Table III. Breakdown of results classified by anti-HBc (+) and anti-HBc (-).

	Subjects with anti-HBc (+) 17		Subjects with anti-HBc (-) 124	
	(n)	(%)	(n)	(%)
Hepatitis B vaccine				
Vaccination yes	1	5.9	67	54.0
Vaccination no	16	94.1	47	37.9
During vaccination (or Drop-out)	0	0.0	4	3.2
Unknown	0	0.0	6	4.8
Sex				
Male	9	52.9	34	27.4
Female	8	47.1	90	72.6
Age				
29 years old	1	5.9	42	33.9
30-39	1	5.9	34	27.4
40-49	2	11.8	34	27.4
50-59	5	29.4	12	9.7
60-69	6	35.3	1	0.8
70-79	2	11.8	0	0.0
80 and older	0	0.0	1	0.8
Type of occupation				
Dentist	9	52.9	33	26.6
Dental hygienist	2	11.8	33	26.6
Dental assistant	2	11.8	39	31.5
Dental mechanic	0	0.0	8	6.5
Clerk	4	23.5	11	8.9
Years engaged in dental care				
<5 years	0	0.0	31	25.0
5-9	2	11.8	33	26.6
10-19	4	23.5	29	23.4
20-29	6	35.3	27	21.8
30 and longer	5	29.4	4	3.2
How to equip oneself with disposable gloves (Plural answers were given)				
Wear new pair with every new patient	1	5.9	8	6.5
Wear new pair with each 2 to 3 patients	1	5.9	30	24.2
Wear new pair when old one is torn	0	0.0	36	29.0
Wear new pair about twice a day	0	0.0	7	5.6
Wear when invasive treatment is performed	7	41.2	23	18.5
Wear when infected patients are treated	9	52.9	20	16.1
Wear when instrument is washed	0	0.0	2	1.6
Do not use	4	23.5	20	16.1
History of jaundice				
Yes	0	0.0	1	0.8
No	17	100.0	116	93.5
Unknown	0	0.0	7	5.6
History of blood transfusion				
Yes	1	5.9	4	3.2
No	15	88.2	118	95.2
Unknown	1	5.9	92	1.6

Table III. Continued.

	Subjects with anti-HBc (+) 17		Subjects with anti-HBc (-) 124	
	(n)	(%)	(n)	(%)
Clinical history of liver diseases				
Yes	1	5.9	5	4.0
No	16	94.1	119	96.0
Unknown	0	0.0	0	0.0
Family history of liver diseases				
Yes	2	11.8	7	5.6
No	15	88.2	109	87.9
Unknown	0	0.0	8	6.5
HBsAg				
Positive (+)	0	0.0	0	0.0
Negative (-)	17	100.0	124	100.0
Anti-HBs				
Positive (+)	16	94.1	57	46.0
Negative (-)	1	5.9	67	54.0
Anti-IgM-HBc				
Positive (+)	0	0.0	-	-
Negative (-)	17	100.0	-	-
HBV DNA quantitative measurement				
≥2.6 log/ml	0	0.0	-	-
<2.6 log/ml	17	100.0	-	-

Discussion

HBV infection is transmitted mostly through blood and body fluid as a result of bites, administration of blood preparations, sexual activities and mother-infant transmission. The principal route of HCV infection is through blood. Medical care workers are always at risk of infection as they are exposed to contaminated fluids from needle sticks and infected blood droplets. Hepatitis B immune globulin (HBIG) has been used since 1981 and hepatitis B vaccination since 1985 (whole virus) and 1988 (recombinant) to prevent infection.

Dental care workers are often exposed to blood because of stomatorrhagia and the use of sharp instruments (11). Meticulous measures should be taken to protect against the spraying of saliva, which contains blood inside the examination room (12,13). Our previous study reported that saliva from HCV carriers contained HCV RNA before and after scaling of dental calculus (14). HCV RNA was detected in exudates from gingival crevicular fluid and on materials used for making dental impressions, a work bench, an air turbine dental hand-piece, holders, suction units, forceps, dental mirrors and cutting bar (15-17). HCV RNA was still detectable on the surface of dental instruments several days after the HCV carriers received treatment (18). Although their risk of infection is high, dental care workers are obligated to prevent cross infection (i.e., from dental care workers to patients and patients to patients). Although there are no documented cases of HCV transmission from dentists to patients, there is one case of the transmission of HBV by an oral surgeon (19).

Whether the disease is contracted depends on the levels of the virus in the blood, source of contamination, route of contact and blood volume transfused (20). The rate of acquiring HBV infection through HBV-contaminated needles is high [12% (21) to 60% (22) in unvaccinated persons]. Wounds caused by needles that are contaminated with HBsAg- and HBeAg-positive blood are associated with a 22-31% risk of developing hepatitis B and a 37-62% probability of establishing HBV infection (23). Wounds caused by needles contaminated with HBsAg-positive and HBeAg-negative blood are associated with a 1-6% risk of developing hepatitis B and a 23-37% probability of establishing HBV infection (21). However, infection can be prevented by HB vaccination and the administration of HBIG after these accidents occur.

Accidental prick with a needle contaminated with HCV-positive blood caused HCV infection in ~1.4 (24) to 10% (25) of cases. The probability of infection due to contaminated needle sticks is lower for HCV than HBV. However, the high risk of developing HCC through horizontal infection of HCV is a concern to often-exposed dentists. Feldman and Schiff found that hepatitis morbidity was 6.7% in dentists and 21% in oral surgeons in the State of Florida, USA (26). Although the risk of hepatitis among dentists is high, a long-term cohort study by Tanaka *et al* reported that liver cancer risk was no higher in Japanese dentists than in the general population (27).

In the present investigation, 51 of the 68 recipients of the HBV vaccine were anti-HBs-positive, indicating that 75% of vaccinated subjects developed an antibody to HBV infection. Of the 63 unvaccinated subjects, 16 (25.4%) were anti-HBc-positive and had no clinical history of HBV-related liver diseases, suggesting that they had been transiently and inapparently infected with HBV in the past. Only 1 (1.5%) of the 68 vaccinated subjects was anti-HBc-positive, indicating the protection rate against HBV infection was higher in vaccinated than unvaccinated subjects and that vaccination was a useful protective measure.

The Japanese Red Cross introduced the Hemagglutination Inhibition Test (HI) in 1989 for the screening of anti-HBc (28) and the Nucleic Acid Amplification Test (NAT) in 1999 for the screening of HBV, HCV and HIV in blood that was HBsAg-, anti-HBc-, anti-HCV- and anti-HIV-negative with ALT values <61 IU/l, dramatically increasing the safety of blood transfusion (29).

