24 Sizmann D, Boeck C, Boelter J, Fischer D, Miethke M, Nicolaus S, Zadak M, Babiel R: Fully automated quantification of hepatitis C virus RNA in human plasma and human serum by the Cobas® AmpliPrep/Cobas® TaqMan® System. J Clin Virol 2007;38:326–333.
25 Kato N, Hijikata M, Ootsuyama Y, Nakagawa M, Ohkoshi S, Sugimura T, Shimotohno K: Molecular cloning of the human hepatitis C virus genome from Japanese patients with non-A, non-B hepatitis. Proc Natl Acad Sci USA 1990;87:9524–9528.
26 Enomoto N, Sakuma I, Asahina Y, Kurosaki M, Murakami T, Yamamoto C, Izumi N, Marumo F, Sato C: Comparison of full-length sequences of interferon sensitive and resistant hepatitis C virus 1b. Sensitivity to interferon is conferred by amino acid substitutions in the NS5A region. J Clin Invest 1995;96:224–230.
27 Enomoto N, Sakuma I, Asahina Y, Kurosaki M, Murakami T, Yamamoto C, Ogura Y, Izumi N, Marumo F, Sato C: Mutations in the nonstructural protein 5A gene and response to interferon in patients with chronic hepatitis C virus 1b infection. N Engl J Med 1996; 334:77–81.
28 Ogata S, Florese RH, Nagano-Fujii M, Hidajat R, Deng L, Ku Y, Yoon S, Saito T, Kawata S, Hotta H: Identification of hepatitis C virus subtype 1b strains that are highly, or only weakly, associated with hepatocellular carcinoma on the basis of the secondary structure of an amino-terminal portion of the HCV NS3 protein. J Clin Microbiol 2003;41:2835–2841.
29 Giménez-Barcons M, Franco S, Suárez Y, Forns X, Ampurdanès S, Puig-Basagoiti F, Sánchez-Fueyo A, Barrera JM, Llovet JM, Bruix J, Sánchez-Tapias JM, Rodés J, Saiz JC: High amino acid variability within the NS5A of hepatitis C virus is associated with hepatocellular carcinoma in patients with HCV-1b-related cirrhosis. Hepatology 2001;34: 158–167.
30 Akuta N, Suzuki F, Kawamura Y, Yatsuji H, Sezaki H, Suzuki Y, Hosaka T, Kobayashi M, Kobayashi M, Arase Y, Ikeda K, Kumada H: Efficacy of low-dose intermittent interferon-α monotherapy in patients infected with hepatitis C virus genotype 1b who were predicted or failed to respond to pegylated interferon + ribavirin combination therapy. J Med Virol 2008;80:1363–1369.
31 Tsukuma H, Hiyama T, Tanaka S, Nakao M, Yabuuchi T, Kitamura T, Nakanishi K, Fujimoto I, Inoue A, Yamazaki H, Kawashima T: Risk factors for hepatocellular carcinoma among patients with chronic liver disease. N Engl J Med 1993;328:1797–1801.
32 Ikeda K, Saitoh S, Koide I, Arase Y, Tsubota A, Chayama K, Kumada H, Kawanishi M: A multivariate analysis of risk factors for hepatocellular carcinogenesis. Hepatology 1993; 18:47–53.
33 Ikeda K, Saitoh S, Arase Y, Chayama K, Suzuki Y, Kobayashi M, Tsubota A, Kobayashi M, Nakamura I, Murashima N, Kumada H, Kawanishi M: Effect of interferon therapy on hepatocellular carcinogenesis in patients with chronic hepatitis type C: a long-term observation study of 1,643 patients using statistical bias correction with proportional hazard analysis. Hepatology 1999;29:1124–1130.
34 Chiba T, Matsuzaki Y, Abei M, Shoda J, Aikawa T, Tanaka N, Osuga T: Multivariate analysis of risk factors hepatocellular carcinoma in patients with hepatitis C virus-related liver cirrhosis. J Gastroenterol 1996;31: 552–558.
35 Di Bisceglie AM: Hepatitis C and hepatocellular carcinoma. Hepatology 1997;26(suppl 1):34–38.
36 Degos F, Christidis C, Ganne-Carrie N, Farmachidi JP, Degott C, Guettier C, Trinchet JC, Beaugrand M, Chevret S: Hepatitis C virus-related cirrhosis: time to occurrence of hepatocellular carcinoma and death. Gut 2000;47:131–136.
37 Aizawa Y, Shibamoto Y, Takagi I, Zeniya M, Toda G: Analysis of factors affecting the appearance of hepatocellular carcinoma in patients with chronic hepatitis C. Cancer (Phila) 2000;89:53–59.
38 Shiratori Y, Ito Y, Yokosuka O, Imazeki F, Nakata R, Tanaka N, Arakawa Y, Hashimoto E, Hirota K, Yoshida H, Ohashi Y, Omata M: Antiviral therapy for cirrhotic hepatitis C: association with reduced hepatocellular carcinoma development and improved survival. Ann Intern Med 2005;142:105–114.

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Original Article

Rapid loss of hepatitis C virus genotype 1b from serum in patients receiving a triple treatment with telaprevir (MP-424), pegylated interferon and ribavirin for 12 weeks

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Aim: To evaluate the efficacy and safety of the triple treatment with telaprevir (MP-424), pegylated interferon (PEG-IFN) and ribavirin during 12 weeks on-treatment.

Methods: The triple treatment was given to 20 patients with chronic hepatitis C who had been infected with hepatitis C virus (HCV)-1b in high viral load (median: 6.8 log IU/mL [range: 5.5–7.2]), with a median age of 54 years (range: 36–65 years). They were followed for early dynamics of HCV RNA in serum during 12 weeks and side-effects.

Results: HCV RNA levels decreased by 4.8 logs by 7 days and 5.5 logs by 14 days. HCV RNA disappeared in 50% (10/20) at 2 weeks, 79% (15/19) at 4 weeks, 88% (14/16) at 6 weeks, 94% (15/16) at 8 weeks and 100% (13/13) at 12 weeks. HCV RNA disappeared equally frequently in 10 treatment-naive patients, six non-responders to IFN monotherapy and four non-responders to PEG-IFN and ribavirin. It was no different in the patients with and without amino acid substitutions reducing the response to IFN. The treatment was withdrawn in seven (35%) patients, mostly due to reduced hemoglobin of less than 8.5 g/dL, of whom six (86%) remained clear of HCV RNA at 12 weeks.

Conclusion: HCV RNA was lost from serum rapidly and universally in patients infected with HCV-1b in high viral loads by the triple treatment. Because an early loss of HCV RNA correlates with high rates of sustained virological response (SVR), it would increase SVR substantially, and merit the patients who have not responded to previous therapies.

Key words: chronic hepatitis, hepatitis C virus, interferon, ribavirin, telaprevir

INTRODUCTION

WORLDWIDE, AN ESTIMATED 170 million people are infected with hepatitis C virus (HCV) persistently.[1] Decompensated cirrhosis and hepatocellular carcinoma (HCC) develop in approximately 30% of individuals infected with HCV, and result in a fatal outcome during the lifetime.[2,3] At present, treatments based on interferon (IFN), in combination with ribavirin, are the mainstay for terminating HCV infection. The response to IFN is influenced by virological factors, such as viral load and genotypes, as well as host factors including sex, age and ethnicity, and responses to previous treatments.[4–6] In Japan, genotype 1b in high viral loads (> 100 KIU/mL) accounts for more than 70% of HCV infections, making it difficult to treat patients with chronic hepatitis C.[7–10] Because HCV started to spread during the turmoil surrounding the World War II (1939–1945) in Japan,[11] patients with chronic hepatitis C in need of treatment are entering their 50s and 60s by now. These backgrounds call for efficient treatments of patients with chronic hepatitis C in Japan.

Even with pegylated IFN (PEG-IFN) combined with ribavirin, the sustained virological response (SVR) lasting over 24 weeks after the withdrawal of treatment is achieved in at most 50% of the patients with high-titer HCV-1b.[12,13] Recently, a new strategy was introduced to the treatment of chronic hepatitis C by means of

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inhibiting protease in NS3/NS4 of the HCV polyprotein. Of them, telaprevir (VX-950) has been selected as a clinical candidate for treatment of chronic hepatitis C.[14] Later, it was found that telaprevir, when combined with PEG-IFN and ribavirin, gains a robust antiviral activity.[15,16] Thus, HCV RNA disappears in 95–100% of the patients infected with HCV-1 during the triple therapy for 14–28 days.[17–19] The SVR, lasting for longer than 24 weeks from the end of triple treatment, was not achieved in all patients who had received the triple treatment, however.[19]

In the present study, the triple therapy was given for 84 days to 20 Japanese patients infected with HCV-1b in high viral loads with the median age of 54 years (range: 36–65), including six non-responders to the standard IFN and four non-responders to PEG-IFN/ribavirin. They all lost HCV RNA from serum without major side-effects, providing a hope for better responses in the patients with chronic hepatitis C who have been refractory to previous IFN-based treatments.

METHODS

THIS DOUBLE-ARM, randomized, open-label study was conducted during April 2008 through March 2009 at the Department of Hepatology in the Toranomon Hospital at Metropolitan Tokyo in compliance with Good Clinical Practice Guidelines and the 1975 Declaration of Helsinki. Before the study, the protocol and informed consent forms were approved by the institutional review board. All patients had given an informed consent in writing after sufficient explanation before they participated in this trial.

Patients

This study was performed on the 20 patients with chronic hepatitis C who met the following inclusion and exclusion criteria. Inclusion criteria for them were: (i) diagnosed with chronic hepatitis C; (ii) HCV-1b confirmed by the sequence analysis in the NS5B region; (iii) possessed HCV RNA levels of 5.0 log IU/mL or more determined with the COBAS TaqMan HCV test (Roche Diagnostics, Tokyo, Japan); (iv) Japanese (Mongoloid) aged 20–65 years at the entry; and (v) had a bodyweight of 35 kg or more and 120 kg or less at the time of registration.

Exclusion criteria were: (i) decompensated liver cirrhosis; (ii) hepatitis B surface antigen (HBsAg) in serum; (iii) HCC or its history; (iv) previous treatment for malignant neoplasm; (v) autoimmune hepatitis, alcohol liver disease, hemochromatosis or chronic liver disease other than chronic hepatitis C; (vi) depression, schizophrenia or suicide attempts; (vii) abnormal hemoglobin disease; (viii) angina pectoris, cardiac insufficiency, myocardial infarction or severe arrhythmia, or their history; (ix) uncontrollable hypertension; (x) chronic renal dysfunction or creatinine clearance of 50 mL/min or less at baseline; (xi) hemoglobin level of 12 g/dL or less, neutrophil count of 1500/mm^3 or less or platelet count of 100 000/mm^3 or less at baseline; (xii) diabetes in need of treatment or fasting glucose level of 110 mg/dL or more at baseline; (xiii) autoimmune disease; (xiv) cerebrovascular disorder or its history; (xv) thyroidal dysfunction uncontrollable by medical treatment; (xvi) chronic pulmonary disease; (xvii) a history of allergy to medication or anaphylactoid symptoms; (xviii) women who were pregnant, breast-feeding or who could become pregnant; and (xix) men with a pregnant partner.

