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ORIGINAL ARTICLE—LIVER, PANCREAS, AND BILIARY TRACT

A multicenter, open-label, dose-ranging study to exploratively evaluate the efficacy, safety, and dose–response of tolvaptan in patients with decompensated liver cirrhosis

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Abstract

Objectives We examined the efficacy of tolvaptan, an orally effective nonpeptide vasopressin V_2 receptor antagonist, in a Japanese clinical study in patients with intractable ascites and/or lower limb edema associated with decompensated liver cirrhosis.

Methods Tolvaptan was orally administrated at titrated doses of 15, 30, and 60 mg once daily after breakfast for 3 days at each dose to 18 liver cirrhosis patients with persistent ascites and/or lower limb edema despite receiving oral furosemide at 40 mg/day or higher.

Results Decreased body weight and abdominal circumference and improvement of ascites and edema were observed following tolvaptan administration beginning from 15 mg. Composite ascites/edema improvement rate was 88.2% at individual maximum doses and 64.7, 80.0, and 90.9%, respectively, after 3-day administration at 15, 30, and 60 mg. Changes in body weight after 3-day administration at 15, 30, and 60 mg were -1.6 ± 0.9, -2.6 ± 1.2, and -3.4 ± 2.1 kg (mean ± SD), respectively, and decreases of 1 kg or more were seen from day 2 (24 h after first dosing). Changes in abdominal circumference ranged from -2.8 to -6.0 cm. Cumulative 24-h urine

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volumes after 3-day administration at 15, 30, and 60 mg were, respectively, 3240.3 ± 1014.5, 3943.3 ± 1060.6, and 4537.4 ± 1621.3 mL/day (mean ± SD). Urine osmolarity was markedly decreased and remained decreased until the end of treatment.

Conclusion Tolvaptan dose-dependently decreased body weight and abdominal circumference and improved ascites and edema beginning from 15 mg, demonstrating a potent aquaretic effect.

Keywords Tolvaptan (OPC-41061) ·
Vasopressin V_2 receptor antagonist ·
Decompensated liver cirrhosis · Intractable ascites ·
Leg edema

Introduction

Arginine vasopressin (AVP) is a neuropeptide synthesized in the paraventricular and supraoptic nuclei of the hypothalamus, transported to the posterior pituitary gland, and released into the bloodstream [1]. AVP causes vasoconstriction via V_{1a} receptors and promotes water reabsorption in the kidney via V_2 receptors, the latter of which are primarily responsible for AVP's antidiuretic effects. Patients with various disorders, including liver cirrhosis and CHF, are at risk of excess water retention or inadequate water disposal due to increased AVP secretion.

Tolvaptan is a novel, orally effective, nonpeptide vasopressin V_2 receptor antagonist developed by Otsuka Pharmaceutical Company [2, 3]. Tolvaptan selectively blocks the binding of vasopressin to V_2 receptors, thus inhibiting water reabsorption in the renal collecting ducts [2] and promoting the excretion of urine with no increase in electrolyte excretion (i.e., aquaresis) and no negative impact on renal function [4]. Unlike peptide V_2 receptor antagonists, tolvaptan possesses no intrinsic agonist activity [2]. Tolvaptan was approved by the United States Food and Drug Administration (US FDA) on 19 May 2009 for the treatment of clinically significant hypervolemic and euvolemic hyponatremia (serum sodium <125 mEq/L, or less marked hyponatremia that is symptomatic and has resisted correction with fluid restriction), including in patients with SIADH, heart failure, and cirrhosis.

Ascites and lower limb edema are commonly associated with decompensated liver cirrhosis. Ascites is caused by obstruction of hepatic lymph drainage, portal hypertension, and hypoproteinemia, and is often intractable. While there are various hypotheses regarding the mechanism of occurrence of ascites secondary to liver cirrhosis [5–8], they are all characterized by a relative decrease in circulating blood volume despite an increase in body fluid

associated with water and sodium retention and by hypoalbuminemia due to impaired albumin synthesis. Treatment for intractable edema often involves the use of loop diuretics such as furosemide. However, administration of loop diuretics can lead to impaired renal function, decreased glucose tolerance, and electrolyte abnormalities such as hyponatremia and hypokalemia. Unlike the loop diuretic furosemide, tolvaptan exerts its aquaretic effect by acting on the V_2 receptors in the blood vessels rather than those in the renal tubules, and it is therefore unaffected by decreased tubular secretion and urine albumin level. When administered in combination with furosemide, tolvaptan further increases urine volume and serum osmolarity due to its aquaretic effect [9], thus enabling excess fluid to be removed from intercellular gaps. Furthermore, because tolvaptan does not increase electrolyte excretion [4], it can be administered to patients with low serum electrolyte levels.

