PO Box 2345, Beijing 100023, China
www.wjgnet.com
wjg@wjgnet.com

World J Gastroenterol 2006 June 21; 12(23): 3756-3759
World Journal of Gastroenterology ISSN 1007-9327

RAPID COMMUNICATION

Risk factors for retinopathy associated with interferon α-2b and ribavirin combination therapy in patients with chronic hepatitis C

Chiaki Okuse, Hiroshi Yotsuyanagi, Yoshihiko Nagase, Yuhtaro Kobayashi, Kiyomi Yasuda, Kazuhiko Koike, Shiro Iino, Michihiro Suzuki, Fumio Itoh

Chiaki Okuse, Yoshihiko Nagase, Yuhtaro Kobayashi, Michihiro Suzuki, Fumio Itoh, Division of Gastroenterology and Hepatology, Department of Internal Medicine, St. Marianna University School of Medicine, Kawasaki, Kanagawa, 216-8511, Japan
Hiroshi Yotsuyanagi, Kazuhiko Koike, Department of Infectious Diseases, Internal Medicine, Faculty of Medicine, University of Tokyo, 7-3-1, Hongo, Bunkyo, Tokyo 113-8655, Japan
Kiyomi Yasuda, Shiro Iino, Center for Liver Diseases, Kiyokawa Hospital, Minamiasagaya, Suginami, Tokyo, 166-0004, Japan
Correspondence to: Dr. Hiroshi Yotsuyanagi, Department of Infectious Diseases, Internal Medicine, Faculty of Medicine, University of Tokyo, 7-3-1, Hongo, Bunkyo, Tokyo 113-8655, Japan. hyotsu-tky@umin.ac.jp
Telephone: +81-3-58008720 Fax: +81-3-58008796
Received: 2006-01-13 Accepted: 2006-02-18

Abstract

AIM: To elucidate the frequency and risk factors for retinopathy in patients with chronic hepatitis C who are treated by interferon-ribavirin combination therapy.

METHODS: We prospectively analyzed 73 patients with histologically confirmed chronic hepatitis C, who underwent combination therapy for 24 wk. Optic fundi were examined before, and 2, 4, 12 and 24 wk after the start of combination therapy.

RESULTS: Fourteen patients (19%) developed retinopathy, which was initially diagnosed by the appearance of a cotton wool spot in 12 patients. Retinal hemorrhage was observed in 5 patients. No patient complained of visual disturbance. Retinopathy disappeared in 9 patients (64%) despite the continuation of combination therapy. However, retinopathy persisted in 5 patients with retinal hemorrhage. A comparison of the clinical background between the groups with and without retinopathy showed no significant differences in age, gender, viral genotype, RNA level, white blood cell count, platelet count, prothrombin time, complications by diabetes mellitus or hypertension, or pretreatment arteriosclerotic changes in the optic fundi. However, multiple logistic regression analysis revealed that complication by hypertension was observed with a high frequency in the group with retinopathy (P = 0.004, OR = 245.918, 95% CI = 5.6-10786.2).

CONCLUSION: Retinopathy associated with combination therapy of interferon α-2b and ribavirin tends to develop in patients with hypertension.

Key words: Retinopathy; Ribavirin; Chronic hepatitis C; Interferon

Okuse C, Yotsuyanagi H, Nagase Y, Kobayashi Y, Yasuda K, Koike K, Iino S, Suzuki M, Itoh F. Risk factors for retinopathy associated with interferon α-2b and ribavirin combination therapy in patients with chronic hepatitis C.*World J Gastroenterol* 2006; 12(23): 3756-3759

http://www.wjgnet.com/1007-9327/12/3756.asp

INTRODUCTION

Chronic hepatitis C, which affects more than 170 million people in the world[1], may eventually lead to cirrhosis and/or hepatocellular carcinoma. The main treatment for this intractable disease is interferon administration. Published guidelines recommend interferon-ribavirin combination therapy as a first-line treatment[2]. Interferon is also used in the treatment of other viral and neoplastic diseases.

