circumference and dysfunction. No cervical lymph node metastasis was detected. After a diagnosis of squamous cell carcinoma of the right tongue (T1N0M0, stage I), tumor resection of the tongue was performed at the Department of Otolaryngology of the Kurume University School of Medicine on June 6, 2006.

During Peg-IFN plus RBV therapy, the patient developed Graves' ophthalmopathy due to hyperthyroidism and tongue cancer resulting from oral leukoplakia. Serum HCV RNA was negative 6 months after the therapy ended, and the case was judged to be one of sustained virological response. Since that time, the patient has been monitored regularly by a hepatologist, an oral surgeon, an otolaryngologist, an endocrinologist and an ophthalmologist. To date, there has been no local recurrence of tongue cancer or late metastasis, and no double vision.

Discussion

IFN therapy for chronic HCV infection has been associated with thyroid dysfunction. The incidence of thyroid dysfunction ranges from 0.6 to 34.3% (25,26) with a mean of 6.6% (27), while in patients treated with IFN α and RBV combination therapy the incidence is higher (12.1%) (28). Recent research indicates that Peg-IFN in combination with RBV does not aggravate thyroid disease in the hepatitis C population (29).

Hypothyroidism is induced more frequently than hyperthyroidism during IFN therapy (3.8 vs. 2.8%), and females appear to be more susceptible to IFN-induced thyroid disorders than males (8.2 vs. 4.8%) (27). Factors predictive of dysthyroidism include female gender and the presence of thyroid autoantibodies before IFN treatment (27,30). TPOAb is considered to be more useful than TgAb in monitoring immunological response in patients treated with IFN (31). Koh *et al* reported that the risk of developing thyroid dysfunction in thyroid antibody-positive patients appears to be 46.1%, whereas only 5% of those who are thyroid antibody-negative at baseline develop thyroid dysfunction (27). They conclude that risk factors for developing thyroid dysfunction with IFN therapy are female gender, receipt of higher doses of IFN for longer durations, and the presence of thyroid autoantibodies prior to or during treatment. However, based on 138 eyes in 105 cases treated with eyelid surgery for Graves' ophthalmopathy, Inoue *et al* reports that the percentage of men with thyroid dysfunction increases as patients age (32).

As shown in Table III, few reported cases of Graves' ophthalmopathy have developed or been exacerbated following IFN treatment for hepatitis C (33-37). The mechanisms by which IFN induces thyroid autoimmunity remain unknown, but infectious agents have long been suspected to trigger thyroid autoimmunity, and HCV has shown the strongest association with autoimmune thyroid disease (38). HCV induces thyroid disease as an extrahepatic manifestation (9). Negative-strand HCV RNA has also been detected in the thyroid (39). IFN receptor activity results in the activation of the JAK-STAT pathway, leading to the activation of numerous IFN-stimulated genes. These effects can induce thyroid autoimmunity, and recent data have suggested that both the immune-mediated and direct thyroid-toxic effects of IFN play a role in its etiology (38). Our previous study found that the expression of thyrotropin receptor (TSH-R) mRNA in orbital fat tissue from patients with Graves' ophthalmopathy significantly correlated with orbital fat volume and the severity of ophthalmopathy (40). These results suggest that the expression of TSH-R in the orbit may play a role in the pathogenesis and clinical manifestations of ophthalmopathy.

Because the symptoms of hypothyroidism, such as fatigue, decreased appetite and depression, and the symptoms of hyperthyroidism, such as nervousness, irritability, fatigue and weight loss, can both be attributed to hepatitis C under IFN therapy, the diagnosis of thyroid disease in these patients may be delayed. This in turn may lead to the development of adverse effects induced by HCV therapy (38).

Our previous large-scale epidemiological survey showed that the incidence of oral pre-cancerous lesions and leukoplakia

was significantly higher in patients with HCV infection (41). Oral leukoplakia are well established as one of the best examples of pre-malignancy in humans. The rate of malignant transformation of these lesions is 3-20% (42). Furthermore, our study suggests the presence and elevation of HCV RNA in oral cancer and OLP tissues (43). Multi-center studies in Japan found that the presence of anti-HCV and HCV RNA was significantly higher in patients with squamous cell carcinoma of the head and neck than in control subjects (14). It has also been demonstrated that oral cancer patients often have carcinoma of the stomach (18%) and liver cancer (16%) as double cancers. Double-cancer patients have significantly higher HCV infection rates than controls (44). In the present case, the patient developed malignant transformation of leukoplakia after testing negative for HCV RNA during Peg-IFN plus RBV therapy. Whether the therapy was the trigger for malignant transformation is unknown.

In conclusion, our patient had Graves' ophthalmopathy, a rare side effect of IFN therapy for hepatitis C, and tongue cancer during Peg-IFN plus RBV therapy. To the best of our knowledge, this is the fifth case of ophthalmopathy newly-induced by IFN therapy (33-36). Thyroid function and pre-existing thyroid autoantibodies should be closely monitored for chronic hepatitis C with IFN therapy. In addition, when patients with HCV infection undergo follow-up, it is important to detect extrahepatic lesions early, refer the patient to specialists and start treatment earlier as well. Finally, we emphasize that medical professionals should perform regular follow-ups, including specialized clinical examinations, on patients with HCV infection.

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Analysis of factors interfering with the acceptance of interferon therapy by HCV-infected patients

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Authors' Contribution:
A Study Design
B Data Collection
C Statistical Analysis
D Data Interpretation
E Manuscript Preparation
F Literature Search
G Funds Collection

Summary

Background: Interferon (IFN) therapy, an antiviral agent, contributes to the prevention of occurrence of hepatocellular carcinoma (HCC) and to improvement in long-term prognosis. However, IFN therapy is not well-implemented in Japan. The present study was conducted to analyze factors preventing the implementation of IFN therapy.

Material/Methods: Questionnaires were sent to patients with hepatitis C virus (HCV)-related liver disease who were treated at 7 clinics (by non liver-specialists) and 1 hospital (by liver specialists) and by their attending physicians.

Results: Of 139 patients for whom attending physicians recommended IFN therapy, 92 (66.2%) agreed to receive the treatment. The proportions of patients who agreed to receive IFN therapy were 74 (86.0%) out of 86 hospital patients and 18 (34%) out of 53 clinic patients. In logistic regression analysis, the adjusted odds ratios on treatment facilities, sex and complications were 18.06, 3.65, and 3.63 respectively, indicating that there were significant differences. Female patients more than male patients declined IFN therapy because of worries over the adverse reactions of IFN therapy.