Thus, tolvaptan in combination with conventional diuretic therapy is expected to promote further diuretic effect and to improve ascites and edema without inducing electrolyte imbalance in patients whose ascites or edema is not improved by treatment with conventional diuretic therapy alone, or in whom conventional diuretics cannot be administered at higher doses or in combination due to the risk of decreased serum electrolyte levels.

In this study, in order to examine the efficacy of tolvaptan in improving ascites and edema by concomitant use with conventional diuretics, we administered tolvaptan to patients who had persistent ascites (diagnosed by ultrasonography) and/or lower limb edema secondary to liver disease despite their use of the conventional diuretic furosemide.

Methods

Subjects

Over a period from 2004 to 2005, 8 study sites and 18 subjects participated in this study conducted in Japan. Of the 18 subjects who received tolvaptan, 17 were included in efficacy analysis, and one subject was excluded due to a deviation from the study protocol (violation of concomitant medication use). Of the 17 subjects included in the efficacy analysis, 17 received 3-day administration of tolvaptan at 15 mg, 15 received 3-day administration at the titrated dose of 30 mg, and 11 received 3-day administration at the titrated dose of 60 mg. All 18 subjects who received tolvaptan were included in the safety analysis.

Demographics and other baseline characteristics are shown in Table 1.

Table 1 Baseline characteristics of subjects included in efficacy analysis

Number of subjects	17
Age (years)[a]	57.6 ± 7.1
Sex (male/female) (n)	14/3
Body weight (kg)[b]	60.69 ± 9.99
Liver disease (cirrhosis) (n)	
Hepatitis B	4
Hepatitis C	6
Alcoholic cirrhosis	5
Primary biliary cirrhosis	1
Other	1
Food restriction [n (%)]	10 (58.8)
Encephalopathy [n (%)]	0 (0.0)
Liver cancer [n (%)]	6 (35.3)
Diabetes mellitus [n (%)]	8 (47.1)
Varicose veins [n (%)]	15 (88.2)

[a] Mean ± SD

[b] At time of screening examination, mean ± SD

Criteria for eligibility

Patients between 20 and 69 years of age who had persistent ascites and/or lower limb edema despite their use of oral furosemide at a dose of 40 mg/day or higher were eligible for enrollment in the study. Subjects were either hospitalized patients or patients who could be hospitalized for the entire study period from the start of the pretreatment observation period until completion of the end-of-treatment examination.

The main exclusion criteria were: (1) complication of: (a) hepatic encephalopathy (Inuyama classification [10] grade II or higher), (b) poorly controlled hepatocellular carcinoma (with imaging-based diagnosis of vascular infiltration of main portal vein, first branch of portal vein, inferior vena cava, or main hepatic vein), (c) esophageal or gastric varices (endoscopic findings within 1 month prior to screening indicating the need for therapy), (d) diabetes mellitus with poorly controlled blood glucose, (e) heart failure (NYHA class III or IV), (f) anuria (urine volume of 100 mL/day or less), (g) impaired urination, or (h) hyponatremia (serum Na <120 mEq/L); (2) body mass index exceeding 35; (3) clinical laboratory values of: (a) hemoglobin <9.0 g/dL, (b) total bilirubin >3.0 mg/dL, (c) serum creatinine >2.0 mg/dL, (d) serum sodium >147 mEq/L, (e) serum potassium >5.5 mEq/L, (f) or prothrombin time <30% (if not using activity ratio, prolonged by 5 s or more above upper limit of normal range or vs. the control value); and (4) patients who had used blood products, including albumins, within 7 days prior to the start of tolvaptan administration.