Various adverse effects have been reported due to use of interferon[3]. An influenza-like syndrome, characterized by fever, chills, myalgias, arthralgias, and headache, is the most common adverse effect. Toxicities of the central nervous, hematopoietic, gastrointestinal, urinary, cardiovascular, musculoskeletal and endocrine systems have also been described. However, ocular toxicity was not reported before the use of interferon for chronic hepatitis[3].

After the introduction of interferon for the treatment of hepatitis, retinal complications have been reported. Hayakawa *et al* showed that 17 of 43 patients developed retinopathy during interferon monotherapy. They also showed that the prevalence of retinopathy was higher in patients with diabetes[4]. Subsequently, several papers have shown that a substantial proportion of patients undergoing interferon monotherapy develop retinopathy[5-7]. However, the prevalence of retinopathy is variable, which is

presumably attributed to the difference in the treatment regimen and/or background of patients.

As mentioned above, interferon-ribavirin combination therapy has become the standard treatment for chronic hepatitis C. Results from recent studies have suggested that the prevalence of retinopathy associated with combination therapy may be higher than that associated with interferon monotherapy, which should be further investigated[8-10].

In spite of the high prevalence, risk factors for interferon-associated retinopathy are still unclear. Diabetes mellitus and the patients' age were reported to be possible risk factors for retinopathy associated with interferon monotherapy[4]. In interferon-ribavirin combination therapy, diabetes, hypertension[8], and response to treatment[10] were considered possible risk factors. However, the results are not conclusive because of the small number of patients examined.

The aim of the present study is to elucidate the prevalence and risk factors for retinopathy associated with interferon-ribavirin combination therapy.

MATERIALS AND METHODS

Patients

Seventy-three consecutive patients with histologically confirmed chronic hepatit is C (47 males and 26 females; median age, 53.4 years; ranges 26-73 years) were enrolled in this study from 2002 to 2004. The clinical backgrounds of the enrolled patients are shown in Table 1. All patients were treated with recombinant interferon α-2b (Intron A, Schering-Plough, Kenilworth, NJ, USA) and ribavirin (Rebetol; Schering-Plough, Kenilworth, NJ, USA) combination therapy. All the patients were treated daily with interferon α-2b at 6 MU for 2 wk followed by three times a wk treatment with interferon α-2b at 6 MU for 22 wk in combination with ribavirin. Ribavirin was given orally twice a day at a total daily dose of 600 mg for patients who weighed 60 kg or less and 800 mg for the remaining patients who weighed more than 60 kg for 24 wk.

All patients were assessed to determine the safety, tolerance, and efficacy of the treatment at the end of wk 1, 2, 4, and every 4 wk during the treatment. After the treatment was completed, patients were followed up on wk 4, 8, 12, and 24. The primary end point was indicated by a sustained loss of detectable HCV-RNA at 24 wk after the treatment.

Methods

Optic fundi were examined before, and 2, 4, 12 and 24 wk after the start of combination therapy. Ophthalmological examinations were carried out before the start of treatment and 2, 4, 12 and 24 wk after the start of treatment until the completion of treatment or until the retinopathy disappeared. Fundus photographs were taken for documentation and comparison when retinal abnormalities were detected.

Informed consent was obtained from each patient. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the Ethics Committees of our institutions.

