

Fig. 1. Cumulative survival rates according to substitution of core amino acid in the elderly group. **a** Cumulative survival rate according to Gln70/His70 was not different compared with that related to Arg70. **b** Cumulative survival rate in Met91 was significantly lower than in Leu91.

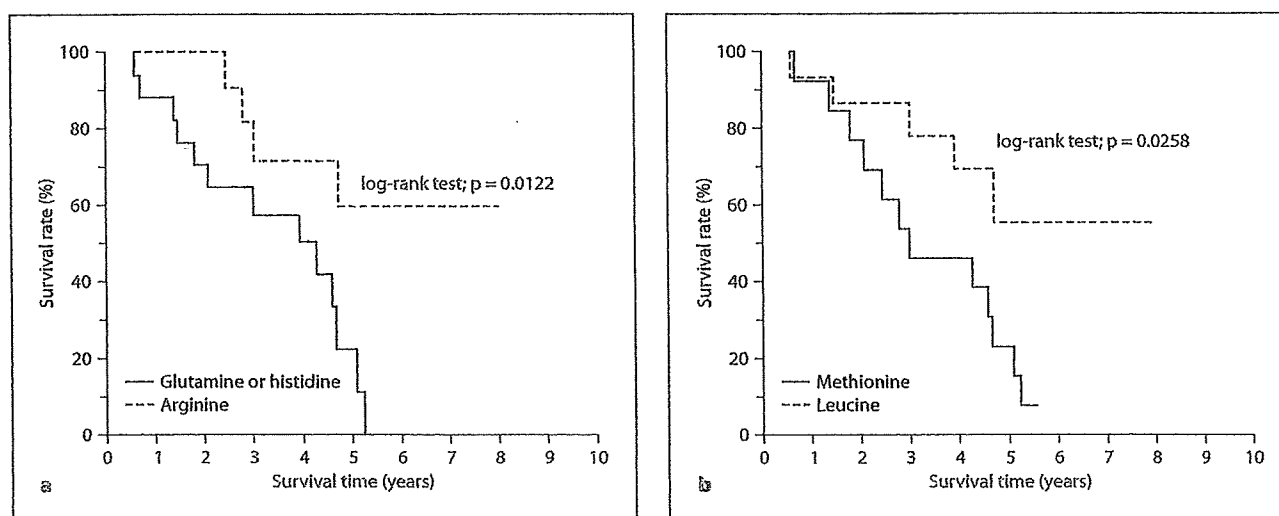


Fig. 2. Cumulative survival rates according to substitution of core amino acid in the young group. **a** The cumulative survival rate according to Gln70/His70 was significantly lower than that related to Arg70. **b** The cumulative survival rate according to Met91 was significantly lower than that related to Leu91.

Discussion

Previous studies reported that elderly patients could develop HCC even when liver histology shows chronic hepatitis and lack of cirrhosis and these patients included

more females, compared with young patients [12, 13]. The present study compared the clinicopathological features of elderly and young patients with HCC based on HCV infection. Glucose metabolism, lipid metabolism, and liver function were preserved regardless of the stage of fi-

Table 3. Factors associated with mortality in elderly patients with HCV genotype 1b infection using multivariate analysis

| Factors | Category | Odds ratio (95% CI) | p value |
|--|------------------------|---------------------|---------|
| Sex | 1: Female | 1 | 0.021 |
| | 2: Male | 3.331 (1.184–7.717) | |
| Core amino acid 91 | 1: Leucine | 1 | 0.012 |
| | 2: Methionine | 3.393 (1.311–8.782) | |
| First therapy for hepatocellular carcinoma | 1: Radical therapy | 1 | 0.085 |
| | 2: Non-radical therapy | 2.500 (0.881–7.098) | |

Radical therapy includes operation, percutaneous ethanol injection, percutaneous microwave coagulation therapy, and radiofrequency ablation.

Non-radical therapy includes transcatheter artery embolization and conservative therapy.

Only variables that achieved statistical significance ($p < 0.05$) or marginal significance ($p < 0.10$) in a multivariate Cox proportional hazard model are shown.