Conclusions: Multivariate analysis showed that factors contributing to the risk that a patient would not consent to receive IFN therapy included a) treatment facilities, b) sex, and c) the presence or absence of complications. It is also essential to devise measures to create cooperation between hospitals and clinics, and to improve communication between physicians and patients.

key words: **hepatitis C virus • interferon therapy • chronic hepatitis C • hepatocellular carcinoma • liver specialist • non liver-specialist**

Abbreviations: **anti-HCV** – anti-bodies to HCV; **HCC** – hepatocellular carcinoma; **HCV** – hepatitis C virus; **IFN** – Interferon

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BACKGROUND

Hepatocellular carcinoma (HCC) is the third most common cause of death from cancer in men and the sixth most common cause in women [1]. An increase in the number of cases of HCC has occurred in the United States over the past two decades [2]. The age-specific incidence of this cancer has progressively shifted toward younger people. Similarly, the number of deaths in Japan from HCC keeps increasing. This trend is expected to continue until 2015 [3]. In Japan, ~80% of HCCs are caused by hepatitis C virus (HCV) and ~10% by hepatitis B virus (HBV). The increase in the number of HCC patients due to HCV contributes to the increase in the deaths in Japan from HCC.

It is presumed that between 1 and 2 million Japanese people are chronically infected with HCV [3]. Because many such people are unaware that they are infected, carriers may develop liver cirrhosis and HCC, and this poses a serious problem. In April 2002, the Ministry of Health, Labour and Welfare began targeting area residents for hepatitis virus screening as part of urgent comprehensive measures for identifying hepatitis C and other infections. Since 2002, antibodies to HCV (anti-HCV) and HBs antigens have been tested in Japanese individuals who receive a basic health check up. This is part of the Elderly Health Project whose goal is to re-test them every 5 years between ages 40 and 70.

The national compliance rate for this health check during 4 years from 2002 to 2005 was about 27% (~5.1 million people). The HCV infection rate at that time was 0.9% (~47,000 people). However, only 6,160 HCV carriers in fact received treatment at secondary medical facilities, while 16% (969/6,160) of carriers were treated with interferon (IFN) at secondary medical facilities during the 4 years. These statistics suggest that not many patients or residents are actually treated with IFN despite the fact that IFN can get rid of HCV [4]. Currently, creation of a network for post-health screening treatment has been in progress.

IFN therapy for chronic hepatitis C is the only treatment for completely eliminating HCV. In recent years, the standard therapy has been the combination of pegylated interferon (Peg-IFN) and ribavirin. Following 1-year administration of this combination, the treatment was found to be markedly effective in~50 to 60% of all HCV-infected patients, including those with conventionally intractable genotype 1b • high titer [5]. It has been demonstrated that IFN therapy contributes to the prevention of occurrence of HCC and to improvement in long-term prognosis [6–9].

Why is IFN therapy for HCV carriers in Japan not used more widely? Reasons remain unclear because no systematic investigation has been conducted.

In our previous study, we sent questionnaires to both 254 pairs of HCV carriers and their attending physicians in different areas in Japan in which we discussed the future state of medical care in which IFN therapy would be used more widely [10]. There was a great difference among types of medical facilities in the proportions of patients who opted to receive IFN therapy. Whereas 78.2% of patients of liver specialists agreed to IFN therapy, the proportion was only 15.7% for patients of non liver-specialists.

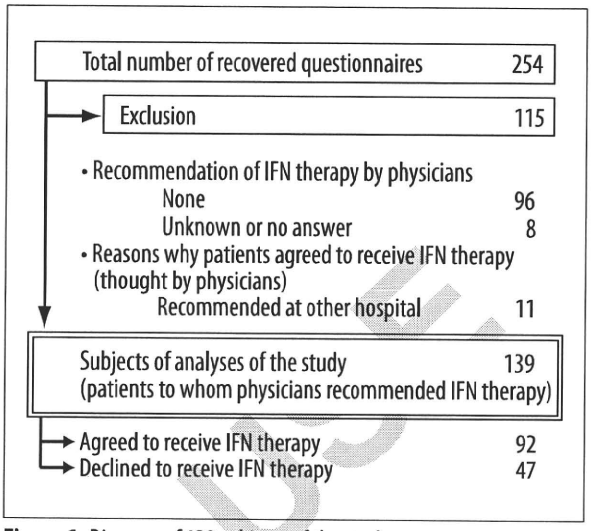

Figure 1. Diagram of 139 subjects of the study.

In the present study, patients who were recommended to receive IFN therapy were defined as "patients who ought to receive IFN therapy." Then, we looked for factors that caused patients who ought to receive IFN therapy to not receive it. That is, we looked for factors interfering with the introduction of IFN therapy. The geographical area where our investigation was conducted was one where we have been conducting successive epidemiological investigations on liver diseases and extrahepatic manifestations since 1990 [11–17].

MATERIAL AND METHODS

Subjects

Between October 1, 2005 and February 28, 2006, unregistered questionnaires were sent to HCV carriers who had been treated at a key hospital in A City, Fukuoka Prefecture and all clinics in H Town in A City and their attending physicians, and 254 pairs of answers were recovered. Subject medical organizations were 7 clinics without liver specialists and 1 hospital where many liver specialists authorized by the Japan Association for the Study of the Liver work full time. We mailed questionnaires directly to these 8 medical organizations. A database for the results of our investigation was compiled at the Office of Pharmaceutical Industry Research (OPIR)/Japan Pharmaceutical Manufacturers Association (JPMA).

The 254 patients were divided into groups depending on whether or not their physicians recommended any of the following IFN therapy: IFN monotherapy, Peg-IFNα-2a monotherapy, IFNα-2b plus ribavirin, and Peg-IFNα-2b plus ribavirin. As shown in Figure 1, 139 patients to whom physicians recommended IFN therapy were selected for the analysis of factors influencing the decision of patients whether or not to receive IFN therapy. Excluded from our analyses were 96 patients to whom physicians did not recommend IFN therapy, and 8 patients for whom it was unclear whether or not physicians recommended IFN therapy, or who did not respond to the questionnaire. Also excluded were 11 patients who received IFN therapy after recommendations from other hospitals. Of 139 patients analyzed, 92 consented to receive IFN therapy and 47 did not.

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Table 1. Items of investigation by questionnaires sent to both physicians and patients.

1. Patients' background
(1) Patients' attributes (age, sex, joining the patient advocacy group for liver disease)
(2) Diagnosis of liver diseases and complications
(3) Nutritional instruction for liver diseases (received, not received)
(4) Health foods and folk medicines (taken, not taken)
(5) Treatment other than IFN therapy (treated, not treated)
2. IFN therapy
(1) Explanation of IFN therapy (given, not given). If yes, when
(2) Implementation of IFN therapy (received, not received)
(3) Frequency of IFN therapy (*)
(4) The nearest place where IFN therapy was given (*)
(5) Reasons why patients decided to receive IFN therapy (*)
(6) The latest therapeutic effects of IFN therapy
(7) Reasons why IFN therapy was discontinued (*)
3. Factors for which IFN therapy was not performed
(1) IFN therapy was recommended (yes, no)
(2) Reasons why IFN therapy was recommended Reasons why IFN therapy was not recommended (*)
(3) Did patients decline IFN therapy? (yes, no)
(4) Reasons why patients declined IFN therapy
4. Comments (write what you think about liver diseases)

(*) Questions asked to physicians only.