In Fukuoka and Kitakyushu Red Cross, 3,647 (1.1%) of 323,799 blood donors screened between April 2003 and October 2004 were anti-HBc-positive. Of these 3,647, a total of 445 were HBsAg-positive (30). In the remaining 3,202 anti-HBc-positive, HBsAg-negative donors, the rates of seroconversion to anti-HBc increased with age (0.10, 0.23, 0.57, 1.38, 2.10 and 2.29%, respectively, in age groups 16-19, 20-29, 30-39, 40-49, 50-59 and 60-69).

Seroconversion to anti-HBc occurred at a significantly higher rate in dental care workers (12.1%) than blood donors ($p<0.05$).

Anti-HBc is a marker of latent hepatitis B (31,32). In previous years, it has been reported that HBV infection was transmitted through a liver transplanted from an anti-HBc-positive donor (32). HBV DNA has been detected in the serum of patients recovered from acute hepatitis B (33). Infection of latent HBV has been associated with the onset of HCV-related HCC (34,35). Therefore, from the standpoint of health safety, the prevalence of latent HBV infection among dental care workers must be acknowledged.

Of the 63 unvaccinated subjects, only 4.8% changed gloves to a new pair for each new patient and 19% never wore gloves. Since dental care workers have a high risk of exposure to the hepatitis virus, a compulsory vaccination for the hepatitis B virus is desirable for all dental care workers. In Japan, hepatitis B vaccination is voluntary. However, from the standpoint of effectiveness and safety and to reduce infection risk, it is important to vaccinate these workers.

Regrettably, no hepatitis C vaccine or immunoglobulin has been developed to prevent HCV infection. Although no persistent carriers of HBV and HCV were detected in the present investigation, the rate of infection is higher in the western portion of Japan, especially in the Saga and Fukuoka prefectures, than eastern Japan. Therefore, further precautions must be taken.

Acknowledgements

This study was supported by a Grant-in-Aid for Scientific Research (C) (No. 18592213) from the Japanese Ministry of Education, Culture, Sports, Science and Technology of Japan. We thank Dr Masahiro Tsuji, Dr Masakatsu Shimada and Dr Masahide Tsuji for support.

References

1. Higuchi M, Tanaka E and Kiyosawa K: Epidemiology and clinical aspects on hepatitis C. Jpn J Infect Dis 55: 69-77, 2002.
2. Batista SM, Andreasi MS, Borges AM, *et al*: Seropositivity for hepatitis B virus, vaccination coverage, and vaccine response in dentists from Campo Grande, Mato Grosso do Sul, Brazil. Mem Inst Oswaldo Cruz 101: 263-267, 2006.
3. Cleveland JL, Siew C, Lockwood SA, Gruninger SE, Gooch BF and Shapiro CN: Hepatitis B vaccination and infection among U.S. dentists, 1983-1992. J Am Dent Assoc 127: 1385-1390, 1996.
4. Ammon A, Reichart PA, Pauli G and Petersen LR: Hepatitis B and C among Berlin dental personnel: incidence, risk factors, and effectiveness of barrier prevention measures. Epidemiol Infect 125: 407-413, 2000.
5. Reingold AL, Kane MA and Hightower AW: Failure of gloves and other protective devices to prevent transmission of hepatitis B virus to oral surgeons. JAMA 259: 2558-2560, 1988.
6. Thomas DL, Gruninger SE, Siew C, Joy ED and Quinn TC: Occupational risk of hepatitis C infections among general dentists and oral surgeons in North America. Am J Med 100: 41-45, 1996.
7. Shinozaki F, Hayatsu Y, Iwai M, *et al*: Investigation of the hepatitis B virus infection among dentist in Hokkaido area (in Japanese). Jpn J Oral Maxillofac Surg 26: 361-365, 1980.
8. Shinozaki F, Hayatsu Y, Iwai M, Kumagai S and Kohama G: A seroepidemiologic survey of hepatitis B virus infection among the dentist in Japan (in Japanese). Jpn J Oral Maxillofac Surg 29: 1865-1871, 1983.
9. Shinozaki F, Hayatsu Y, Fukuda T, Suetsugu M and Mizugaki Y: A seroepidemiologic survey of hepatitis C virus infection among the dentist in Japan (in Japanese). J Jpn Stomatol Soc 44: 438-441, 1995.
10. Klein RS, Freeman K, Taylor PE and Stevens CE: Occupational risk for hepatitis C virus infection among New York City dentists. Lancet 338: 1539-1542, 1991.
11. Siew C, Gruninger SE, Miaw CL and Neidle EA: Percutaneous injuries in practicing dentists: a prospective study using a 20-day diary. J Am Dent Assoc 126: 1227-1234, 1995.
12. Davison F, Alexander GJ, Trowbridge R, Fagan EA and Williams R: Detection of hepatitis B virus DNA in spermatozoa, urine, saliva and leucocytes, of chronic HBsAg carriers. A lack of relationship with serum markers of replication. J Hepatol 4: 37-44, 1987.
13. Komiyama K, Moro I, Mastuda Y, *et al*: HCV in saliva of chronic hepatitis patients having dental treatment. Lancet 338: 572-573, 1991.
14. Nagao Y, Seki N, Tamatsukuri S and Sata M: Detection of hepatitis C virus in saliva before and after scaling of dental calculus. Kansenshogaku Zasshi 74: 961-965, 2000.
15. Furuya H: A fact-finding on dental care of suspected hepatitis C patients-Hepatitis and Other Diseases Conquest Emergency Measures Study Project (hepatitis division). Study on reduction of infection risk of hepatitis C in dental care. Summary of assignment reports (in Japanese). Health and Labour Sciences Research Grants, Ministry of Health, Labour, and Welfare, Japan, pp6-11, 2002.
16. Piazza M, Borgia G, Picciotto L, Nappa S, Cicciarello S and Orlando R: Detection of hepatitis C virus-RNA by polymerase chain reaction in dental surgeries. J Med Virol 45: 40-42, 1995.
17. Maticic M, Poljak M, Kramar B, *et al*: Detection of hepatitis C virus RNA from gingival crevicular fluid and its relation to virus presence in saliva. J Periodontol 72: 11-16, 2001.
18. Fong TL, Charboneau F, Valinluck B and Govindarajan S: The stability of serum hepatitis C viral RNA in various handling and storage conditions. Arch Pathol Lab Med 117: 150-151, 1993.
19. Rimland D, Parkin WE, Miller GB Jr and Schrack WD: Hepatitis B outbreak traced to an oral surgeon. Hepatitis B outbreak traced to an oral surgeon. N Engl J Med 296: 953-958, 1977.
20. Chiarello LA and Bartley JB: Prevention of blood exposure in health care personnel. Semin Infect Control 1: 30-43, 2001.
21. Werner BG and Grady GF: Accidental hepatitis-B-surface-antigen-positive inoculations. Use of e antigen to estimate infectivity. Ann Intern Med 97: 367-369, 1982.