Table 4. Factors associated with mortality in young patients with HCV genotype 1b infection using multivariate analysis

| Factors | Category | Odds ratio (95% CI) | p value |
|------------------------------|------------------------|---------------------|---------|
| First therapy | 1: Radical therapy | 1 | 0.002 |
| | 2: Non-radical therapy | 22.04 (3.175–153.0) | |
| AFP, $\mu\text{g/l}$ | 1: <21 | 1 | 0.021 |
| | 2: ≥ 21 | 4.507 (1.251–16.23) | |
| ALT, IU/l | 1: ≥ 51 | 1 | 0.045 |
| | 2: <51 | 3.401 (1.031–11.24) | |
| Fasting blood glucose, mg/dl | 1: <111 | 1 | 0.019 |
| | 2: ≥ 111 | 4.857 (1.295–18.21) | |
| Core amino acid 91 | 1: Leucine | 1 | 0.011 |
| | 2: Methionine | 6.091 (1.516–24.47) | |
| Tumor number | 1: Multiple | 1 | 0.084 |
| | 2: Solitary | 3.546 (0.845–14.95) | |

Radical therapy includes operation, percutaneous ethanol injection, percutaneous microwave coagulation therapy, and radiofrequency ablation.

Non-radical therapy includes transcatheter artery embolization and conservative therapy.

AFP = α -Fetoprotein; ALT = alanine aminotransferase.

Only variables that achieved statistical significance ($p < 0.05$) or marginal significance ($p < 0.10$) in a multivariate Cox proportional hazard model are shown.

brosis in elderly patients. A previous study reported that liver histology was a significant variable between elderly and young groups [12], but in the present study, liver histology was not a significant variable. The discrepancy between our result and that of the previous study may be due to two reasons. One reason may be the larger number of patients in this study than the previous study. The other

reason may be that preserved liver function, glucose and lipid metabolism suggested better liver histology in our study. To our knowledge, the present study is the first to report preservation of glucose and lipid metabolism in elderly HCC patients. Further studies of larger number of patients are required to determine more distinct differences between the two groups.

The viral factors associated with hepatocarcinogenesis in patients infected with HCV are still incompletely investigated, though some have been clarified in recent studies. Ogata et al. [28] reported that HCV genotype 1b strains might be associated with HCC based on the secondary structures of the amino-terminal portion of the HCV NS3 protein. Giménez-Barcons et al. [29] reported that high aa variability within the NS5A of HCV might be associated with HCC in patients with HCV-1b-related cirrhosis. Our previous study also reported that aa substitutions of the HCV-1b core region were important predictor of hepatocarcinogenesis [21, 22]. Whereas the association of viral factor and hepatocarcinogenesis has been gradually clarified, the association of viral factor and mortality has not been investigated. In the present study, substitutions of Met91 in the core region were associated with mortality of elderly HCV-1b patients after first treatment for HCC. In young HCV-1b-HCC patients, substitutions of Met91 and/or Gln70/His70 were also associated with mortality. To our knowledge, our study is the first to report that aa substitutions of the HCV-1b core region could be related to mortality after first treatment of HCC in elderly and young patients. Admittedly, we did not investigate the clinical impact of other virological factors on survival, except for HCV core region and NS5A-ISDR. Therefore, further studies should be performed to investigate the clinical impact of other viral regions of HCV on survival.

Previous studies identified substitutions in aa70 and/or aa91 in the HCV-1b core region and elevated AFP levels as predictors of poor virological response to peginterferon + ribavirin therapy [14–20], and also as risk factors and surrogate markers of hepatocarcinogenesis [21, 22]. Our study is the first to report that aa substitutions of core region are associated with mortality of elderly and young patients with HCV-1b-HCC. Especially Met91 in the core region was a significant factor of mortality in elderly patients. The reason might be the higher recurrence rate after radical treatment for elderly Met91 patients with first developed HCC (data not shown). A previous study reported that substitution of aa70 in the core region was a more important predictor of elevated AFP as a surrogate marker of hepatocarcinogenesis than that of aa91 [22]. However, in this study, substitution of aa70 (Gln70/His70) in the core region was not a significant variable of mortality in the elderly group. This discrepancy might be explained by the higher levels of malignant potentiality of substitution in aa70. Accordingly, because patients with Gln70/His70 in the core region had already developed HCC at a younger age, this might tend to decrease

the number of patients with Gln70/His70 in the elderly group and increase the number of patients with Met91 in the elderly group.

A previous study of low-dose intermittent IFN monotherapy showed that ALT normalization rates did not differ according to core aa substitutions, which is a poor response to peginterferon + ribavirin combination therapy and risk factor of hepatocarcinogenesis [30]. Thus, a low-dose intermittent IFN monotherapy for patients with aa substitutions (Met91 and/or Gln70/His70) is an efficacious therapeutic regimen for normalization of ALT and thus reduction of risk of hepatocarcinogenesis, and probably improvement of survival. Especially since female patients with Met91 and/or Gln70/His70 are a high-risk group of hepatocarcinogenesis when they age, such a group should receive low-dose intermittent IFN monotherapy to reduce the risk of hepatocarcinogenesis.

