Table 2 Rate of the ribavirin reduction or discontinuance due to adverse effects according to CL/F level

	No reduction	Dose reduction	Discontinuance	
			All cases	Cases due to severe anemia
$20 \leq CL/F$ ($n = 12$)	67% (8/12)	25% (3/12)	8% (1/12)	0
$15 \leq CL/F < 20$ ($n = 23$)	57% (13/23)	30% (7/23)	13% (3/23)	0
$10 \leq CL/F < 15$ ($n = 39$)	46% (18/39)	31% (12/39)	23% (9/39)	5% (2/39)
$CL/F < 10$ ($n = 42$)	33% (14/42)	40% (17/42)	26% (11/42)	5% (2/42)

$P = 0.031$ (Mantel–Haenszel χ^2-test).

Table 3 Minimum hemoglobin levels during PegIFN/ribavirin combination therapy according to CL/F level

	10 g/dL < Hb	8.5 < Hb ≤ 10 g/dL	Hb ≤ 8.5 g/dL
$20 \leq CL/F$ ($n = 12$)	92% (11/12)	12% (1/12)	0
$15 \leq CL/F < 20$ ($n = 23$)	83% (19/23)	17% (4/23)	0
$10 \leq CL/F < 15$ ($n = 39$)	72% (28/39)	23% (9/39)	5% (2/39)
$CL/F < 10$ ($n = 42$)	50% (21/42)	43% (18/42)	7% (3/42)

$P = 0.009$ (Mantel–Haenszel χ^2-test).

non-responders, 61% (23/38) in relapsers, and 58% (37/64) in naïve patients. The relationship between dose reduction or discontinuance of PegIFN and ribavirin and the SVR rate on ITT analysis is shown in Figure 1. Similar SVR rates were obtained in the groups without dose reduction of PegIFN and ribavirin (64%, 25/39) and with reduction of PegIFN and/or ribavirin (66%, 35/53); in detail, the SVR rate was 79% (11/14) in the group with reduction of only PegIFN, 55% (11/20) with reduction of only ribavirin, and 63% (12/19) with reduction of both PegIFN and ribavirin. In the group where both drugs were discontinued, the SVR rate was 25% (6/24), significantly lower than the group without reduction of both drugs ($P = 0.003$), and the group with reduction of PegIFN and/or ribavirin ($P = 0.001$).

CL/F and dose reduction or discontinuance of ribavirin

CL/F calculated for all patients showed a median of 12.6 L/h (range 4.5–27.9). At the start of the treatment, 36% (42/116) were under 10 L/h, 34% (39/116) were 10–15 L/h, 20% (23/116) were 15–20 L/h and 10% (12/116) were 20 L/h or more.

The rate of dose reduction or discontinuance of ribavirin is shown in Table 2 for different levels of CL/F. The rate of discontinuance of ribavirin in all cases was 8% (1/12) for the $CL/F \geq 20$, 13% (3/23) for the $15 \leq CL/F < 20$, 23% (9/39) for the $10 \leq CL/F < 15$, and 26% (11/42) for the $CL/F < 10$ group. Ribavirin did not have to be discontinued due to severe anemia among patients with $15 \leq CL/F$, but did for the 18% (2/11) of those with $CL/F < 10$ and 22% (2/9) of those with $10 \leq CL/F < 15$. The rate of reduction and discontinuance of ribavirin correlated significantly with the CL/F level.

CL/F and minimum hemoglobin level during treatment

To examine the relationship between anemia and the cessation of ribavirin in further detail, we evaluated the minimum hemoglobin level during treatment. Table 3 presents the different levels in relation to CL/F. The patients with minimum Hb ≤ 8.5 g/dL, the criterion for discontinuance of ribavirin, accounted for 7% (3/42) of the group of $CL/F < 10$, and 5% (2/39) of the group of $10 \leq CL/F < 15$. No patients of the group of $CL/F \geq 15$ showed minimum Hb ≤ 8.5 g/dL.

Early decline of Hb and progression of anemia during combination therapy

Following the initiation of combination therapy, the Hb concentration decreased rapidly until the end of four-weeks. At the end of two weeks, Hb had decreased by 1.1 ± 1.0 g/dL among the patients without dose reduction of ribavirin ($n = 53$), 1.6 ± 1.2 g/dL among those with dose reduction ($n = 39$), and 1.8 ± 1.0 g/dL among

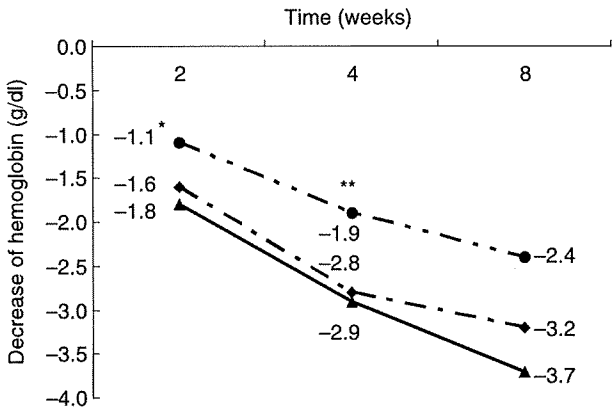


Figure 2 Course of ΔHb in the initial phase. (—··—), No reduction; (—·—·), reduction; (——), discontinuance. *Significantly different between patients with discontinuance and patients with no reduction ($P = 0.04$). **Significantly different between patients with discontinuance and patients with no reduction ($P = 0.008$), and between patients with discontinuance and patients with reduction ($P = 0.003$).

those who had discontinued ribavirin ($n = 24$). It was significantly different between the patients with no reduction and those with discontinuance of therapy ($P = 0.04$). At the end of four weeks, Hb had decreased by 1.9 ± 1.2 g/dL among the patients without dose reduction of ribavirin, 2.8 ± 1.2 g/dL among those with dose reduction, and 2.9 ± 1.2 g/dL among those who had discontinued ribavirin. Hb decline at the end of four weeks was significantly greater in the patients who had discontinued treatment and those who had reduced it, than in those with no reduction ($P = 0.008$, $P = 0.003$, respectively) (Fig. 2).

In this study, we selected the Hb decrease at the end of two weeks as the predictive factor for anemia progression. This is because the judgment of Hb decrease at the end of four weeks is too late to prevent progression of anemia or to perform appropriate counter-measures, such as the administration of epoetin or reduction of ribavirin. Next, we tried to use two borderlines of ΔHb: ΔHb 2.0 indicates a 2 g/dL Hb decrease at the end of two weeks and ΔHb 1.5 indicates a 1.5 g/dL Hb decrease. When ΔHb 2.0 was adopted, the rate of discontinuance of drugs was 31% (12/39) in the ΔHb ≥ 2.0 and 14% (11/76) in the ΔHb < 2.0. When ΔHb 1.5 was adopted, it was 23% (14/60) in the ΔHb ≥ 1.5 and 16% (9/55) in the ΔHb < 1.5. Comparison of the ΔHb 2.0 and ΔHb 1.5 standards showed the sensitivity to be 52% (12/23) and 61% (14/23), and the specificity to be 71% (65/92) and 50% (46/92), respectively. With respect to discontinuance due to anemia, both ΔHb 2.0 and ΔHb 1.5 gave 100% sensitivity (3/3), and the specificities were 68% (76/112) using ΔHb 2.0 and 49% (55/112) using ΔHb 1.5. We decided to adopt the standard of ΔHb 2 g/dL at the end of two weeks from the start of the pegylated IFN and ribavirin combination therapy as the predictive factor for anemia progression ("2 by 2" standard), which has been taken as a predictive factor for anemia in the IFN and ribavirin combination therapy.[25]

Applying the "2 by 2" standard to PegIFN plus ribavirin combination therapy, the rate of reduction or discontinuance of the ribavirin dose was examined with respect to the Hb decrease level (Table 4). Only one patient was excluded from this study, because the treatment was discontinued on the 11th day. In the group of ΔHb (the decrease in Hb concentration at two weeks from the baseline) ≥ 2 g/dL ($n = 39$), the doses were reduced for 18 patients (46%) and discontinued for 12 (31%), three of whom (8%) had severe anemia. For the group of ΔHb < 2 g/dL (76 patients), the doses were reduced for 21 patients (28%) and discontinued for 11 (14%); none due to severe anemia.

Early decline of Hb and minimum hemoglobin level during treatment

As in the case of ΔHb, we evaluated the minimum hemoglobin level during treatment, as shown in Figure 3. The patients with minimum Hb ≤ 8.5 g/dL accounted for 10% (4/39) of the group of ΔHb ≥ 2 g/dL, and there was no patient with minimum Hb ≤ 8.5 g/dL

Table 4 Rate of the ribavirin reduction or discontinuance due to adverse effects according to Hb decrease levels

	No reduction	Dose reduction	Discontinuance	
			All cases	Cases due to severe anemia
ΔHb < 2 g/dL ($n = 76$)	58% (44/76)	28% (21/76)	14% (11/76)	0
ΔHb ≥ 2 g/dL ($n = 39$)	23% (9/39)	46% (18/39)	31% (12/39)	8% (3/39)

$P = 0.004$ (Mantel–Haenszel χ^2-test).

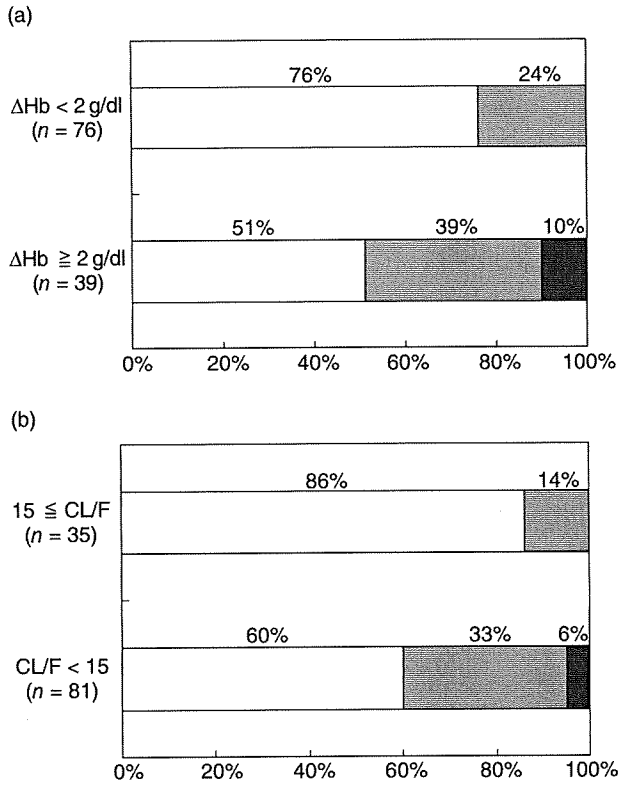


Figure 3 Minimum hemoglobin levels during PegIFN/ribavirin combination therapy. (□), 10 g/dL < minimum Hb; (▩), 8.5 < minimum Hb ≤ 10 g/dL; (■), minimum Hb ≤ 8.5 g/dL. (a) According to the "2 by 2" standard (Hb 2 g/dL decrease at two weeks from the baseline). $P = 0.009$ (Mantel–Haenszel χ^2-test). (b) according to CL/F levels. $P = 0.001$ (Mantel–Haenszel χ^2-test).

in the ΔHb < 2 g/dL group (Fig. 3a). The patients with minimum Hb ≤ 8.5 g/dL accounted for 6% (5/81) of the group of CL/F < 15, and there was no patient with minimum Hb ≤ 8.5 g/dL in the 15 ≤ CL/F group (Fig. 3b). The number of patients with minimum Hb ≤ 8.5 g/dL during PegIFN and ribavirin combination therapy according to "2 by 2" standard and CL/F levels is shown in Table 5. The patients with minimum Hb ≤ 8.5 g/dL were found only in the "2 by 2" standard-positive and low CL/F (<15) group (4/29, 14%).