Study design

The 20 patients were randomly allocated to two groups with different doses of telaprevir (MP-424; Mitsubishi Tanabe Pharma, Osaka, Japan) by a third party institute, Bellsystem24 (Tokyo, Japan). MP-424 was administered in doses of 750 mg (group A) or 500 mg (group B) three times a day at an 8-h (q8) interval after the meal. PEG-IFN-α-2b (PEG-Intron; Schering Plough, Kenklworth, NJ, USA) was injected s.c. at a median dose of 1.5 μg/kg (range: 1.250–1.739 μg/kg) once a week. Ribavirin (Rebetol; Schering Plough) was administered at a dose of 200–600 mg twice a day after breakfast and dinner (daily dose: 600–1000 mg). These three drugs were administered for 12 weeks. After completion or discontinuation of the triple therapy, a follow-up observation was performed for 24 weeks.

Doses of PEG-IFN and ribavirin were reduced or their administration discontinued, as required, based on the reduction of hemoglobin levels, white blood cell count, neutrophil count or platelet count, or the development of adverse events. Thus, the dose of PEG-IFN was reduced to one half, when leukocyte count decreased below 1500/mm^3, neutrophil count below 750/mm^3 or platelet count below 80×10^3/mm^3; PEG-IFN was withdrawn when they decreased below 1000/mm^3, 500/mm^3 or 50×10^3/mm^3, respectively. When hemoglobin decreased below 10 g/dL, the daily dose of ribavirin was reduced from 600 to 400 mg, from 800 to 600 mg and 1000 to 600 mg, depending on the initial dose of each patient. Ribavirin was withdrawn when hemoglobin decreased below 8.5 g/dL. The decrease of telaprevir (MP-424) dose was not permitted, and its administra-

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tion was stopped when the discontinuation was appropriate for the development of adverse events. In cases when the administration of MP-424 was stopped, the administration of PEG-IFN-α-2b and ribavirin was terminated, also.

HCV RNA measurements

Antiviral effects of telaprevir (MP-424) on HCV were assessed by measuring plasma HCV RNA levels. Blood samples were obtained on day 1 before dosing and at 2.5, 4, 8, 16 and 24 h after the first dose (the 8-h sample was collected before administration of dose 2, and the 16-h sample was collected before administration of dose 3). Pre-dose samples were obtained on days 2, 3, 8, 14, 29, 43, 57, 86, 92, 99, 113, 141, 169, 197, 225 and 253. HCV RNA concentrations were determined using the COBAS TaqMan HCV test (Roche Diagnostics). The linear dynamic range of the assay was 1.2–7.8 log IU/mL.

Safety assessments

During the on-study period, patients were monitored for safety at regular intervals from the start of dosing through every hospital visit. Safety assessments included physical examinations, clinical laboratory tests and adverse events. After the treatment was completed or aborted, patients were monitored for safety by the standard practice of investigators.

Statistical analysis

No prospective calculations of the statistical power were made. The sample size was selected to provide information on the safety and tolerability during 12 weeks of dosing. Descriptive statistics were reported for clinical laboratory and vital sign data. Categorical presentation was used for adverse events. HCV RNA values in log IU/mL were summarized using descriptive statistics for each treatment group and scheduled time point.

RESULTS

Baseline demographic and virological characteristics of the 20 patients with chronic hepatitis C who received the triple treatment

TABLE 1 LISTS baseline characteristics of the 20 patients who received the triple treatment with telaprevir (MP-424), PEG-IFN and ribavirin for 12 weeks. They all were infected with HCV-1b in high viral loads with a median of 6.8 log IU/mL. They were aged with a median of 54 years, and 14 (70%) of them were older than 50 years.

Table 1 Baseline characteristics of patients with chronic hepatitis C who received a triple therapy with telaprevir (MP-424), PEG-IFN and ribavirin

Male	10 (50%)
Age (years)	54 (36–65)
Hemoglobin (g/dL)	14.2 (12.1–16.8)
Platelets ($\times 10^3/mm^3$)	163 (102–243)
Albumin (g/dL)	4.2 (3.7–4.6)
Total bilirubin (mg/dL)	0.8 (0.3–1.1)
Creatinine (mg/dL)	0.76 (0.45–0.93)
Total cholesterol (mg/dL)	184 (114–253)
Fasting blood sugar (mg/dL)	112 (84–146)
Aspartate aminotransferase (IU/L)	40 (23–99)
γ-Glutamyl transpeptidase (IU/L)	39 (7–142)
Alanine aminotransferase (IU/L)	50 (26–167)
Hepatitis C virus RNA (log IU/mL)	6.8 (5.5–7.2)

Values are number with percentage in parentheses or median with range in parentheses.

Factors influencing the response to antiviral treatments are listed in Table 2. Of the 20 patients, 10 (50%) had not received antiviral treatments before, six (30%) had not responded to previous monotherapy with the standard IFN, and four (20%) had failed to respond to PEG-IFN and ribavirin before. Substitution of amino acid 70 in the HCV core protein from arginine to glutamine, as well as that of aa91 from leucine to methionine, interferes with the response to IFN-based treatments.[20,21] Such substitutions were detected in HCV RNA sequences from 10 (50%) patients. Amino acid substitutions in the IFN sensitivity determining region (ISDR) in the NS5A region, which increase the sensitivity to IFN,[22] were found in HCV RNA sequences from six (30%) patients.

Higher ages and poor responses to previous IFN-based treatments as well as high HCV-1b loads of the 20 patients, combined with virological characteristics diminishing the response in substantial subpopulations, forecast that they would likely be refractory to antiviral therapies.

Dynamics of HCV RNA in patients during the triple treatment

Figure 1 illustrates dynamics of HCV RNA in the 20 patients who had received the triple therapy with telaprevir (MP-424), PEG-IFN and ribavirin during 12 weeks. The effect of triple therapy in suppressing

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Table 2 Amino acid substitutions interfering the response to IFN in patients who received telaprevir (MP-424)/PEG-IFN/ribavirin

Group and case no.	Age/Sex	Amino acids 70/91 in the core protein†	Amino acid substitutions in ISDR‡
(A) Treatment-naive patients (n = 10)			
1	36/F	Arg/Leu	1
2	47/F	Arg/Leu	0
3	47/F	Glu/Leu	1
4	54/F	Arg/Leu	1
5	60/F	Arg/Leu	0
6	62/F	Arg/Leu	1
7	44/M	Arg/Met	1
8	46/M	Glu/Leu	0
9	54/M	Glu/Leu	0
10	64/M	Glu/Leu	6
(B) Relapsers to previous IFN monotherapy (n = 6)			
11	54/F	Arg/Leu	0
12	56/F	Arg/Met	0
13	60/F	Arg/Leu	0
14	42/M	Glu/Leu	0
15	47/M	Arg/Leu	0
16	65/M	Arg/Leu	0
(C) Non-responders to combined PEG-IFN and ribavirin (n = 4)			
17	56/F	Glu/Met	0
18	47/M	Arg/Leu	0
19	52/M	Glu/Met	0
20	54/M	Glu/Met	0

†Substituted amino acids are marked in the boldface. ‡Numbers of amino acid substitutions in the interferon sensitivity determining region is shown. Arg, arginine; Glu, glutamine; IFN, interferon; ISDR, interferon sensitivity determining region; Leu, leucine; Met, methionine; PEG, pegylated.

HCV RNA levels was rapid, robust and universal. During the initial few days, HCV RNA dropped sharply (rapid phase) followed by slower decrease until 2 weeks (slow phase). The loss of detectable HCV RNA from serum (< 1.2 log IU/mL) occurred in 10 (50%) patients by 2 weeks. It gradually increased thereafter, and all of the 13 patients were freed of serum HCV RNA at the end of the 12-week therapy.

Viral dynamics during the triple therapy and previous PEG-IFN/ribavirin treatment in the four non-responders to combined treatment are illustrated in Figure 2. After the triple therapy, HCV RNA levels dropped sharply within 1 week in them all. The loss of HCV RNA from serum occurred at 2, 3, 4 and 8 weeks in them, respectively. In outstanding contrast, HCV RNA stayed in high

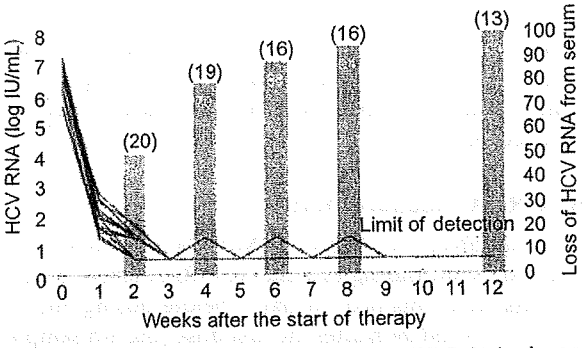

Figure 1 Dynamics of hepatitis C virus (HCV) RNA in the 20 patients with chronic hepatitis C during the triple treatment with telaprevir (MP-424), pegylated interferon (PEG-IFN) and ribavirin. The course of HCV RNA individual patients are indicated by lines, and loss of HCV RNA from serum by columns. The number of patients is indicated on the top of each column in parentheses, and areas below the sensitivity of detection are indicated by a shaded bar (< 1.2 log IU/mL).

levels during previous PEG-IFN and ribavirin treatment in all of them.

Early decreases in HCV RNA levels at 7 and 14 days during the triple treatment

Table 3 compares the average HCV RNA titers at baseline, 7 and 14 days during the triple treatment. Overall, HCV RNA decreased by 5.0 logs at 7 days and by 5.7 logs at 14 days. Similar decreases were achieved in subgroups of patients with various records of previous IFN-based treatment, and with or without amino-acid substitutions for a poor response to IFN. Early virological response was no different, either, between men and women (before: 6.63 ± 0.56 vs 6.50 ± 0.56; 1 week: 1.87 ± 0.57 vs 1.37 ± 0.41; and 2 weeks: 1.04 ± 0.44 vs 0.68 ± 0.30 log copies/mL, respectively), between the patients aged below and above 50 years of age, or between the patients who received two different doses of telaprevir (MP-424) (data not shown).