All patients gave written informed consent to participate in the study, and the study was approved by the institutional review board (IRB) of each study site.

Treatment protocol

The study consisted of a pretreatment observation period and a treatment period. The pretreatment observation period began 3 days prior to the start of tolvaptan administration, and from that time the dosage regimen of the conventional diuretics being used was fixed until completion of the end-of-treatment examination. Of 19 enrolled subjects, 18 subjects whose fluid volume expansion status (change in body weight) showed no or little change (change of within ±1.0 kg in pre-breakfast body weight from day 2 to day 3 of pretreatment observation period) during the pretreatment observation period were eligible to advance to the treatment period. One subject was judged to be ineligible to advance to the treatment period due to excessive weight decrease during the pretreatment observation period. During the treatment period, tolvaptan was orally administered once daily after breakfast in combination with the fixed regimen of conventional diuretics, including furosemide, and administration of tolvaptan was continued in a dose-titration manner until either ascites (as verified by ultrasonography) and lower limb edema symptoms disappeared or administration at the highest dose was completed.

Administration of tolvaptan was initiated at 15 mg/day and assessment was performed after 3 days to determine whether or not to titrate. If ascites and edema disappeared after 3-day repeated administration at 15 mg/day, administration was stopped. If ascites or edema persisted, the dose of tolvaptan was titrated to 30 mg/day and administration was continued for another 3 days, after which the same procedure was repeated for titration to 60 mg/day. The maximum dose was set at 60 mg/day and each dose was administered for 3 days only, for a maximum total administration period of 9 days.

The end-of-treatment examination in each subject was performed on the day following the final tolvaptan administration. A follow-up assessment was performed at 7–10 days after the final tolvaptan administration.

The primary efficacy endpoint for this study was composite ascites/edema improvement rate. Secondary efficacy endpoints were change in body weight, change in abdominal circumference, ascites improvement rate, lower limb edema improvement rate, and ascites/edema resolution rate.

Improvement of ascites was defined as a decrease of at least 2 cm in abdominal circumference. Improvement of lower limb edema was determined based on the difference in edema severity assessment between before and after administration according to 4 grades: (1) "none"—no observable pitting; (2) "mild"—barely visible pitting; (3) "moderate"—observable pitting; and (4) "severe"—obvious edema at first sight.

The grading criteria for determining improvement of ascites were: "improved" abdominal circumference decreased by 2 cm or more; "unchanged" change in abdominal circumference of less than 2 cm; "worsened" abdominal circumference increased by 2 cm or more or emergence of ascites. The grading criteria for determining improvement of lower limb edema were: "markedly improved"—resolution or improvement by 2 grades or more; "improved"—improvement by one grade; "unchanged"—symptoms unchanged or no symptoms at baseline; "worsened"—worsened by one grade or more.

The improvement rate for each symptom was calculated as: (number of subjects with a grading of "improved" or "markedly improved")/(number of subjects with corresponding symptom) × 100. The composite ascites/edema improvement rate combined the ascites improvement rate and the lower limb edema improvement rate.

The ascites/edema resolution rate was defined as the percentage of subjects who had ascites and/or edema at baseline and whose ascites and edema were confirmed by the investigator to be resolved at the time of physical examination. Ascites/edema resolution rate was calculated as: (number of subjects who showed resolution of ascites and edema)/(number of subjects included in efficacy analysis) × 100 (Table 3).

Pharmacodynamic endpoints were cumulative 24-h urine volume, urine osmolarity, serum sodium level, and plasma AVP level.

Statistical analysis

In the analysis of the primary efficacy endpoint, for subjects with ascites and/or lower limb edema at baseline (day −1), the point estimate and two-sided 95% confidence interval for the composite ascites/edema improvement rate at individual maximum doses were determined.

In the analysis of secondary efficacy endpoints, for change in body weight and abdominal circumference, the mean and standard deviation of the amount of change and of the percent change from baseline (day 1) at each postdose time point were calculated and a t test was performed at baseline and at each postdose time point. For subjects with ascites/edema at baseline (day −1), the point estimate

and two-sided 95% confidence interval for the ascites/edema resolution rate were determined.