Table 5 The number of patients with minimum hemoglobin ≤8.5 g/dL during PegIFN/ribavirin combination therapy according to "2 by 2" standard and CL/F levels

	ΔHb < 2 g/dL ($n = 76$)	ΔHb ≥ 2 g/dL ($n = 39$)
CL/F ≥ 15 ($n = 35$)	0/25	0/10
CL/F < 15 ($n = 80$)	0/51	4/29 (14%)

DISCUSSION

PREDICTION OF THE progression of anemia is necessary to decide whether drugs can be continued, with minimization of the disadvantages induced by anemia. Recently, CL/F has been used as a marker of progressing anemia that necessitates discontinuance of treatment. For example, if the patients have a low CL/F level, they should start treatment with a low ribavirin dose. In this study, we attempted to use the CL/F level measurement for our patients. To predict which patients might have to discontinue the treatment, the target range had to be CL/F < 15 because 6% of patients ($n = 5$) in this range showed minimum Hb ≤ 8.5 g/dL, which is the level at which ribavirin should be discontinued. No patients of the CL/F ≥15 group showed minimum Hb ≤ 8.5 g/dL. Our findings showed that 70% of the patients (81/116) with CL/F < 15 should be discriminated from the others (Table 3). In the same manner, using ΔHb as the marker, 34% of the target patients in the ΔHb ≥ 2 g/dL group were identified because 10% in this range showed minimum Hb ≤ 8.5 g/dL. No patients in the ΔHb < 2 g/dL group showed minimum Hb ≤ 8.5 g/dL. Compared to CL/F, ΔHb is considered to be more sensitive and convenient for identifying the high risk patients for whom treatment would need to be discontinued. Furthermore, the application of "2 by 2" standard in the group with low level of CL/F < 15 can be the most sensitive method for this (Table 5), since no patients with progression of anemia were found in the "2 by 2" standard-negative group with CL/F < 15.

In Japan, ribavirin doses are set at 600 mg for <60 kg, 800 mg for 60–80 kg, and 1000 mg for ≥80 kg, which are lower doses than those used in Europe and the USA. In this study, the mean ribavirin level at the start of treatment was 743 mg per day, while the AASLD practice guideline for genotype 1 hepatitis C is a daily dose of 1000 mg for body weight ≤ 75 kg and 1200 mg if >75 kg[26] In Japan, the use of lower doses is why fewer patients treated with PegIFN and ribavirin combination therapy are forced to discontinue the treatment due to severe anemia. Since the "2 by 2" model and/or CL/F can identify the patients who are prone to develop severe anemia, the other patients could be candidates for ribavirin dose-up strategies to raise SVR rates.

A considerable number of patients with chronic hepatitis C are over 60 years old in Japan (mean age is

around 55 years old),[27] although the mean age of this study was 50.6 years old. The number of aged patients with chronic hepatitis C is expected to increase in Europe and the USA, as well as in Japan. In IFN and ribavirin combination therapy, the discontinuance rate due to anemia was significantly higher in aged patients (≥60 years old, 21%) than in younger patients (<60 years old, 9%) ($P < 0.001$).[25] Earlier prediction of anemia is necessary to reduce the ribavirin dose in order to prevent the progression of severe anemia or to start epoetin alfa administration as needed, especially with aged patients. The "2 by 2" standard in PegIFN and ribavirin combination therapy should be a useful and convenient device for predicting the progress of anemia and treatment discontinuance in Europe and the USA, as well as in Japan.

CONCLUSION

IN CONCLUSION, THIS paper has shown that the SVR rate can be raised by preventing the discontinuance of ribavirin in PegIFN and ribavirin combination therapy. What is now needed is a prospective study of whether the early reduction of ribavirin in "2 by 2" standard-positive patients can improve the SVR rates, to ascertain the utility of the "2 by 2" standard in PegIFN and ribavirin combination therapy.

REFERENCES

1 Kasahara A, Hayashi N, Mochizuki K *et al.* Risk factors for hepatocellular carcinoma and its incidence after interferon treatment in patients with chronic hepatitis C. Osaka Liver Disease Study Group. *Hepatology* 1998; **27**: 1394–402.

2 Imai Y, Kasahara A, Tanaka H *et al.* Interferon therapy for aged patients with chronic hepatitis C: improved survival in patients exhibiting a biochemical response. *J Gastroenterol* 2004; **39**: 1069–77.

3 Hayashi N, Takehara T. Antiviral therapy for chronic hepatitis C: past, present, and future. *J Gastroenterol* 2006; **41**: 17–27.

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* 1998; **352**: 1426–32.

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* 1998; **339**: 1485–92.

6 Manns MP, McHutchison JG, Gordon SC *et al.* Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. *Lancet* 2001; **358**: 958–65.

7 Fried MW, Shiffman ML, Reddy KR *et al.* Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. *N Engl J Med* 2002; **347**: 975–82.

8 Hiramatsu N, Kasahara A, Nakanishi F *et al.* The significance of interferon and ribavirin combination therapy followed by interferon monotherapy for patients with chronic hepatitis C in Japan. *Hepatol Res* 2004; **29**: 142–7.

9 Bruno S, Camma C, Di Marco V *et al.* Peginterferon alfa-2b plus ribavirin for naïve patients with genotype 1 chronic hepatitis C: a randomized controlled trial. *J Hepatol* 2004; **41**: 474–81.

10 Hadziyannis SJ, Sette H Jr, Morgan TR *et al.* Peginterferon-alpha2a and ribavirin combination therapy in chronic hepatitis C: a randomized study of treatment duration and ribavirin dose. *Ann Intern Med* 2004; **140**: 346–55.

11 Berg T, Von Wagner M, Nasser S *et al.* Extended treatment duration for Hepatitis C virus type 1: comparing 48 versus 72 weeks of peginterferon-alfa-2a plus ribavirin. *Gastroenterology* 2006; **130**: 1086–97.

12 Lodato F, Azzaroli F, Brillanti S *et al.* Higher doses of peginterferon alpha-2b administered twice weekly improve sustained virological response in difficult-to-treat patients with chronic hepatitis C: results of a pilot randomized study. *J Viral Hepat* 2005; **12**: 536–42.

13 Lindahl K, Stahle L, Bruchfeld A, Schvarcz R. High-dose ribavirin in combination with standard dose peginterferon for treatment of patients with chronic hepatitis C. *Hepatology* 2005; **41**: 275–9.

14 Bodenheimer HC Jr, Lindsay KL, Davis GL *et al.* Tolerance and efficacy of oral ribavirin treatment of chronic hepatitis C: a multicenter trial. *Hepatology* 1997; **26**: 473–7.

15 De Franceschi L, Fattovich G, Turrini F *et al.* Hemolytic anemia induced by ribavirin therapy in patients with chronic hepatitis C virus infection: role of membrane oxidative damage. *Hepatology* 2000; **31**: 997–1004.

16 Van Vlierbergh H, Delanghe JR, De Vos M, Leroux-Roel G. Factors influencing ribavirin-induced hemolysis. *J Hepatol* 2001; **34**: 911–16.

17 Tappero G, Ballare M, Farina M, Negro F. Severe anemia following combined alpha-interferon/ribavirin therapy of chronic hepatitis C. *J Hepatol* 1998; **29**: 1033–4.

18 Afdhal NH, Dieterich DT, Pockros PJ *et al.* Epoetin alfa maintains ribavirin dose in HCV-infected patients: a prospective, double-blind, randomized controlled study. *Gastroenterology* 2004; **126**: 1302–11.

19 Pockros PJ, Shiffman ML, Schiff ER *et al.* Epoetin alfa improves quality of life in anemic HCV-infected patients receiving combination therapy. *Hepatology* 2004; **40**: 1450–8.

20 Dieterich DT, Wasserman R, Brau N *et al.* Once-weekly epoetin alfa improves anemia and facilitates maintenance

of ribavirin dosing in hepatitis C virus-infected patients receiving ribavirin plus interferon alfa. *Am J Gastroenterol* 2003; **98**: 2491–9.
21 Lindahl K, Schvarcz R, Bruchfeld A, Stahle L. Evidence that plasma concentration rather than dose per kilogram body weight predicts ribavirin-induced anaemia. *J Viral Hepat* 2004; **11**: 84–7.
22 Jen JF, Glue P, Gupta S, Zambas D, Hajian G. Population pharmacokinetic and pharmacodynamic analysis of ribavirin in patients with chronic hepatitis C. *Ther Drug Monit* 2000; **22**: 555–65.
23 Kamar N, Chatelut E, Manolis E, Lafont T, Izopet J, Rostaing L. Ribavirin pharmacokinetics in renal and liver transplant patients: evidence that it depends on renal function. *Am J Kidney Dis* 2004; **43**: 140–6.
24 Karino Y, Kato T, Arakawa T *et al.* Total clearance (CL/F) of ribavirin is the factor most influencing the incidence of hemolytic anemia during IFN plus ribavirin therapy. *Hepatology* 2004; **40** (Suppl 1): 358.
25 Oze T, Hiramatsu N, Kurashige N *et al.* Early decline of hemoglobin correlates with progression of ribavirin-induced hemolytic anemia during interferon plus ribavirin combination therapy in patients with chronic hepatitis C. *J Gastroenterol* 2006; **41**: 862–72.
26 Strader DB, Wright T, Thomas DL, Seeff LB. Diagnosis, management, and treatment of hepatitis C. *Hepatology* 2004; **39**: 1147–67.
27 Hiramatsu N, Oze T, Tsuda N *et al.* Should aged patients with chronic hepatitis C be treated with interferon and ribavirin combination therapy? *Hepatol Res* 2006; **35**: 185–9.

ARTICLE | Annals of Internal Medicine

Declining Incidence of Hepatocellular Carcinoma in Osaka, Japan, from 1990 to 2003

Hideo Tanaka, MD; Yasuharu Imai, MD; Naoki Hiramatsu, MD; Yuri Ito, PhD; Kazuho Imanaka, MD; Masahide Oshita, MD; Taizo Hijioka, MD; Kazuhiro Katayama, MD; Iwao Yabuuchi, MD; Harumasa Yoshihara, MD; Atsuo Inoue, MD; Michio Kato, MD; Tetsuo Takehara, MD; Shinji Tamura, MD; Akinori Kasahara, MD; Norio Hayashi, MD; and Hideaki Tsukuma, MD

Background: Japan has the highest incidence rate of primary liver cancer attributed to chronic hepatitis C virus (HCV) infection among developed countries. Molecular clock analysis of HCV sequences revealed that the spread of HCV took place earlier in Japan than in other countries. This might influence recent temporal trends in hepatocellular carcinoma (HCC) incidence.

Objective: To characterize the contribution of HCV-related hepatocellular carcinoma (HCC) to recent changes in HCC incidence in Osaka, Japan.

Design: Population-based survey.

Setting: Osaka Cancer Registry and 10 hospitals in Osaka.

Participants: 63 862 patients with HCC that was diagnosed between 1981 and 2003 in Osaka Prefecture, including 5253 HCV-seropositive patients with HCC that was diagnosed between 1990 and 2003 at 10 hospitals.

Measurements: Incidence of HCC and estimated incidence rate of HCV-related HCC, measured by multiplying the prevalence of anti-HCV by the corresponding HCC incidence rate.

Results: Between 1981 and 2003, peak incidence of HCC among men age 50 to 59 years, 60 to 69 years, and 70 to 79 years occurred in 1986, 1995, and 2000, respectively, with marked downward trends thereafter (average annual change, −7.9, −22.3, and −12.4 per 100 000 persons, respectively). Similar trends were observed in women. Estimated sex- and age-specific incidence of HCV-related HCC (per 100 000 persons) decreased from 255 to 92 cases at the maximum in men age 60 to 69 years and from 61 to 34 cases in women age 60 to 69 years, whereas estimated incidence of non-HCV–related HCC did not change between 1990 and 2003.

Limitation: Infection was determined only by HCV seropositivity.

Conclusion: The incidence of HCC in Osaka started to decrease by 2000, mainly because of decreased HCV-related HCC.

Ann Intern Med. 2008;148:820-826. www.annals.org
For author affiliations, see end of text.

Primary liver cancer was the fifth most common cancer worldwide by 2000, with approximately 551 000 new cases recorded (1). In most countries, hepatocellular carcinoma (HCC) comprises 85% to 90% of primary liver cancer cases. With some exceptions, developed countries, including the United States, have been experiencing an increase in the incidence of primary liver cancer, considered to be due at least in part to increased prevalence of chronic hepatitis C virus (HCV) infection (2).

Japan has had one of the highest incidence rates of primary liver cancer among developed countries (age-standardized incidence rate in 1995, 25.5 per 100 000 men and 7.7 per 100 000 women) (3). Approximately 90% of liver cancer cases are HCC, which, in Japan, is mainly caused by chronic HCV infection rather than chronic hepatitis B virus infection (4). A recent report on the age-standardized incidence of primary liver cancer among Japanese men, which was calculated from 6 population-based cancer registries, showed a sharp increase that started in the mid-1970s but leveled off in the mid-1990s (5). These distinctive trends were thought to be due to the spread of HCV infection, which began in the 1920s and increased after World War II (6–8). Thus, HCV penetrated Japan earlier than Spain, Egypt, the United States, the former Soviet Union, South Africa, and Hong Kong, as evidenced by molecular clock analysis of the sequences of HCV isolates (8). However, recent temporal trends regarding incidence rates of HCC and the contribution of HCV infection have not been clearly documented in the Japanese population.