22. U.S. National Heart and Lung Institute Collaborative Study Group and Phoenix Laboratories Division, Bureau of Epidemiology, Center for Disease Control: Relation of e antigen to infectivity of HBsAg-positive inoculations among medical personnel. Lancet 1: 492-494, 1976.
23. CDC. Updated U.S. Public Health Service Guidelines for the Management of Occupational Exposures to HBV, HCV, and HIV and Recommendations for Postexposure Prophylaxis. 50 (RR11): 1-42, 2001.
24. Sodeyama T, Kiyosawa K, Urushihara A, *et al*: Detection of hepatitis C virus markers and hepatitis C virus genomic-RNA after needlestick accidents. Arch Intern Med 153: 1565-1572, 1993.
25. Mitsui T, Iwano K, Masuko K, *et al*: Hepatitis C virus infection in medical personnel after needlestick accident. Hepatology 16: 1109-1114, 1992.
26. Feldman RE and Schiff ER: Hepatitis in dental professionals. JAMA 232: 1228-1230, 1975.
27. Tanaka H, Nishio N, Tokunaga R and Tsukuma H: Liver cancer risk in Japanese male dentists: a long-term retrospective cohort study. J Occup Health 46: 398-402, 2004.
28. Iizuka H, Ohmura K, Ishijima A, *et al*: Correlation between anti-HBc titers and HBV DNA in blood units without detectable HBsAg. Vox Sang 63: 107-111, 1992.
29. Japanese Red Cross NAT Screening Research Group: Nationwide nucleic acid amplification testing of hepatitis B virus, hepatitis C virus and human immunodeficiency virus type 1 for blood transfusion and follow-up study of nucleic acid amplification positive donors. Jpn J Infect Dis 53: 116-123, 2000.
30. Yamasaki H, Manabe K, Matsumoto K, *et al*: The effect of notification of antibody to hepatitis B core antigen to voluntary donors (in Japanese). Ketsuekijigyo 28: 413-419, 2005.
31. Joller-Jemelka HI, Wicki AN and Grob PJ: Detection of HBs antigen in 'anti-HBc alone' positive sera. J Hepatol 21: 269-272, 1994.
32. Dickson RC, Everhart JE, Lake JR, *et al*: Transmission of hepatitis B by transplantation of livers from donors positive for antibody to hepatitis B core antigen. The National Institute of Diabetes and Digestive and Kidney Diseases Liver Transplantation Database. Gastroenterology 113: 1668-1674, 1997.
33. Michalak TI, Pasquinelli C, Guilhot S and Chisari FV: Hepatitis B virus persistence after recovery from acute viral hepatitis. J Clin Invest 93: 230-239, 1994.
34. Marusawa H, Osaki Y, Kimura T, *et al*: High prevalence of anti-hepatitis B virus serological markers in patients with hepatitis C virus related chronic liver disease in Japan. Gut 45: 284-288, 1999.
35. Tanaka K, Nagao Y, Ide T, Kumashiro R and Sata M: Antibody to hepatitis B core antigen is associated with the development of hepatocellular carcinoma in hepatitis C virus-infected persons: a 12-year prospective study. Int J Mol Med 17: 827-832, 2006.

Graves' ophthalmopathy and tongue cancer complicated by peg-interferon α-2b and ribavirin therapy for chronic hepatitis C: A case report and review of the literature

YUMIKO NAGAO[1], YUJI HIROMATSU[2], TADASHI NAKASHIMA[3] and MICHIO SATA[1,4]

[1]Department of Digestive Disease Information and Research, [2]Division of Endocrinology and Metabolism, Department of Medicine, [3]Department of Otolaryngology, [4]Division of Gastroenterology, Department of Medicine, Kurume University School of Medicine, Asahi-machi, Kurume, Fukuoka 830-0011, Japan

Received May 30, 2008; Accepted July 17, 2008

DOI: 10.3892/mmr_00000003

Abstract. Hepatitis C virus (HCV) infection induces not only chronic liver disease, but also extrahepatic manifestations such as thyroid disease and oral cancer. Thyroid dysfunction is also a complication known to be associated with interferon (IFN) therapy for HCV infection. We report on a 69-year-old Japanese man who developed Graves' ophthalmopathy and tongue cancer (malignant transformation of leukoplakia) while receiving peg-interferon (Peg-IFN) α-2b and ribavirin (RBV) treatment for chronic hepatitis C. This patient had no history of thyroid disease before the combination therapy, but did have bilateral leukoplakia of the tongue. The leukoplakia lesions did not change until 20 weeks after the start of the combination therapy, and ophthalmopathy was not diagnosed until 47 weeks later. As ophthalmopathy is considered to be a severe adverse event induced by Peg-IFN α-2b plus RBV, therapy was discontinued after 47 weeks. The patient received a partial glossectomy to remove the malignant neoplasm as well as extraocular muscle surgery for the ophthalmopathy, and was treated with an antithyroid agent and steroids. In conclusion, it is necessary to clinically examine organs other than the liver in patients with HCV infection.