Table 1 Profiles and initial laboratory data of patients with and without retinopathy during IFN-ribavirin combination therapy[1]

	Total	Retinopathy (+)	Retinopathy (-)
Patients			
Number	73	14	59
Age (yr)	53.4 ± 10.9	56.3 ± 10.5	52.8±38.6
Gender (M/F)	47/26	10/4	37/22
Hypertension (Yes/No)[a]	15/58	5/8	10/49
Diabetes mellitus (Yes/No)	2/71	1/13	1/58
Peripheral blood count			
Platelet count ($\times 10^4/mm^3$)	15.3 ± 6.0	12.5 ± 10.5	15.9 ± 38.6
White blood cell ($\times 10^3/mm^3$)	46.9 ± 12.6	46.5 ± 13.0	48.6 ± 10.9
Hemoglobin (×g/dL)	14.0 ± 1.3	14.0 ± 1.0	14.0 ± 1.4
Prothrombin time (%)	90.2 ± 13.3	87.1 ± 13.3	90.8 ± 13.3
ALT (IU/L)	109.4 ± 78.2	104.1 ± 41.0	110.4 ± 83.6
Viral factors			
Genotype (type 1/type 2)[2]	45/26	33/24	12/2
Viral load (kcopies/mL)	592.3 ± 271.2	505.6 ± 309.1	607.5 ± 271.2
Pretreatment/ Arteriosclerotic	12/61	7/7	5/54
changes in optic fundi (Yes/No)			
Response to therapy (SVR/non-SVR)	38/35	5/9	33/26

[1] Data are expressed as mean ± SD.
[2] Genotype could not be determined in 2 patients.
[a] $P = 0.004$

RESULTS

Before the start of the combinaiton therapy, one patient had scars from laser coagulation of a previous interferon-associated retinopathy and another patient had retinal central vein occlusion. Arteriosclerotic changes of the optic fundi were observed in 12 patients.

After the start of interferon-ribavirin combination therapy, 14 out of 73 patients (19%) developed retinopathy. The clinical profiles and laboratory data of the patients with and without retinopathy are shown in Table 1.

We compared the characteristics of patients who developed retinopathy and those who did not. The two groups showed no statistical differences in age, gender, subtype of virus, RNA level, white blood cell count, platelet count, prothrombin time before treatment or prevalence of pretreatment fundic arteriosclerotic changes. The patients with retinopathy were more frequently complicated by hypertension ($P = 0.004$) (Table 1).

Logistic regression analysis of factors affecting retinopathy was also carried out. Hypertension was found to be a factor for predicting retinopathy (Table 2).

Table 3 shows the optic fundi findings of the 14 patients with retinopathy. Retinopathy was initially diagnosed by the appearance of a cotton wool spot in 12 patients. In three of the 12 patients, retinal hemorrhage was also observed simultaneously or sequentially. Two of the 14 patients who developed retinopathy were diagnosed by retinal hemorrhage without a cotton wool spot. No patient complained of the visual disturbance.

Table 2 Logistic regression analysis of factors associated with retinopathy

Factor	*P*	Odds ratio	95% confidennce interval
Sex	0.68	1.699	0.1-21.0
Age	0.203	1.099	1.0-1.3
Genotype	0.776	1.621	0.1-45.5
Levels of HCV RNA	0.114	1.006	0.99-1.0
Hypertension	0.004	246.32	5.5-10977.8
Diabetes mellitus	0.211	0.122	0.1-3.3
Abnormal findings in pretreatment optic fundi	0.904	1.192	0.1-20.3
Platelet	0.059	1.391	1.0-1.9
Prothrombin time	0.747	0.982	0.9-1.1
ALT	0.992	1	0.98-1.0
WBC	0.964	1.027	0.4-2.9
Response to therapy (SVR or non-SVR)	0.123	0.016	0.0-3.1

Table 3 Optic fundi findings of patients with retinopathy

No	Age	Sex	Underlying disease		Optic fundi before treatment		Optic fundi after treatment	
			Hyper tension	Diabetes mellitus	H	S	Cotton wool spot	Retinal hemorrhage
1	38	M	+	+	0	0	4 wk-	4 wk-
2	52	M	+	−	1	0	4-12 wk	−
3	40	M	−	−	0	0	6-36 wk	−
4	62	F	−	−	0	0	4-36 wk	−
5	61	M	+	−	0	0	12 wk-	−
6	58	M	−	−	1	1	12 wk-	−
7	73	M	−	−	2	2	4-28 wk	−
8	65	F	+	−	0	0	24-36 wk	−
9	59	F	+	−	2	2	2 wk-	4-24 wk
10	40	M	−	−	0	0	4-20 wk	−
11	62	F	−	−	1	2	2 wk-	4 wk-
12	65	M	−	−	1	1	2-24 wk	−
13	40	M	−	−	0	0	−	8-16 wk
14	40	M	−	−	0	0	−	2-4 wk

Retinopathy disappeared in 9 of the 14 patients despite the continuation of combination therapy. However, it continued in three patients with retinal hemorrhage and two without retinal hemorrhage.