The investigation was conducted in accordance with the "ethical guidelines on epidemiological studies" by the Ministry of Education and Science and the Ministry of Health, Labour and Welfare and observed the spirit of the Helsinki Declaration. Physicians at study facilities explained to patients the content and significance of the study and obtained consent in accordance with rules at each facility.

Items of investigation

Unregistered questionnaires asked patients and their attending physicians to respond to the following items.

1) Patients' background, 2) IFN therapy, and 3) factors determining the decision to not implement IFN therapy.

Items of investigation are listed in Table 1.

Statistical analysis

Crude odds ratios and adjusted odds ratios were calculated for factors possibly related to consenting to IFN therapy. Adjusted odds ratios were calculated using logistic regression analysis. Candidate factors for logistic regression analysis were selected by using a strategy that was recommended by Hosmer, DW, et al. [18], and secondary interactions among the selected factors were also assessed. Selection of factors for the final model was performed in a stepwise method, and the significance level for entering or removing of factors into or from regression models were both 0.15. The fitting of models was assessed using the Hosmer-Lemeshow test.

We tabulated reasons why patients declined IFN therapy, and therapeutic effects in patients who received IFN therapy.

All statistical analyses were conducted using SAS for Windows Version 8.2 (SAS Institute, Cary, NC, USA). The level of statistical significance was defined as 0.05.

Results

Patients' background

Table 2 lists clinical information for patients who were recommended to receive IFN therapy. Physicians recommended IFN therapy to 139 patients; 53 at clinics (non liver-specialists) and 86 at a hospital (liver specialists). For patients older than 60, 36 were recommended at clinics (67.9%) and 55 at a hospital (64.0%). The number of patients who joined the patient advocacy group for liver disease was zero at clinics and 13 (15.1%) at a hospital. The number of patients who were female were 30 (56.6%) at clinics and 45 (52.3%) at a hospital. The number of patients with concomitant medical complications were 36 (67.9%) at clinics and 65 (75.6%) at a hospital. Patients in the two groups were well-matched for baseline characteristics.

Univariate analysis

Of 139 subjects of analyses to whom physicians recommended IFN therapy, 92 (66.2%) agreed to receive the therapy (Table 2). Whereas 74 of 86 hospital patients (86.0%) agreed to receive IFN therapy, only 18 of 53 clinic patients (34.0%) did so.

In univariate analyses (Table 3), the crude odds ratio of treatment facilities (clinic/hospital) was calculated as 11.99, demonstrating a significant difference in the proportion agreeing to receive IFN therapy between clinic patients and hospital patients. As for other factors, the crude odds ratio for sex (female/male) was 1.96 and that for joining the Liver Society (or not) was 0.14, suggesting that the associations between these factors and the decision to receive IFN therapy were not statistically significant.

Multivariate analysis

According to multivariate analysis, three factors, treatment facilities (clinic/hospital), sex (female/male) and complications (yes/no), were identified as factors that influenced patients' decisions to receive IFN therapy. The adjusted odds ratios for these 3 factors were 18.06, 3.65 and 3.63, respectively, and each was statistically significant. Among all of the selected factors, the adjusted odds ratios were increased over the crude odds ratios. Factors of sex and complications were not statistically significant in the crude odds ratios but significant following multivariate adjustment.

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Table 2. Clinical information of 139 patients to whom IFN therapy was recommended.

		Total n=139 (%)		Clinic (Non liver-specialist) n=53 (%)		Hospital (Liver specialist) n=86 (%)	
IFN therapy	Accepted	92	(66.2)	18	(34.0)	74	(86.0)
	Not accepted	47	(33.8)	35	(66.0)	12	(14.0)
Treatment facilities	Hospital (liver-specialist)	86	(61.9)				
	Clinic (non liver-specialist)	53	(38.1)				
Age	20–29 years old	2	(1.4)	0	(0.0)	2	(2.3)
	30–39	3	(2.2)	0	(0.0)	3	(3.5)
	40–49	10	(7.2)	4	(7.5)	6	(7.0)
	50–59	33	(23.7)	13	(24.5)	20	(23.3)
	60–69	44	(31.7)	14	(26.4)	30	(34.9)
	70–79	45	(32.4)	22	(41.5)	23	(26.7)
	80 years or older	2	(1.4)	0	(0.0)	2	(2.3)
Sex	Male	63	(45.3)	22	(41.5)	41	(47.7)
	Female	75	(54.0)	30	(56.6)	45	(52.3)
	No answer	1	(0.7)	1	(1.9)	0	(0.0)
Diagnosis of liver diseases (choose one)	Chronic hepatitis C alone	103	(74.1)	34	(64.2)	69	(80.2)
	Other than chronic hepatitis C alone	36	(25.9)	19	(35.8)	17	(19.8)
	No answer	0	(0.0)	0	(0.0)	0	(0.0)
Diagnosis of liver diseases (choose all applicable)	Chronic hepatitis C	117	(84.2)	41	(77.4)	76	(88.4)
	HCV-related liver cirrhosis	22	(15.8)	10	(18.9)	12	(14.0)
	HCC type C	7	(5.0)	4	(7.5)	3	(3.5)
	Asymptomatic HCV carrier	1	(0.7)	1	(1.9)	0	(0.0)
	History of HCV infection	3	(2.2)	2	(3.8)	1	(1.2)
	Others	7	(5.0)	4	(7.5)	3	(3.5)
	Uncertain	0	(0.0)	0	(0.0)	0	(0.0)
	No answer	0	(0.0)	0	(0.0)	0	(0.0)
Concomitant medical complications	No	36	(25.9)	15	(28.3)	21	(24.4)
	Yes	101	(72.7)	36	(67.9)	65	(75.6)
	Hypertension	68	(48.9)	27	(50.9)	41	(47.7)
	Diabetes mellitus	28	(20.1)	11	(20.8)	17	(19.8)
	Heart diseases	10	(7.2)	3	(5.7)	7	(8.1)
	Cerebrovascular diseases	4	(2.9)	1	(1.9)	3	(3.5)
	Thyroid diseases	7	(5.0)	1	(1.9)	6	(7.0)
	Rheumatism	0	(0.0)	0	(0.0)	0	(0.0)
	Stomatitis	2	(1.4)	0	(0.0)	2	(2.3)
	Others	33	(23.7)	7	(13.2)	26	(30.2)
	No answer	2	(1.4)	2	(3.8)	0	(0.0)
Patient advocacy group for liver disease	Joined	13	(9.4)	0	(0.0)	13	(15.1)
	Not joined	126	(90.6)	53	(100.0)	73	(84.9)

HCC – Hepatocellular carcinoma.