Previous studies examined patients with HCV and identified age, the extent of liver fibrosis, male sex, alcohol consumption, positivity for hepatitis B surface antigen, and high levels of AFP and γ -GTP as risk factors for hepatocarcinogenesis [31–38]. Furthermore, radical therapy improved survival of elderly HCV patients after first development of HCC [12]. In the present study, multivariate analysis in elderly patients with HCV-1b-related HCC identified viral factor (Met91), host factor (male sex), and therapeutic factor (non-radical therapy) as factors of mortality after treatment for HCC. Furthermore, in their young counterparts, multivariate analysis also identified viral factor (Met91), host factors (low levels of ALT and high levels of FBG), therapeutic factor (non-radical therapy), and tumor factors (high levels of AFP and solitary HCC) as factors of mortality. To our knowledge, this study is the first to report that viral factors are associated with mortality of HCV patients after first treatment for HCC. Further studies should be performed to investigate the association between virological factors and mortality of HCV patients.

The limitations of the present study were that it did not investigate dominant group of HCC (i.e., from 51 to 74 years of age), basic mechanism of association between aa substitutions of the core region and mortality, other genotypes apart from HCV-1b, the geographic diversities of HCV-1b core region, and the study of other races apart from Asians in Japan. Further prospective studies, matched for HCV genotype, aa substitutions of the core region, and race of a large group of patients are required to determine the association between viral factors and mortality.

In conclusion, the results of the present study compared the characteristics of elderly and young patients with HCV-related HCC and found that aa substitutions of the HCV-1b core region might be related to mortality

of patients after first treatment of HCC. This finding highlights the importance of low-dose intermittent IFN monotherapy in reducing the risk of hepatocarcinogenesis in this group of patients.

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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

Fumitaka Suzuki,¹ Norio Akuta,¹ Yoshiyuki Suzuki,¹ Hitomi Sezaki,¹ Hiromi Yatsuji,¹ Yusuke Kawamura,¹ Tetsuya Hosaka,¹ Masahiro Kobayashi,¹ Yasuji Arase,¹ Kenji Ikeda,¹ Rie Mineta,² Satomi Iwasaki,² Sachiyo Watahiki,² Mariko Kobayashi,² Yuzo Miyakawa³ and Hiromitsu Kumada¹

¹Department of Hepatology and ²Research Institute for Hepatology, Toranomon Hospital, Kawasaki City, and ³Miyakawa Memorial Research Foundation, Tokyo, Japan

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-naïve 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

Correspondence: Dr Fumitaka Suzuki, Department of Hepatology, Toranomon Hospital, 1-3-1, Kajigaya, Takatsu-ku, Kawasaki City 213-8587, Japan. Email: fumitakas@toranomon.gr.jp
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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/mm³ or less or platelet count of 100 000/mm³ 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, Kenilworth, NJ, USA) was injected s.c. at a median dose of 1.5 μ g/kg (range: 1.250–1.739 μ g/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/mm³, neutrophil count below 750/mm³ or platelet count below 80×10^3 /mm³; PEG-IFN was withdrawn when they decreased below 1000/mm³, 500/mm³ or 50×10^3 /mm³, 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-

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

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 ($\times 10^3/\text{mm}^3$) | 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.

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.

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

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-naïve 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 ($< 1.2 \log \text{ IU/mL}$) 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

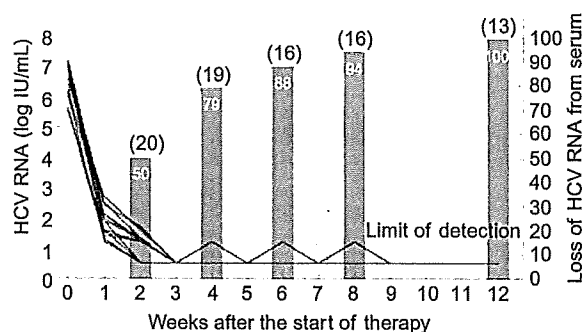


Figure 1 Dynamics of hepatitis C virus (HCV) RNA in the 20 patients with chronic hepatitis C during the triple treatment with telaprevir (MP-424), pegylated interferon (PEG-IFN) and ribavirin. The course of HCV RNA individual patients are indicated by lines, and loss of HCV RNA from serum by columns. 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 ($< 1.2 \log \text{ IU/mL}$).