Ocular manifestations other than retinopathy (e.g., ocular pain, a mild watery eye and conjunctivitis) were not observed in any patients.

DISCUSSION

Interferon associated retinopathy was first recognized in 1990 when Ikebe and associates reported a 39-year-old patient who developed retinal hemorrhages and cotton wool spots following intravenous administration of interferon[11].

The exact mechanism of interferon-induced-retinopathy is not known but is presumably related to the disturbance in retinal microcirculation[12]. Therefore, preexisting arteriosclerosis that affects microcirculation may promote interferon-induced retinopathy.

Our study shows that hypertension is a more frequent complication in patients with interferon-induced-retinopathy. Chronic hypertension is associated with the thickening of the walls of the arteries and small arterioles[13]. Therefore, systemic hypertension predisposes patients to interferon-induced-retinopathy. The fact that hypertensive retinopathy induces the formation of flame-shaped hemorrhages and white cotton wool spots, which are also seen in interferon-induced-retinopathy, implies that systemic hypertension and interferon-induced-retinopathy may be related each other.

Statistical analysis did not indicate pretreatment optic fundic changes or diabetes as predictive factors of retinopathy. This may be attributed to the following reasons: (1) pretreatment changes in the optic fundi as a predictive factor are included in hypertension; and (2) the number of patients with diabetes is too small. Regardless of these reasons, systemic hypertension is an important risk factor for interferon-related retinopathy.

The frequencies of interferon-induced retinopathy associated with interferon monotherapy and interferon-ribavirin combination therapy are reported to be 24%-58%[4-7,14,15] and 16%-64%[8-10,16], respectively. The frequency in the present study (20%) was lower than that in previous reports. Furthermore, the ocular side effects of ribavirin, which include a mild watery eye and conjunctivitis, were not seen in this study. Therefore, the frequency of induced retinopathy associated with combination therapy may be considered as high as that associated with interferon monotherapy.

Retinopathy developed by 12 wk in most (13/14, 93%) of the patients after the start of combination therapy and disappeared in majority (10/14, 71%) of the patients during the 4-8 wk period, in which the patients were receiving the treatment. This suggests that treatment can be continued despite the development of retinopathy in many patients. However, two patients who developed cotton wool spots early in the therapy (2 wk) therafter suffered from retinal hemorrhage in a prolonged manner. Therefore, patients who develop cotton wool spots early in the therapy should be carefully monitored. However, as reported in previous studies[4,8,17], most of the patients with retinopathy in this study were asymptomatic. Therefore, combination therapy may be continued in most patients.

The fact that retinopathy occurred more frequently in patients with hypertension, suggests that these patients should be carefully monitored. With periodic examination of the optic fundi, major bleeding that causes visual symptoms may be prevented or detected at an early stage. Therefore, patients who undergo interferon-ribavirin combination therapy, particularly those with hypertension, should undergo periodic examination of the optic fundi.

To conclude, retinopathy associated with combination therapy of interferon α-2b and ribavirin tends to develop in patients with hypertension.