We analyzed temporal trends for HCC incidence rates between 1981 and 2003 in Osaka Prefecture (population in 2005, 8.8 million) and interpreted these in the context of HCV infection rates.

See also:

Print
Editors' Notes 821

Web-Only
Conversion of graphics into slides

METHODS

Data Collection on Incident HCC Cases

We obtained data on incident HCC cases from the Osaka Cancer Registry, which was established by the Osaka Prefectural Government in 1962. The registry collects reports on patients with newly diagnosed cancer, including demographic and cancer-related information, from all medical institutions in Osaka Prefecture (9). These have been routinely supplemented by death certificates gathered

by the Osaka Prefectural Government (9). For patients with cancer who were enrolled in the registry on the basis of their death certificate, we contacted the issuing hospital to obtain information on diagnosis and treatment and to establish the date of HCC incidence, which we determined to be the time of diagnosis at that hospital. We site-coded the data according to the International Classification of Diseases for Oncology, Third Edition (10). We included patients with HCC (codes 8170 through 8180). The protocol was approved by the ethics committee of the Osaka Medical Center for Cancer and Cardiovascular Diseases.

From 1981 to 2003, 48 166 men and 15 696 women with HCC were documented in the Osaka Cancer Registry. We calculated the annual age-standardized incidence rates of HCC (world population as a standard population) by sex between 1981 and 2003. To characterize temporal trends for HCC, we assessed 10-year, age-specific incidence rates of HCC between 1981 and 2003 in individuals age 50 to 79 years. We studied these particular age-specific rates because most HCV-related HCC cases in the Japanese population occur between the ages of 50 and 79 years (4). We used the annual population estimates from 1981 to 2003, which were based on the average population in each sex and age category for the Osaka Prefecture during the particular period, as denominators for calculating incidence rates. The annual population estimates were based on data from the 1980, 1985, 1990, 1995, 2000, and 2005 Japanese population censuses, with linear interpolation for the years in between.

Statistical Analysis

To identify years when a statistically significant change in the slope of the temporal trend in the incidence occurred, we applied the joinpoint regression model by using the Joinpoint Regression Program, version 3.0 (U.S. National Cancer Institute, Bethesda, Maryland). We assumed constant variance and uncorrelated errors (11) because we could not detect heteroskedasticity by the White test or autocorrelation by the Durbin-Watson test in men or women in any age group.

We computed the estimated slopes describing the average annual change of incidence rate per 100 000 persons and the corresponding 95% CIs for each trend by fitting a piecewise regression line to the rates, using calendar year as a regression variable. We used the permutation test method to identify years when a statistically significant change had occurred ($P < 0.05$) and set the number of randomly permuted data sets at 4499. We set the number of joinpoints to a minimum of 0 and a maximum of 3 in the Joinpoint Regression Program.

Data Collection on Prevalence of HCV Infection among Patients with HCC

The Osaka Cancer Registry does not collect serologic data on HCV infection in the registered patients. Therefore, we used data on HCV seropositivity from patients with HCC that was diagnosed at 10 hospitals in Osaka Prefecture (1 university hospital, 2 cancer centers, and 7 general hospitals) to estimate the prevalence of HCV infection in patients with HCC. We considered the HCC diagnosis confirmed when the patient had positive histologic or positive radiologic results by enhanced computed tomography or hepatic angiography. We collected data on the patient's sex, date of birth, date of diagnosis between 1990 and 2003, first Chinese letter of the family name, and presence of hepatitis B surface antigen and antibody to hepatitis C (anti-HCV) as assessed by any commercially available kit. We did not collect the full first and family name for reasons of confidentiality. Because anti-HCV testing first became available in Japan in 1990, we collected data on patients whose HCC diagnosis was between 1990 and 2003. One investigator checked for duplication of the data set, because some patients might have been registered multiple times among the participating hospitals as a result of referrals and recurrence of HCC. We defined HCV-related HCC as occurring in patients who were HCV-seropositive at the time of diagnosis.

We calculated the sex-specific, age-specific (50 to 59, 60 to 69, or 70 to 79 years), and period-specific (1990 to 1992, 1993 to 1995, 1996 to 1998, 1999 to 2001, or 2002 to 2003) prevalences of HCV seropositivity for patients with HCC. We then multiplied prevalence rates by the corresponding strata of the HCC incidence rate obtained from the Osaka Cancer Registry data. Thus, we derived the denominators from the general population in Osaka through the denominators of the HCC incidence rate and obtained the numerators by multiplying the prevalence rates by the HCC incidence rate. We calculated the incidence rate of non–HCV-related HCC by subtracting HCV-related HCC from total HCC. Thus, we describe trends for the estimated incidence rates of HCV-related

Context

Hepatitis C virus (HCV) infection in Japan began to spread during the 1920s, increased after World War II with an explosion in parenteral amphetamine use and paid blood donation, and decreased in the 1950s to 1960s with voluntary blood donation and penalties against amphetamine use. Evidence linking the trends in HCV infection to hepatocellular carcinoma rates in Japan is limited.

Contribution

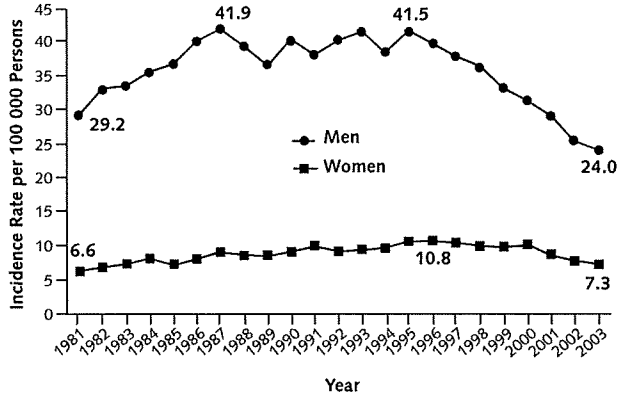
Data from the Osaka Cancer Registry and 10 Osaka hospitals suggest that hepatocellular carcinoma rates began to decrease in 2000, mainly because of a decrease in HCV-associated cancer.

Implication

Control of HCV transmission within a population seems to be followed by a decrease in hepatocellular carcinoma.

—The Editors

Figure 1. **Trends in age-standardized (world population) incidence of hepatocellular carcinoma in Osaka, Japan, 1981–2003.**



and non–HCV-related HCC between 1990 and 2003 in Osaka Prefecture. We calculated the CI of the estimated rates by multiplying the lower and upper limits of the CI of the prevalence based on SE by the corresponding HCC incidence rate.

Role of the Funding Source

This study was supported by the Osaka Prefectural Government between 1990 and 2000 and Grants-in-Aid for Hepatitis Research of the Japanese Ministry of Health, Labor, and Welfare. There is no conflict of interest in the study. The funding sources had no role in the collection, management, or analysis of data.

RESULTS

The age-standardized incidence rate of HCC in men increased between 1981 and 1987 from 29.2 to 41.9 cases per 100 000 persons, then fluctuated until 1995. After that, it steadily decreased to 24.0 cases per 100 000 persons in 2003 (**Figure 1**). Among women, the age-standardized incidence rate of HCC increased between 1981 and 1996 from 6.6 to 10.8 cases per 100 000 persons, then gradually decreased to 7.3 cases per 100 000 persons in 2003 (**Figure 1**).

Figure 2 shows the trends in the incidence of HCC among men and women age 50 to 59 years, 60 to 69 years, and 70 to 79 years in Osaka between 1981 and 2003. The HCC incidence rate increased from 1981 to 1986 among men age 50 to 59 years, from 1981 to 1995 among men age 60 to 69 years, and from 1981 to 2000 among men age 70 to 79 years (average annual change of the incidence rate [per 100 000 persons], 10.0, 10.7, and 6.2, respectively) (**Table 1**). A striking downward trend occurred after the year of peak incidence in the 3 age groups (−7.9 until 1996, −22.3 until 2003, and −12.4 until 2003, respectively). Among men age 50 to 59 years, there was a second joinpoint (a change from rapid to moderate decrease) in 1996, resulting in a slope of −3.1 until 2003. Among women age 50 to 59 years, 60 to 69 years, and 70 to 79 years, the incidence rates of HCC peaked in 1991, 1997, and 2000, respectively (**Table 1**). The rates in women seemed to increase slightly from 1981 until the year of the joinpoint, with slopes of 0.43, 2.07, and 3.10, respectively. Thereafter, HCC incidence rates in women decreased through 2003 at a statistically significant average annual rate of −0.9, −5.7, and −7.9, respectively (**Table 1**).

Figure 2. **Joinpoint analysis of the incidence rate of hepatocellular carcinoma among individuals age 50 to 79 years in Osaka, Japan, 1981–2003.**

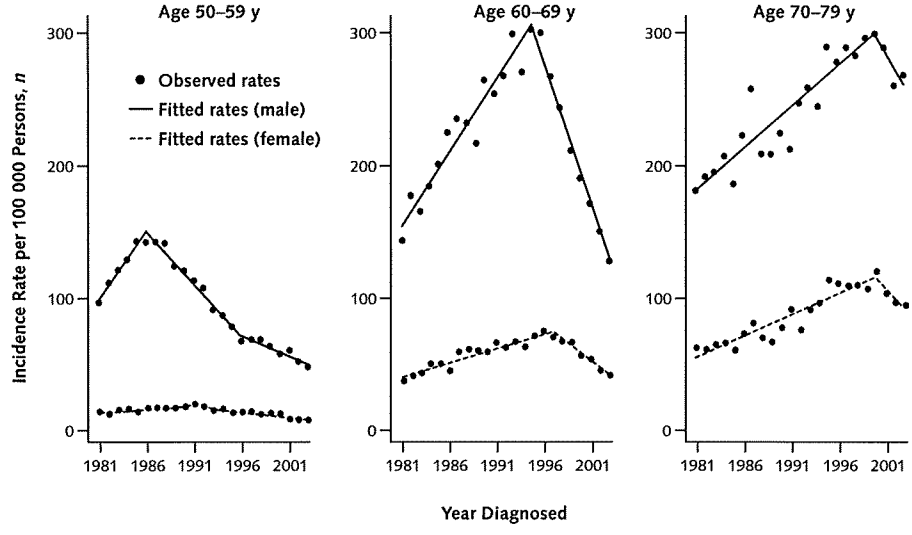


Table 1. **Joinpoint Analysis of the Hepatocellular Carcinoma Incidence Rate per 100 000 Persons in Osaka, Japan, 1981–2003**

Age Range	Peak Year	Incidence Rate per 100 000 Persons	Trend 1		Trend 2		Trend 3	
			Years	Slope (95% CI)	Years	Slope (95% CI)	Years	Slope (95% CI)
Men								
50–59 y	1986	142.0	1981–1986	10.0 (8.2 to 11.8)*	1986–1996	−7.9 (−8.6 to −7.1)*	1996–2003	−3.1 (−4.2 to −2.1)*
60–69 y	1995	299.6	1981–1995	10.7 (9.1 to 12.3)*	1995–2003	−22.3 (−26.0 to −18.6)*	–	–
70–79 y	2000	296.4	1981–2000	6.2 (4.8 to 7.5)*	2000–2003	−12.4 (−35.7 to 10.9)	–	–
Women								
50–59 y	1991	19.7	1981–1991	0.4 (0.2 to 0.7)*	1991–2003	−0.9 (−1.1 to −0.7)*	–	–
60–69 y	1997	68.5	1981–1997	2.1 (1.7 to 2.4)*	1997–2003	−5.7 (−7.3 to −4.1)*	–	–
70–79 y	2000	118.1	1981–2000	3.1 (2.5 to 3.7)*	2000–2003	−7.9 (−18.1 to 2.4)	–	–

* $P < 0.001$.

Table 2 shows the prevalence of anti-HCV antibodies among 5253 patients age 50 to 79 years with HCC that was diagnosed at 10 hospitals in Osaka between 1990 and 2003. The prevalence was highest in men with HCC that was diagnosed in 1993 to 1995 (82.4%). The proportion of HCV-seronegative patients ranged from 18% to 29% through the observation period. The prevalence of anti-HCV was almost constant (81% to 83%) among women with HCC that was diagnosed between 1993 and 2003 (Table 2).