Correspondence to: Dr Yumiko Nagao, Department of Digestive Disease Information and Research, Kurume University School of Medicine, 67 Asahi-machi, Kurume 830-0011, Japan
E-mail: nagao@med.kurume-u.ac.jp

Abbreviations: HCV, hepatitis C virus; IFN, interferon; Peg-IFN, peg-interferon; RBV, ribavirin; HCC, hepatocellular carcinoma; MRI, magnetic resonance imaging; HBsAg, hepatitis B surface antigen; TSH, thyroid stimulating hormone; FT_3, free tri-iodothyronine; FT_4, free thyroxine; TPOAb, thyroid peroxidase antibodies; TgAb, thyroglobulin antibodies; anti-HCV, HCV antibody; RBC, red blood cell; Hb, hemoglobin; WBC, white blood cell; AST, aspartate aminotransferase; ALT, alanine aminotransferase; γ-GTP, γ-glutamyl transpeptidase; LDH, lactate dehydrogenase; TRAb, TSH receptor antibody; TSAb, thyroid stimulating antibody; hTRAb, human TSH receptor antibody

Key words: hepatitis C virus, peg-interferon, ribavirin, Graves' ophthalmopathy, extrahepatic manifestation, oral squamous cell carcinoma

Introduction

Hepatitis C virus (HCV) frequently causes persistent infection, which leads to chronic liver disease and hepatocellular carcinoma (HCC). HCV-related HCC represents 80% of all HCC cases in Japan (1) and primary liver cancer, 95% of which is HCC-related, ranks third in men and fifth in women as the cause of death from malignant neoplasms. Interferon (IFN) α monotherapy for chronic hepatitis C infection leads to a sustained virological response in only 10-15% of HCV-infected patients (2,3). A substantial improvement in response of approximately 2-fold over IFN monotherapy was noted using the combination of IFN α plus ribavirin (RBV) (4,5). Recently, a combination treatment of peg-interferon (Peg-IFN) plus RBV has been adopted as standard care for patients with chronic hepatitis C, as it is associated with significant improvements in the rate of sustained virological response (50%) as compared to IFN α plus RBV or Peg-IFN α alone (6).

HCV infection has also been associated with extrahepatic manifestations and immune-mediated phenomena (7), including mixed cryoglobulinemia (8), thyroid disease (9), Sjögren's syndrome (10), porphyria cutanea tarda (11), lichen planus (12), oral cancer (13,14) and type 2 diabetes mellitus (15). The incidence of HCV infection in oral squamous cell carcinoma in Japanese patients has been reported as being 16.7-24.0% (13,14).

The side effects of IFN therapy for HCV have been well documented (16,17). Flu-like symptoms such as fever, chills, muscle ache, nausea, vomiting and fatigue are common side effects of treatment. Depression and related symptoms, such as anxiety, irritability, insomnia and mental confusion, are not rare and, in patients with a previous history, may be significant. Withdrawal rates in IFN-based combination studies due to side effects have ranged from 6 to 7% (5). Various side effects have been reported in patients treated with this cytokine, including the appearance or exacerbation

of underlying autoimmune diseases and the development of a variety of organ- and non-organ-specific autoantibodies (18). Auto-immune thyroid disease is a common side effect of IFN treatment of viral hepatitis C, affecting 2-19% of IFN-treated patients (19). We previously reported the case of a patient with chronic hepatitis C who developed worsening lichen planus lesions during treatment with IFN plus RBV (20), and the case of a patient who developed oral cancer after IFN therapy (21).

We now describe a patient with chronic hepatitis C infection who developed hyperthyroidism, Graves' ophthalmopathy and malignant transformation of tongue leukoplakia during combination therapy with Peg-IFN α-2b and RBV. This patient was treated successfully.

Case report

A 67-year-old Japanese man, diagnosed in 1998 with chronic hepatitis C, consulted the Digestive Disease Center of Kurume University on June 6, 2003 for treatment of his chronic liver disease. The patient had received a right upper lobectomy for lung tuberculosis at the age of 23 (in 1958), and had been administered blood transfusions of 600 ml during the procedure. Hypertension was noted at the age of 67, and antihypertensive treatment was started at 68. Hemangioma of the right middle finger was diagnosed at 69. For 20 years, he smoked 50 cigarettes a day, though he had not smoked for the last 30 years. His alcohol consumption was 500 ml of beer daily for 49 years. His family history was non-contributory.

Periodic blood tests and abdominal ultrasound exams were conducted by a hepatologist at Kurume University. As the patient's aminotransferase levels were in the normal range, he was monitored regularly for chronic hepatitis C. On July 30, 2004, at the age of 69, his aminotransferase levels were found to be elevated and a liver biopsy revealed chronic active hepatitis, diagnosed as F2A2 according to the new Inuyama classification (22). As of June 14, 2005, for a period of 1-3 months, the patient was treated by a family doctor with a combination of peg-IFN α-2b (Peg-Intron®; Schering-Plough, Kenilworth, NJ, USA) (40-100 μg/week) plus RBV (Rebetol®; Schering-Plough) (300-800 mg/day). During this time, he was examined by a hepatologist once.

At the start of Peg-IFN α-2b plus RBV therapy, laboratory data regarding hepatitis virus markers indicated that the patient was negative for hepatitis B surface antigen (HBsAg), but positive for HCV antibody (anti-HCV) and HCV RNA. Both free thyroxine (FT_4) and thyroid stimulating hormone (TSH) levels before Peg-IFN plus RBA therapy were within normal ranges (Table I).

In March 2006, while undergoing Peg-IFN plus RBV therapy, the patient experienced double vision. He did not consult a family doctor or a hepatologist, but was examined by an ophthalmologist, and then by a neurosurgeon who prescribed magnetic resonance imaging (MRI) followed by a neurological examination at Kurume University Hospital on May 9, 2006. Thyroid function tests on February 10, 2006 revealed suppressed TSH at 0.016 μIU/ml (normal value 0.21-3.85) and elevated free tri-iodothyronine (FT_3) at 4.1 pg/ml (normal value 1.9-3.5), but the hepatologist did not diagnose thyroid disease. Over the next 3 months, thyroid function tests revealed hyperthyroidism of autoimmune etiology, indicated by the following laboratory values from a test taken on May 16, 2006: TSH, 0.007 μIU/ml (normal value 0.21-3.85); FT_3, 4.6 pg/ml (normal value 1.9-3.5); FT_4, 1.58 ng dl (normal value 0.88-1.56); positive thyroid peroxidase antibodies (TPOAb), 92.2 IU/ml (normal value <5); thyroglobulin

Table I. Laboratory data of patient with hepatitis C virus infection at the time of admission for Peg-IFN and RBV therapy.