Normalization of alanine aminotransferase levels during the triple treatment

Normalization of alanine aminotransferase (ALT) levels in male and female patients during the triple treatment is summarized in Table 4. ALT levels were normalized (≤ 40 IU/L) in 80–90% of men at 2 weeks and thereafter. The normalization stayed below 60% in women due to dropouts increasing with the duration of triple treatment. Of the six women who had normalized ALT at 2 weeks, the triple treatment was terminated in one by

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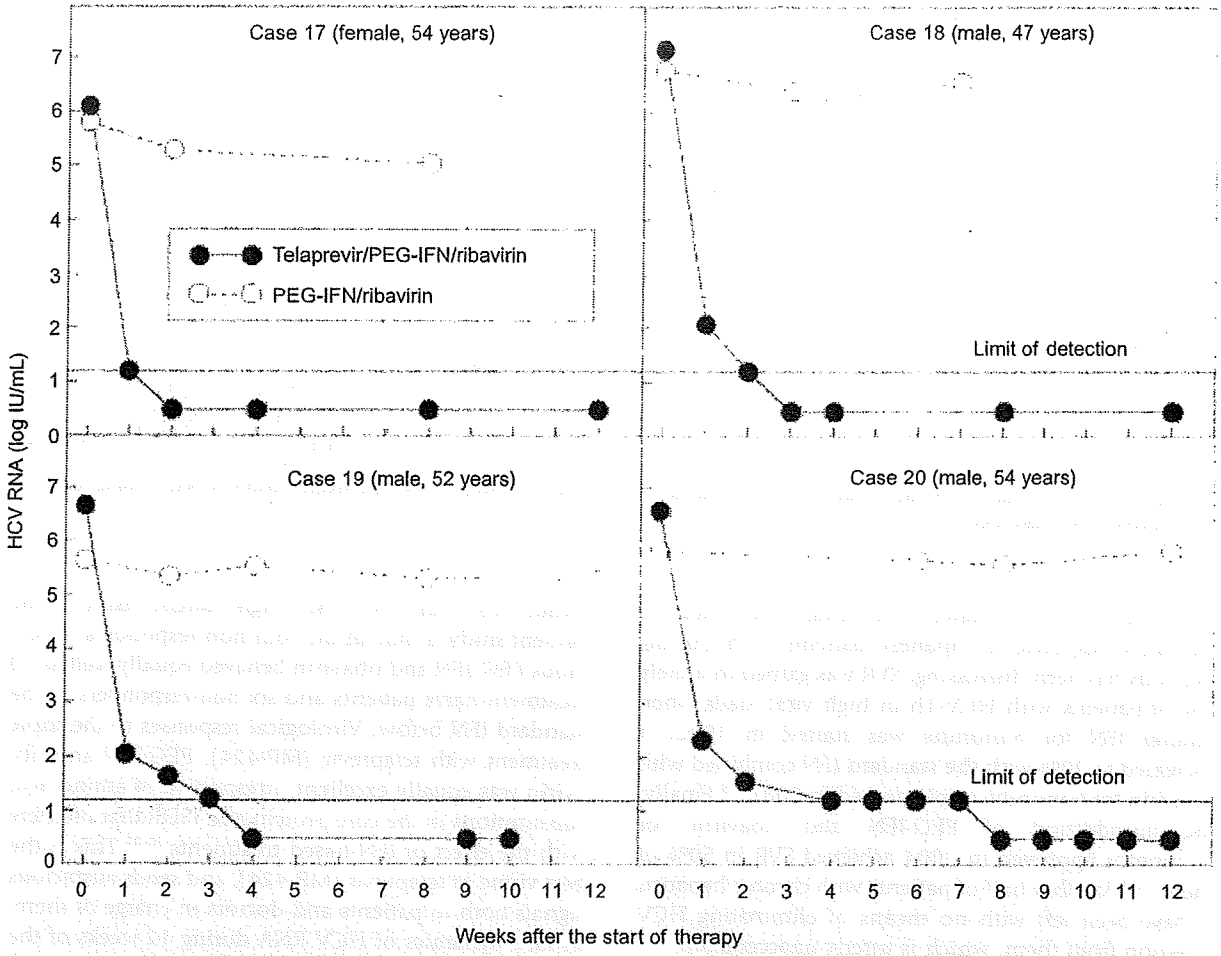

Figure 2 Dynamics of hepatitis C virus (HCV) RNA in non-responders to pegylated interferon (PEG-IFN) and ribavirin during the triple treatment. Black dots represent HCV RNA levels during the triple therapy, and open dots indicate HCV RNA levels during PEG-IFN and ribavirin they had received before.

4 weeks, four by 8 weeks and one by 12 weeks. Thus, the triple treatment was withdrawn in six of the 10 (60%) women, in remarkable contrast to only one of the 10 (10%) men. Overall, the normalization of ALT levels was achieved in 10 of the 13 (77%) patients who had completed the triple treatment for 12 weeks.

Side-effects during the triple treatment for 12 weeks

The triple treatment had to be stopped due to side-effects in seven of the 20 (35%) patients due to following reasons. Levels of hemoglobin during the triple treatment in each patient are illustrated in Figure 3. Five patients (one man and four women [cases 2, 13, 6, 1 and 9 in Table 2]) developed low hemoglobinemia (< 8.5 g/dL) at day 22, 29, 36, 78 and 84, respectively, after the start of triple treatment. One patient (female, 54 years [case 4]) came down with IFN-related symptoms including general malaise, and another (female, 56 years [case 12]) developed generalized dermatitis that was unable to be treated with topical steroid ointments.

DISCUSSION

IN JAPAN, THE majority of patients with chronic hepatitis C are infected with HCV-1b in high titers. Combined with their ages being approximately 20 years

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Table 3 Early virological response to telaprevir (MP-424)/PEG-IFN/ribavirin in the patients with risk factors for non-response to therapy

Risk factors	*n*	HCV RNA (log IU/mL)†		
		Before	At 7 days	At 14 days
Previous interferon-based therapy				
Treatment-naive	10	6.4 ± 0.6	1.5 ± 0.5	0.8 ± 0.4
Non-responders to the standard IFN	6	6.8 ± 0.4	1.6 ± 0.6	0.9 ± 0.4
Non responders to PEG-IFN/ribavirin	4	6.7 ± 0.5	1.9 ± 0.6	1.1 ± 0.5
Amino acid substitutions in positions 70 and 91 in the core protein				
Arg/Leu	10	6.7 ± 0.5	1.6 ± 0.4	0.7 ± 0.3
Others	10	6.4 ± 0.6	1.7 ± 0.7	1.0 ± 0.5
Amino acid substitutions in the interferon sensitivity determining region (ISDR)				
0	14	6.8 ± 0.4	1.8 ± 0.6	1.0 ± 0.4
≥ 1	6	6.1 ± 0.6	1.3 ± 0.3	0.6 ± 0.2
Total	20	6.6 ± 0.5	1.6 ± 0.5	0.9 ± 0.4

†Values indicate the mean ± SD. Arg, arginine; HCV, hepatitis C virus; IFN, interferon; ISDR, interferon sensitivity determining region; Leu, leucine; PEG, pegylated.

older than those in Western countries,[11] the history of treatment response in Japanese patients with chronic hepatitis has been distressing. SVR was gained in merely 6% of patients with HCV-1b in high viral loads when natural IFN for 6 months was started in 1992; it increased to 20% with the standard IFN combined with ribavirin for 6 months implemented in 2001.[7–9] Finally, the introduction of PEG-IFN and ribavirin for 12 months approved in 2004 achieved SVR in 50% of them.[12,13] Another half of patients with chronic hepatitis C have been left with no means of eliminating HCV infection from them, which is utterly unacceptable.

Instigated by favorable results of short-term telaprevir in combination with PEG-IFN and ribavirin,[17–19] a Phase-I PK (pharmacokinetics) trial was started in the Department of Hepatology in the Toranomon Hospital in Metropolitan Tokyo. The results of the 20 patients with high-load HCV-1b infections, who had received the triple treatment for 12 weeks, are even more promising than those in previous reports with a treatment duration up to 4 weeks.[17–19]

Non-responders to IFN-based treatments, as well as relapsers among responders, are refractory to re-treatments with IFN.[4] The single salient result of the present study is that all the four non-responders to previous PEG-IFN and ribavirin behaved equally well as 10 treatment-naive patients and six non-responders to the standard IFN before. Virological responses to the triple treatment with telaprevir (MP-424), PEG-IFN and ribavirin was equally excellent, irrespective of amino acid substitutions in the core protein and ISDR that interfere with the effect of IFN-based treatments.[20–22] This is the best virtue of telaprevir (MP-424), and sends auspicious signals both to patients and doctors in charge of them. In fact, dynamics of HCV RNA during 12 weeks of the triple treatment was no different among treatment-naive patients, non-responders to previous treatment with the standard IFN or PEG-IFN and ribavirin (Fig. 1). The average HCV RNA titers of 6.4 log IU/mL at the baseline decreased by 5.0 logs at 7 days and by 5.7 logs at 14 days after the start of triple treatment (Table 3). Similar rapid and forceful decreases in HCV RNA levels have been reported unanimously in previous studies.[17–19]

Rapid, universal and robust antiviral activity of the triple therapy was not without costs. Anemia with

Table 4 Normalization of alanine aminotransferase levels during the triple treatment

	Before	2 weeks	4 weeks	8 weeks	12 weeks
Men	20% (2/10)	80% (8/10)	90% (9/10)	80% (8/10)	89% (8/9)
Women	20% (2/10)	60% (6/10)	56% (5/9)	33% (2/6)	50% (2/4)
Total	20% (4/20)	70% (14/20)	74% (14/19)	63% (10/16)	77% (10/13)

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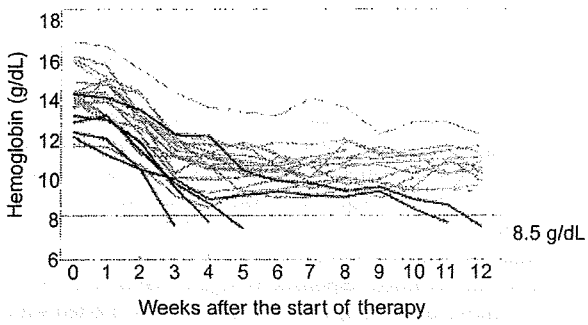

Figure 3 Levels of hemoglobin in the patients who received the triple treatment during 12 weeks. Black lines represent the patients in whom hemoglobin decreased below 8.5 g/dL and who were placed off the triple treatment at that point.

hemoglobin levels of less than 8.5 g/dL developed in five of them including one (10% [1/10]) man and four (40% [4/10]) women, and one each developed severe generalized dermatitis that could not be treated with topical steroids and general malaise that was ascribable to PEG-IFN. Thus, the triple treatment was withdrawn from seven of the 20 (35%) patients. Ribavirin dose would need to be monitored more closely and modified as soon as reduction is required. Such precaution would prevent aged women, who are especially prone to anemia, from discontinuing the triple treatment. Despite withdrawal of the triple treatment 22–89 days after the start, HCV RNA stayed below detectable levels (< 1.2 log IU/mL) in six (86%) of them at 12 weeks.

No virological breakthroughs with increases in HCV RNA levels occurred in any of the 20 patients during a 12-week triple therapy. Hence, HCV mutants with amino acid conversions for resistance to telaprevir, such as the 156S mutation,[23] would not have developed in them. Should they have elicited, they must have been suppressed by PEG-IFN given to the 20 patients under the triple therapy; telaprevir-resistant HCV mutants are susceptible to IFN in both *in vivo* and *in vitro* studies.[17,24]

Sustained virological response is the gold standard for evaluating the response to antiviral treatments. In large-scale follow-up studies, 99.2% of the patients who had achieved an SVR remained HCV RNA undetectable at a median of 4.1 years (range: 0.4–7.0).[25] There is a close correlation between the velocity of HCV RNA clearance and chances for SVR. Thus, SVR is achieved more often in the patients who did than who did not lose HCV RNA from serum within 12 weeks after the start of IFN-based treatment;[26] the faster HCV RNA is lost, the higher a chance for SVR.[21,27] In view of a rapid loss of HCV RNA from serum, the 20 patients studied will therefore have a great chance of achieving SVR, although this needs to be ascertained by follow ups longer than 24 weeks after the completion of triple therapy. In fact, SVR was not achieved in all patients who had received the triple treatment for 28 days.[19] It is a matter of conjecture how long the triple therapy should be continued and whether or not PEG-IFN and ribavirin need to be maintained after the withdrawal of telaprevir (MP-424). In any case, the duration of the triple treatment is reasonably expected to be shortened to less than that of PEG-IFN and ribavirin in the current use, towards ensuring less chances for telaprevir-resistant HCV variants to prevail and induce breakthrough hepatitis.

In conclusion, the triple treatment of the 20 patients with telaprevir (MP-424), PEG-IFN and ribavirin for 12 weeks suppressed HCV RNA in serum rapidly, universally and robustly, irrespective of previous responses to antiviral treatments or mutations decreasing the sensitivity to IFN. Promoted by few grave side-effects, the triple therapy is hoped to gain an excellent efficacy in treatment-resistant patients who are infected with HCV-1 in high viral loads.