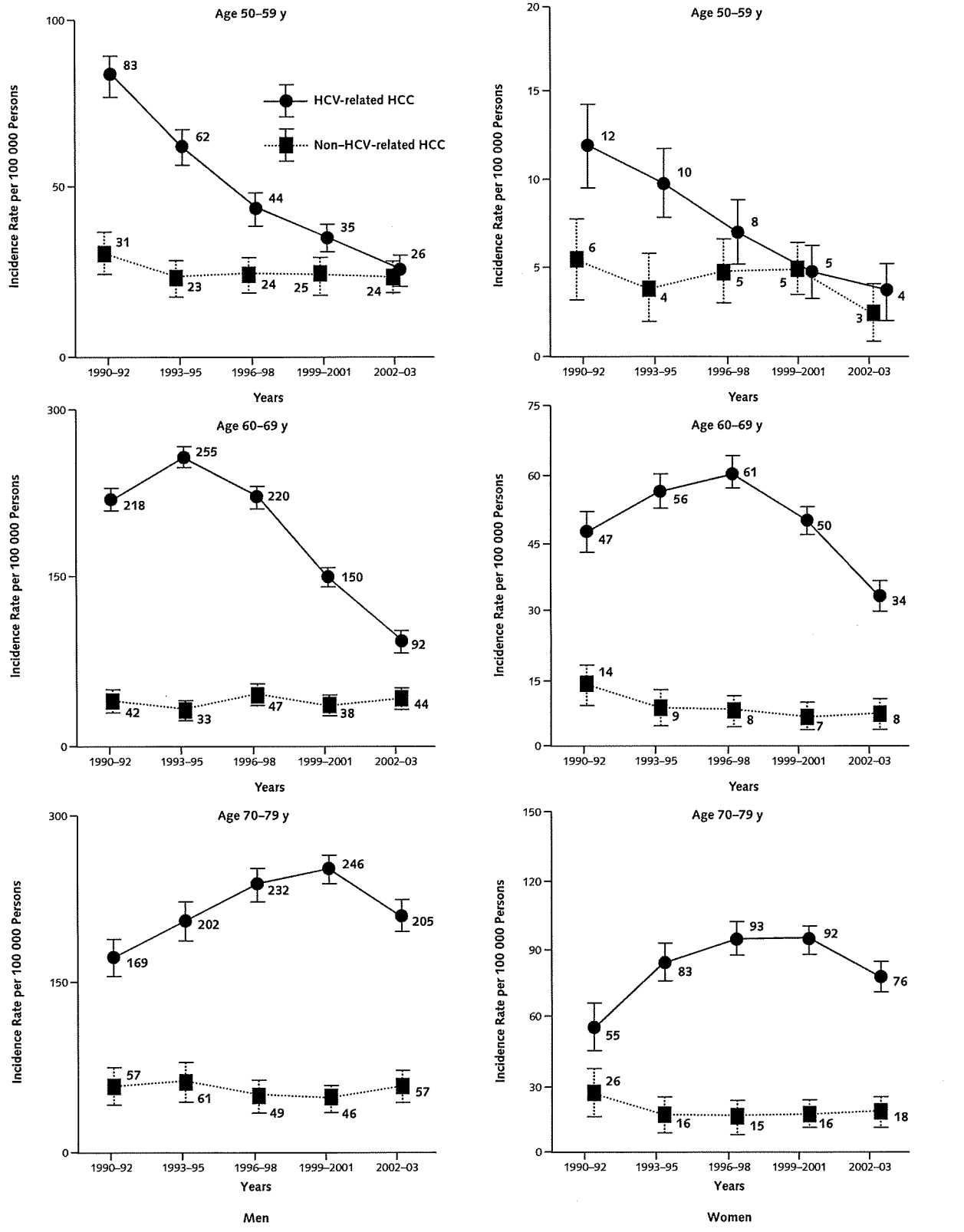
Figure 3 shows changes in the estimated incidence rate of HCV-related and non–HCV-related HCC from 1990 to 2003. Among men, the estimated incidence rate of HCV-related HCC steadily decreased among Osaka residents age 50 to 59 years from 83 (95% CI, 77 to 89) cases per 100 000 persons in 1990 to 1992 to 26 (CI, 21 to 30) cases per 100 000 persons in 2002 to 2003. Among men age 60 to 69 years, incidence seemed to peak (255 [CI, 247 to 264] cases per 100 000 persons) from 1993 to 1995. Among men age 70 to 79 years, the incidence rate increased from 1990 to 1992 (169 [CI, 153 to 186] cases per 100 000 persons) to 1999 to 2001 (246 [CI, 234 to 258] cases per 100 000 persons) and leveled off afterward. The estimated incidence rate of HCV-related HCC among women age 50 to 59 years decreased from 12.4 (CI, 10.1 to 14.7) cases per 100 000 persons during 1990 to 1992 to 4.2 (CI, 2.5 to 5.8) cases per 100 000 persons during 2002 to 2003, whereas among women age 60 to 69 years, the incidence peaked (61 [CI, 57 to 64] cases per 100 000 persons) during 1996 to 1998. The trend in women age 70 to 79 years seemed to be similar to that in men of the same age: increasing during the 1990s and leveling off in the early 2000s (Figure 3). The estimated incidence rate of non–HCV-related HCC was lower than that of HCV-

Table 2. **Prevalence of Anti-HCV among 5253 Patients Age 50 to 79 Years with Hepatocellular Carcinoma at 10 Hospitals in Osaka, Japan, 1990–2003***

Variable	1990–1992		1993–1995		1996–1998		1999–2001		2002–2003	
	Patients, *n*	Prevalence (±SE), %	Patients, *n*	Prevalence (±SE), %	Patients, *n*	Prevalence (±SE), %	Patients, *n*	Prevalence (±SE), %	Patients, *n*	Prevalence (±SE), %
Men										
Anti-HCV(+)	602	78.3 ± 1.5	677	82.4 ± 1.3	651	78.7 ± 1.4	709	76.6 ± 1.4	385	70.9 ± 1.9
Anti-HCV(+) and HBsAg(+)	18	2.3 ± 0.5	17	2.1 ± 0.5	11	1.3 ± 0.4	16	1.7 ± 0.4	8	1.5 ± 0.5
Anti-HCV(+) and HBsAg(−)	584	75.9 ± 1.5	660	80.3 ± 1.4	640	77.4 ± 1.5	693	74.8 ± 1.4	377	69.4 ± 2.0
Anti-HCV(−)	167	21.7 ± 1.5	145	17.6 ± 1.3	176	21.3 ± 1.4	217	23.4 ± 1.4	158	29.1 ± 1.9
Anti-HCV(−) and HBsAg(+)	60	7.8 ± 1.0	57	6.9 ± 0.9	71	8.6 ± 1.0	106	11.4 ± 1.0	68	12.5 ± 1.4
Anti-HCV(−) and HBsAg(−)	107	13.9 ± 1.2	88	10.7 ± 1.1	105	12.7 ± 1.2	111	12.0 ± 1.1	90	16.6 ± 1.6
Total	769	100.0	822	100.0	827	100.0	926	100.0	543	100.0
Women										
Anti-HCV(+)	165	73.0 ± 3.0	211	82.7 ± 2.4	248	82.9 ± 2.2	274	80.8 ± 2.1	200	81.0 ± 2.5
Anti-HCV(+) and HBsAg(+)	8	3.5 ± 1.2	2	0.8 ± 0.6	5	1.7 ± 0.7	2	0.6 ± 0.4	2	0.8 ± 0.6
Anti-HCV(+) and HBsAg(−)	157	69.5 ± 3.1	209	82.0 ± 2.4	243	81.3 ± 2.3	272	80.2 ± 2.2	198	80.2 ± 2.5
Anti-HCV(−)	61	27.0 ± 3.0	44	17.3 ± 2.4	51	17.1 ± 2.2	65	19.2 ± 2.1	47	19.0 ± 2.5
Anti-HCV(−) and HBsAg(+)	21	9.3 ± 1.9	17	6.7 ± 1.6	29	9.7 ± 1.7	29	8.6 ± 1.5	18	7.3 ± 1.7
Anti-HCV(−) and HBsAg(−)	40	17.7 ± 2.5	27	10.6 ± 1.9	22	7.4 ± 1.5	36	10.6 ± 1.7	29	11.7 ± 2.0
Total	226	100.0	255	100.0	299	100.0	339	100.0	247	100.0

* HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus.

Figure 3. **Trends in estimated incidence rates of hepatitis C virus (*HCV*)–related and non–HCV-related hepatocellular carcinoma (*HCC*) in Osaka, Japan, 1990–2003.**



Information on anti-HCV status only became available after 1989. Error bars indicate 95% CIs.

related HCC in most strata. We observed no distinctive changes in the temporal trends for non–HCV-related HCC during the study period.

Discussion

Our analysis of HCC incidence in the Japanese population between 1981 and 2003 identified calendar years in which significant changes in temporal trends occurred. The HCC incidence rates in men and women age 50 to 59 years peaked during 1986 and 1991, respectively; in men and women age 60 to 69 years during 1995 and 1997, respectively; and in men and women age 70 to 79 years in 2000. We also found that temporal trends for HCC incidence between 1990 and 2003 by age group were mainly determined by trends in the incidence rates of HCV-related HCC.

The most likely explanation for these observations is the particular mode of HCV transmission in Japanese society. According to a study on molecular tracing of endemic HCV (8), the exponential spread of HCV-1b infection, a dominant genotype of HCV in Japan, started in the 1920s. This was associated with treatment of *Schistosoma japonicum* beginning in 1921 (12). Later, HCV infection coincided with an increase in parenteral amphetamine use in the devastated country during and after World War II (6, 7). Subsequently, viral spread was considered to be amplified through blood transfusions and parenteral medical procedures in the 1950s and 1960s (6, 7). Data on first-time blood donor candidates in Osaka indicate that the prevalence of anti-HCV antibodies among those born in 1925 to 1935 was much higher (7% to 10%) than that in the younger generation born in 1936 to 1955 (13). It is plausible that Japanese people born between 1925 and 1935, who were adolescents in the early 1950s, were most susceptible to HCV transmission under these circumstances. Age groups with peak incidence of HCC in men and women in the current study (1986 and 1991, respectively, for 50 to 59 years; 1995 and 1997, respectively, for 60 to 69 years; and 2000 for 70 to 79 years) included the generation for which prevalence of anti-HCV was high in Osaka (born in 1925 and 1935) (13). Stiffening of legal penalties against amphetamine use starting in 1954 and conversion from paid to voluntary blood donation in the late 1960s may have reduced HCV transmission, thereby resulting in the lower prevalence of HCV infection in generations born after 1935. Indeed, the spread of HCV in Japan essentially ended by the early 1990s at the latest, as evidenced by the current very low incidence of HCV infection among repeat blood donors (14, 15). Better detection methods introduced in the early 1980s for HCC in patients with cirrhosis through ultrasonography and measurement of α-fetoprotein may have contributed to the apparent increase in the incidence of HCC found in this study. However, the distinctive changes we observed in the age-specific incidence of HCC during the 1990s through the early 2000s cannot be explained by the increased ability to detect HCC, because the different joinpoints in age-specific incidence rates would not be derived from a single period effect of detection of HCC.

Increases in the incidence of and deaths from liver cancer in the 1970s to 1990s have been reported in Japan (5, 16), Australia (2), the United Kingdom (17), France (2, 18), Italy (2, 18), and the United States (2, 19). The increases in Japan and the United States are attributable to increased seroprevalence of HCV (6, 13, 20, 21), whereas this relationship has not been clearly established in the other countries.

Certain limitations of this study should be considered. First, because cancer reporting in Osaka is not mandated by law, HCC could have been underreported. However, because it is fatal, most of the unreported cases should have been detected by examination of the death certificate. In addition, because the proportion of persons with HCC included only on the basis of their death certificate was almost constant (22% to 25%) during the observation period (22–24), such underreporting would not be expected to affect the temporal trends for HCC incidence rates shown in our study. Second, the proportion of HCV-seropositive patients among the 5253 cases diagnosed at 10 hospitals might differ somewhat from the entire cohort of patients with HCC in Osaka. However, all Japanese patients, including those with HCC, have easy access to hospitals because of the national medical insurance system, and the 10 participating hospitals did not select patients with HCC on the basis of their etiologic background. Therefore, it is realistic to suppose that selection bias on prevalence of anti-HCV among these 5253 patients would have been limited. Finally, the temporal trends seen in the present study might differ from those among the entire Japanese population. We previously reported age-specific incidence rates of liver cancer by birth year in Japanese men between 1962 and 1997 (5) by using 6 population-based cancer registries from Cancer Incidence in Five Continents (9) (registries for Miyagi, Yamagata, Osaka, Hiroshima, Saga, and Nagasaki). Our previous study found the peak incidence of HCC among those born between 1931 and 1935 (5). In addition, the age-dependent prevalence of anti-HCV among first-time blood donors in Osaka (13) was similar to those in other areas of Japan (25). These findings may indicate that the timing of the outbreak of HCV infection and its reduction were similar in the different geographic areas of the country.