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 $0.68 \pm 0.30 \log \text{ copies/mL}$, 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 ($\leq 40 \text{ IU/L}$) 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

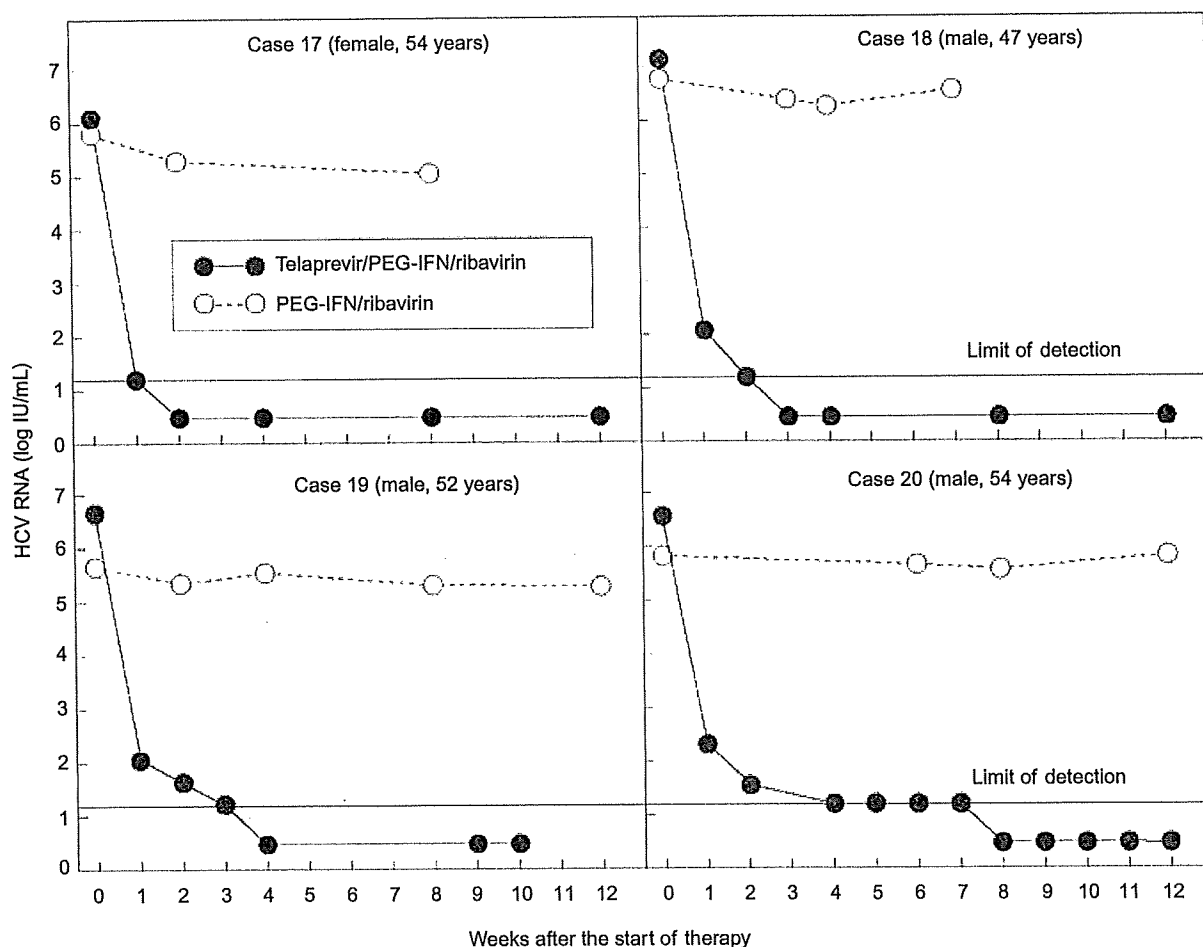


Figure 2 Dynamics of hepatitis C virus (HCV) RNA in non-responders to pegylated interferon (PEG-IFN) and ribavirin during the triple treatment. Black dots represent HCV RNA levels during the triple therapy, and open dots indicate HCV RNA levels during PEG-IFN and ribavirin they had received before.