Laboratory assay	Value	Unit	Standard value
RBC	483	$x10^4/mm^3$	430-570
Hb	16.0	g/dl	14.0-18.0
Ht	46.9	%	40.0-52.0
WBC	63	$x10^4/mm^3$	40-90
Plt	17.4	$x10^4/mm^3$	13.0-36.0
AST	32	U/l	13-33
ALT	32	U/l	8-42
LDH	170	U/l	119-229
ALP	209	U/l	115-359
γ-GTP	90	U/l	10-47
TP	7.21	g/dl	6.70-8.30
Alb	4.11	g/dl	4.00-5.00
ChE	160	IU/l	107-233
TC	140	mg/dl	128-256
TB	1.14	mg/dl	0.00-1.50
DB	0.12	mg/dl	0.00-0.60
BUN	15.3	mg/dl	8.0-22.0
Crea	0.72	mg/dl	0.60-1.10
Na	139	mEq/l	138-146
K	4.0	mEq/l	3.6-4.9
Cl	104	mEq/l	99-109
Fe	190	μg/dl	80-170
UIBC	68	μg/dl	180-274
Ferritin	167.7	ng/ml	23.0-183.0
CRP	0.04	mg/dl	0.00-0.40
IgA	225	mg/dl	103-409
IgM	65	mg/dl	40-221
IgG	1856	mg/dl	918-1742
FT_4	1.24	ng/dl	0.88-1.56
TSH	2.970	μIU/ml	0.210-3.850
AFP (L3)	3.3	ng/dl	0.0-8.7
HbA1c	5.1	%	4.3-5.8
HBsAg	Negative		
Anti-HBc	Negative		
Anti-HCV	Positive		
HCV RNA level	2400	KIU/ml	
HCV genotype	1b		

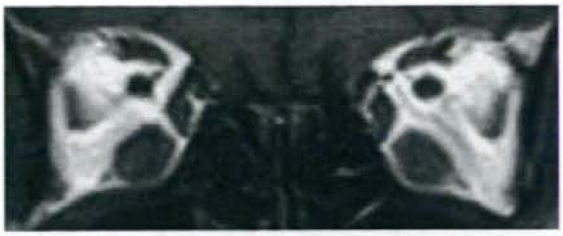
June 14, 2005.

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

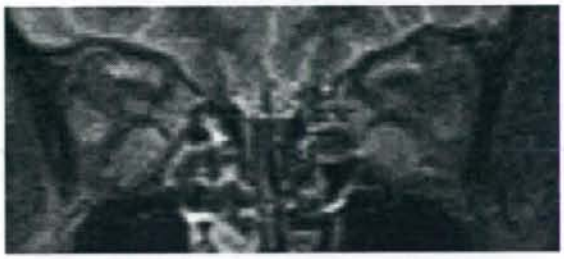
Laboratory assay	Value	Unit	Standard value
RBC	376	x10⁴/mm³	430-570
Hb	11.9	g/dl	14.0-18.0
Ht	35.8	%	40.0-52.0
WBC	43	x10⁴/mm³	40-90
Plt	18.3	x10⁴/mm³	13.0-36.0
AST	12	U/l	13-33
ALT	9	U/l	8-42
LDH	122	U/l	119-229
ALP	233	U/l	115-359
γ-GTP	17	U/l	10-47
TP	7.47	g/dl	6.70-8.30
Alb	3.94	g/dl	4.00-5.00
ChE	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.



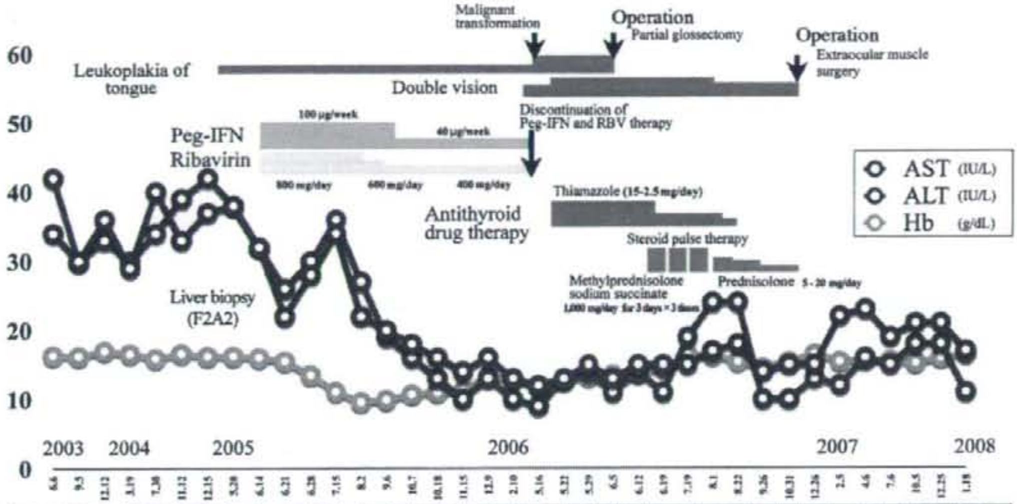
T1 weighted image



STIR image

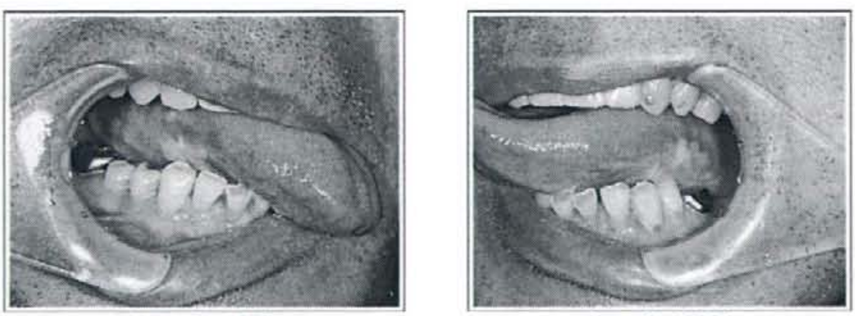
Figure 1. MRI of the orbits shows conspicuous enlargement of the bilateral inferior rectus muscles before steroid pulse therapy (coronal view).

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.



	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
HCV RNA level (KIU/mL)	MT 500	1900	MT 500	1100	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	3.2	2.2	-	1.1	-	2.3	3.3	3.3	-	3.1	3.0	-	3.6	2.9	2.9	3.1	3.3	3.3
FT4 (ng/dL)	-	-	-	1.29	1.24	-	-	-	-	-	-	-	-	-	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)	-	-	-	[illegible]	[illegible]	-	-	-	-	-	-	-	-	[illegible]	0.007	[illegible]	0.147	[illegible]	-	[illegible]	-	[illegible]	[illegible]	[illegible]	-	[illegible]	[illegible]	-	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
TgAb (IU/mL)	-	-	-	-	-	-	-	-	-	-	-	-	-	7.5	8.5	-	-	-	-	-	-	-	3.9	-	9.1	-	-	-	-	-	-	-	-	-
TPOAb (IU/mL)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	93.2	-	-	-	-	-	-	59.5	-	-	13.6	-	-	-	-	-	-	-	-	-
TRAb (%)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	19.7	-	-	-	23.1	-	-	16.4	-	11.2	-	-	-	12.9	-	-	-	7.3	-	8.3
TSAb (%)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	139	-	-	-	199	-	-	378	-	126	-	-	-	119	-	-	-	128	-	184
hTRAb (IU/L)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	7.8	-	-	-	4.8	-	-	5.0	-	1.9	-	-	-	1.6	-	-	-	1.3	-	<1.0