In conclusion, our calculation of HCC incidence rates demonstrated that they are already decreasing in both sexes in Osaka, Japan. That the outbreak of HCV infection in Japan after World War II and its termination occurred earlier in Japan than in the rest of the world is the most likely explanation for these observations. These findings confirm that HCV-related HCC is a preventable disease that can be decreased by controlling parenteral HCV transmission. In the early 1990s, interferon therapy for patients

with chronic HCV infection was started in Japan to reduce the risk for HCC (26, 27). A nationwide, community-based anti-HCV screening system targeting individuals age 40 to 70 years was introduced by municipal governments in Japan in 2002. Further observation of the temporal trends of HCC incidence is needed to assess the efficacy of these interventions in Japan.

From Osaka Medical Center for Cancer and Cardiovascular Diseases, Ikeda Municipal Hospital, Osaka University Graduate School of Medicine, Osaka Police Hospital, National Hospital Organization Osaka Minami Medical Center, Osaka Koseinenkin Hospital, Otemae Hospital, Osaka Rousai Hospital, Osaka General Medical Center, and National Hospital Organization Osaka National Hospital, Osaka, Japan.

Acknowledgment: The authors thank the Osaka Cancer Registry for allowing use of their data and Ms. Yasue Kotani for assistance with statistical analysis.

Grant Support: By the Osaka Prefectural Government (1999–2000) and Grants-in-Aid for Hepatitis Research of the Japanese Ministry of Health, Labor, and Welfare.

Potential Financial Conflicts of Interest: None disclosed.

Reproducible Research Statement: *Study protocol:* Available by contacting Dr. Tanaka (e-mail, hitanaka@aichi-cc.jp). The protocol is only available in Japanese. *Statistical code and data set:* Not available.

Requests for Single Reprints: Hideo Tanaka, MD, 1-1 Kanokoden, Chikusa-ku Nagoya-shi, Aichi, Japan 464-8681; e-mail, hitanaka@aichi-cc.jp.

Current author addresses and author contributions are available at www.annals.org.

References

1. **Ferlay J, Bray F, Pisani P, Parkin DM, Ferlay J.** GLOBOCAN 2000: Cancer Incidence, Mortality and Prevalence Worldwide, Version 1.0. IARC Cancer Base No. 5. Lyon, France: International Agency for Research on Cancer; 2001.

2. **McGlynn KA, Tsao L, Hsing AW, Devesa SS, Fraumeni JF Jr.** International trends and patterns of primary liver cancer. Int J Cancer. 2001;94:290-6. [PMID: 11668511]

3. **The Research Group for Population-based Cancer Registration in Japan.** Cancer incidence and incidence rates in Japan in 1995: estimates based on data from nine population-based cancer registries. Jpn J Clin Oncol. 2000;30:318-21. [PMID: 11007166]

4. **Tanaka H, Tsukuma H.** Hepatitis C virus. In: Newton R, Beral V, Weiss RA, Tooze J, eds. Cancer Surveys Vol. 33: Infections and Human Cancer. New York: Cold Spring Harbor Laboratory Pr; 1999:213-35.

5. **Tanaka H, Uera F, Tsukuma H, Ioka A, Oshima A.** Distinctive change in male liver cancer incidence rate between the 1970s and 1990s in Japan: comparison with Japanese-Americans and US whites. Jpn J Clin Oncol. 2007;37:193-6. [PMID: 17332055]

6. **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. [PMID: 11868791]

7. **Tsukuma H, Tanaka H, Ajiki W, Oshima A.** Liver cancer and its prevention. Asian Pac J Cancer Prev. 2005;6:244-50. [PMID: 16235981]

8. **Tanaka Y, Kurbanov F, Mano S, Orito E, Vargas V, Esteban JI, et al.** Molecular tracing of the global hepatitis C virus epidemic predicts regional patterns of hepatocellular carcinoma mortality. Gastroenterology. 2006;130:703-14. [PMID: 16530512]

9. **Parkin DM, Whelan SL, Ferlay J, Teppo L, Thomas DM, eds.** Cancer Incidence in Five Continents. vol. VIII. IARC Scientific Publications No. 155. Lyon, France: International Agency for Research on Cancer; 2002:264-5.

10. **Fritz A, Percy C, Jack A, Shanmugaratnam K, Sobin L, Parkin DM, Whelans, eds.** The International Classification of Diseases for Oncology, Third Edition. Geneva: World Health Organization; 2000.

11. **Kim HJ, Fay MP, Feuer EJ, Midthune DN.** Permutation tests for joinpoint regression with applications to cancer rates. Stat Med. 2000;19:335-51. [PMID: 10649300]

12. **Iida F, Iida R, Kamijo H, Takaso K, Miyazaki Y, Funabashi W, et al.** Chronic Japanese schistosomiasis and hepatocellular carcinoma: ten years of follow-up in Yamanashi Prefecture, Japan. Bull World Health Organ. 1999;77:573-81. [PMID: 10444881]

13. **Tanaka H, Hiyama T, Tsukuma H, Okubo Y, Yamano H, Kitada A, et al.** Prevalence of second generation antibody to hepatitis C virus among voluntary blood donors in Osaka, Japan. Cancer Causes Control. 1994;5:409-13. [PMID: 7999962]

14. **Sasaki F, Tanaka J, Moriya T, Katayama K, Hiraoka M, Ohishi K, et al.** Very low incidence rates of community-acquired hepatitis C virus infection in company employees, long-term inpatients, and blood donors in Japan. J Epidemiol. 1996;6:198-203. [PMID: 9002386]

15. **Tanaka H, Tsukuma H, Hori Y, Nakade T, Yamano H, Kinoshita N, et al.** The risk of hepatitis C virus infection among blood donors in Osaka, Japan. J Epidemiol. 1998;8:292-6. [PMID: 9884479]

16. **Tanaka H, Tsukuma H.** Characteristics of Japanese patients with liver cancer—epidemiological study based on a comparison between male and female patients. Hepatol Res. 2002;24:S11-20.

17. **Taylor-Robinson SD, Foster GR, Arora S, Hargreaves S, Thomas HC.** Increase in primary liver cancer in the UK, 1979-94 [Letter]. Lancet. 1997;350:1142-3. [PMID: 9343506]

18. **La Vecchia C, Lucchini F, Franceschi S, Negri E, Levi F.** Trends in mortality from primary liver cancer in Europe. Eur J Cancer. 2000;36:909-15. [PMID: 10785597]

19. **El-Serag HB, Davila JA, Petersen NJ, McGlynn KA.** The continuing increase in the incidence of hepatocellular carcinoma in the United States: an update. Ann Intern Med. 2003;139:817-23. [PMID: 14623619]

20. **El-Serag HB, Mason AC.** Risk factors for the rising rates of primary liver cancer in the United States. Arch Intern Med. 2000;160:3227-30. [PMID: 11088082]

21. **Davila JA, Morgan RO, Shaib Y, McGlynn KA, El-Serag HB.** Hepatitis C infection and the increasing incidence of hepatocellular carcinoma: a population-based study. Gastroenterology. 2004;127:1372-80. [PMID: 15521006]

22. **Parkin DM, Muir CS.** Comparability and quality of data. In: Parkin DM, Muir CS, Whelan SL, Gao YT, Ferlay J, Powell J, eds. Cancer Incidence in Five Continents. vol. VI. IARC Scientific Publications No. 120. Lyon, France: International Agency for Reseach on Cancer; 1992:45-173.

23. Indices of data quality. In: Parkin DM, Whelan SL, Ferlay J, Raymond L, Young J, eds. Cancer Incidence in Five Continents. vol. VII. IARC Scientific Publications No. 143. Lyon, France: International Agency for Research on Cancer; 1997:1146.

24. Indices of data quality. In: Parkin DM, Whelan SL, Ferlay J, Raymond L, Teppo L Thomas DB, eds. Cancer Incidence in Five Continents. vol. VII. IARC Scientific Publications No. 143. Lyon, France: International Agency for Research on Cancer; 2002:719.

25. **Yoshizawa H.** Trends of hepatitis virus carriers. Hepatology Research 2002; 24: S28-39.

26. **Imai Y, Kawata S, Tamura S, Yabuuchi I, Noda S, Inada M, et al.** Relation of interferon therapy and hepatocellular carcinoma in patients with chronic hepatitis C. Osaka Hepatocellular Carcinoma Prevention Study Group. Ann Intern Med. 1998;129:94-9. [PMID: 9669992]

27. **Tanaka H, Tsukuma H, Kasahara A, Hayashi N, Yoshihara H, Masuzawa M, et al.** Effect of interferon therapy on the incidence of hepatocellular carcinoma and mortality of patients with chronic hepatitis C: a retrospective cohort study of 738 patients. Int J Cancer. 2000;87:741-9. [PMID: 10925370]

Current Author Addresses: Drs. Tanaka, Ito, Imanaka, and Tsukuma: 1-3-3 Nakamichi, Higashinari-ku, Osaka 537-8511, Japan.
Dr. Imai: 3-1-18 Johnan, Ikeda, Osaka 563-0025, Japan.
Drs. Hiramatsu and Takehara: 2-2 Yamadaoka, Suita, Osaka 565-0871, Japan.
Dr. Oshita: 10-31 Kitayama-cho, Tennouji-ku, Osaka 543-0035, Japan.
Dr. Hijioka: 2-1 Kido-Higashi-cho, Kawashinagano, Osaka 586-0008, Japan.
Dr. Katayama: 4-2-78 Fukushima, Fukushima-ku, Osaka 553-0003, Japan.
Dr. Yabuuchi: 1-5-34 Otemae, Chuo-ku, Osaka 540-0008, Japan.
Dr. Yoshihara: 1179-3 Nagasone-cho, Kita-ku, Sakai, Osaka 591-8025, Japan.
Dr. Inoue: 3-1-56 Bandai-Higashi, Sumiyoshi-ku, Osaka 558-0056, Japan.
Dr. Kato: 2-1-14 Hoenzaka, Chuo-ku, Osaka 540-0006, Japan.
Dr. Tamura: 5-7-1 Kayano, Minoh, Osaka 562-0014, Japan.
Drs. Kasahara and Hayashi: 2-15 Yamadaoka, Suita, Osaka 565-0871, Japan.

Author Contributions: Concept and design: H. Tanaka, Y. Imai, N. Hiramatsu.
Analysis and interpretation of the data: Y. Imai, K. Imanaka, M. Oshita, T. Hijioka, K. Katayama, I. Yabuuchi, H. Yoshihara, A. Inoue, M. Kato, T. Takehara, S. Tamura, A. Kasahara, H. Tsukuma.
Drafting of the article: H. Tanaka.
Final approval of the article: H. Tanaka, Y. Imai, N. Hiramatsu, Y. Ito, K. Imanaka, M. Oshita, T. Hijioka, K. Katayama, I. Yabuuchi, H. Yoshihara, A. Inoue, M. Kato, T. Takehara, S. Tamura, A. Kasahara, N. Hayashi, H. Tsukuma.
Statistical expertise: Y. Ito.

doi:10.1111/j.1440-1746.2008.05319.x

HEPATOLOGY

Association between the treatment length and cumulative dose of pegylated interferon alpha-2b plus ribavirin and their effectiveness as a combination treatment for Japanese chronic hepatitis C patients: Project of the Kyushu University Liver Disease Study Group

Norihiro Furusyo,* Eiji Kajiwara,† Kazuhiro Takahashi,‡ Hideyuki Nomura,§ Yuichi Tanabe,¶ Akihide Masumoto,** Toshihiro Maruyama,†† Makoto Nakamuta,‡‡ Munechika Enjoji,§§ Koichi Azuma,¶¶ Junya Shimono,*** Hironori Sakai,††† Shinji Shimoda‡‡‡ and Jun Hayashi* for the Kyushu University Liver Disease Study (KULDS) Group

*Department of General Medicine, Kyushu University Hospital, ‡Department of Medicine, Hamanomachi Hospital, ¶Department of Medicine, Fukuoka City Hospital, ††Departments of Gastroenterology, National Hospital Organization Kyushu Medical Center, Departments of §§Medicine and Bioregulatory Science, ¶¶Medicine and Clinical Science and ‡‡‡Medicine and Biosystemic Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka, †Department of Internal Medicine, Nippon Steel Yawata Memorial Hospital, §The Center for Liver Diseases, Shin-Kokura Hospital, **Department of Clinical Research, National Hospital Organization Kokura Hospital, ††Department of Medicine, Kitakyushu Municipal Medical Center, ***Departments of Medicine, Yahata Saiseikai Hospital, Kitakyushu, and †††Department of Gastroenterology, National Hospital Organization Beppu Medical Center, Beppu, Japan

Key words
hepatitis C virus, pegylated interferon alpha-2b, ribavirin.