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Table 3. Results of univariate analysis (crude odds ratio).

		Number of patients		Crude odds ratio (95% confidence intervals)		P value
		Not accepted	Accepted			
Treatment facilities	Hospital	12	74	1.00		
	Clinic	35	18	11.99	(5.21–27.60)	<0.0001
Age	20–59	16	32	1.00		
	60–69	12	32	0.75	(0.31–1.84)	0.5286
	70 years or older	19	28	1.36	(0.59–3.13)	0.4742
Sex	Male	16	47	1.00		
	Female	30	45	1.96	(0.94–4.07)	0.0718
	No answer	1	0			
Diagnosis of liver diseases	Chronic hepatitis C alone	33	70	1.00		
	Other than chronic hepatitis C alone	14	22	1.35	(0.61–2.97)	0.4553
Concomitant medical complications	No	10	26	1.00		
	Yes	37	64	1.50	(0.65–3.46)	
	No answer	0	2			0.3383
Patient advocacy group for liver disease	Joined	46	80	1.00		
	Not joined	1	12	0.14	(0.65–3.46)	0.0677

Table 4. Acknowledgement by patients who did not agree to receive IFN therapy upon recommendation.

	Patients who did not agree to receive IFN therapy	Treatment facilities		Sex			Complications	
		Clinic (non liver-specialist)	Hospital (liver specialist)	Male	Female	No answer	No	Yes
	n=47 (%)	n=35 (%)	n=12 (%)	n=16 (%)	n=30 (%)	n=1 (%)	n=10 (%)	n=37 (%)
To recommendation by physicians of IFN therapy								
Patients acknowledged it	30 (63.8)	20 (57.1)	10 (83.3)	11 (68.8)	18 (60.0)	1 (100.0)	8 (80.0)	22 (59.5)
Patients did not acknowledge it	13 (27.7)	13 (37.1)	0 (0.0)	5 (31.3)	8 (26.7)	0 (0.0)	2 (20.0)	11 (29.7)
Uncertain or no answer	4 (8.5)	2 (5.7)	2 (16.7)	0 (0.0)	4 (13.3)	0 (0.0)	0 (0.0)	4 (10.8)

The Hosmer-Lemeshow goodness-of-fit test indicated that the model fits (P=0.6025).

Reasons why patients declined IFN therapy

Of 47 patients who declined IFN therapy despite recommendation by their physicians, 30 (11 males, 18 female and 1 no answer) acknowledged that "IFN therapy was recommended to them by physicians" (Table 4).

Table 5 lists 17 reasons used by patients to decline IFN therapy. Of 29 patients (11 males and 18 females) who declined IFN therapy, 2 (18.2%) out of 11 males and 6 (33.3%) out of 18 females mentioned "worries over adverse reactions" as the biggest reason for declining. A higher proportion of female patients worried over adverse reactions than the proportion of male patients who did. Ten reasons including "didn't want other people to know about my illness" were not selected as the most accurate reason for declining IFN therapy (Table 5).

Therapeutic effects of IFN

Of 92 patients who agreed to receive IFN therapy upon recommendation by their physician, 28 could not be eval-

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Table 5. Reasons why patients who acknowledged that physicians recommended IFN therapy but patients did not agree to receive the therapy (the reason expressing their feelings most accurately).

	Patients who declined IFN therapy despite acknowledging recommendation of physicians	Treatment facilities		Sex			Complications	
		Clinic (non liver-specialist)	Hospital (liver-specialist)	Male	Female	No answer	No	Yes
	n=30 (%)	n=20 (%)	n=10 (%)	n=11 (%)	n=18 (%)	n=1 (%)	n=8 (%)	n=22 (%)
Worries over adverse reactions	8 (26.7)	6 (30.0)	2 (20.0)	2 (18.2)	6 (33.3)	–	4 (50.0)	4 (18.2)
High cost	2 (6.7)	2 (10.0)	–	–	1 (5.6)	1 (100)	–	2 (9.1)
Seemed to be unnecessary because of being asymptomatic	2 (6.7)	1 (5.0)	1 (10.0)	2 (18.2)	–	–	–	2 (9.1)
Was busy	2 (6.7)	2 (10.0)	–	2 (18.2)	–	–	–	2 (9.1)
Was anxious	2 (6.7)	1 (5.0)	1 (10.0)	1 (9.1)	1 (5.6)	–	–	2 (9.1)
Didn't want other people to know about my illness	–	–	–	–	–	–	–	–
Seemed to be unsuitable because of old age	1 (3.3)	–	1 (10.0)	–	1 (5.6)	–	–	1 (4.5)
Seemed to be not urgent	2 (6.7)	1 (5.0)	1 (10.0)	2 (18.2)	–	–	–	2 (9.1)
Was reluctant to go to other hospitals or clinics	–	–	–	–	–	–	–	–
Was satisfied with current treatment	–	–	–	–	–	–	–	–
Family objection	–	–	–	–	–	–	–	–
Seemed to be unsuitable because of the presence of other illnesses	–	–	–	–	–	–	–	–
Seemed to be bothersome to go to clinics more often	–	–	–	–	–	–	–	–
Seemed to be ineffective	–	–	–	–	–	–	–	–
Did not like injection	–	–	–	–	–	–	–	–
Explanation by physicians was insufficient	–	–	–	–	–	–	–	–
Could not understand the explanation by physicians	–	–	–	–	–	–	–	–
Others	3 (10.0)	3 (15.0)	–	–	3 (16.7)	–	3 (37.5)	–
No answer	8 (26.7)	4 (20.0)	4 (40.0)	2 (18.2)	6 (33.3)	–	1 (12.5)	7 (31.8)

uated for the effect of IFN because the therapy was in progress. Therapeutic effects of IFN for the remaining 64 patients are as follows (Table 6). "Sustained virological response (SVR) (negative HCV RNA and normal transaminase in tests conducted 6 months after the completion of IFN therapy)" was found for 46.9% (30/64) of the patients; "biological response (BR) (positive HCV RNA and normal transaminase in tests conducted 6 months after the completion of IFN therapy)" for 14.1% (9/64); "no response (NR)" for 34.4% (22/64); and "Unclear or no answer" for 4.7% (3/64).