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

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-naïve | 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-naïve 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-naïve 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) |

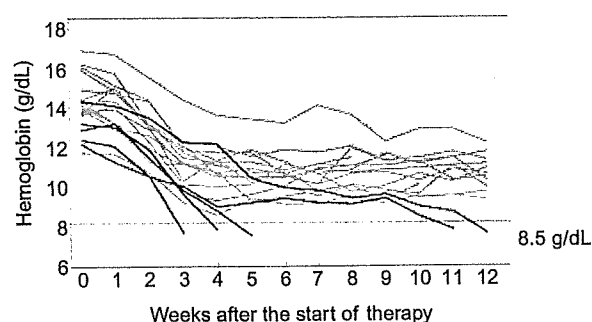


Figure 3 Levels of hemoglobin in the patients who received the triple treatment during 12 weeks. Black lines represent the patients in whom hemoglobin decreased below 8.5 g/dL and who were placed off the triple treatment at that point.

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 ($< 1.2 \log \text{ IU/mL}$) 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.

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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

MARIKO KOBAYASHI¹, FUMITAKA SUZUKI², NORIO AKUTA², YOSHIYUKI SUZUKI², HITOMI SEZAKI², HIROMI YATSUJI², YUSUKE KAWAMURA², TETSUYA HOSAKA², MASAHIRO KOBAYASHI², YASUJI ARASE², KENJI IKEDA², RIE MINETA¹, SATOMI IWASAKI¹, SACHIYO WATAHIKI¹, YUZO MIYAKAWA³ & HIROMITSU KUMADA²

¹Research Institute for Hepatology, ²Department of Hepatology, Toranomon Hospital, Tokyo, Japan, and ³Miyakawa Memorial Research Foundation, Japan

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-naïve patients aged ≥ 65 years with platelet counts $> 120 \times 10^3/\text{mm}^3$ 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

Correspondence: Mariko Kobayashi, BS, Research Institute for Hepatology, Toranomon Hospital, 1-3-1, Kajigaya, Takatsu-ku, Kawasaki City 213-8587, Japan. Tel: +81 44 8605 111. Fax: +81 44 8601 623. E-mail: vj7m-kbys@asahi-net.or.jp

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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 ≤ 40 IU/l (group A) and the 212 with ASAT and/or ALAT ≥ 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 ≥ 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 $< 120 \times 10^3/\text{mm}^3$ were excluded. The remaining 332 patients were classified into the 120 with ASAT and ALAT levels ≤ 40 IU/l (Group A) and the 212 with ASAT and/or ALAT levels ≥ 41 IU/l (group B); they included 22 patients (10.4%) with ASAT levels ≤ 40 IU/l and 18 (8.5%) with ALAT

levels ≤ 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 -fetoprotein (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).

Results

Treatment-naïve 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

HCC developing in the elderly infected with HCV 977

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 ($\times 10^3/\text{mm}^3$) | 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.

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 ($\times 10^3/\text{mm}^3$) | 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 ≥ 41 IU/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 transaminase 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 ($\times 10^3/\text{cm}^3$) | 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.

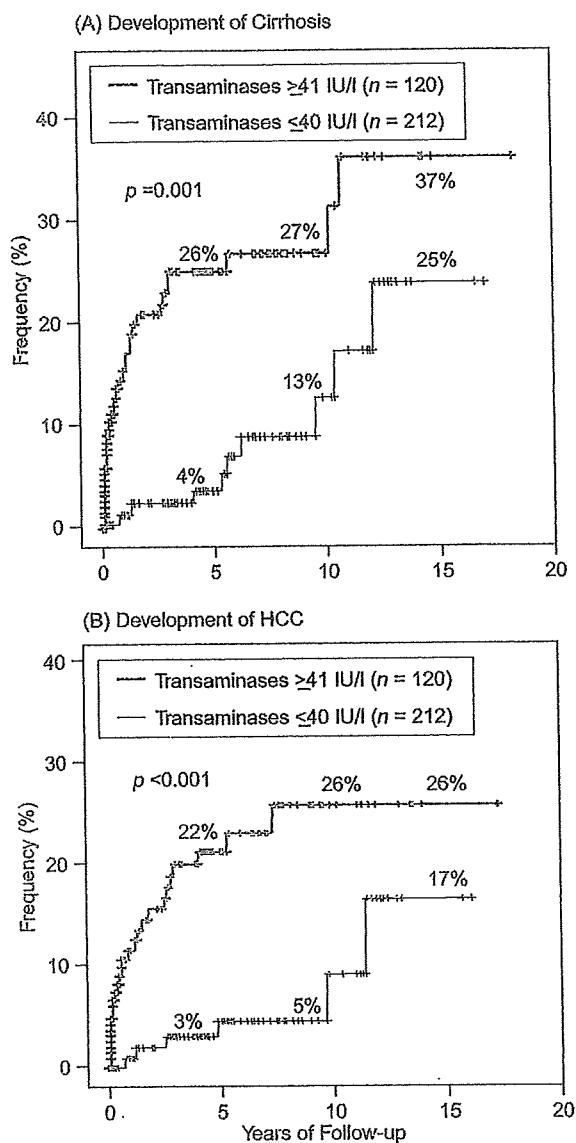


Figure 1. Development of cirrhosis (A) and HCC (hepatocellular carcinoma) (B) in patients over 65 years of age with chronic hepatitis C who were followed-up without receiving antiviral treatment. Patients with and without elevated baseline transaminase levels are compared.