Accepted for publication 8 November 2007.

Correspondence
Professor Jun Hayashi, Department of General Medicine, Kyushu University Hospital, Higashi-Ku, Fukuoka 812-8582, Japan. Email: hayashij@genmedpr.med.kyushu-u.ac.jp

Abstract

Aim: The aim of the present study was to investigate the association between the length of the treatment period and the cumulative dose of pegylated interferon alpha-2b (peg-IFN alpha-2b) plus ribavirin (RBV) and their effectiveness in the treatment of chronic hepatitis C.

Methods: Seven hundred and fifteen patients received peg-IFN alpha-2b plus RBV treatment for 48 weeks and 24 weeks for genotypes 1 ($n = 586$) and 2 ($n = 129$), respectively.

Results: Sustained virological responses (SVR), defined as serum hepatitis C virus (HCV)-RNA undetectable at 24 weeks after the end of treatment, were 42.4% and 74.4% in genotypes 1 and 2, respectively, on an intention-to-treat analysis. SVR significantly increased with treatment length (4.7%, 36.4%, and 51.8% for < 24 weeks, 24–47 weeks, and 48 weeks, respectively, for genotype 1; and 28.6%, 57.1%, 78.3% for < 12 weeks, 12–23 weeks, and 24 weeks, respectively, for genotype 2). SVR significantly increased with total cumulative treatment dose (21.1%, 36.5%, and 52.9% with < 60%, 60–79%, and ≥ 80% in peg-IFN dose; 29.6%, 51.1%, and 59.2% with < 60%, 60–79%, and ≥ 80% in RBV dose) in genotype 1, although it did not differ significantly for genotype 2.

Conclusions: In peg-IFN alpha-2b plus RBV treatment for chronic hepatitis C, it is important to complete the target length of treatment and to continue the target dosage to achieve SVR, especially for genotype 1 patients.

Introduction

Hepatitis C virus (HCV) is a major cause of chronic liver disease, with perhaps 200 million persons infected worldwide. Approximately 1.8 million patients have chronic HCV infection in Japan. The severity of disease varies widely, from asymptomatic chronic infection to cirrhosis and hepatocellular carcinoma (HCC).[1,2] Eradication of HCV by antiviral treatment improves liver histology and patient survival.[3] A currently popular antiviral treatment regimen for the treatment of chronic HCV infection worldwide is pegylated interferon alpha (peg-IFN alpha) in combination with ribavirin (RBV). The combination treatment has resulted in a higher rate of sustained virological response (SVR), over 50% in Caucasian patients, than standard interferon (IFN) monotherapy.[4,5] However, there are no data concerning the response and safety of the combination treatment for a large number of Japanese patients with chronic HCV infection because this treatment was only approved by the Japanese Ministry of Health, Labor and Welfare in December 2004.

The HCV genotype has been reported to be the most important predictor of IFN treatment response.[4–14] Patients infected with genotypes 2 and 3 achieved approximately 65% SVR in a 24-week

Journal of Gastroenterology and Hepatology 23 (2008) 1094–1104

trial of non-peg-IFN alpha in combination with RBV, in contrast to patients with genotype 1 who had < 30% SVR.[13,14] SVR is also achieved consistently more often by patients with a low HCV-RNA level.[4–14] Moreover, host factors affect the chance of SVR, albeit less so than the genotype.[10] These factors include age, race, sex, obesity, and the degree of hepatic fibrosis and steatosis.[15] In a racial analysis, African Americans were shown to have response rates only one-half to one-third those of Caucasians.[15] In addition, Asian patients were more likely to achieve an SVR by treatment with peg-IFN alpha-2a and RBV than Caucasian patients.[16] The reasons for the racial differences in response rates to peg-IFN alpha plus RBV treatment are not well known.

Peg-IFN alpha was a substantive breakthrough in therapy because of the longer effect; the lasting, steady therapeutic blood level is a major pharmacokinetic advance.[4,5] The most frequent adverse effects during peg-IFN alpha plus RBV treatment are depression and hematological disorders such leukopenia, anemia, and thrombocytopenia. Therefore, the peg-IFN alpha plus RBV treatment often results in discontinuation or the need for a reduction of the dosage due to the adverse effects.

To investigate the efficacy and safety of antiviral treatments for Japanese chronic hepatitis B and C patients, a multicenter study, the Kyushu University Liver Disease Study (KULDS), was launched in 2003. Our group has previously reported several clinical studies.[17–21] The present report is a prospective, multicenter study carried out to analyze the association between the treatment length and the cumulative dose and effectiveness of peg-IFN alpha-2b plus RBV treatment for a large number of Japanese patients with chronic hepatitis C.

Methods

Patients

Treatment of chronic hepatitis C with a combination of peg-IFN alpha-2b and RBV was accepted by the Japanese Ministry of Health in October, 2004. A prospective study of 715 Japanese patients aged 18 years or older (586 and 129 patients with genotypes 1b and 2, respectively) treated with peg-IFN alpha-2b plus RBV between December 2004 and February 2007 who were all positive for antibody to HCV and HCV-RNA for over 6 months was carried out. The respective distribution rates were 82.0% and 18.0% for genotypes 1b and 2, similar to the reported epidemiological distribution.[22]

Criteria for exclusion were: (i) clinical or biochemical evidence of hepatic decompensation, advanced cirrhosis identified by large esophageal varices (F2 or F3), history of gastrointestinal bleeding, ascites, encephalopathy, or hepatocellular carcinoma; (ii) hemoglobin level < 115 g/L, white blood cell count $< 3 \times 10^9$/L, and platelet count $< 50 \times 10^9$/L; (iii) concomitant liver disease other than hepatitis C (hepatitis B surface antigen positive or HIV positive); (iv) excessive active alcohol consumption > 60 g/day or drug abuse; (v) severe psychiatric disease; and (vi) antiviral or corticosteroid therapy within 12 months prior to the enrollment. Patients who fulfilled the above criteria were recruited at Kyushu University Hospital and 32 affiliated hospitals in the northern Kyushu area of Japan.

Within the 3 months before the start of the treatment and every 3 months during the treatment period, each patient was tested for alpha-fetoprotein (AFP) and had abdominal ultrasonographic examination. If an abnormal AFP level of ≥ 40 ng/mL and/or an appearance of focal lesions at ultrasonographic examination was found at any testing, further testing for hepatocellular carcinoma (HCC) was done, which included dynamic computed tomography (CT), angiography, and/or tumor biopsy. Patients so confirmed to have HCC within 3 months after the start of the treatment were excluded from this study.

Table 1 shows the baseline characteristics of the enrolled patients. The median age was 58.0 years. Of the 715 patients, 198 (27.6%) were aged 65 years or over. In Japan, many older patients with chronic hepatitis C are candidates for antiviral treatment, different from many other countries. The rates of prior non-peg-IFN monotherapy significantly differed among the genotype-classified patients (genotype 1, 40.8% and genotype 2, 28.7%).

Table 1 Characteristics of 715 chronic hepatitis C patients treated with a combination of pegylated IFN alpha-2b and ribavirin, classified by HCV genotype

Characteristics	Total $n = 715$	Genotype 1 $n = 586$	Genotype 2 $n = 129$	*P*-value
Male *n* (%)	388 (54.3)	321 (54.8)	67 (51.9)	0.6250
Age (years)	56.8 ± 11.7	57.8 ± 10.3	52.6 ± 14.1	0.0004
Body mass index (kg/m^2)	23.4 ± 3.2	23.5 ± 3.1	23.5 ± 3.3	0.4999
Prior IFN monotherapy *n* (%)	276 (38.6)	239 (40.8)	37 (28.7)	0.0140
Prior combined IFN plus RBV treatment *n* (%)	69 (9.7)	60 (10.9)	5 (3.9)	0.0221
Alanine aminotransferase (IU/L)	77.1 ± 55.4	77.5 ± 52.8	70.9 ± 55.3	0.0594
γ-Glutamyltranspeptidase (IU/L)	60.6 ± 60.3	61.8 ± 58.6	50.8 ± 45.2	0.0241
Albumin (g/dL)	4.1 ± 0.4	4.1 ± 0.3	4.1 ± 0.3	0.1305
White blood cell (/mm^3)	5030.8 ± 1439.2	4993.0 ± 140.8	5260.6 ± 1658.2	0.3005
Hemoglobin (g/dL)	13.9 ± 1.4	13.9 ± 1.4	13.9 ± 1.5	0.7092
Platelet count (10^9/L)	165 ± 56	161 ± 52	185 ± 69	0.0013
Creatinine (mg/dL)	0.70 ± 0.16	0.70 ± 0.17	0.71 ± 0.16	0.1230
Creatinine clearance (mL/min)	97.9 ± 29.9	97.1 ± 29.8	101.3 ± 31.3	0.3621

Data are shown as the mean ± standard deviation.
HCV, hepatitis C virus; IFN, interferon; RBV, rivabirin.

Also, the rates of prior non-peg-IFN alpha plus RBV treatment significantly differed (genotype 1, 10.9% and genotype 2, 3.9%). These differences are explained by the necessity of re-treatment of patients with genotype 1 who had lower SVR by the standard IFN monotherapy than did non-genotype 1 patients, and because the RBV combination treatment with peg-IFN alpha-2b was approved in stages, first for patients with genotype 1 in October 2004, then for those with non-genotype 1 in January 2006. The means for age, platelet count, and γ-glutamyltranspeptidase (γ-GTP) in genotype 1 patients were significantly different than those of genotype 2 patients.

Informed consent was obtained from all patients before enrollment in this study. The study was approved by the institutional ethics committees of the hospitals involved and conducted in accordance with the ethical guidelines of the Declaration of Helsinki and the International Conference on Harmonization of guidelines for good clinical practice.

Treatment regimen

All patients were treated with a weight-based, 1.5 μg/kg weekly dose of subcutaneous peg-IFN alpha-2b (PegIntron A; Schering-Plough, Osaka, Japan). In combination with peg-IFN alpha-2b, RBV (Rebetol; Schering-Plough) was given orally at a daily dose of 600–1000 mg based on bodyweight (600 mg for patients weighing < 60 kg, 800 mg for those weighing 60–80 kg, and 1000 mg for those weighing ≥ 80 kg). The lengths of treatment were 48 weeks and 24 weeks for HCV genotypes 1 and 2 patients, respectively. The above durations and dosages are those approved by the Japanese Ministry of Health, Labor and Welfare. Patients were considered to have RBV-induced anemia if the hemoglobin level decreased to < 100 g/L. In such cases, a reduction in the dose of RBV was required. Some patients also had peg-IFN alpha-2b-induced psychological adverse effects or a decrease of white blood cell and platelet count. In such cases, a reduction in the dosage of peg-IFN alpha-2b was required. Both peg-IFN alpha-2b and RBV were discontinued if the hemoglobin level, white blood cell count, or platelet count fell below 85 g/L, 1×10^9/L, and 2.5×10^9/L, respectively. The treatment was discontinued if severe general fatigue, hyperthyroidism, interstitial pneumonia, or severe hemolytic problems developed, continuation of treatment was judged not to be possible by the attending physician, or the patient desired discontinuation of treatment.

Clinical and laboratory assessment

Body mass index (BMI) was calculated as weight in kilograms/height in square meters. Blood samples were taken on enrollment, in the morning after 12 h overnight fasting. Serum levels of alanine aminotransferase (ALT), γ-GTP, white blood cell count, hemoglobin, and platelet count were measured by standard laboratory techniques at a commercial laboratory.