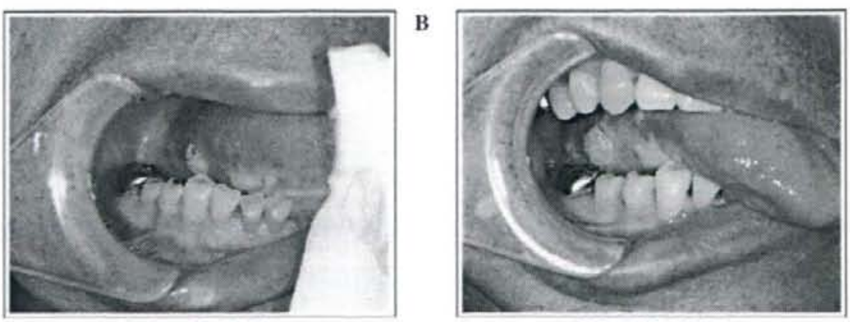
Figure 2. Clinical course of the patient.



June 21, 2005　　June 21, 2005

Figure 3. Bilateral oral leukoplakia of the tongue.

A　B



May 10, 2006　　May 23, 2006

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.

References

1. Yoshizawa H: Hepatocellular carcinoma associated with hepatitis C virus infection in Japan: projection to other countries in the foreseeable future. Oncology 62 (Suppl 1): 8-17, 2002.
2. Carithers RL Jr and Emerson SS: Therapy of hepatitis C: meta-analysis of interferon alfa-2b trials. Hepatology 26 (3 Suppl 1): 83-88, 1997.
3. Everson GT, Jensen DM, Craig JR, *et al*: Efficacy of interferon treatment for patients with chronic hepatitis C: comparison of response in cirrhotics, fibrotics, or nonfibrotics. Hepatology 30: 271-276, 1999.
4. Poynard T, Marcellin P, Lee SS, *et al*: Randomised trial of interferon alpha2b plus ribavirin for 48 weeks or for 24 weeks versus interferon alpha2b plus placebo for 48 weeks for treatment of chronic infection with hepatitis C virus. International Hepatitis Interventional Therapy Group (IHIT). Lancet 352: 1426-1432, 1998.
5. McHutchison JG, Gordon SC, Schiff ER, *et al*: Interferon alfa-2b alone or in combination with ribavirin as initial treatment for chronic hepatitis C. Hepatitis Interventional Therapy Group. N Engl J Med 339: 1485-1492, 1998.
6. Fried MW, Shiffman ML, Reddy KR, *et al*: Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. N Engl J Med 347: 975-982, 2002.
7. Pawlotsky JM, Yahia MB, Andre C, *et al*: Immunological disorders in C virus chronic active hepatitis: a prospective case-control study. Hepatology 19: 841-848, 1994.
8. Misiani R, Bellavita P, Fenili D, *et al*: Hepatitis C virus infection in patients with essential mixed cryogloblinemia. Ann Intern Med 117: 573-577, 1992.
9. Huang MJ, Wu SS and Liaw YF: Thyroid abnormalities in patients with chronic viral hepatitis. Hepatology 20: 1651-1652, 1994.
10. Haddad J, Deny P, Munz-Gotheil C, *et al*: Lymphocytic sialadenitis of Sjögren's syndrome associated with chronic hepatitis C virus liver disease. Lancet 339: 321-323, 1992.
11. Piperno A, D'Alba R, Roffi L, *et al*: Hepatitis C virus infection in patients with idiopathic hemochromatosis (IH) and porphyria cutanea tarda (PCT). Arch Virol Suppl 4: 215-216, 1992.
12. Nagao Y, Sata M, Tanikawa K, Itoh K and Kameyama T: Lichen planus and hepatitis C virus in the northern Kyushu region of Japan. Eur J Clin Invest 25: 910-914, 1995.
13. Nagao Y, Sata M, Tanikawa K, Itoh K and Kameyama T: High prevalence of hepatitis C virus antibody and RNA in patients with oral cancer. J Oral Pathol Med 24: 354-360, 1995.
14. Nagao Y, Sata M, Itoh K, *et al*: High prevalence of hepatitis C virus antibody and RNA in patients with head and neck squamous cell carcinoma. Hepatol Res 7: 206-212, 1997.
15. Petit JM, Bour JB, Galland-Jos C, *et al*: Risk factors for diabetes mellitus and early insulin resistance in chronic hepatitis C. J Hepatol 35: 279-283, 2001.
16. Reddy KR, Wright TL, Pockros PJ, *et al*: Efficacy and safety of pegylated (40-kd) interferon alpha-2a compared with interferon alpha-2a in noncirrhotic patients with chronic hepatitis C. Hepatology 33: 433-438, 2001.
17. Okanoue T, Sakamoto S, Itoh Y, *et al*: Side effects of high-dose interferon therapy for chronic hepatitis C. J Hepatol 25: 283-291, 1996.
18. Gatselis NK, Georgiadou SP, Tassopoulos N, *et al*: Impact of parietal cell autoantibodies and non-organ-specific autoantibodies on the treatment outcome of patients with hepatitis C virus infection: a pilot study. World J Gastroenterol 11: 482-487, 2005.
19. Carella C, Mazziotti G, Amato G, Braverman LE and Roti E: Interferon-alpha-related thyroid disease: pathophysiological, epidemiological, and clinical aspects. J Clin Endocrinol Metab 89: 3656-3661, 2004.
20. Nagao Y, Kawaguchi T, Tanaka K, Kumashiro R and Sata M: Extrahepatic manifestations and insulin resistance in an HCV hyperendemic area. Int J Mol Med 16: 291-296, 2005.
21. Nagao Y, Sata M, Fukuizumi K, Harada H and Kameyama T: Oral cancer and hepatitis C virus (HCV): can HCV alone cause oral cancer? A case report. Kurume Med J 43: 97-100, 1996.
22. Ichida F, Tsuji T, Omata M, *et al*: New Inuyama classification: new criteria for histological assessment of chronic hepatitis. Int Hepatol Commun 6: 112-119, 1996.
23. Werner SC: Modification of the classification of the eye changes of Graves' disease: recommendations of the Ad Hoc Committee of the American Thyroid Association. J Clin Endocrinol Metab 44: 203-204, 1977.
24. Mourits MP, Koornneef L, Wiersinga WM, Prummel MF, Berghout A and van der Gaag R: Clinical criteria for the assessment of disease activity in Graves' ophthalmopathy: a novel approach. Br J Ophthalmol 73: 639-644, 1989.
25. Fattovich G, Giustina G, Favarato S and Ruol A: A survey of adverse events in 11,241 patients with chronic viral hepatitis treated with alfa interferon. J Hepatol 24: 38-47, 1996.
26. Preziati D, La Rosa L, Covini G, *et al*: Autoimmunity and thyroid function in patients with chronic active hepatitis treated with recombinant interferon alpha-2a. Eur J Endocrinol 132: 587-593, 1995.
27. Koh LK, Greenspan FS and Yeo PP: Interferon-alpha induced thyroid dysfunction: three clinical presentations and a review of the literature. Thyroid 7: 891-896, 1997.
28. Bini EJ and Mehandru S: Incidence of thyroid dysfunction during interferon alfa-2b and ribavirin therapy in men with chronic hepatitis C: a prospective cohort study. Arch Intern Med 164: 2371-2376, 2004.
29. Tran HA, Attia JR, Jones TL and Batey RG: Pegylated interferon-alpha2beta in combination with ribavirin does not aggravate thyroid dysfunction in comparison to regular interferon-alpha2beta in a hepatitis C population: meta-analysis. J Gastroenterol Hepatol 22: 472-476, 2007.
30. Watanabe U, Hashimoto E, Hisamitsu T, Obata H and Hayashi N: The risk factor for development of thyroid disease during interferon-alpha therapy for chronic hepatitis C. Am J Gastroenterol 89: 399-403, 1994.
31. Carella C, Amato G, Biondi B, *et al*: Longitudinal study of antibodies against thyroid in patients undergoing interferon-alpha therapy for HCV chronic hepatitis. Horm Res 44: 110-114, 1995.
32. Inoue Y, Inoue R, Kouzaki A and Koumoto N: Ophthalmic surgery on Graves' ophthalmopathy. Nippon Rinsho 64: 2291-2296, 2006.
33. Huet D, Entremont A and Hautecouverture M: Basedow's disease and interferon for hepatitis C. Recurrence as Basedow's ophthalmopathy after interferon reintroduction. Presse Med 29: 82, 2000.
34. Villanueva RB and Brau N: Graves' ophthalmopathy associated with interferon-alpha treatment for hepatitis C. Thyroid 12: 737-738, 2002.