For analysis of pharmacodynamic endpoints, for cumulative 24-h urine volume, urine osmolarity, and plasma AVP level, the mean and standard deviation of the percent change from baseline (day −1 or day 1) at each postdose time point were calculated and a t test was performed at baseline and at each postdose time point.

Results

Pharmacodynamic assessment

The aquaretic action of tolvaptan significantly increased urine volume at all postdose measurement time points compared with the baseline (1445 ± 420 mL/day), with cumulative 24-h urine volumes of 3240.3 ± 1014.5, 3943.3 ± 1060.6, and 4537.4 ± 1621.3 mL/day (mean ± SD) following 3-day repeated administration at 15, 30, and 60 mg, respectively, indicating a dose-dependent diuretic effect throughout the treatment period (Fig. 1).

Administration of tolvaptan also significantly decreased urine osmolarity (Fig. 2) and increased serum sodium level (Fig. 3) and plasma AVP level (Fig. 4) at all postdose measurement time points compared with the baseline.
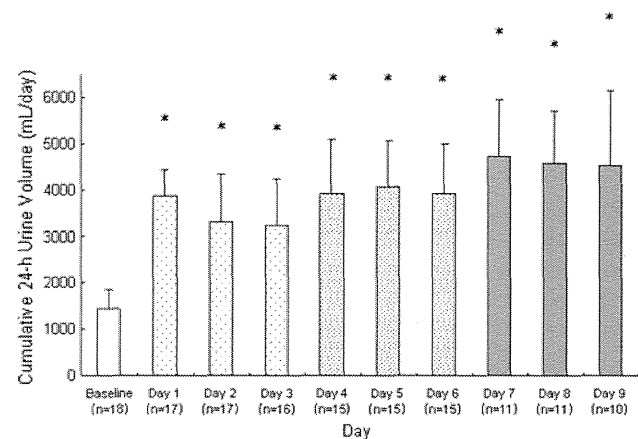

Fig. 1 Cumulative 24-h urine volume (mean ± SD). Urine was cumulatively collected during the 24-h period after each dosing (15 mg on days 1 through 3, 30 mg on days 4 through 6, and 60 mg on days 7 through 9). Statistically significant (*$P < 0.05$) increases in urine volume compared with the baseline were observed at all measurement time points following the start of tolvaptan administration. Urine volume was markedly increased from the first day of administration at 15 mg, and remained increased until the final administration at that dose. In addition, further increases in urine volume were observed with dose titration from 15 to 30 mg and again with dose titration from 30 to 60 mg
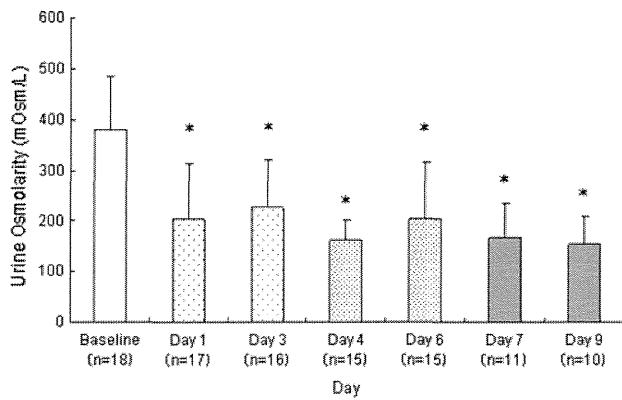
Fig. 2 Urine osmolarity (mean ± SD). Urine osmolarity was measured at 24 h after each dosing (15 mg on days 1 through 3, 30 mg on days 4 through 6, and 60 mg on days 7 through 9). Statistically significant (*$P < 0.05$) decreases in urine osmolarity compared with the baseline were observed at all measurement time points following the start of tolvaptan administration. Urine osmolarity was markedly decreased from the first day of administration at 15 mg, and remained decreased until completion of treatment
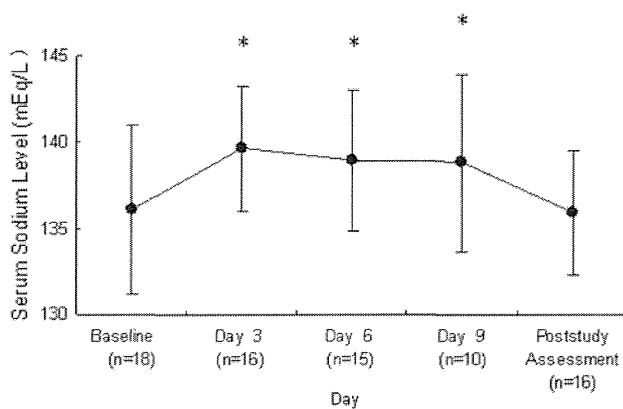