ACKNOWLEDGMENT

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REFERENCES

1 Di Bisceglie AM. Hepatitis C. *Lancet* 1998; 351: 351–5.
2 Alberti A, Chemello L, Benvegnu L. Natural history of hepatitis C. *J Hepatol* 1999; 31: S17–24.
3 Seeff LB. Natural history of chronic hepatitis C. *Hepatology* 2002; 36: S35–46.
4 Shiffman ML. Retreatment of patients with chronic hepatitis C. *Hepatology* 2002; 36: S128–34.
5 Backus LI, Boothroyd DB, Phillips BR, Mole LA. Predictors of response of US veterans to treatment for the hepatitis C virus. *Hepatology* 2007; 46: 37–47.
6 Kanwal F, Hoang T, Spiegel BM *et al.* Predictors of treatment in patients with chronic hepatitis C infection – role of patient versus nonpatient factors. *Hepatology* 2007; 46: 1741–9.
7 Iino S, Tomita E, Kumada H *et al.* Impact of daily high-dose IFNalpha-2b plus ribavirin combination therapy on reduction of ALT levels in patients with chronic hepatitis C with genotype 1 and high HCV RNA levels. *Hepatol Res* 2005; 31: 88–94.
8 Tsubota A, Arase Y, Someya T *et al.* Early viral kinetics and treatment outcome in combination of high-dose interferon

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induction vs. pegylated interferon plus ribavirin for naive patients infected with hepatitis C virus of genotype 1b and high viral load. *J Med Virol* 2005; 75: 27–34.
9 Tsubota A, Arase Y, Suzuki F *et al.* High-dose interferon alpha-2b induction therapy in combination with ribavirin for Japanese patients infected with hepatitis C virus genotype 1b with a high baseline viral load. *J Gastroenterol* 2004; 39: 155–61.
10 Kumada T, Toyoda H, Honda T *et al.* Treatment of chronic hepatitis C with interferon alone or combined with ribavirin in Japan. *Intervirology* 2006; 49: 112–18.
11 Yoshizawa H, Tanaka J, Miyakawa Y. National prevention of hepatocellular carcinoma in Japan based on epidemiology of hepatitis C virus infection in the general population. *Intervirology* 2006; 49: 7–17.
12 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.
13 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.
14 Lin C, Kwong AD, Perni RB. Discovery and development of VX-950, a novel, covalent, and reversible inhibitor of hepatitis C virus NS3.4A serine protease. *Infect Disord Drug Targets* 2006; 6: 3–16.
15 Modi AA, Hoofnagle JH. New therapies for hepatitis C. *Hepatology* 2007; 46: 615–17.
16 Zeuzem S. Telaprevir, peginterferon alfa-2a, and ribavirin for 28 days in chronic hepatitis C patients. *J Hepatol* 2008; 49: 157–9.
17 Forestier N, Reesink HW, Weegink CJ *et al.* Antiviral activity of telaprevir (VX-950) and peginterferon alfa-2a in patients with hepatitis C. *Hepatology.* 2007; 46: 640–8.
18 Kieffer TL, Sarrazin C, Miller JS *et al.* Telaprevir and pegylated interferon-alpha-2a inhibit wild-type and resistant genotype 1 hepatitis C virus replication in patients. *Hepatology* 2007; 46: 631–9.
19 Lawitz E, Rodriguez-Torres M, Muir AJ *et al.* Antiviral effects and safety of telaprevir, peginterferon alfa-2a, and ribavirin for 28 days in hepatitis C patients. *J Hepatol* 2008; 49: 163–9.
20 Akuta N, Suzuki F, Sezaki H *et al.* Predictive factors of virological non-response to interferon-ribavirin combination therapy for patients infected with hepatitis C virus of genotype 1b and high viral load. *J Med Virol* 2006; 78: 83–90.
21 Akuta N, Suzuki F, Kawamura Y *et al.* Predictive factors of early and sustained responses to peginterferon plus ribavirin combination therapy in Japanese patients infected with hepatitis C virus genotype 1b: amino acid substitutions in the core region and low-density lipoprotein cholesterol levels. *J Hepatol* 2007; 46: 403–10.
22 Enomoto N, Sakuma I, Asahina Y *et al.* Mutations in the nonstructural protein 5A gene and response to interferon in patients with chronic hepatitis C virus 1b infection. *N Engl J Med* 1996; 334: 77–81.
23 Lin C, Gates CA, Rao BG *et al.* In vitro studies of cross-resistance mutations against two hepatitis C virus serine protease inhibitors, VX-950 and BILN 2061. *J Biol Chem* 2005; 280: 36784–91.
24 Zhou Y, Muh U, Hanzelka BL *et al.* Phenotypic and structural analyses of hepatitis C virus NS3 protease Arg155 variants: sensitivity to telaprevir (VX-950) and interferon alpha. *J Biol Chem* 2007; 282: 22619–28.
25 Lang L. HCV findings presented at EASL: long-term follow-up and the criteria of a cure. *Gastroenterology* 2007; 132: 2282–3.
26 Davis GL. Monitoring of viral levels during therapy of hepatitis C. *Hepatology* 2002; 36: S145–51.
27 Jensen DM, Morgan TR, Marcellin P *et al.* Early identification of HCV genotype 1 patients responding to 24 weeks peginterferon alpha-2a (40 kd)/ribavirin therapy. *Hepatology* 2006; 43: 954–60.

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ORIGINAL ARTICLE

Development of hepatocellular carcinoma in elderly patients with chronic hepatitis C with or without elevated aspartate and alanine aminotransferase levels

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Abstract

Objective. Hepatocellular carcinoma (HCC) in the elderly infected with hepatitis C virus (HCV) is expected to increase globally within the next two decades. The purpose of the study was to define the natural history of elderly patients with chronic hepatitis C needs in order to prevent HCC from arising in these patients. ***Material and methods.*** Treatment-naive patients aged ≥65 years with platelet counts $>120\times10^3/mm^3$ were classified as 120 with aspartate and alanine aminotransferase (ASAT and ALAT) levels ≦40 IU/l (group A) and 212 with either or both levels ≥41 (group B) and followed-up for 3 years or longer without antiviral treatment. ***Results.*** Cirrhosis and HCC developed more frequently in group B than in group A ($p<0.001$ for both). In particular, of the patients aged 65–69 years at entry, cirrhosis and HCC developed more frequently in group B than in group A ($p<0.001$ and $p=0.001$, respectively). Liver-related causes of death were more common in group B than in group A (20/34 (59%) versus 1/9 (11%), $p=0.021$). HCC developed more frequently in men than in women ($p=0.033$). ***Conclusions.*** In elderly patients with chronic hepatitis C, cirrhosis and HCC develop more frequently in those with elevated transaminase levels than in those without elevated transaminase levels. Therefore, transaminase levels need to be suppressed below ≦40 IU/l, using antiviral treatments or other agents, in order to prevent cirrhosis and HCC arising in these patients. In view of rare liver-related deaths, aggressive antiviral treatment would not be necessary in the elderly with chronic hepatitis C who have normal transaminase levels.

Key Words: *Age, chronic hepatitis, cirrhosis, hepatitis C virus, hepatocellular carcinoma*

Introduction

There are an estimated 170 million people persistently infected with hepatitis C virus (HCV) worldwide, and approximately 30% of them develop serious complications during their lifetime, such as decompensated cirrhosis and hepatocellular carcinoma (HCC) [1]. The incidence of HCC in HCV carriers increases with age and is particularly high in those aged 65 years or older. Based on the shift in age-specific distribution of HCV carriers with time [2–4], HCC is expected to increase in the next 20 years, globally.

The natural history of infection with HCV is influenced by host and virological factors including age and gender [5–7], as well as viral loads and genotypes [8–10]. Thus, hepatitis proceeds slowly in HCV infections contracted by children and young women. During follow-ups carried out over 20 years, liver damage developed in a mere 3% of children who were infected with HCV during heart surgery [7], and cirrhosis emerged in only 2% of pregnant women infected with anti-D immune globulin contaminated with HCV [5].

As the average life span of human beings continues to extend, owing to improvements in sanitary

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conditions and efficient management of ailments, difficulties in the treatment of chronic hepatitis C in elderly individuals are increasingly coming to the fore. This is attributable, at least in part, to liver fibrosis accelerating in parallel with age [11], as well as less tolerability and more side effects of combined interferon (IFN) and ribavirin in these patients [6,11,12].

These constraints notwithstanding, there is a pressing need for treatment of aged individuals with antiviral agents in order to prevent the development of cirrhosis and HCC and to promote better survival with an increased quality of life. When planning antiviral treatment of the elderly, weighing its merits against untoward effects, it is essential to understand the natural history of HCV infection in these patients. However, there have been virtually no reports on the natural history of HCV infection in older adults, nor are there any solid guidelines for antiviral treatment in these patients [13].

In the 42 years from 1964 to 2005, we have followed-up 332 patients who were persistently infected with HCV and had not received any antiviral treatment. They included the 120 patients with aspartate and alanine aminotransferase (ASAT and ALAT) levels $\leqq$40 IU/l (group A) and the 212 with ASAT and/or ALAT $\geq$41 (group B), and were followed-up for 3 years or longer without receiving any antiviral treatment. It is hoped that the evolution of chronic hepatitis in these patients, with special reference to the baseline transaminase levels, will shed light on how they should be treated for the prevention of cirrhosis and HCC in the coming era of global longevity.

Material and methods

Patients

During 42 years, from 1964 through 2005, 7358 patients with HCV-RNA in the serum visited the Department of Hepatology at the Toranomon Hospital in Metropolitan Tokyo. Of these patients, 843 (11.5%) were $\geq$65 years of age at presentation, and 512 (60.7% of the elderly) had not received antiviral agents or other drugs that might suppress the replication of HCV. In order to rule out cirrhosis, 180 patients with platelet counts $<120\times10^3/mm^3$ were excluded. The remaining 332 patients were classified into the 120 with ASAT and ALAT levels $\leqq$40 IU/l (Group A) and the 212 with ASAT and/or ALAT levels $\geqq$41 IU/l (group B); they included 22 patients (10.4%) with ASAT levels $\leqq$40 IU/l and 18 (8.5%) with ALAT levels $\leqq$40 IU/l. Baseline transaminase levels were determined at least twice, 2–3 months apart, in the course of 6 months. The patients were followed-up for 3 years or longer without receiving any antiviral treatment, and tested monthly for liver function, HCV-RNA and α-fetprotein (AFP) or protein induced by the absence of vitamin K or antagonist-II (PIVKA-II). Screening for cirrhosis and HCC was carried out yearly using ultrasonography and/or computed tomography. Angiography was implemented when HCC was strongly suspected by imaging modalities. During follow-ups, herbal medicine (intravenous Stronger Neo-Minophagen C (SNMC) or oral Shousaikotou) and/or ursodeoxycholic acid was given to 51 (42.5%) patients in group A and 139 (65.6%) patients in group B. Three (2.5%) patients in group A and 24 (11.2%) patients in group B, in whom IFN was started after they had been followed-up for 3 years or longer, left the study cohorts at the initiation of treatment. Informed consent was obtained from each patient who participated in this study, and the protocol conformed to the ethics guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the Human Research Committee of the institution.