Of 64 patients in whom therapeutic effects of IFN could be evaluated, 18 were treated at clinics (non liver-specialists) and 46 at a hospital (liver specialists). For these two groups, IFN therapy was evaluated as SVR in 44.4% (8/18) and 47.8% (22/46) of patients. This shows that effects of IFN therapy were comparable in the two groups despite

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Table 6. Therapeutic effects of IFN to patients who agreed to receive IFN therapy upon recommendation by their physicians (excluding patients in whom the therapy is in progress).

	Patients who agreed to receive IFN therapy (excluding patients who could not be evaluated)	Treatment facilities	
		Clinic (non liver-specialist)	Hospital (liver specialist)
	n=64 (%)	n=18 (%)	n=46 (%)
SVR	30 (46.9)	8 (44.4)	22 (47.8)
BR	9 (14.1)	2 (11.1)	7 (15.2)
NR	22 (34.4)	7 (38.9)	15 (32.6)
Unclear or no answer	3 (4.7)	1 (5.6)	2 (4.3)

SVR – sustained virological response; BR – biological response; NR – no response.

their having attended different treatment facilities (clinics vs hospital).

Discussion

We have reported studies done in an HCV hyperendemic area [10–17]. In 1990, 10% (739 people) of the adult population (7,389) in the area were selected randomly, of whom 509 people were tested for liver disease. The positive rates of anti-HCV, HCV RNA and HBs antigen were, respectively, 23.6%, 17.9% and 2.6% [11].

Findings concerning the area obtained so far are as follows. Medical activities are regarded as the original source of HCV dissemination in the area [12]. Many HCV carriers die of HCC or cirrhosis [13]. Follow up from 1990 to 2002 found that the yearly onset rate of HCC from chronic hepatitis C was 1.7% and that of HCC from cirrhosis was 6.7% [14]. Nineteen percent of HCV carriers were under the care of liver specialists and 75% of residents with a history of IFN therapy were treated by liver specialists [15]. HCV carriers had extrahepatic manifestations including lichen planus and diabetes mellitus more frequently than non-carriers [16,17].

Telephone interviews were conducted to determine the reasons why some carriers who knew the facts did not participate in screenings or declined to receive treatment. Reasons included high medical cost, being asymptomatic, secrecy from families, and being busy [15].

In our previous reports of the same area [10], according to responses by physicians to questionnaires, 59.1% (150/254) of patients were recommended IFN therapy by physicians and 40.6% (103/254) of patients received IFN therapy. The proportions of these patients receiving IFN therapy were 78.2% for patients of liver specialists and 15.7% for patients of non liver-specialists, revealing that the two differed by approximately 5 fold. The difference was due to the intensity of the effort and the strength of the explanations or recommendations given by physicians to patients. It was also found that liver specialists offered to patients information on new therapies, influencing the decision by patients to receive IFN therapy. Liver specialists also explained and recommended IFN therapy to patients even though the patients were elderly with complications [10].

In the present paper, factors were studied statistically that influenced the decision by patients with chronic hepatitis C whether or not to receive IFN therapy after it was recommended by their physician. We could collect unbiased answers from groups that have relatively homogenous medical environments and living customs, as many medical facilities in the subject area were cooperative. Of 139 patients to whom physicians recommended IFN therapy, 92 (66.2%) agreed to receive IFN therapy. Whereas 74 (86.0%) of 86 hospital patients (treated by liver specialists) agreed to receive IFN therapy, only 18 (34.0%) of 53 clinic patients (treated by non liver-specialists) did so.

Multivariate analysis demonstrated that treatment facilities, sex and the presence or absence of complications were factors associated with the risk that patients would decline IFN therapy. In other words, age (elderly) and stages of liver diseases which physicians answered as factors for which IFN therapy was not recommended did not influence the decision by patients. Analysis suggested that differences in sex influenced the decision by patients.

The most frequently mentioned reason for not receiving IFN therapy even though physicians recommended it and patients acknowledged the recommendation was "worries over adverse reactions." A higher proportion of females than males worried about adverse reactions (male: 18.2%, female: 33.3%), as shown in Table 5. Although the risk of HCC in males was higher than that in females, treatment of HCC in elderly females has become an issue because of HCC patients' aging [19]. It has been reported concerning IFN therapy for female patients that IFN monotherapy for females over 40 years old was not markedly effective [20], and caution should be exercised for hemolytic anemia as an adverse reaction of ribavirin [21]. It may be necessary for physicians to explain and recommend IFN therapy to female patients while keeping in mind that females are more anxious about the therapy than are males.

It is understandable that it is difficult for non-specialists to explain well to patients about diseases and treatments outside their specialties. However, there was no difference between treatment facilities in therapeutic effects of IFN therapy in patients who agreed to receive the therapy upon recommendation by physicians. In other words, therapeutic effects were not affected greatly whether attending phy-

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sicians were liver specialists or not. Therefore, it is essential, in order to facilitate patients' decision to receive IFN therapy, for physicians to strive to explain it as thoroughly as possible.

Conclusions

It is important, in order to facilitate patients decisions to receive IFN therapy, to improve communication between physicians and patients. It is also important for physicians and patients to strive to establish trust between themselves. It is hoped that specialists and non-specialists in all areas will hold discussions to create cooperation between hospitals and clinics.

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原　著

HCVあるいはHBV感染者における歯科治療時の自己申告調査

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Key words: hepatitis C virus (HCV), hepatitis B virus (HBV), dental care, cross infection, self-disclosure

要　旨

C型肝炎ウイルス（HCV）もしくはB型肝炎ウイルス（HBV）感染を認識し，慢性肝疾患を治療する目的で久留米大学病院消化器病センターを受診した患者を対象に，歯科医療機関を受診した際に肝疾患の病歴を申告しているかどうかの有無を調査した．2006年10月24日から2007年4月24日までに209名の患者が調査に参加した．そのうち，感染者であることをいつも申告する患者の割合は59.8%（125名），申告することもあるが，しないこともある患者の割合は12.0%（25名），申告しない患者の割合は28.2%（59名）であった．申告しない最大の理由は，「基礎疾患の有無を質問されなかったから」（71.2%）であった．「歯科医院で嫌がられるかもしれないから」という理由や（11.9%），「肝疾患の罹患を知られたくなかったから」という隠蔽理由は10.2%であり，これらの理由を挙げる割合は，女性よりも男性の方が多かった．

以上の結果から，肝臓専門医は肝疾患患者が歯科治療に際し，どのように対処すればよいかなどの助言を行うべきだと考えられる．さらに何よりも重要なのは，歯科医療の安全を確保して感染を防止するために，歯科医療従事者が全患者にスタンダードプレコーションを実施することであり，また，歯科医による院内感染対策を奨励し，援助するために国が適切な措置を講じることが望まれる．