Determination of baseline HCV-RNA level and HCV genotype

The pretreatment, baseline, serum HCV-RNA level was measured by a quantitative HCV-RNA polymerase chain reaction (PCR) assay (COBAS Amplicor HCV Monitor Test v2.0 using the 10-fold dilution method; Roche Diagnostics, Tokyo, Japan), which has a lower limit of quantitation of 5000 IU (1350 copies)/mL (5 kIU/mL) and an outer limit of quantitation of 5 100 000 IU/mL (5100 kIU/mL). The HCV genotype was determined by a type-specific primer from the core region of the HCV genome. The protocol for genotyping was carried out as previously described.[23]

Efficacy of treatment

Sustained virological response was defined as serum HCV-RNA undetectable at 24 weeks after the end of treatment. Patients who had undetectable HCV-RNA within the initial 12 weeks of treatment were considered to have had an early virological response (EVR). These efficacy variables, SVR and EVR, were defined as non-detectable HCV-RNA as measured by the COBAS Amplicor HCV Monitor Test v2.0, and the results were labeled as positive or negative. The lower limit of detection was 50 IU/mL (0.5 kIU/mL). The analysis of SVR and EVR was done on an intention-to-treat basis.

Statistical analysis

Continuous data were expressed as mean values, the values ± standard deviation (SD), or the values ± standard error (SE) of the mean. The following statistics were done using a commercially available software package (BMDP Statistical Software Inc., Los Angeles, CA, USA) for the IBM 3090 system computer. The chi-squared or Fisher's exact test was used to examine the association between baseline characteristics and SVR. The Mann–Whitney *U*-test was also used to compare responders and non-responders with regard to various characteristics, when appropriate. The Cochran-Mantel-Haenszel test was used to test for statistical significance among the subgroups. A *P*-value of less than 0.05 was considered significant.

Results

Discontinuation of peg-IFN alpha-2b plus RBV treatment and adverse effects

Of the 715 patients, 152 (21.2%) did not complete peg-IFN alpha-2b plus RBV treatment due to adverse effects or for other reasons (Table 2). Although anemia, as a cause of discontinuation, was followed by general fatigue and depression, most patients discontinued the treatment because of general fatigue and depression together with anemia (hemoglobin 85–100 g/L).

The discontinuation rate was higher for patients with genotype 1 (138 of 586, 23.5%) than those with genotype 2 (14 of 129, 10.8%). The genotype 1 patients included 55 who stopped receiving treatment without virological effect (positive for serum HCV-RNA or no more than 2-$\log_{10}$ reduction from the pretreatment viral level) at 24 or more weeks after the start ($n = 22$), economic problems related to the high cost of treatment ($n = 6$), and other reasons (drop out, moving, nursing ill family members, and being arrested for a crime) ($n = 27$). Thus, the discontinuation rates for patients with adverse effects were only 14.1% (83 of 586) and 7.7% (10 of 129) for genotypes 1 and 2, respectively, with no significant difference. The majority were patients aged 65 years or

Table 2 Reasons for discontinuation of pegylated IFN plus ribavirin treatment, classified by HCV genotype

	Genotype 1	Genotype 2	Total
Adverse effects			
General fatigue	29	0	29
Depression	10	1	11
Encephalopathy	2	0	2
Anemia	11	0	11
Thrombocytopenia	1	1	2
Hyperthyroidism	5	1	6
Rash	6	3	9
Retinopathy	2	0	2
Interstitial pneumonia	1	1	2
Articular rheumatism	1	0	1
Brain infarction	0	1	1
Proteinuria	1	0	1
Hepatocellular carcinoma	11	2	13
Malignancy (extra-liver)†	2	0	2
Pulmonary tuberculosis	1	0	1
Other reasons			
No effect of treatment	22	2	24
Economic problems	6	0	6
Others‡	27	2	29
Total	138	14	152

†Includes one patient with gastric cancer and one patient with lung cancer.

‡Includes drop out ($n = 16$), patients who moved ($n = 6$), who nursed ill family members ($n = 3$), or who were arrested for criminal activity ($n = 2$).

over: 68 (73.1%) of the 93 discontinued due to adverse effects. The discontinuation rate due to adverse effects was significantly higher for patients aged 65 years or over (68 of 198, 34.3%) than for those aged under 65 years (25 of 517, 4.8%) ($P < 0.0001$). The mean times to discontinuation (± SD) were 23.0 ± 13.1 weeks and 20.2 ± 15.4 weeks for patients with genotypes 1 and 2, respectively.

SVR by intention-to-treat analysis

Of the 715 patients, 345 (48.2%) achieved SVR in the intention-to-treat analysis. SVR was significantly higher in genotype 2 (96 of 129, 74.4%) than in genotype 1 (249 of 586, 42.4%) ($P < 0.0001$). No significant differences in SVR were found between patients with and without prior non-peg-IFN monotherapy or non-peg-IFN plus RBV treatment between the genotype-classified patients.

An analysis of the association between SVR and the length of treatment showed that patients who completed the combination treatment had a significantly higher rate of SVR than did those with a shortened period of treatment (Fig. 1). Completing the 48-week combination treatment resulted in a significantly higher rate of SVR than either 1–11-week and 12–23-week treatments (both $P < 0.0001$), but there was no significant difference between 24 and 47 weeks and the complete 48 weeks of treatment ($P = 0.1260$). The SVR of patients with genotype 1 was significantly associated with a ≥ 24-week treatment period when compared with treatment < 24 weeks (244 of 481, 50.7% *vs* 5 of 105, 4.7%, $P < 0.0001$). In genotype 2 patients, SVR significantly increased with the treatment period: 28.6%, 57.1%, and 78.3% by 1–11-week, 12–23-week, and 24-week periods, respectively ($P = 0.0018$ by the Cochran-Mantel-Haenszel test).

The combination treatment was done for 443 (75.5%) and 110 (85.2%) of genotype 1 and 2 patients, respectively (Fig. 2). The rates of SVR for genotype 1 and 2 patients were significantly higher in those who continued the combination treatment than in those who discontinued RBV treatment: 230 of 443 (51.9%) versus 19 of 143 (13.2%) genotype 1 ($P < 0.0001$) and 89 of 110 (80.9%) versus seven of 19 (36.8%) genotype 2 ($P = 0.0002$). In genotype 1, 286 patients who required a reduced dosage during treatment (Groups B, C, and D) were able to complete the full 48 weeks of combination treatment. There were no significant differences in SVR among Groups A to D patients with genotypes 1 and 2. Of the patients who discontinued RBV treatment (143 with genotype 1 and 19 with genotype 2), most patients (138 (96.5%) with genotype 1 and 14 (73.7%) with genotype 2) did not complete combination treatment because there was no viral effect, because of adverse effects, or because they dropped out. The remaining patients discontinued the RBV treatment but completed the combination treatment without a reduction of the peg-IFN alpha-2b target dosage (three with genotype 1 and five with genotype 2), or discontinued the RBV treatment and completed their peg-IFN alpha-2b treatment with a reduction of the target dosage (two with genotype 1 and none with genotype 2).

An analysis of the association between SVR and the total dosage of peg-IFN alpha-2b and RBV during the treatment showed that patients with a higher total dosage of the combination treatment had a significantly higher rate of SVR than those with a lower dosage only for genotype 1 patients, although no significant difference was found in genotype 2 (Fig. 3). In genotype 1, reducing the total dosage of peg-IFN alpha-2b during the treatment significantly reduced the rate of SVR: 52.9% (187 of 353) for patients with ≥ 80% of the peg-IFN alpha-2b dosage, 36.5% (30 of 82) for those ≥ 60% but < 80% of the peg-IFN alpha dosage, and 21.1% (32 of 151) for those < 60% of the peg-IFN alpha dosage (both $P < 0.0001$). In genotype 1, the SVR rate of patients < 60% of the RBV dosage (91 of 307, 29.6%) was significantly lower than that of patients ≥ 80% of the RBV dosage (112 of 189, 59.2%) and those ≥ 60% but < 80% of the RBV dosage (46 of 90, 51.1%) (both $P < 0.0001$), although no significant difference was found between those ≥ 80% of the RBV dosage and those ≥ 60% but < 80% of the dosage. In genotype 2, neither a dosage reduction of peg-IFN nor RBV significantly influenced SVR.

An analysis of the association between SVR and the total combined dosage of peg-IFN alpha-2b plus RBV showed that patients with a higher total combined dosage of the combination treatment had a significantly higher rate of SVR than those with a lower dosage for genotype 1 patients only, although no significant difference was found in genotype 2 (Fig. 4). In genotype 1, the SVR rate of patients ≥ 80% of peg-IFN alpha-2b and ≥ 80% of RBV was significantly higher (78 of 122, 63.9%) than those without these combined dosages (171 of 464, 36.8%) ($P < 0.0001$). Moreover, the SVR rate of patients ≥ 80% of peg-IFN alpha-2b and ≥ 60% of RBV was significantly higher (116 of 187, 62.0%) than those without these dosages (133 of 399, 33.3%) ($P < 0.0001$). However, in genotype 2, neither a dosage reduction of peg-IFN nor RBV significantly influenced SVR.

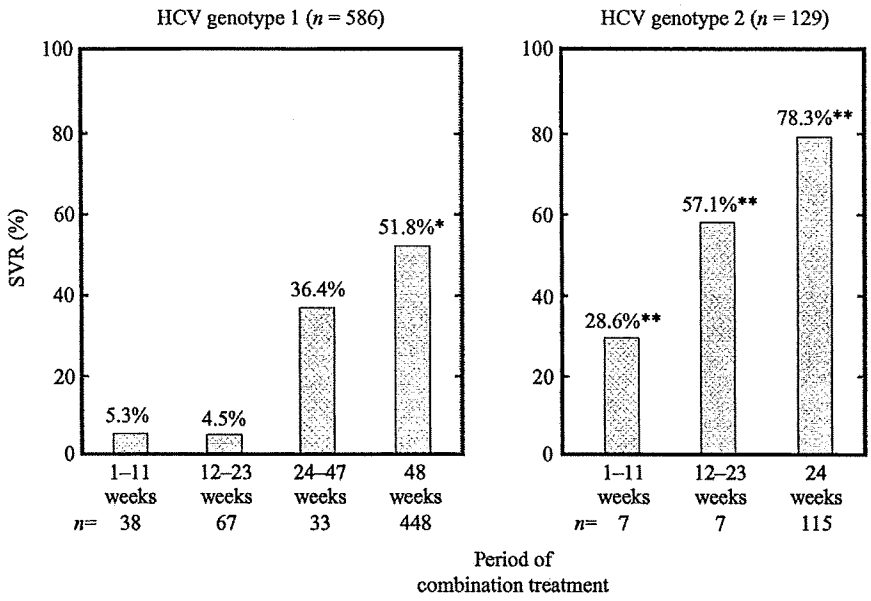


Figure 1 Sustained virological response (SVR) rates classified by length of pegylated interferon-alpha-2b (peg-IFN alpha-2b) plus ribavirin (RBV) combination treatment and by hepatitis C virus (HCV) genotype: An intention-to-treat analysis.

Analysis of EVR and the first 12-week adherence

An EVR was significantly higher in patients with genotype 2 (119 of 129, 92.2%) than in those with genotype 1 (307 of 586, 52.3%) ($P < 0.0001$). An analysis of the association between SVR and EVR showed that patients with EVR had a significantly higher rate of SVR than did patients without EVR for both genotypes 1 and 2: 220 of 309 (71.1%) versus 29 of 277 (10.4%) in genotype 1, and 96 of 119 (80.6%) versus none of 10 (0%) in genotype 2 (all $P < 0.0001$).

An analysis of the association between EVR and the first 12-week combined dosage of peg-IFN alpha-2b plus RBV showed that patients with a higher total combined dosage of the combination treatment had a significantly higher rate of SVR than those with a lower dosage for genotype 1 patients only, although no significant difference was found in genotype 2 (Fig. 5). In genotype 1, the EVR rate of patients ≥ 80% of peg-IFN alpha-2b and ≥ 80% of RBV was significantly higher (217 of 357, 60.7%) than those without these dosages (92 of 229, 40.1%) ($P < 0.0001$). Moreover, the SVR rate of patients ≥ 80% of peg-IFN alpha-2b and ≥ 60% of RBV was significantly higher (262 of 445, 58.8%) than those without these dosages (47 of 141, 33.3%) ($P < 0.0001$). However, in genotype 2, neither a dosage reduction of peg-IFN nor RBV influenced EVR.