Markers of HCV infection

Qualitative assay for HCV-RNA was performed using polymerase chain reaction (PCR) with nested primers and the results were recorded as positive or negative, with the detection limit at 100 copies/ml. Quantification of HCV-RNA was carried out with the branched-DNA assay version 2.0 (Chiron Corp., Calif., USA), and the results were expressed in megaequivalents (MEq) per milliliter over a range from <0.5 to 120 MEq/ml.

Statistical analysis

Since certain data in the analysis were regarded to comply with non-Gaussian distribution, categorical variables at baseline were compared with the Fisher exact test and numerical values were analyzed with the Mann-Whitney U-test and the Kruskal-Wallis test. Cumulative rates of cirrhosis, HCC, and death were calculated using the Kaplan-Meier technique, and differences between curves were evaluated by the log-rank test. A p-value <0.05 with the two-tailed test was considered significant. All the analyses were carried out using the computer program SPSS ver.11.0 (SPSS Inc., Ill., USA).

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Results

Treatment-naive patients older than 65 years infected with HCV

During the 42 years from 1964 through 2005, the Department of Hepatology at the Toranomon Hospital in Metropolitan Tokyo admitted 332 patients aged 65 years or older with HCV who had not received any antiviral treatment, and in whom cirrhosis had not developed. In Table I we compare demographic, clinical, and virological characteristics between the 120 patients with baseline transaminase levels ≦40 IU/l and the 212 patients with levels ≧41 IU/l. ASAT and ALAT levels were higher, while platelet counts were lower in the patients with elevated transaminase levels compared with in patients without elevated transaminase levels.

When patients with baseline transaminase levels ≦40 IU/l were stratified by age, the median follow-up period was shorter in those aged 75–80 years than in those aged 65–69 or 70–74 years (4.5 versus 8.6 or 7.0 years, $p=0.011$) (Table II). Although the baseline transaminase levels were within normal limits in all of them, the median ASAT level was higher in patients aged 70–74 years than in those aged 65–70 or 75–80 years (35 versus 27 or 28 IU/l, $p=0.040$). In patients with baseline levels of both or either transaminase ≧41 IU/l, the median albumin level was lower in those aged 75–80 years than in those aged 65–69 or 70–74 years (3.9 versus 4.1 or 4.1 g /dl, $p=0.005$) (Table III).

Development of cirrhosis and HCC

Cirrhosis developed more frequently in elderly patients aged 65 years or older, with elevated transaminase levels at baseline, during follow-ups for longer than 3 years (Figure 1A). At 5 and 10 years of follow-up, cirrhosis developed in, respectively, 26% and 27% of the patients with the baseline transaminase levels ≧41 IU/l in contrast to only 4% and 13% of the patients with levels ≦40 IU/l ($p<0.001$). Likewise, HCC developed more frequently in elderly patients with elevated transaminase levels at baseline (Figure 1B). At 5 and 10 years of follow-up, HCC developed in, respectively, 22% and 26% of the patients with the baseline transaminase levels ≧41 IU/l, contrasting with only 3% and 5% of the patients with levels ≦40 IU/l ($p<0.001$).

Development of cirrhosis is compared between patients with and without elevated transaminase levels at baseline who were stratified by age (Figure 2). Cirrhosis developed more frequently in the patients with elevated transaminase levels than in those without elevated transaminase levels who were aged 65–69 years ($p<0.001$). In patients aged 70–74 years, cirrhosis tended to occur more often in those with elevated transaminase levels than in those without elevated transaminase levels during 5 years (27% versus 0%), but the difference fell short of being significant owing to the small number of patients in both groups.

Likewise, development of HCC is compared between patients with and those without elevated transaminase levels at baseline who were stratified by age (Figure 3). HCC developed more frequently in the patients with elevated transaminase levels than in those without elevated transaminase levels who were aged 65–69 years ($p=0.001$). In patients aged 70–74 and 75–80 years, HCC tended to occur more often in those with elevated transaminase levels than in those without elevated transaminase levels during 5 years (20% versus 5% and 19% versus 0%, respectively), but the difference was not significant, owing to the small number of patients in both groups.

Influence of gender on the development of cirrhosis and HCC

Figure 4 shows a comparison of the development of cirrhosis and HCC between 155 male and 177

Table I. Characteristics of patients with HCV-RNA aged 65 years or older with or without elevated transaminase (ASAT and ALAT) levels.

Features	≦40 IU/ml ($n=120$)	≧41 IU/l ($n=212$)	Differences p-value
Men	51 (42.5%)	104 (49.1%)	0.513
Follow-up (years)	7.8 (3–31.5)	8.7 (3–18.9)	0.181
ASAT (IU/l)	23 (6–40)	76 (27–496)	<0.001
ALAT (IU/l)	28 (11–40)	63 (22–411)	<0.001
Albumin (g/dl)	4.1 (2.4–4.9)	4.1 (3.2–5.3)	0.189
Platelets ($\times 10^3/mm^3$)	184 (120–343)	173 (120–313)	0.001
HCV RNA (MEq/ml)	4.5 (<0.5–120)	5.6 (<0.5–49)	0.168
HCV genotypes (1b:2a:2b:ND)	85:20:3:7	176:28:12:9	0.970

Abbreviations: HCV = hepatitis C virus; ASAT = aspartate aminotransferase; ALAT = alanine aminotransferase; MEq = megaequivalents; ND = not determined. Data are expressed as the number (%) or the median with the range in parentheses.

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Table II. Characteristics of patients aged 65 years or older with HCV-RNA and without elevated baseline transaminase levels (ASAT and ALAT ≤40 IU/l) stratified by the age.

Features	65–69 years (n=79 (65.8%))	70–74 years (n=25 (20.8%))	75–80 years (n=16 (13.3%))	Differences p-value
Men	29 (36.7%)	11 (44.0%)	11 (68.8%)	0.062
Follow-up (years)	8.6 (3–31.5)	7.0 (3–12.6)	4.5 (3–17.6)	0.011
ASAT (IU/l)	27 (11–39)	35 (16–40)	28 (15–40)	0.004
ALAT (IU/l)	22 (6–40)	25 (9–40)	22 (9–37)	0.604
Albumin (g/dl)	4.1 (3.2–4.9)	4.1 (3.0–4.4)	4.0 (2.4–4.5)	0.247
Platelets ($\times 10^3$/mm^3)	193 (120–298)	177 (120–343)	182 (120–263)	0.408
HCV RNA (MEq/ml)	4.2 (<0.5–34.6)	6.5 (<0.5–120)	4.0 (<0.5–17.1)	0.181
HCV genotypes (1b:2a:2b:ND)	51:19:2:4	21:1:1:1	13:0:0:2	0.074

Abbreviations: HCV = hepatitis C virus; ASAT = aspartate aminotransferase; ALAT = alanine aminotransferase; MEq = megaequivalents; ND = not determined. Data are expressed as the number (%) or the median with the range in parentheses.

female patients aged 65 years or older. Cirrhosis tended to occur more frequently in male than in female patients. There were marked gender differences in the development of HCC. At 5 and 10 years of follow-up, HCC occurred more frequently in men than in women (18% and 25% versus 9% and 9%, respectively, p=0.033).

Complications and death in patients with the baseline transaminase levels ≦40 IU/l and ≧41IU/l

Of the 120 patients with baseline transaminase levels ≦40 IU/l, 33 (27.5%) developed complications during follow-up (hypertension in 9 (27%), diabetes in 7 (21%), both complications in 1 (3%), pulmonary disease in 4 (12%), heart disease in 4 (12%), and other illnesses in the remaining 8 (24%)). At 5, 10, and 15 years of follow-up, respectively, death occurred more frequently in the patients with complications than in those without complications (10%, 18%, and 45% versus 0%, 5%, and 5%, p=0.015) (Figure 5).

Among 9 of the 120 (7.5%) patients who died, liver disease was the cause of death in only one. Of the remaining 8 (89%) patients, 4 died of heart failure or infarction, and one each of pneumonia, cerebral hemorrhage, renal insufficiency, and decrepitude. Death was more frequent in the patients aged ≥70 years than in those aged <70 years at presentation (p=0.006) (Figure 6).

Complications and death in patients with the baseline transaminase levels ≧41 IU/l

Of the 212 patients with baseline tranasaminase levels ≧41 IU/l, 83 (39.2%) developed complications during follow-up (hypertension in 18 (22%), diabetes in 23 (28%), both complications in 10 (12%), extrahepatic malignancies in 12 (15%), and other diseases in the remaining 20 (24%)). There were no differences in the frequency of death between the patients with and those without complications, however (Figure 7).

Among 34 of the 212 (14.0%) patients who died, liver disease was the most frequent cause of death and occurred in 20 (59%); the frequency was higher than that (11% (1/9)) in the patients with transaminase levels ≦40 IU/l at baseline (p=0.021). There were no differences in the frequency of death among

Table III. Characteristics of patients with HCV-RNA aged 65 years or older and with elevated baseline transaminase levels (ASAT and/or ALAT ≥41 IU/l) stratified by the age.

Features	65–69 years (n=140 (66.0%))	70–74 years (n=48 (22.6%))	75–80 years (n=24 (11.3%))	Differences p-value
Men	63 (45.0%)	25 (52.1%)	16 (66.7%)	0.707
Follow-up (years)	9.0 (3–18.9)	8.4 (3–17.2)	7.7 (3–14.7)	0.061
ALAT (IU/l)	82 (28–496)	74 (27–440)	64 (30–269)	0.959
ASAT (IU/l)	67 (22–411)	67 (34–309)	71 (35–172)	0.201
Albumin (g/dl)	4.1 (3.2–5.3)	4.1 (3.4–4.6)	3.9 (3.4–4.7)	0.005
Platelets ($\times 10^3$/cm^3)	171 (120–313)	180 (120–289)	157 (120–263)	0.398
HCV RNA (MEq/ml)	5.9 (<0.5–44.8)	5.6 (<0.5–30.0)	3.0 (<0.5–49.0)	0.251
HCV genotypes (1b:2a:2b:ND)	121:19:8:6	37:7:4:1	18:2:0:2	0.294

Abbreviations: HCV = hepatitis C virus; ASAT = aspartate aminotransferase; ALAT = alanine aminotransferase; MEq = megaequivalents; ND = not determined.

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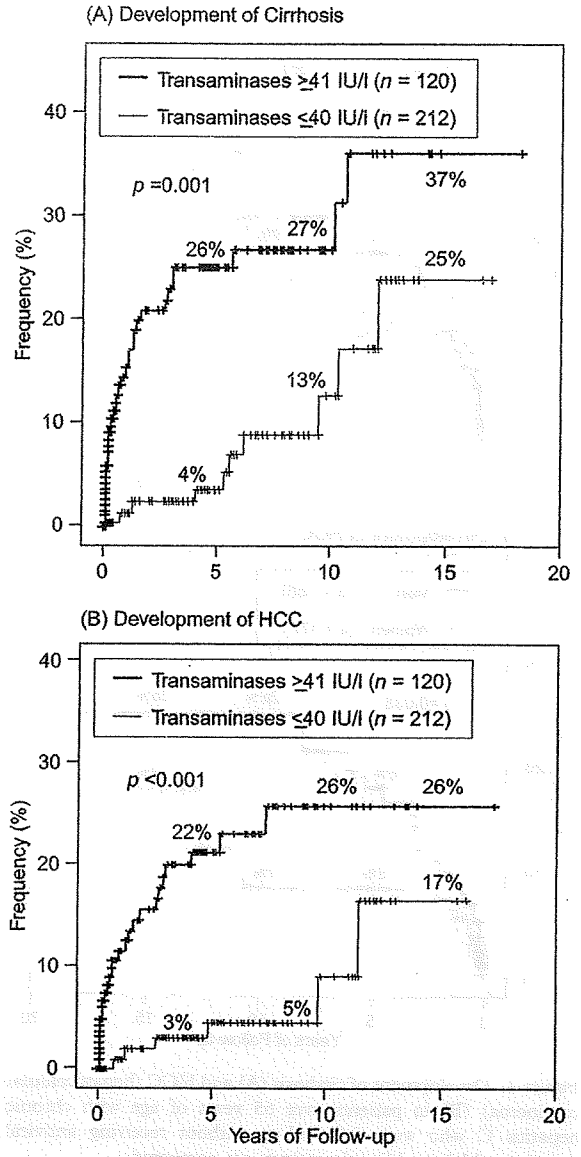

Figure 1. Development of cirrhosis (A) and HCC (hepatocelllular carcinoma) (B) in patients over 65 years of age with chronic hepatitis C who were followed-up without receiving antiviral treatment. Patients with and without elevated baseline transaminase levels are compared.

the patients in distinct age groups who had elevated baseline transaminase levels at baseline (Figure 8).