〔感染症誌　82：213～219，2008〕

序　文

現在，日本における肝細胞癌（肝癌）の死亡者数は増加の一途をたどっている[1]．日本では，肝癌の原因の約8割がC型肝炎ウイルス（HCV）に起因し，約1割がB型肝炎ウイルス（HBV）に起因している．HCVによる肝癌患者の増加が，本邦における肝癌死亡者数の増加の原因である．

厚生労働省は，肝癌撲滅を目的として，2002年4月より老人保健法に基づく保健事業における肝炎ウイルス検診（節目検診と節目外検診）を開始した．しかしその一方で，検診受診率が低いこと，肝炎ウイルス検査で要精密検査と判断された者が医療機関を受診しないこと，またたとえ医療機関を受診しても，必ずしも適切な医療が提供されていないという問題点が指摘されている[2]．そのため，2007年より都道府県における肝疾患診療ネットワークの構築が推し進められている．

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本邦におけるC型慢性肝疾患患者の増加に伴い，歯科診療上，院内感染対策の再徹底が急務とされ，2001年度より肝炎等克服緊急対策研究事業（肝炎分野）として「歯科診療におけるC型肝炎の感染リスク低減に関する研究」が開始された[3]．歯科治療におけるHCVの水平感染を防ぐ方策が検討され，スタンダードプレコーションの考えに基づき歯科医療機関の院内感染対策ガイドラインが策定された[4)5)]．

一般歯科診療では，病原体を含む血液あるいは唾液に接触することで，患者から歯科医療従事者へ，歯科医療従事者から患者へ，あるいは汚染された器械・器具を通じて患者から別の患者へと病原体の伝播が拡大する可能性がある．歯科医療施設において，血液媒介病原体（HBVもしくはHCVもしくはヒト免疫不全ウイルス：HIV）の院内感染が実際に起こった事例は少ない[6]ものの，感染伝播の可能性を看過することはできない．歯科医師にとってまず求められるのは，患者の全身状態や既往疾患を認識して必要な情報を得るために，的確な問診と得られた資料を十分に考察することである．初診時の問診を丁寧に行うことは，感染

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防止対策の第一歩となるのと同時に，患者との信頼関係を築くことにもつながる．さらに，必要に応じて各専門医と対診し，治療方針を決定することもできるからである．しかし，日本の一般歯科外来診療の現状では，歯科医師が全患者の感染症の実態を把握することは不可能である．また，患者自身が自分の疾患に気づいていない場合も多く，いかにこれをスクリーニングするかが問題となる．したがって，感染対策についてはスタンダードプレコーションの適用が重要視される．

私どもが過去に報告した調査の中で，HCV 感染者が医師からインターフェロン（IFN）治療を推奨されても拒否する理由として「他人に病気のことを知られたくないから」という理由が 9.4%（3/32 名）存在した[7]．また福岡県 X 町における 12 年間の追跡疫学調査の中で，HCV 持続感染者と認識しているにもかかわらず，12 年間のうち検診も通院もしないと回答した感染者がいたが，その理由の 1 つは，HCV 感染を家族に知られたくないからということが電話インタビューによってわかっている[8]．つまり，私どもは，肝炎ウイルス感染患者が自分自身の感染を隠蔽する事態があり得るのではないかと考えた．

そこで，私どもは久留米大学病院消化器病センターを受診している肝炎ウイルス感染患者を対象に，歯科医療機関を受診した際に肝疾患の病歴を申告しているかどうかを調査した．

対象と方法

1．対象

対象は，2006 年 10 月 24 日から 2007 年 4 月 24 日までに，肝疾患の治療目的に久留米大学病院消化器病センターを受診した HCV もしくは HBV による慢性肝疾患を有する患者で，自身の肝炎ウイルス感染を認識し，かつ歯科受診をしたことのある患者とした．ただし，肝炎ウイルス感染者であることを自覚していなかった患者，歯科受診の経験がない患者，肝疾患名が正確ではない患者，あるいは認知症を認める患者は対象外とした．全対象者は，社団法人日本肝臓学会が認定した肝臓専門医の診察を受けた後，本アンケートに無記名で回答した．

2．方法

患者が来院した際に，外来主治医が「歯科受診時のアンケート」への回答を依頼し，主治医が医師記入欄の診断名を記入したのち，患者は無記名でアンケートに回答し，アンケート回収ボックスに投函した．

下記の調査項目につき，アンケートを実施した．

1）患者背景

①年齢

②性別

③肝疾患の診断名（医師のみアンケートに回答）

2）歯科受診時の肝炎ウイルス感染の申告有無

①申告する

②申告することもあるが，しないこともある

③申告しない

3）歯科受診時に肝炎ウイルス感染を必ずしも申告しない理由（複数回答可）

①肝臓の病気と歯科治療は，関係ないと思ったから

②歯科医院で，全身的な病気があるかどうか質問されなかったから

③肝炎ウイルスを持ってはいるが，肝機能の値が安定しているので，伝える必要はないと思ったから

④IFN 治療によってウイルスを駆除でき，現在ウイルスは消えているため，伝える必要はないと思ったから

⑤歯科医院で，肝臓病を患っていることを伝えたら，嫌がられるかもしれないと考えたから

⑥歯科医院で，肝臓病を患っていることを伝えたら，過去に嫌がられた経験があるから

⑦肝臓の病気を伝えるのが面倒くさかったから

⑧肝臓の病気を知られたくなかったから

⑨その他

⑩無回答

4）自由回答（歯科治療について望むこと）

統計解析は，$\chi 2$ 乗検定法を用いた．

成　績

患者自身が HCV もしくは HBV による慢性肝疾患患者と認識し，歯科受診をしたことのある患者は 209 名（男性 95 名，女性 114 名）（59.5 歳±12.7 歳）であった（アンケート回収率は 100%）．HCV 感染者 162 名，HBV 感染者 46 名，HCV 並びに HBV 感染者 1 名であった．肝疾患の内訳は，Table 1に示すように HCV，HBV 感染いずれも慢性肝炎が最も多く，各々 67.9%（110/162 名），45.7%（21/46 名）であった．

自身が肝炎ウイルス感染者であることを歯科医師に申告するかどうかの有無については，いつも「申告する」59.8%（125/209 名），「申告することもあるが，しないこともある」12.0%（25/209 名），「申告しない」28.2%（59/209 名）であった（Table 2）．なお，「申告する」（125 名），「申告することもあるが，しないこともある」（25 名），「申告しない」（59 名）の 3 グループにおいて，HCV もしくは HBV の感染別，あるいは性別には差異は認められなかった．

歯科医師に感染者であることを「申告しない」と答えた患者（59 名）の理由を Table 3に示す．複数回答において，最大の理由は，「歯科医院で，全身的な病気があるかどうかを質問されなかったから」であり，71.2%（42/59 名）を占めた．その他の理由として，「肝