35. Binaghi M, Lévy C, Douvin C, Guittard M, Soubrane G and Coscas G: Severe thyroid ophthalmopathy related to interferon alpha therapy. J Fr Ophtalmol 25: 412-415, 2002.
36. Su DH, Chang YC, Liao SL and Chang TC: Lanreotide treatment in a patient with interferon-associated Graves' ophthalmopathy. Graefes Arch Clin Exp Ophthalmol 243: 269-272, 2005.
37. DeMartelaere SL, Green MK and Shore JW: Exacerbation of Graves ophthalmopathy with interferon-alpha therapy. Ophthal Plast Reconstr Surg 23: 319-321, 2007.
38. Tomer Y, Blackard JT and Akeno N: Interferon alpha treatment and thyroid dysfunction. Endocrinol Metab Clin North Am 36: 1051-1066, 2007.
39. Laskus T, Radkowski M, Wang LF, Vargas H and Rakela J: Search for hepatitis C virus extrahepatic replication sites in patients with acquired immunodeficiency syndrome: specific detection of negative-strand viral RNA in various tissues. Hepatology 28: 1398-1401, 1998.
40. Hiromatsu Y, Sato M, Inoue Y, *et al*: Localization and clinical significance of thyrotropin receptor mRNA expression in orbital fat and eye muscle tissues from patients with thyroid-associated ophthalmopathy. Thyroid 6: 553-556, 1996.
41. Nagao Y, Sata M, Fukuizumi K, Tanikawa K and Kameyama T: High incidence of oral precancerous lesions in a hyperendemic area of hepatitis C virus infection. Hepatol Res 8: 173-177, 1997.
42. Bouquot JE: Reviewing oral leukoplakia: clinical concepts. J Am Dent Assoc 122: 80-82, 1991.
43. Nagao Y, Sata M, Noguchi S, *et al*: Detection of hepatitis C virus RNA in oral lichen planus and oral cancer tissues. J Oral Pathol Med 29: 259-266, 2000.
44. Yoshida M, Nagao Y, Sata M, Kusukawa J and Kameyama T: Multiple primary neoplasms and HCV infection in oral cancer patients. Hepatol Res 9: 75-81, 1998.

© Med Sci Monit, 2008; 14(11): PI45-52
PMID: 18971882

www.MEDSCIMONIT.COM
Product Investigation

Received: 2008.04.09
Accepted: 2008.07.07
Published: 2008.11.01

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

Yumiko Nagao[1ABDEF], Yutaka Kawakami[2ABE], Tamotsu Yoshiyama[2G], Michio Sata[1ABG]

[1] Department of Digestive Disease Information & Research, Kurume University School of Medicine, Kurume, Fukuoka, Japan
[2] Pfizer Global R&D, Tokyo Laboratories, Pfizer Japan Inc., Shibuya-ku, Tokyo, Japan

Source of support: The study was made possible by a Grant-in-Aid for Scientific Research (C) (No. 18592213) from the Ministry of Education, Culture, Sports, Science and Technology of Japan and the Second Award Fukuoka Field of Medicine from Medical Care Education Research Foundation

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

PI

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

Full-text PDF: http://www.medscimonit.com/fulltxt.php?ICID=869425
Word count: 2570
Tables: 6
Figures: 1
References: 21

Author's address: Yumiko Nagao, Department of Digestive Disease Information & Research, Kurume University School of Medicine, 67 Asahi-machi, Kurume 830-0011, Japan, e-mail: nagao@med.kurume-u.ac.jp

PERSONAL USE
This copy is for personal use only - distribution prohibited. This copy is for personal use only - distribution prohibited.
Electronic PDF security powered by IDR clearcom

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.