Discussion

To the best of our knowledge, no reports have been written on the efficacy and safety of peg-IFN alpha-2b plus RBV treatment for a large number of Japanese HCV patients. The present study by intention-to-treat analysis included over 700 Japanese patients with chronic hepatitis C, a sufficient number to provide a meaningful statistical analysis and to be of interest to clinical physicians. Our findings show that in peg-IFN alpha-2b plus RBV treatment for chronic hepatitis C it is important to complete the target treatment duration and to use the full dosage to achieve virological efficacy.

A recent study showed Asian patients with chronic hepatitis C were more likely to achieve an SVR by treatment with peg-IFN alpha-2a and RBV than were Caucasian patients, suggesting a genetic influence on the antiviral response.[16] A significant difference between Asian and Caucasian patients with genotype 1 infections (65% and 36%) was also reported. However, the study included only 52 Asian patients and had no analysis concerning dosage of peg-IFN and RBV. Because our study included a large number of Japanese patients and an analysis of the complete combination treatment and the dosage of peg-IFN alpha and RBV, the present study provides for meaningful statistical analysis.

Our analysis showed that the discontinuation of RBV was significantly associated with a marked decline in SVR. We also showed that a < 60% reduction of the total dosage was associated with a poor outcome. Several adverse reactions are strongly associated with RBV. One of the most significant problems is hemolytic, especially anemia.[14] Most patients with anemia have general fatigue. Careful administration is necessary for patients > 60 years old, female patients, and patients receiving an RBV dosage by bodyweight of ≥ 12 mg/kg.[24] In fact, most of our patients who required a reduction in the total dosage or who discontinued RBV had anemia or fatigue. Also, discontinuation in this study was frequently found in patients aged ≥ 65 years. In Japan, many older patients with chronic hepatitis C are candidates for antiviral treatment, different from other countries. It is important to reduce the dosage of RBV at an early a stage as possible to allow the safe continuation of the combination treatment, as shown by data that a reduction of up to 60% of the total dosage of RBV does not appear to adversely influence SVR in Japanese patients.

The duration and dose of antiviral treatment are the most important factors influencing treatment outcome, especially in

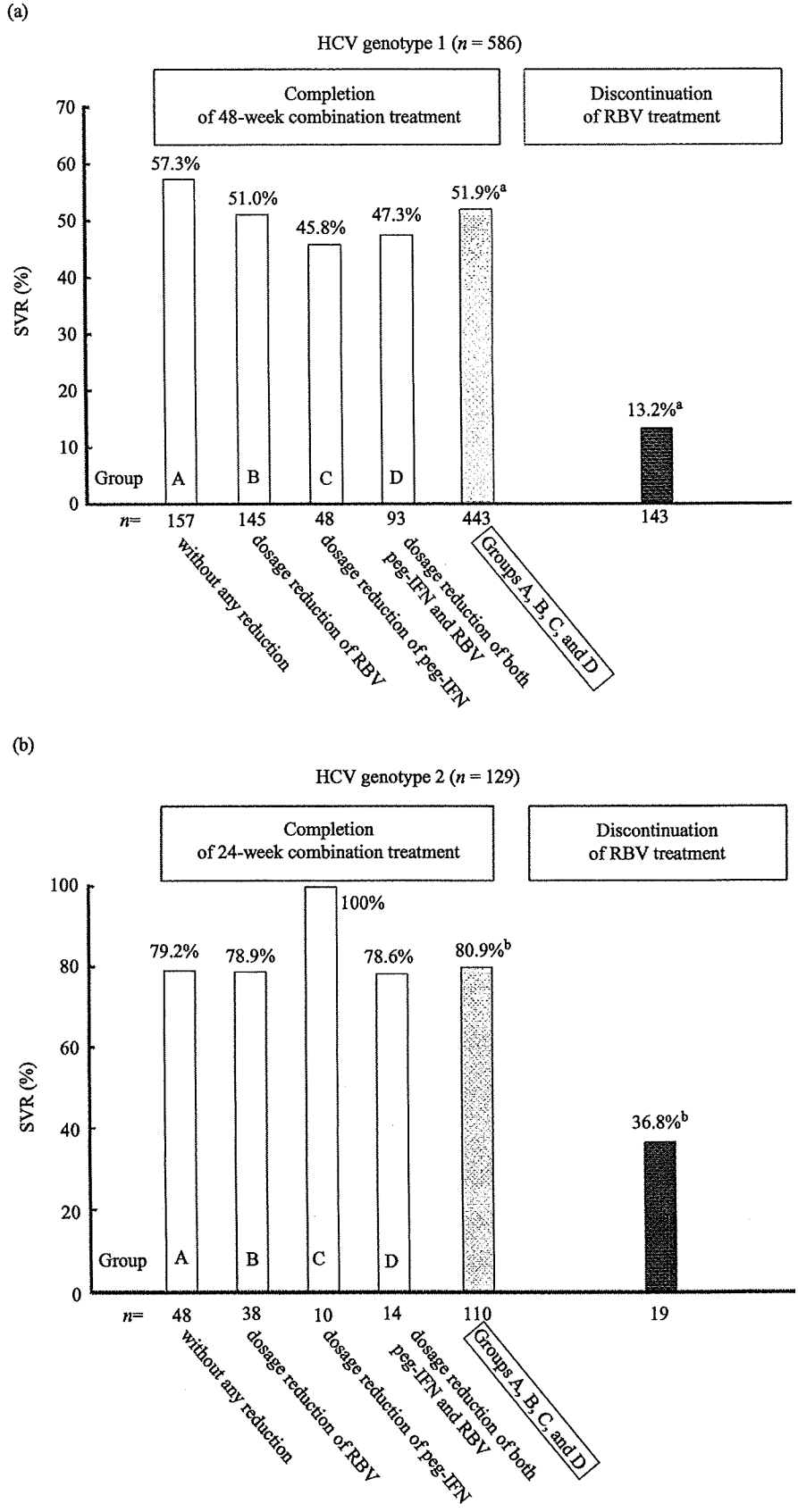


Figure 2 Sustained virological response (SVR) rates classified by continuation, reduction of the dosage, discontinuation of pegylated interferon-alpha-2b (peg-IFN alpha-2b) plus ribavirin (RBV) treatment, and hepatitis C virus (HCV) genotype: An intention-to-treat analysis (Fig. 2a for genotype 1 and Fig. 2b for genotype 2). The following groups A, B, C, and D consisted of patients who completed their scheduled combination treatment (48 weeks for genotype 1 patients [$n = 443$] and 24 weeks for genotype 2 patients [$n = 110$]) and patients who discontinued RBV treatment (genotype 1 patients [$n = 143$] and genotype 2 patients [$n = 19$]). Group A patients well tolerated the combination treatment with peg-IFN alpha-2b and RBV without any reduction in the target dosage of either drug; Group B patients completed the combination treatment and had no reduction of peg-IFN alpha-2b dose, but needed a reduction of the RBV target dosage; Group C patients completed the combination treatment and had no reduction of RBV dosage, but needed a reduction of the target dosage of peg-IFN alpha-2b; Group D patients completed the combination treatment, but needed a reduction of the target dosage of both peg-IFN alpha-2b and RBV. 'a' and 'b' indicate significant differences between completion of the full combination treatment and discontinuation of RBV treatment ($P < 0.0001$ and $P = 0.0002$, respectively).

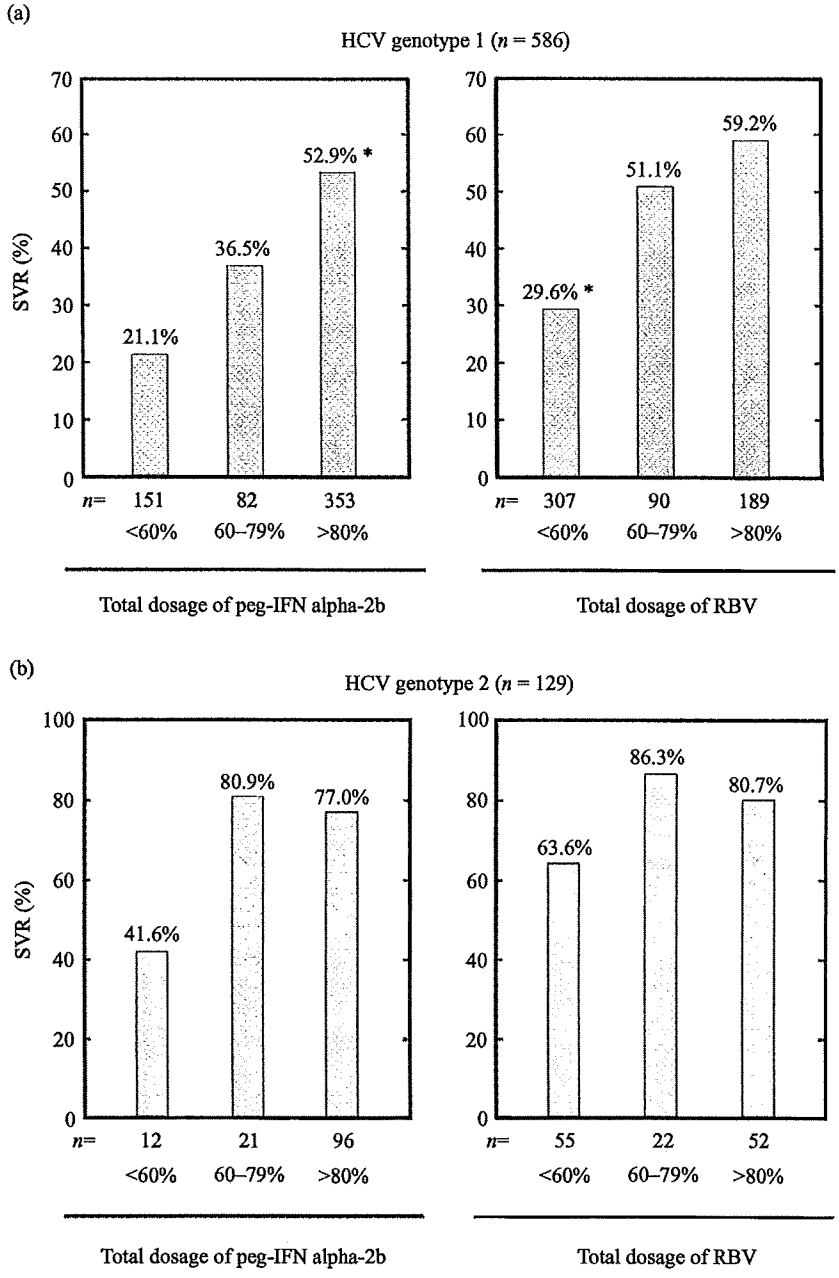


Figure 3 Sustained virological response (SVR) rates classified by percentage of total dosage of pegylated interferon-alpha2b (peg-IFN alpha-2b) plus ribavirin (RBV) treatment and by hepatitis C virus (HCV) genotype: An intention-to-treat analysis (Fig. 3a for genotype 1 and Fig. 3b for genotype 2). *indicates a significant difference between the groups.

HCV genotype 1-infected patients.[25,26] Shiffman and colleagues reported that reducing the total dose of peg-IFN alpha-2a to < 80% within the first 20 weeks of therapy significantly reduced SVR, but reducing the dose of RBV appeared to have little impact on SVR.[25] For our patients with genotype 1, the treatment period and total dosage were important to gaining SVR with peg-IFN alpha-2b plus RBV treatment. The 48-week combination treatment is the minimum requirement for SVR by these patients. Moreover, it is necessary to give ≥ 80% of the target dosage of peg-IFN alpha-2b (suitable for the weekly ≥ 0.9–1.2 μg/kg) and ≥ 60% of the target RBV (suitable for the daily 6–8 mg/kg) throughout the treatment.

Our previous report showed that a 24-week non-peg-IFN alpha plus RBV treatment regimen produced a high rate of SVR in Japanese genotype 2-infected patients.[19] The 24-week peg-IFN alpha-2b plus RBV treatment regimen used in the present study also demonstrated a remarkable rate of SVR (74.4%) for genotype 2 patients, as expected. This can be explained by the fact that genotype 2 patients have an extremely high rate of EVR, over 80%, with this combination treatment. Another important finding was that the total dosages of peg-IFN alpha-2b and RBV during the treatment for genotype 2 patients did not significantly influence SVR, although a dosage < 60% of the target resulted in a lower rate of SVR than a dosage ≥ 60%, without

Journal of Gastroenterology and Hepatology **23** (2008) 1094–1104