Table 1 Liver disease among 209 patients

Diagnosis	n	HCV n = 162 (%)	HBV n = 46 (%)	HCV and HBV n = 1 (%)
Asymptomatic carrier	14	5 (3.1)	9 (19.6)	0 (0)
Chronic hepatitis (CH) alone	131	110 (67.9)	21 (45.7)	0 (0)
CH post-IFN SVR	17	17 (10.5)	n/a	0 (0)
Liver cirrhosis (LC)	35	20 (12.3)	15 (32.6)	0 (0)
Hepatocellular carcinoma (HCC)	6	5 (3.1)	1 (2.2)	0 (0)
CH and HCC	2	2 (1.2)	0 (0)	0 (0)
CH post-IFN SVR and HCC	1	1 (0.6)	n/a	0 (0)
LC and HCC	2	2 (1.2)	0 (0)	0 (0)
HBV asymptomatic carrier and CH-C post-IFN SVR	1	0 (0)	0 (0)	1 (100)

IFN: interferon
SVR: sustained virological response
CH: chronic hepatitis
LC: liver cirrhosis
HCC: hepatocellular carcinoma
n/a: not applicable

Table 2 Disclosure questionnaire of dental patients with liver disease

Disclosure	Subjects	Hepatitis virus			Gender	
		HCV	HBV	HCV and HBV	Male	Female
	n = 209 (%)	n = 162 (%)	n = 46 (%)	n = 1 (%)	n = 95 (%)	n = 114 (%)
Yes	125 (59.8)	98 (60.5)	26 (56.5)	1 (100)	54 (56.8)	71 (62.3)
Depends on situation	25 (12.0)	18 (11.1)	7 (15.2)	0 (0)	16 (16.8)	9 (7.9)
No	59 (28.2)	46 (28.4)	13 (28.3)	0 (0)	25 (26.3)	34 (29.8)

臓の病気と歯科治療は，関係ないと思ったから」52.5% (31/59名)，「肝炎ウイルスを持ってはいるが，肝機能の値が安定しているので，伝える必要はないと思ったから」22.0% (13/59名)，「歯科医院で，肝臓病を患っていることを伝えたら，嫌がられるかもしれないと考えたから」11.9% (7/59名)，「肝臓の病気を知られたくなかったから」10.2% (6/59名) などが挙がっていた．

歯科医院で，全身的な病気の有無を質問されなかったために，自身の肝炎ウイルス感染を申告しない患者は，男女ともに高率であった（男性60.0%，女性79.4%）．しかし，「肝臓の病気を知られたくないから」という理由や「歯科医院で嫌がられるかもしれないから」という理由で申告しない患者は，各々男性8.0%・女性1.2%，男性16.0%・女性8.8%であり，女性よりも男性の方が多かった．

ウイルス感染別にみると，HBV感染者はHCV感染に比べて，歯科医院で申告すると嫌がられるかもしれないと考える患者が有意に多かった．肝疾患別では，肝疾患の病期が進展した肝硬変患者であっても申告しない患者が存在した．

考　察

わが国の歯科治療における感染予防では，特に感染者の多い肝炎ウイルス対策が重要となる．本邦には約200万人のHCV持続感染者，約150万人のHBV持続感染者が存在すると考えられているからである．その中には自分自身が感染していることを自覚していない者も多い．

歯牙を切削する高速回転器機（エアータービン）は，毎分30～40万回転しており，摩擦熱を冷却するための水と空気の混合スプレーが放出される．注水下に歯や骨を切削すると，唾液や血液等の体液を周囲に飛散させる機会が多く，歯科医療従事者は自身への感染に注意するだけでなく，交叉感染を防止する院内感染対策にも留意する必要がある．HCV持続感染者の歯科治療では，HCV RNAが血液だけでなく唾液，歯肉溝滲出液，印象採得時の印象材，診療台の作業台，エアータービンのハンドピース，ホルダー，吸引嘴管，鉗子，デンタルミラー，切削バーからも検出されることが報告されている[9)~13)]．また歯石除去前後の唾液にHCV RNAが検出されることもわかっている[14)]．ただし，唾液中に検出されるウイルス量は血中のウイルス量よりも少ないため[15)16)]，唾液中のHCVによる感染が必ずしも成立するとは限らない．

どんなに詳細で丁寧な問診を行っても，患者自身が感染者であることを自覚していない症例も存在するため，全患者をスクリーニングすることはできない．問診によって患者から得られる情報と事実には，どれほ

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Table 3 Reasons why infection-aware patients did not disclose medical histories (multiple answers allowed)

Reasons	Nondisclosure	Gender			hepatitis virus			Diagnosis of liver diseases						
		Male	Female	p value	HCV	HBV	p	Asymptomatic	Chronic hepatitis (CH)	CH post IFN SVR	Liver cirrhosis	Hepatocellular carcinoma (HCC)	CH post- IFN SVR and HCC	p
	n = 59 (%)	n = 25 (%)	n = 34 (%)		n = 46 (%)	n = 13 (%)		n = 9 (%)	n = 36 (%)	n = 3 (%)	n = 9 (%)	n = 1 (%)	n = 1 (%)	
· Liver disease seemed unrelated to dental treatment	31 (52.5)	16 (64)	15 (44.1)	NS	25 (54.3)	6 (46.2)	NS	5 (55.6)	20 (55.6)	1 (33.3)	5 (55.6)	—	—	NS
· Not asked to provide information about medical history including systemic disease	42 (71.2)	15 (60.0)	27 (79.4)	NS	32 (79.4)	10 (76.9)	NS	6 (66.7)	26 (72.2)	2 (66.7)	7 (77.8)	—	1 (100.0)	NS
· Seemed to be unnecessary to disclose because the liver function was stable	13 (22.0)	5 (20.0)	8 (23.5)	NS	9 (19.6)	4 (30.8)	NS	4 (44.4)	6 (16.7)	1 (33.3)	2 (22.2)	—	—	NS
· Seemed to be unnecessary to disclose because able to get rid of hepatitis virus by IFN therapy	4 (6.8)	4 (16.0)	—	NS	4 (8.7)	—	NS	—	1 (2.8)	2 (66.7)	1 (11.1)	—	—	NS
· Seemed to receive negative reaction from dental healthcare workers if disclosed	7 (11.9)	4 (16.0)	3 (8.8)	NS	3 (6.5)	4 (30.8)	< 0.05	2 (22.2)	3 (8.3)	1 (33.3)	1 (11.1)	—	—	NS
· Received negative reactions from dental healthcare workers when disclosed	1 (1.7)	—	1 (2.9)	NS	1 (2.2)	—	NS	—	1 (2.8)	—	—	—	—	NS
· Nuisance to disclose illness	3 (5.1)	—	3 (8.8)	NS	2 (4.3)	1 (7.7)	NS	1 (11.1)	2 (5.6)	—	—	—	—	NS
· Did not want dentist or staff to know about illness	6 (10.2)	2 (8.0)	4 (1.2)	NS	5 (10.9)	1 (7.7)	NS	—	4 (11.1)	1 (33.3)	1 (11.1)	—	—	NS
· Other	4 (6.8)	3 (12.0)	1 (2.9)	NS	3 (6.5)	1 (7.7)	NS	—	3 (8.3)	—	—	1 (100.0)	—	< 0.01
· No response	2 (3.4)	—	2 (5.9)	NS	2 (4.3)	—	NS	—	2 (5.6)	—	—	—	—	NS