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

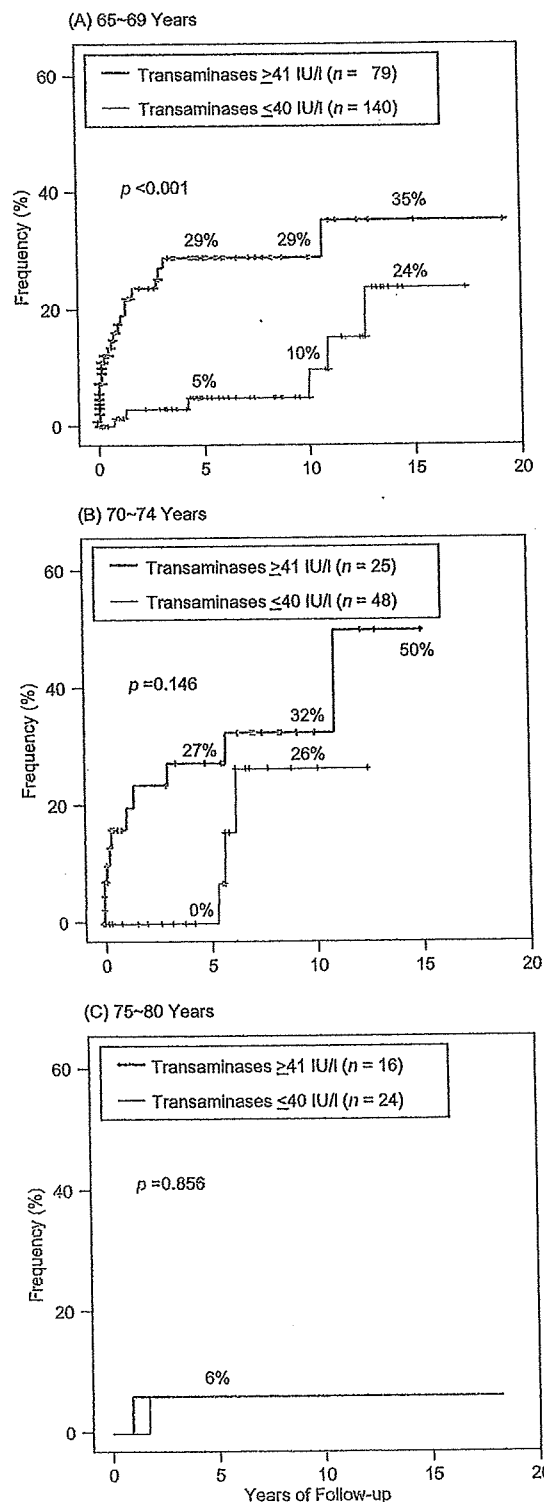


Figure 2. Development of cirrhosis in patients of more than 65 years of age with chronic hepatitis C who were followed-up without receiving antiviral treatment. Patients in different age groups are compared between those with and those without elevated transaminase levels.