Discussion

The World Health Organization defines elderly individuals as those aged ≥65 years. In general, IFN is indicated for patients under 65 years of age, in view of frequent side effects and safety precautions. HCC develops increasingly with age and in the majority after 65 years, and in Japan approximately

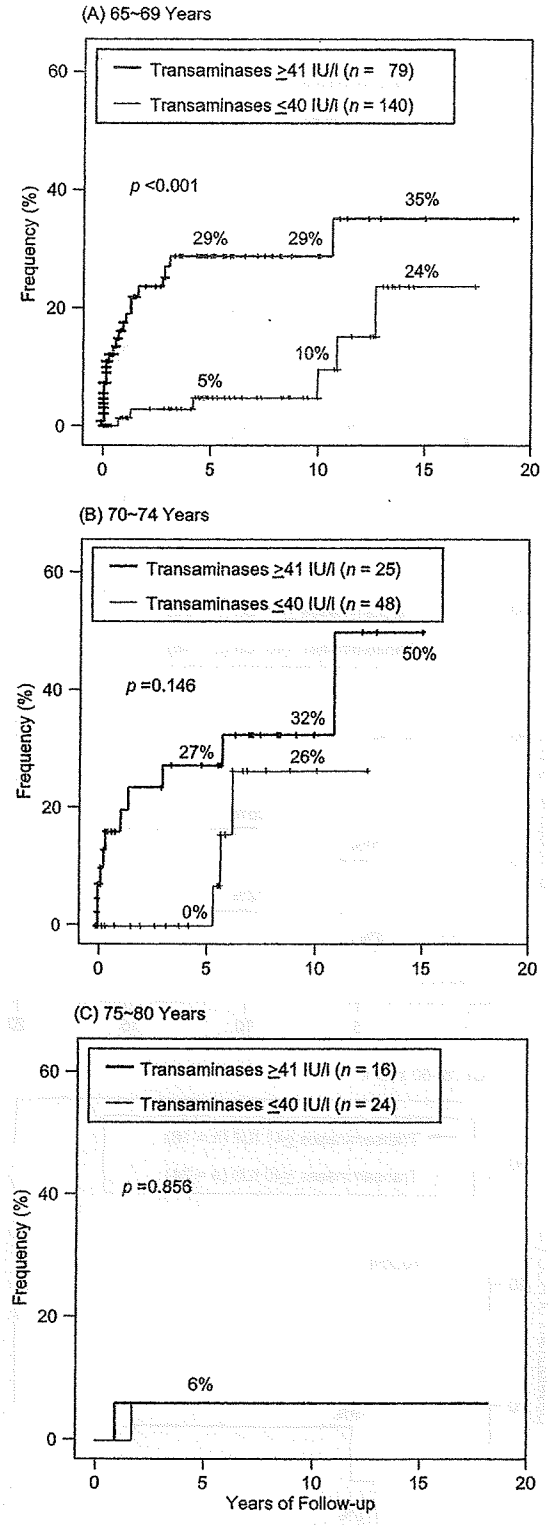

Figure 2. Development of cirrhosis in patients of more than 65 years of age with chronic hepatitis C who were followed-up without receiving antiviral treatment. Patients in different age groups are compared between those with and those without elevated transaminase levels.

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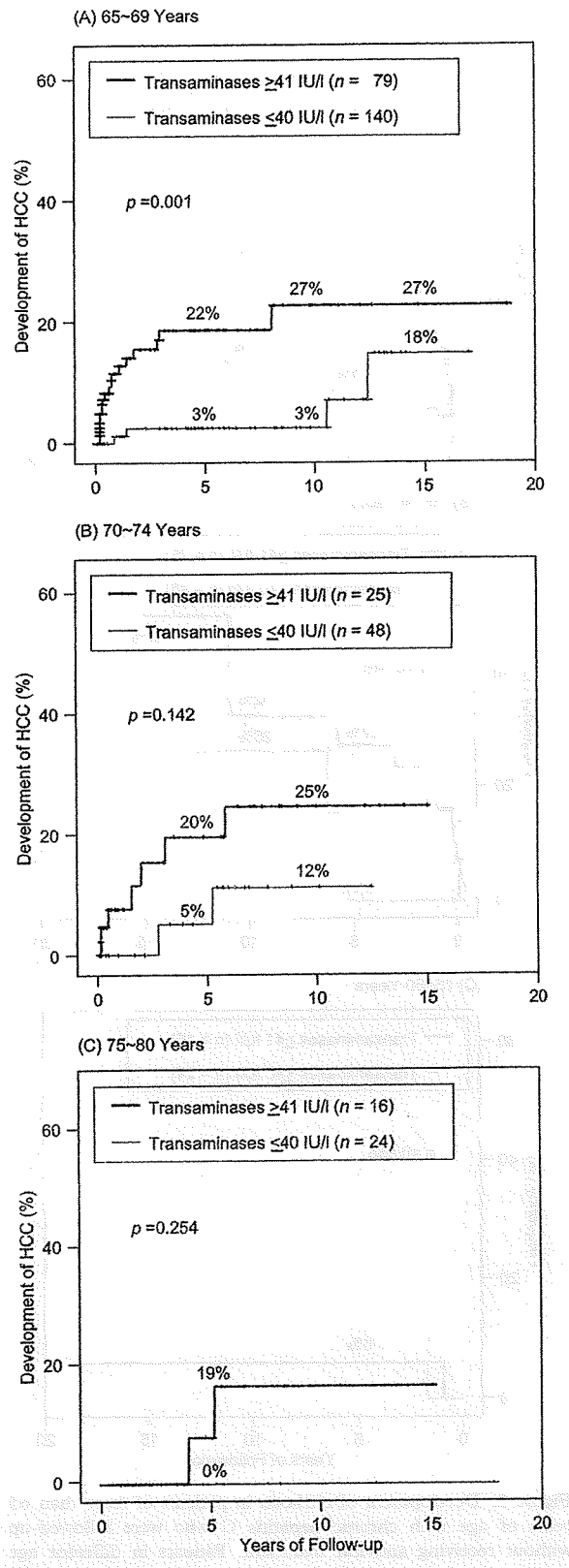

Figure 3 (*Continued*)

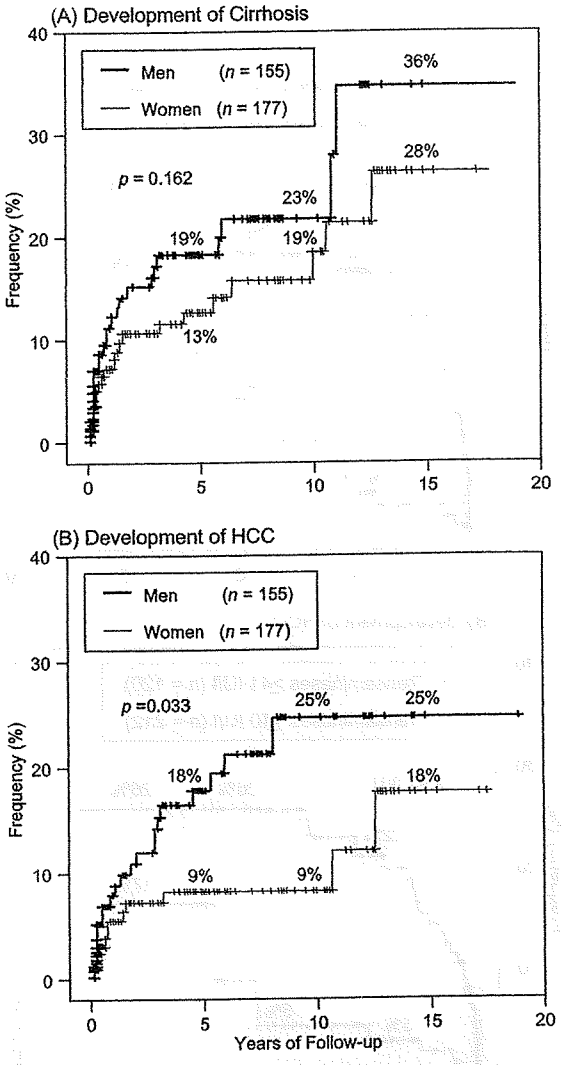

Figure 4. Development of cirrhosis (A) and HCC (hepatocelllular carcinoma) (B) in patients over 65 years of age with chronic hepatitis C who were followed-up without receiving antiviral treatment. Male and female patients are compared.

30,000 patients infected with HCV die yearly [14]. Furthermore, HCC is steadily increasing in the United States, and the incidence is expected to double or triple in the next two decades [15]. Hence, HCV carriers aged 65 years or older should be given IFN treatment, which is proven to be efficacious in preventing the development of HCC [16,17]. Previously, we have evaluated the efficacy and safety of IFN monotherapy in patients aged 65 years or older [18]. Of the 84 patients studied, the sustained virological response was reached in 30 (36%), while

Figure 3. Development of hepaptocelluar carcinoma (HCC) in patients over 65 years of age with chronic hepatitis C who were followed-up without receiving antiviral treatment. Patients in different age groups are compared between those with and those without elevated transaminase levels.

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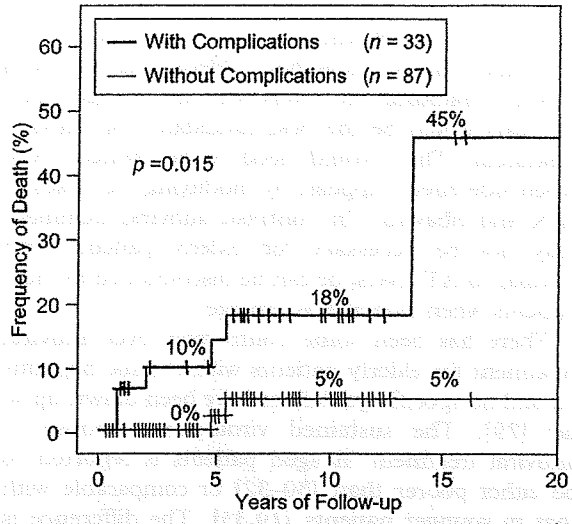

Figure 5. Deceased patients without elevated baseline transaminase levels (ASAT and ALAT <40 IU/l). Patients with and without complications other than liver disease are compared.