どの差があるのだろうか？　増田らは，ある一定の期間に病院歯科口腔外科を受診した975名，延べ1,657件における梅毒，HBV，並びにHCV感染症の有無について，血液検査，および他の医療機関での検査，問診によって調査した[17]．彼らによると，感染症の有無を把握できたのは，対象者の約60%（581/975名）に留まっている．梅毒感染者7名，HBV感染者4名，HCV感染者20名のうち，問診での判明率は，各々14.3%（1/7名），50.0%（2/4名），40.0%（8/20名）であり，病院歯科でさえ問診のみで患者の感染症を把握することは困難である．まして一般歯科診療所では，全患者の感染症有無を把握することは不可能であろう．岸本らによると，大学病院口腔外科外来を受診した270名の患者のうち，問診上は問題なしと考えられた輸血歴，透析歴，肝疾患の既往，肝疾患の家族歴を認めない227名において，梅毒・HBV・HCV感染症いずれかの保有率は4.1%（9/227名）であったと報告している（梅毒1名，HCV感染8名）[18]．また今井らは，対象患者2,198名のうち，問診にて判明したHBVもしくはHCV感染者等を除外した，問診上では感染症を認めない2,167名について検索を行ったところ，感染者は103名（4.8%）認められたと報告している[19]．HBs抗原陽性率0.78%，HCV抗体陽性率3.97%であった．これらのデータから，問診だけでは把握できない潜在感染患者が予想以上に多いことがわかり，院内感染対策の重要性を認識させられる．

本調査における対象患者は，大学病院で肝臓専門医による診察を受けている患者であり，先進的医療を希望して受診しているため，肝疾患の病態についての知識も高いと思われるが，歯科医院を受診する際に，肝炎ウイルス感染者であることを必ず申告すると答えた患者の割合は，約60%であった．約30%は，自らの感染を自覚しているのにもかかわらず，申告するわけではなかった．つまり，肝臓専門医のいない医療機関に通院している患者では，歯科医院で感染の申告を行っていない割合が，もっと高い可能性がある．よって，歯科治療の現場では，患者自身が感染者であることを自覚していない場合以外に，感染者であっても申告しない場合があることを念頭に置く必要がある．肝炎ウイルス感染者が，自分自身の感染を自覚しながら，歯科治療受診時に申告しないと答えた59名（28.2%，59/209名）のうち，その理由として最も多いものは，歯科医院で全身的な病気があるかどうか質問されなかったからだと答えている（71.2%，42/59名）．はたしてこの事実は正しいのだろうか？

本稿のアンケートは，患者と歯科医師双方を対象に実施したものではないため，患者と歯科医師の認識の一致率を正当に評価したものではない．私どもが2007年1月20日に実施した福岡県南地区歯科医学会に参加した開業医の歯科医師を対象に行った調査によると，必ず基礎疾患の問診を行う歯科医師は89.7%（61/68名）に留まっていた．基礎疾患に対する問診実施率を上げる工夫も必要である．歯学部の学生における肝炎ウイルスの知識や器具の消毒と滅菌に関する理解は，必ずしも高くないこともわかっており[20]，歯科医療の安全と感染防止対策を図るために患者全員に対するスタンダードプレコーションの実施に取り組むと同時に，歯科医師の生涯教育が大切であると考えられる．

昨今，スタンダードプレコーションの実施が重要視されているが，一般歯科診療所における院内対策のための保険点数は認められていない．感染防止対策に対する歯科診療報酬は「再診料」38点（380円）の中にしか含まれておらず，歯科医療の安全・感染防止対策が適切に行われるとは考えがたい．患者が安心して治療を受けられるためにも，院内感染対策として国が十分な措置を講じる必要がある．

一方，あえて肝炎ウイルス感染者であることを申告しない患者の中には，肝臓の病気を知られたくない，病気を伝えることが面倒くさい，歯科治療とは関係ないと思ったと認識している患者も存在していた．このような認識による感染の未申告は，歯科医院での交叉感染のリスクを上げるだけでなく，観血処置や投薬等に影響を及ぼすため，危険である．HBV感染者の方がHCV感染者よりも，嫌がられるかもしれないからという理由で感染者であることを申告しない患者が有意に多かった．このことは，患者自身がHCVよりもHBVの方が感染力が強いという事実を認識している可能性がある．肝臓専門医は肝疾患を有する患者が歯科治療を受ける際にどのように対処すればよいかなどの助言を日常診療の中で患者に行うことも大切であろう．

今回の結果より，歯科治療を受ける際にHCVあるいはHBV感染を認識しているにもかかわらず，申告しない患者が存在する実態が明らかとなった．このことを解決するには，歯科治療を受療する際の肝臓専門医による患者への助言，歯科医療の安全と感染防止対策のための歯科医療従事者によるスタンダードプレコーションの実施，歯科医療に関する院内感染対策を援助するための国による支援と措置が必要と考えられた．

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HCV or HBV Infection Self-disclosure to Dentists

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We distributed a questionnaire to 209 patients who visited the Digestive Disease Center of Kurume University for liver disease treatment from October 2006 to April 2007 to determine whether patients with hepatitis C virus (HCV) or hepatitis B virus (HBV) disclosed their disease status to dental clinics personnel. We found that 59.8% (125/209) always did so, 12.0% (25/209) sometimes did so, and 28.2% (59/209) never did so. The main reason (71.2%) for nondisclosure was failure of dental healthcare workers to ask whether patients had systemic disease. Other reasons included fear of negative reactions from healthcare workers (11.9%) and not wanting dentists or staff to know their specific liver ailment (10.2%). Men were less likely than women to disclose status for these reasons.

It thus cannot be over emphasized that liver disease patients be advised by medical specialists to make known their HCV or HBV status when undergoing dental care. Above all, it is important for dental workers to take standard precautions with all patients to ensure medical safety and to prevent infection in dental practice. The government should take appropriate measures to encourage and support dentists who use precautions to prevent nosocomial infection.

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