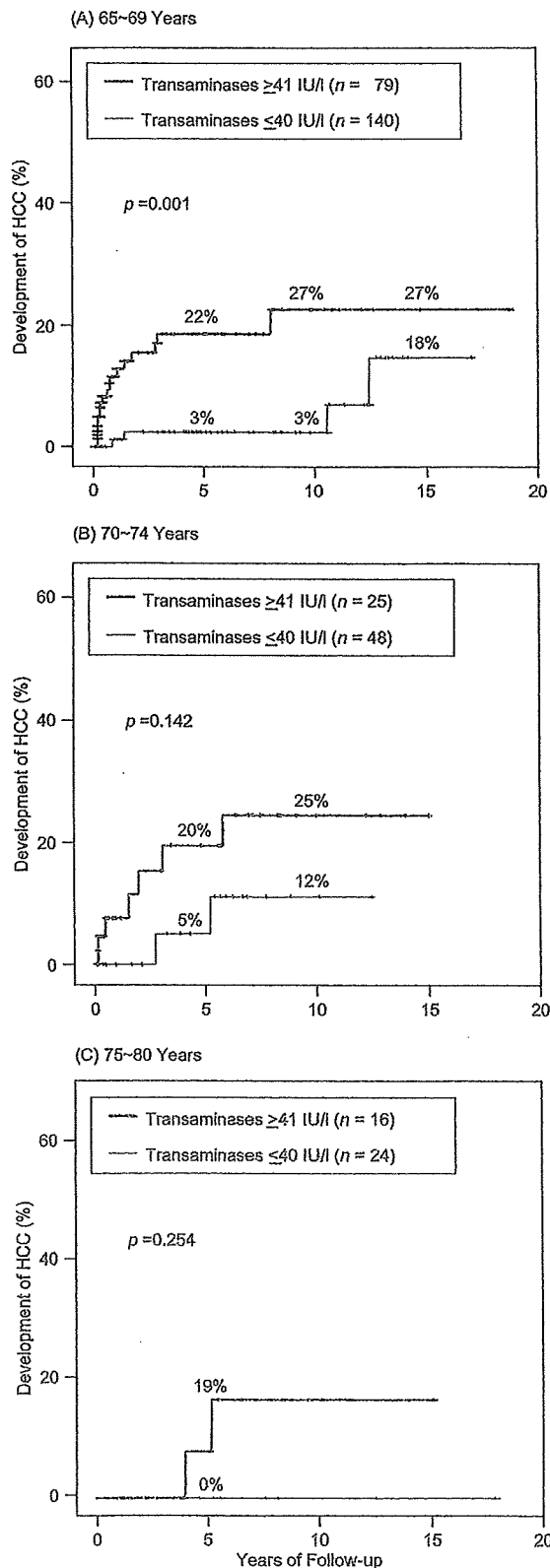


Figure 3 (Continued)

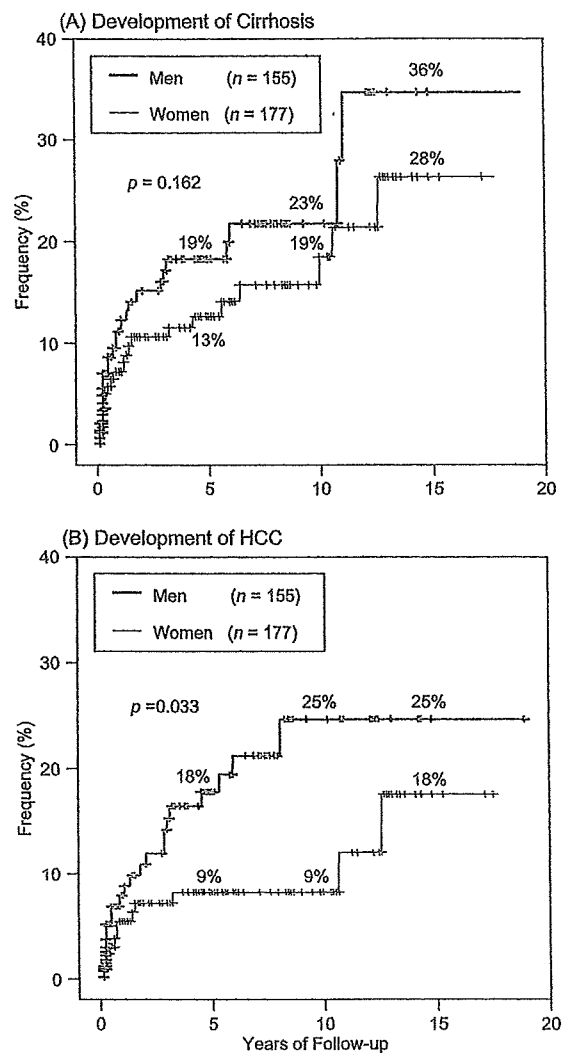


Figure 4. Development of cirrhosis (A) and HCC (hepatocellular carcinoma) (B) in patients over 65 years of age with chronic hepatitis C who were followed-up without receiving antiviral treatment. Male and female patients are compared.

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 hepatocellular 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.