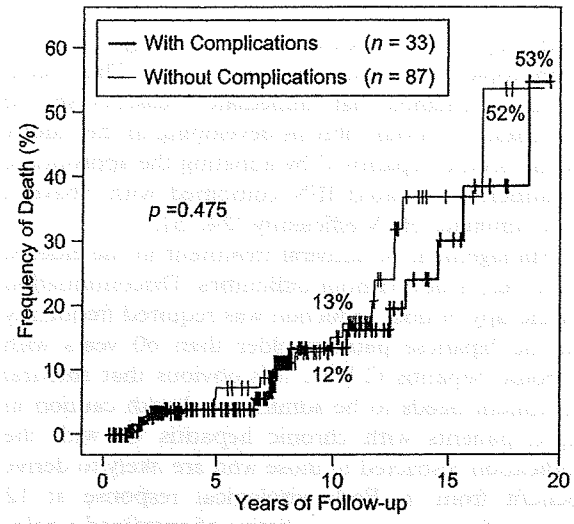

Figure 7. Deceased patients without elevated baseline transaminase levels (ASAT and ALAT <40 IU/l). Patients with and without complications other than liver disease are compared.

IFN was discontinued owing to adverse events in 11 (13%). Remarkably, the sustained virological response to combined IFN and ribavirin was comparable between the 66 patients aged ≥60 years and the 154 aged <60 years (31.8% versus 38.3%), although ribavirin had to be discontinued more frequently in the older patients (33.3% versus 20.8%, $p<0.05$) [19].

HCV spread widely in Japan around the end of World War II, at least 20 years earlier than in the other countries [4,14]. As a consequence, patients given combined IFN and ribavirin are 10–15 years older than those in Western countries [20–22]. Throughout the world, there are increasing numbers of individuals who are infected with HCV and entering the elder years. By the year 2010, the number of the elderly infected with HCV is estimated to account for 0.48 (54%) of the entire 0.89 million infected in Japan, and that in the United States for 0.78 (22%) of the 3.61 million [2–4]. These numbers will continue to increase for some time thereafter. As sequellae to this, cirrhosis and HCC will continue to increase, demanding higher medical costs. In the USA already, HCV-related

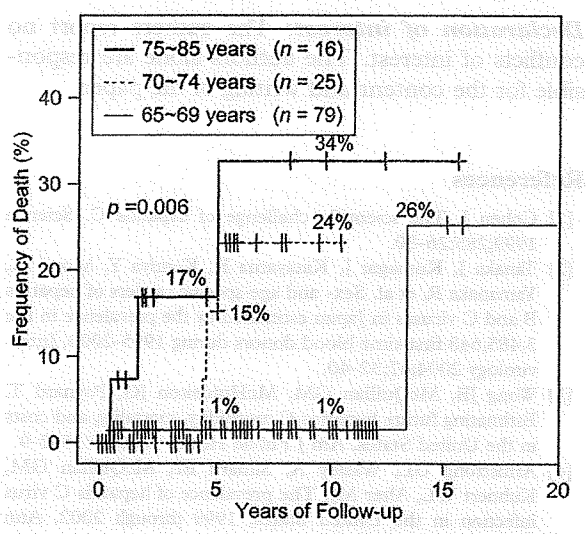

Figure 6. Deceased patients with elevated baseline transaminase levels (ASAT and/or ALAT >41 IU/l). Patients in the different age groups are compared.

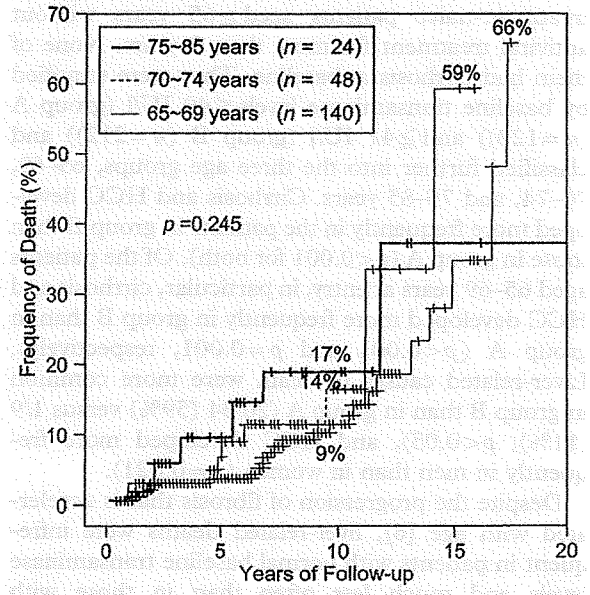

Figure 8. Deceased patients with elevated baseline transaminase levels (ASAT and/or ALAT >41 IU/l). Patients in the different age groups are compared.

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end-stage liver disease is the leading cause of orthotopic liver transplantation [23]. This background demands that immediate measures should be taken to prevent fibrosis developing in the elderly with chronic hepatitis C by initiating the appropriate treatment; pegylated IFN combined with ribavirin can eliminate HCV efficiently [24,25].

Management of antiviral treatment in the elderly, however, is not without difficulties. Discontinuation of therapy or dose reduction was required frequently in the Japanese patients older than 60 years with chronic hepatitis C [21]. It is obvious that antiviral treatment needs to be administered with caution in aged patients with chronic hepatitis C, with the indication restricted to those who are likely to derive benefit from it. Early virological response at 12 weeks of treatment is predictive of sustained virological response [26]. The influence of HCV genotypes on the response to combined therapy, which increases with age [27], would have to be taken into consideration, also. In the Japanese patients infected with HCV genotype 1b, substitutions of amino acids at positions 70 and 91 are associated with a better response to combined treatment [28]. In view of the more frequent and serious side effects in elderly patients, these predictors would need to be taken into account when deciding whether to continue or discontinue combined treatment with IFN and ribavirin in elderly patients with chronic hepatitis C.

In order to plan the treatment of elderly patients, the natural history of HCV infection in these patients needs to be elucidated, which has not been done as yet. In the present study, we have followed-up treatment-naive patients aged ≥ 65 years without antiviral treatment for more than 3 years. None of them had cirrhosis at baseline. They were stratified by baseline transaminase levels ≤ 40 IU/l (group A ($n=120$)) and ≥ 41 IU/l (group B ($n=212$)) and classified further into the three age groups, 65–69, 70–74, and 75–85 years. Cirrhosis and HCC developed more frequently in the patients in group B than those in group A ($p<0.001$ for both). Of the patients aged 65–69 years at entry, in particular, cirrhosis and HCC developed more frequently in group B than in group A ($p<0.001$ and $p=0.001$, respectively). Liver-related causes of death were more common in group B than in group A (20/34 (59%) versus 1/9 (11%), $p<0.05$), and HCC developed more frequently in men than in women ($p=0.021$).

Despite the progression of fibrosis that is accelerated with age [6], liver-related deaths were infrequent in patients with normal baseline transaminase levels and much less often than in those with elevated baseline transaminase levels (1/120 (0.8%) versus 20/212 (9.4%), $p=0.002$). Development of cirrhosis or HCC was no different between patients in groups A and B who were aged 70 years or older at entry. Taken altogether, elderly patients with elevated transaminase levels who are younger than 70 years would be the best candidates for antiviral treatment. They would need to be treated, even when side effects appear, by modifying the doses of IFN and ribavirin. In contrast, antiviral treatment may not be necessary for elderly patients with normal ALAT levels, or can be discontinued in these patients when side effects emerge.

There has been some controversy over antiviral treatment for elderly patients with chronic hepatitis C, and no specific guidelines have been drawn up so far [29]. The sustained virological response to antiviral treatment in aged patients is reported to be either poorer than [30–32] or comparable with that in younger patients [19,33]. The difference is most likely ascribed to careful selection of the aged patients who would benefit from treatment [13]. Based on the natural history of elderly patients with chronic hepatitis C described herein, those with elevated transaminase levels would need treatment to prevent progression to cirrhosis and HCC, while others with normal levels may not require treatment. It is to be hoped that the results in this study might be of help in planning a reasonable treatment strategy towards the longevity, without development of cirrhosis or HCC, in elderly patients with chronic hepatitis C, whose numbers are expected to increase progressively in the foreseeable future.

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References

[1] Cohen J. The scientific challenge of hepatitis C. Science 1999;285:26–30.

[2] Tanaka J, Kumagai J, Katayama K, Komiya Y, Mizui M, Yamanaka R, et al. Sex- and age-specific carriers of hepatitis B and C viruses in Japan estimated by the prevalence in the 3,485,648 first-time blood donors during 1995–2000. Intervirology 2004;47:32–40.

[3] Wong JB, McQuillan GM, McHutchison JG, Poynard T. Estimating future hepatitis C morbidity, mortality, and costs in the United States. Am J Public Health 2000;90:1562–9.

[4] Armstrong GL, Wasley A, Simard EP, McQuillan GM, Kuhnert WL, Alter MJ. The prevalence of hepatitis C virus infection in the United States, 1999 through 2002. Ann Intern Med 2006;144:705–14.

[5] Kenny-Walsh E. Clinical outcomes after hepatitis C infection from contaminated anti-D immune globulin. Irish Hepatology Research Group. N Engl J Med 1999;340:1228–33.