Fig. 3 Serum sodium level (mean ± SD). Serum sodium level was measured at 24 h after the final dosing of 3-day repeated oral administration at each dose (15 mg on days 1 through 3, 30 mg on days 4 through 6, and 60 mg on days 7 through 9). Statistically significant (*$P < 0.05$) increases in serum sodium level compared with the baseline were observed at all measurement time points following the start of tolvaptan administration at 15 mg on day 1. The increased serum sodium level showed a tendency to return to the baseline level after completion of treatment

Efficacy of tolvaptan against intractable ascites and edema

Decreases in body weight and abdominal circumference and improvement of ascites and lower limb edema were observed following administration of tolvaptan beginning from 15 mg. Decreases in mean body weight of 1 kg or more were seen from Day 2 (24 h after first dosing). Changes in body weight following 3-day repeated administration at 15, 30, and 60 mg were, respectively, −1.6 ± 0.9, −2.6 ± 1.2, and −3.4 ± 2.1 kg (mean ± SD),
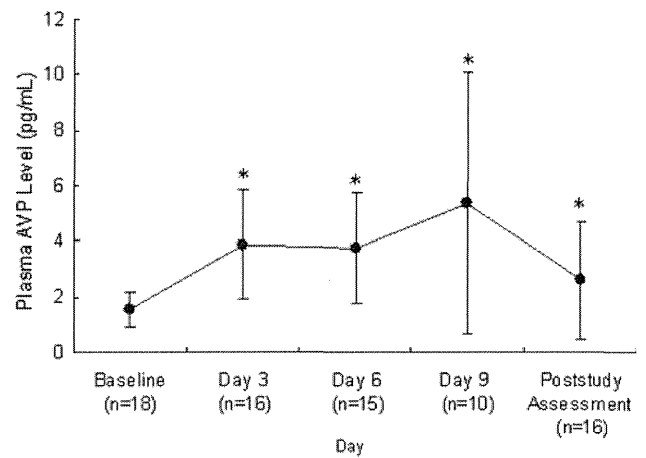

Fig. 4 Plasma AVP level (mean ± SD). Plasma AVP level was measured at 24 h after the final dosing of 3-day repeated oral administration at each dose (15 mg on days 1 through 3, 30 mg on days 4 through 6, and 60 mg on days 7 through 9). Statistically significant (*$P < 0.05$) increases in plasma AVP level compared with the baseline were observed at all measurement time points following the start of tolvaptan administration at 15 mg on day 1. The increased plasma AVP level showed a tendency to return to the baseline level after completion of treatment
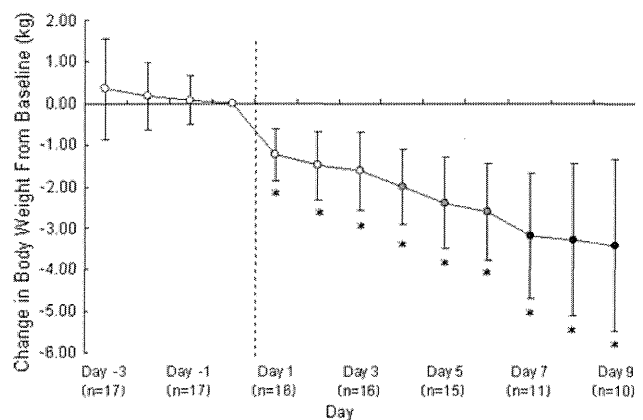