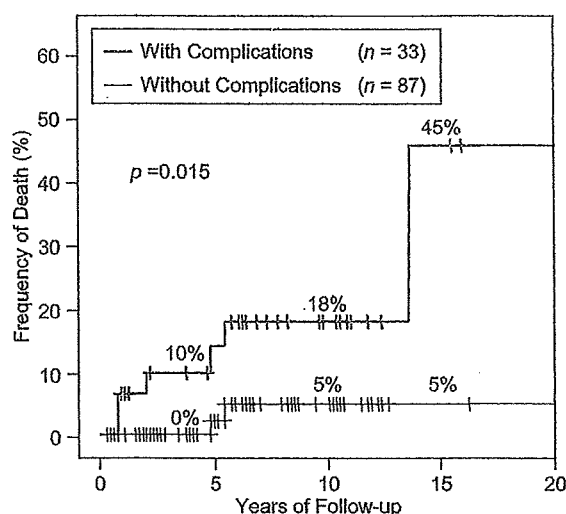


Figure 5. Deceased patients without elevated baseline transaminase levels (ASAT and ALAT < 40 IU/l). Patients with and without complications other than liver disease are compared.

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

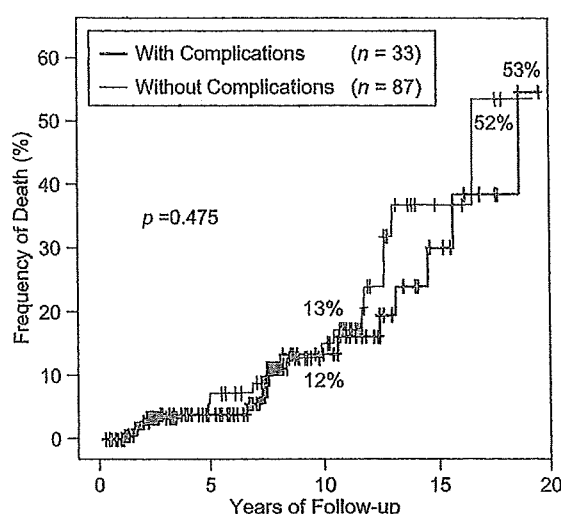


Figure 7. Deceased patients without elevated baseline transaminase levels (ASAT and ALAT < 40 IU/l). Patients with and without complications other than liver disease are compared.

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 sequelae to this, cirrhosis and HCC will continue to increase, demanding higher medical costs. In the USA already, HCV-related

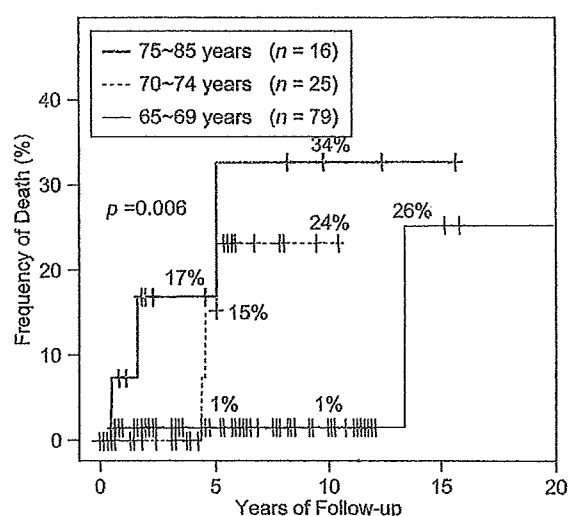


Figure 6. Deceased patients with elevated baseline transaminase levels (ASAT and/or ALAT > 41 IU/l). Patients in the different age groups are compared.

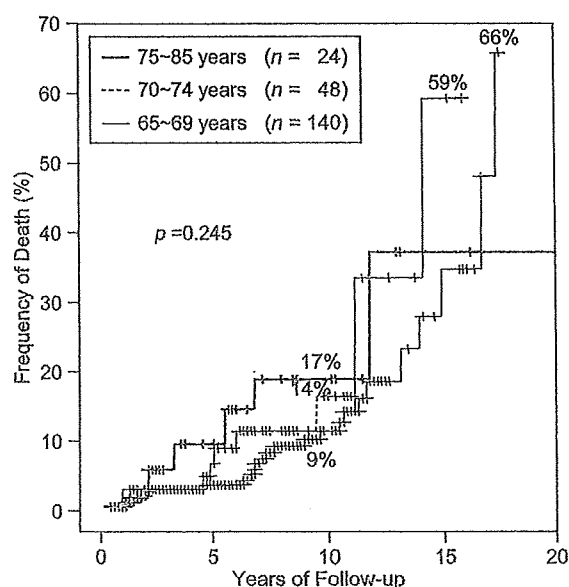


Figure 8. Deceased patients with elevated baseline transaminase levels (ASAT and/or ALAT > 41 IU/l). Patients in the different age groups are compared.