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[6] Poynard T, Bedossa P, Opolon P. Natural history of liver fibrosis progression in patients with chronic hepatitis C. Lancet 1997;349:825–32.
[7] Vogt M, Lang T, Frosner G, Klingler C, Sendl AF, Zeller A, et al. Prevalence and clinical outcome of hepatitis C infection in children who underwent cardiac surgery before the implementation of blood-donor screening. N Engl J Med 1999;341:866–70.
[8] Feray C, Gigou M, Samuel D, Paradis V, Mishiro S, Maertens G, et al. Influence of the genotypes of hepatitis C virus on the severity of recurrent liver disease after liver transplantation. Gastroenterology 1995;108:1088–96.
[9] Garcia-Samaniego J, Soriano V, Castilla J, Bravo R, Moreno A, Carbo J, et al. Influence of hepatitis C virus genotypes and HIV infection on histological severity of chronic hepatitis C. Am J Gastroenterol 1997;92:1130–4.
[10] Pageaux GP, Ducos J, Mondain AM, Costes V, Picot MC, Perrigault PF, et al. Hepatitis C virus genotypes and quantitation of serum hepatitis C virus RNA in liver transplant recipients: relationship with severity of histological recurrence and implications in the pathogenesis of HCV infection. Liver Transpl Surg 1997;3:501–5.
[11] Wali M, Harrison RF, Gow PJ, Mutimer D. Advancing donor liver age and rapid fibrosis progression following transplantation for hepatitis C. Gut 2002;51:248–52.
[12] Kumada T, Toyoda H, Honda T, Kuzuya T, Katano Y, Nakano I, et al. Treatment of chronic hepatitis C with interferon alone or combined with ribavirin in Japan. Intervirology 2006;49:112–8.
[13] Marcus EL, Tur-Kaspa R. Chronic hepatitis C virus infection in older adults. Clin Infect Dis 2005;41:1606–12.
[14] Yoshizawa H, Tanaka J, Miyakawa Y. National prevention of hepatocellular carcinoma in Japan based on epidemiology of hepatitis C virus infection in the general population. Intervirology 2006;49:7–17.
[15] 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.
[16] Arase Y, Ikeda K, Suzuki F, Suzuki Y, Kobayashi M, Akuta N, et al. Interferon-induced prolonged biochemical response reduces hepatocarcinogenesis in hepatitis C virus infection. J Med Virol 2007;79:1485–90.
[17] Ikeda K, Saitoh S, Arase Y, Chayama K, Suzuki Y, Kobayashi M, et al. Effect of interferon therapy on hepatocellular carcinogenesis in patients with chronic hepatitis type C: a long-term observation study of 1,643 patients using statistical bias correction with proportional hazard analysis. Hepatology 1999;29:1124–30.
[18] Koyama R, Arase Y, Ikeda K, Suzuki F, Suzuki Y, Saitoh S, et al. Efficacy of interferon therapy in elderly patients with chronic hepatitis C. Intervirology 2006;49:121–6.
[19] Honda T, Katano Y, Urano F, Murayama M, Hayashi K, Ishigami M, et al. Efficacy of ribavirin plus interferon-alpha in patients aged (60 years with chronic hepatitis C. J Gastroenterol Hepatol 2007;22:989–95.
[20] Davis GL, Esteban-Mur R, Rustgi V, Hoefs J, Gordon SC, Trepo C, et al. Interferon alfa-2b alone or in combination with ribavirin for the treatment of relapse of chronic hepatitis C. International Hepatitis Interventional Therapy Group. N Engl J Med 1998;339:1493–9.
[21] Iwasaki Y, Ikeda H, Araki Y, Osawa T, Kita K, Ando M et al. Limitation of combination therapy of interferon and ribavirin for older patients with chronic hepatitis C. Hepatology 2006;43:54–63.
[22] Poynard T, Marcellin P, Lee SS, Niederau C, Minuk GS, Ideo G, 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. Lancet 1998;352:1426–32.
[23] Verna EC, Brown RS Jr. Hepatitis C and liver transplantation: enhancing outcomes and should patients be retransplanted? Clin Liver Dis 2008;12:637–59.
[24] Fried MW, Shiffman ML, Reddy KR, Smith C, Marinos G, Goncales FL Jr, et al. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. N Engl J Med 2002;347: 975–82.
[25] Manns MP, McHutchison JG, Gordon SC, Rustgi VK, Shiffman M, Reindollar R, 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.
[26] Davis GL, Wong JB, McHutchison JG, Manns MP, Harvey J, Albrecht J. Early virologic response to treatment with peginterferon alfa-2b plus ribavirin in patients with chronic hepatitis C. Hepatology 2003;38:645–52.
[27] Antonucci G, Longo MA, Angeletti C, Vairo F, Oliva A, Comandini UV, et al. The effect of age on response to therapy with peginterferon alpha plus ribavirin in a cohort of patients with chronic HCV hepatitis including subjects older than 65 years. Am J Gastroenterol 2007;102:1383–91.
[28] Akuta N, Suzuki F, Kawamura Y, Yatsuji H, Sezaki H, Suzuki Y, et al. Predictors of viral kinetics to peginterferon plus ribavirin combination therapy in Japanese patients infected with hepatitis C virus genotype 1b. J Med Virol 2007;79:1686–95.
[29] Wright TL. Treatment of patients with hepatitis C and cirrhosis. Hepatology 2002;36:S185–94.
[30] Floreani A, Minola E, Carderi I, Ferrara F, Rizzotto ER, Baldo V. Are elderly patients poor candidates for pegylated interferon plus ribavirin in the treatment of chronic hepatitis C? J Am Geriatr Soc 2006;54:549–50.
[31] Hayashi J, Kishihara Y, Ueno K, Yamaji K, Kawakami Y, Furusyo N, et al. Age-related response to interferon alfa treatment in women vs men with chronic hepatitis C virus infection. Arch Intern Med 1998;158:177–81.
[32] Hiramatsu N, Oze T, Tsuda N, Kurashige N, Koga K, Toyama T, et al. Should aged patients with chronic hepatitis C be treated with interferon and ribavirin combination therapy? Hepatol Res 2006;35:185–9.
[33] Tsui JI, Currie S, Shen H, Bini EJ, Brau N, Wright TL. Treatment eligibility and outcomes in elderly patients with chronic hepatitis C: results from the VA HCV-001 Study. Dig Dis Sci 2008;53:809–14.

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＜特別寄稿＞

免疫抑制・化学療法により発症するB型肝炎対策 —厚生労働省「難治性の肝・胆道疾患に関する調査研究」班 劇症肝炎分科会および「肝硬変を含めたウイルス性肝疾患の 治療の標準化に関する研究」班合同報告—

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索引用語：　劇症肝炎　HBV再活性化　*de novo* B型肝炎　核酸アナログ製剤　リツキシマブ

近年，化学療法，免疫療法，移植療法の進歩に伴い，多様な抗癌剤や免疫抑制剤を使用する機会が増加している．以前よりB型肝炎ウイルス（HBV）キャリアに合併した悪性腫瘍患者に対し，ステロイドを併用した化学療法を施行した場合，HBVの急激な増殖すなわちHBVの再活性化（reactivation）により致死的な重症肝炎が発症することが知られていた[1)2)]．HBV遺伝子にはglucocorticoid enhancement elementが存在するため[3)]，ステロイドにより直接的にウイルス複製が助長されるだけでなく，化学療法による免疫抑制や治療終了後に生じる免疫学的な均衡の破綻により，HBVの増殖とともに広範な感染肝細胞の破壊を伴う重症肝炎が惹起される．このようなHBVキャリアに対する化学療法時にはラミブジンなどの核酸アナログを予防投与してHBV再活性化を避けることが必要である[4)]．

一方，HBs抗原陰性でHBc抗体ないしHBs抗体陽性例は従来HBV既往感染とされ，臨床的には治癒の状態と考えられてきた．しかしこのような既往感染例でも肝臓や末梢血単核球中では低レベルながらHBV-DNAの複製が長期間持続することが明らかになっている[5)~7)]．最近，移植後やB細胞表面抗原CD20に対する抗体であるリツキシマブなど強力な免疫抑制剤の使用により，このような既往感染例からもHBV再活性化により重症肝炎が発症することが報告され，de novo B型肝炎と呼ばれている[8)~10)]．厚生労働省「肝硬変を含めたウイルス性肝疾患の治療の標準化に関する研究」班の全国調査によりこのようなde novo B型肝炎は通常のB型肝炎

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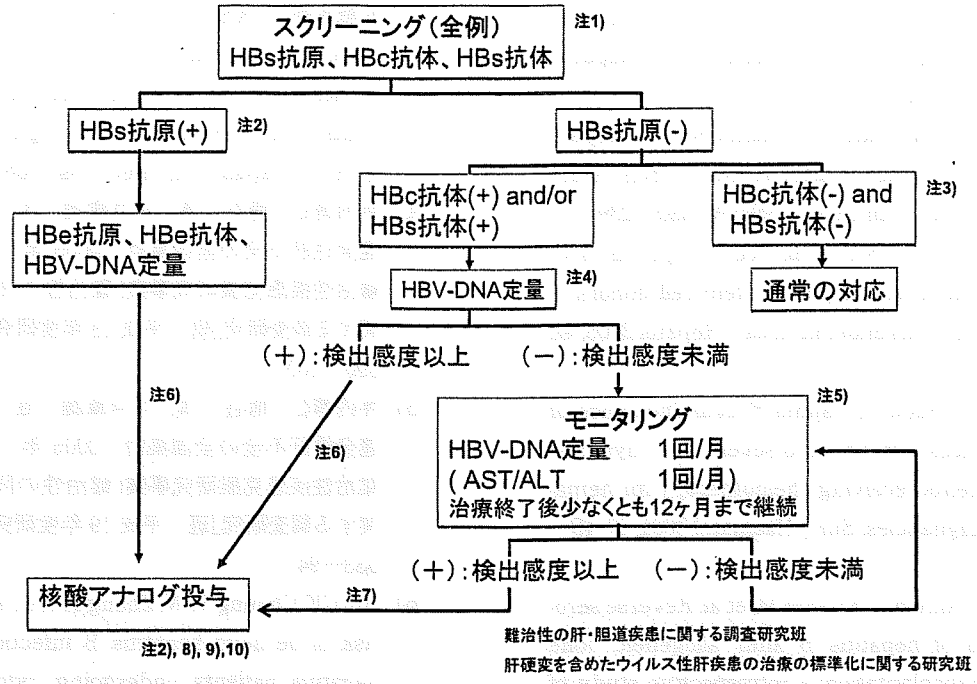

Fig. 1　免疫抑制・化学療法により発症するB型肝炎対策ガイドライン*

補足

*血液悪性疾患に対する強力な免疫・抑制化学療法中あるいは終了後にHBs抗原陽性あるいはHBs抗原陰性例の一部にHBV再活性化によりB型肝炎が発症し，その中には劇症化する症例があり，注意が必要である．その他の疾患においても治療によるHBV再活性化のリスクを考慮して対応する必要がある．また，ここで推奨する核酸アナログ予防投与のエビデンスはなく，劇症化予防効果を完全に保証するものではない．

注1)　CLIA法で測定することが望ましい．

注2)　HBs抗原陽性例は肝臓専門医にコンサルトすること．全ての症例で核酸アナログ投与にあたっては肝臓専門医にコンサルトするのが望ましい．

注3)　初回治療時にHBc抗体，HBs抗体未測定の再治療例では抗体価が低下している場合があり，HBV-DNA定量検査などによる精査が望ましい．

注4)　PCR法およびリアルタイムPCR法により実施する．より検出感度の高いリアルタイムPCR法が望ましい．

注5)　リツキシマブ・ステロイド使用例，造血細胞移植例はHBV再活性化の高リスクであり，注意が必要である．フルダラビンは強力な免疫抑制作用を有するが，HBV再活性化のリスクは不明であり，今後注意が必要である．

注6)　免疫抑制・化学療法を開始する前，できるだけ早期に投与を開始するのが望ましい．

注7)　免疫抑制・化学療法中はHBV-DNA定量検査が検出感度以上になった時点で直ちに投与を開始する．

注8)　核酸アナログはエンテカビルの使用を推奨する．

注9)　下記の条件を満たす場合には核酸アナログ投与の終了を検討して良い．
スクリーニング時にHBs抗原（+）例ではB型慢性肝炎における核酸アナログ投与終了基準を満たす場合．スクリーニング時にHBc抗体（+）and/or HBs抗体（+）例では，(1) 免疫抑制・化学療法終了後，少なくとも12カ月間は投与を継続すること．(2) この継続期間中にALT（GPT）が正常化していること．（但しHBV以外にALT異常の原因がある場合は除く）(3) この継続期間中にHBV-DNAが持続陰性化していること．

注10)　核酸アナログ投与終了後12カ月間は厳重に経過観察する．経過観察方法は各核酸アナログの使用上の注意に基づく．経過観察中にHBV-DNA定量検査が検出感度以上になった時点で直ちに投与を再開する．

に比して劇症化する頻度が高率で，死亡率も高いことが明らかになった[11)~13)]．また，厚生労働省「難治性の肝・胆道疾患に関する調査研究」班で実施している劇症肝炎・遅発性肝不全（LOHF）の全国調査でもここ数年，特に悪性リンパ腫に対しリツキシマブとステロイドを併用したR-CHOP治療例からの劇症化やde novo B型肝炎が増加傾向にあり，予後不良であった[14)15)]．以上のような経緯から，早急なHBV再活性化対策が必要となり，両研究班が合同でワーキンググループを立ち上げ，Fig. 1に示すガイドラインを作成した．

ガイドラインの要旨は以下のとおりである．まずHBV再活性化リスク群の同定を目的にスクリーニング検査として，全ての症例にHBs抗原およびHBc抗体，HBs抗体を測定する．HBs抗原が陽性の場合はさらにHBe抗原，HBe抗体，HBV-DNA定量検査を実施する．HBs抗原陽性例では，無症候性キャリアだけではなく，慢