REFERENCES

1 Hepatitis C-global prevalence (update). Wkly Epidemiol Rec 1999; **74**: 425-427

2 **Strader DB**, Wright T, Thomas DL, Seeff LB. Diagnosis, management, and treatment of hepatitis C. *Hepatology* 2004; **39**: 1147-1171
3 **Quesada JR**, Talpaz M, Rios A, Kurzrock R, Gutterman JU. Clinical toxicity of interferons in cancer patients: a review. *J Clin Oncol* 1986; **4**: 234-243
4 **Hayasaka S**, Fujii M, Yamamoto Y, Noda S, Kurome H, Sasaki M. Retinopathy and subconjunctival haemorrhage in patients with chronic viral hepatitis receiving interferon alfa. *Br J Ophthalmol* 1995; **79**: 150-152
5 **Sugano S**, Suzuki T, Watanabe M, Ohe K, Ishii K, Okajima T. Retinal complications and plasma C5a levels during interferon alpha therapy for chronic hepatitis C. *Am J Gastroenterol* 1998; **93**: 2441-2444
6 **Kawano T**, Shigehira M, Uto H, Nakama T, Kato J, Hayashi K, Maruyama T, Kuribayashi T, Chuman T, Futami T, Tsubouchi H. Retinal complications during interferon therapy for chronic hepatitis C. *Am J Gastroenterol* 1996; **91**: 309-313
7 **Saito H**, Ebinuma H, Nagata H, Inagaki Y, Saito Y, Wakabayashi K, Takagi T, Nakamura M, Katsura H, Oguchi Y, Ishii H. Interferon-associated retinopathy in a uniform regimen of natural interferon-alpha therapy for chronic hepatitis C. *Liver* 2001; **21**: 192-197
8 **Cuthbertson FM**, Davies M, McKibbin M. Is screening for interferon retinopathy in hepatitis C justified? *Br J Ophthalmol* 2004; **88**: 1518-1520
9 **Schulman JA**, Liang C, Kooragayala LM, King J. Posterior segment complications in patients with hepatitis C treated with interferon and ribavirin. *Ophthalmology* 2003; **110**: 437-442
10 **Jain K**, Lam WC, Waheeb S, Thai Q, Heathcote J. Retinopathy in chronic hepatitis C patients during interferon treatment with ribavirin. *Br J Ophthalmol* 2001; **85**: 1171-1173
11 **Ikebe T**, Nakatsuka K and Goto M. A case of retinopathy induced by intravenous administration of interferon. *Folia Ophthalmol Jpn (Ganka-Kiyo)* 1990; **41**: 2291-2296 (in Japanese)
12 **Guyer DR**, Yannuzzi LA, Chang S, Shields JA, Green WR. Rerina-Vitreous-Macula. 1st ed. Philadelphia: W.B. Saunders, 1999: 864
13 **Sharrett AR**, Hubbard LD, Cooper LS, Sorlie PD, Brothers RJ, Nieto FJ, Pinsky JL, Klein R. Retinal arteriolar diameters and elevated blood pressure: the Atherosclerosis Risk in Communities Study. *Am J Epidemiol* 1999; **150**: 263-270
14 **Hejny C**, Sternberg P, Lawson DH, Greiner K, Aaberg TM Jr. Retinopathy associated with high-dose interferon alfa-2b therapy. *Am J Ophthalmol* 2001; **131**: 782-787
15 **Kadayifcilar S**, Boyacioglu S, Kart H, Gursoy M, Aydin P. Ocular complications with high-dose interferon alpha in chronic active hepatitis. *Eye (Lond)* 1999; **13** (Pt 2): 241-246
16 **Chisholm JA**, Williams G, Spence E, Parks S, Keating D, Gavin M, Mills PR. Retinal toxicity during pegylated alpha-interferon therapy for chronic hepatitis C: a multifocal electroretinogram investigation. *Aliment Pharmacol Ther* 2005; **21**: 723-732
17 **Guyer DR**, Tiedeman J, Yannuzzi LA, Slakter JS, Parke D, Kelley J, Tang RA, Marmor M, Abrams G, Miller JW. Interferon-associated retinopathy. *Arch Ophthalmol* 1993; **111**: 350-356

S- Editor Pan BR **E- Editor** Liu Y