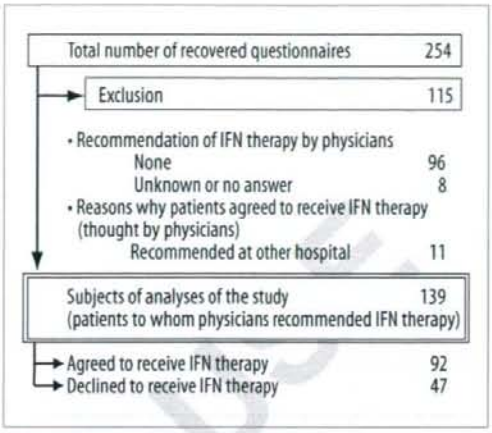


Figure 1. Diagram of 139 subjects of the study.

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.

Electronic PDF security powered by IS-science.com

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.

PI

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.

This PDF is for personal use only - distribution prohibited. This copy is for personal use only - distribution prohibited. This copy is for personal use only - distribution prohibited. Electronic PDF security powered by IST-compliance

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.

Electronic PDF security powered by IS-rulesets.com

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

PERSONAL USE ONLY

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-

Electronic PDF security powered by ISL-science.com

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

Electronic PDF security powered by IST-science.com

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-

Electronic PDF security powered by ISI-science.com

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.

Acknowledgements

We are deeply in debt to Mr. Yoshindo Takahashi, Director, Mr. Fumio Suzuki, Research Fellow, and Mr. Haruhiko Nobayashi, Research Fellow, at OPIR in JPMA for their cooperation in the investigation by questionnaires and in building the database.

REFERENCES:

1. Parkin DM, Bray F, Ferlay J, Pisani P: Estimating the world cancer burden: Globocan 2000. Int J Cancer, 2001; 94: 153–56
2. El-Serag HB, Mason AC: Rising incidence of hepatocellular carcinoma in the United States. N Engl J Med, 1999; 340: 745–50
3. Yoshizawa H: Hepatocellular carcinoma associated with hepatitis C virus infection in Japan: projection to other countries in the foreseeable future. Oncology, 2002; 62 (Suppl.1): 8–17
4. Okita K: Clinical study on standardization of treatment of carriers of hepatitis B and C viruses; the current status of hepatitis virus screening and future problems of guidance for patients who require thorough examination. Research on Hepatitis. Health and Labour Sciences Research Grants, Ministry of Health, Labour, and Welfare, Japan, 2007; 204–7 (in Japanese)
5. Muir AJ, Bornstein JD, Killenberg PG: Atlantic Coast Hepatitis Treatment Group. Peginterferon alfa-2b and ribavirin for the treatment of chronic hepatitis C in blacks and non-Hispanic whites. N Engl J Med, 2004; 350: 2265–71
6. Yoshida H, Shiratori Y, Moriyama M et al: Interferon therapy reduces the risk for hepatocellular carcinoma: national surveillance program of cirrhotic and noncirrhotic patients with chronic hepatitis C in Japan. IHIT Study Group. Inhibition of Hepatocarcinogenesis by Interferon Therapy. Ann Intern Med, 1999; 131: 174–81
7. Yoshida H, Arakawa Y, Sata M et al: Interferon therapy prolonged life expectancy among chronic hepatitis C patients. Gastroenterology, 2002; 123: 483–91
8. Okanoue T, Itoh Y, Minami M et al: Interferon therapy lowers the rate of progression to hepatocellular carcinoma in chronic hepatitis C but not significantly in an advanced stage: a retrospective study in 1148 patients. Viral Hepatitis Therapy Study Group. J Hepatol, 1999; 30: 653–59
9. Mazzaferro V, Romito R, Schiavo M et al: HCC Italian Task Force. Prevention of hepatocellular carcinoma recurrence with alpha-interferon after liver resection in HCV cirrhosis. Hepatology, 2006; 44: 1543–54
10. Nagao Y, Sata M, Suzuki F et al: Toward more widespread use of novel drug therapies -Current status of interferon therapy in patients with hepatitis C and discussion of strategies to propagate its use. Office of Pharmaceutical Industry Research. Research Paper Series, 2006; 32: 1–81 (in Japanese)
11. Sata M, Nakano H, Suzuki H et al: Sero-epidemiologic study of hepatitis C virus infection in Fukuoka, Japan. J Gastroenterol, 1998; 33: 218–22
12. Fukuizumi K, Sata M, Suzuki H et al: Hepatitis C virus seroconversion rate in a hyperendemic area of HCV in Japan: a prospective study. Scand J Infect Dis, 1997; 29: 345–47
13. Nagao Y, Fukuizumi K, Kumashiro R et al: The prognosis for life in an HCV hyperendemic area. Gastroenterology, 2003; 125: 628–29
14. Nagao Y, Tanaka K, Kobayashi K et al: A cohort study of chronic liver disease in an HCV hyperendemic area of Japan: a prospective analysis for 12 years. Int J Mol Med, 2004; 13: 257–65
15. Nagao Y, Tanaka K, Kobayashi K et al: Analysis of approach to therapy for chronic liver disease in an HCV hyperendemic area of Japan. Hepatol Res, 2004; 28: 30–35
16. Nagao Y, Sata M, Fukuizumi K et al: High incidence of oral precancerous lesions in a hyperendemic area of hepatitis C virus infection. Hepatol Res, 1997; 8: 173–77
17. Nagao Y, Sata M, Fukuizumi K et al: High incidence of oral lichen planus in an HCV hyperendemic area. Gastroenterology, 2000; 119: 882–83
18. Hosmer DW, Lemeshow S: Applied Logistic Regression. 2nd ed. New York: John Wiley & Sons; 2000; 91–116
19. Ohishi W, Kitamoto M, Aikata H et al: Impact of aging on the development of hepatocellular carcinoma in patients with hepatitis C virus infection in Japan. Scand J Gastroenterol, 2003; 38: 894–900
20. Hayashi J, Kishihara Y, Ueno K et al: Age-related response to interferon alfa treatment in women vs men with chronic hepatitis C virus infection. Arch Intern Med, 1998; 158: 177–81
21. Hung CH, Lee CM, Lu SN et al: Anemia associated with antiviral therapy in chronic hepatitis C: incidence, risk factors, and impact on treatment response. Liver Int, 2006; 26: 1079–86

Electronic PDF security powered by IST-science.com

肝臓病の方の皮膚や粘膜には、さまざまな症状が現れます。
とくにインターフェロン治療中には注意が必要です。

－ 肝臓病と皮膚・粘膜の病気 －

編著：長尾由実子（久留米大学医学部消化器疾患情報講座）
今福　信一（福岡大学医学部皮膚科学講座）
佐田　通夫（久留米大学医学部内科学講座　消化器内科部門）

肝外病変シリーズ No.2
初版発刊　2008年11月
編集・発行　久留米大学医学部消化器疾患情報講座