Fig. 5 Change in body weight from baseline (mean ± SD). Body weight was measured at 24 h after each dosing (15 mg on days 1 through 3, 30 mg on days 4 through 6, and 60 mg on days 7 through 9), and changes from the baseline were calculated. Although body weight showed almost no decrease during the pretreatment observation period, statistically significant (*$P < 0.05$) decreases compared with the baseline were observed from the start of tolvaptan administration at 15 mg on day 1. Body weight continued to gradually decrease until the final administration, at which time a statistically significant (*$P < 0.05$) difference from the baseline was observed

and body weight at all postdose measurement time points was significantly decreased compared with the baseline (Fig. 5). As was observed for body weight, decreases in mean abdominal circumference were also observed following tolvaptan administration, with statistically significant differences from the baseline seen at all postdose measurement time points (Fig. 6).
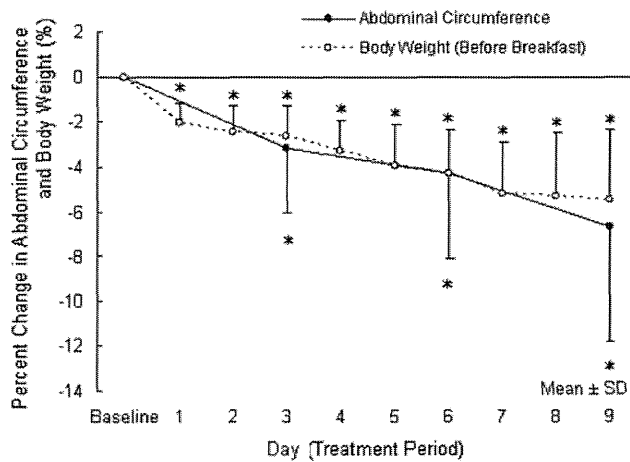
Fig. 6 Time courses of percent change in body weight and abdominal circumference from baseline (mean ± SD). Body weight and abdominal circumference were measured at 24 h after each dosing (15 mg on days 1 through 3, 30 mg on days 4 through 6, and 60 mg on days 7 through 9), and percent change from the baseline was calculated. Both body weight and abdominal circumference showed dose-dependent percent decreases from the baseline with administration of tolvaptan, and statistically significant (*$P < 0.05$) percent decreases from the baseline were observed at all measurement time points

At individual maximum doses, the ascites improvement rate was 87.5% (14 of 16 subjects) and the lower limb edema improvement rate was 83.3% (5 of 6 subjects). The composite ascites/edema improvement rate (primary efficacy endpoint) was 88.2% (15 of 17 subjects) at individual maximum doses or at discontinuation of administration (Table 2a), and 64.7, 80.0, and 90.9%, respectively, after 3-day administration at 15, 30, and 60 mg (Table 2b). In addition, the ascites/edema resolution rate at individual maximum doses was 41.2% (7 of 17 subjects) (Table 3).

Dose–response in this study was evaluated based on the results for changes in cumulative 24-h urine volume, body weight, and abdominal circumference and for improvement of ascites/edema. Regarding body weight, a further body weight decrease of 500 g or more was seen in 8 of 15 subjects following dose titration from 15 to 30 mg/day and in 6 of 11 subjects following dose titration from 30 to 60 mg/day. Decreases in body weight were greater on the first day of administration after dose titration than on the second and third days of administration at the same dose. Regarding abdominal circumference, a further abdominal circumference decrease of 2 cm or more was seen in 7 of 15 subjects following dose titration from 15 to 30 mg/day and in 4 of 11 subjects following dose titration from 30 to 60 mg/day. Of the 7 subjects in whom ascites was not improved (abdominal circumference decrease of less than 2 cm) by 3-day repeated administration at 15 mg/day, 5 subjects showed improvement or resolution of ascites following dose

titration to 30 mg/day. Regarding improvement of ascites/edema, although 6 of 17 subjects were assessed as "unchanged" at 15 mg/day, 4 of those 6 subjects showed improvement following dose titration to 30 mg/day. In addition, 2 of 3 subjects assessed as "unchanged" at 30 mg/day showed improvement of ascites/edema following dose titration to 60 mg/day (Fig. 7).

Safety evaluation

Following administration of tolvaptan in a dose-titration manner (15–60 mg/day) to subjects with ascites and/or lower limb edema associated with decompensated liver cirrhosis, adverse events were observed in all 18 subjects who received tolvaptan, for a total of 69 episodes. However, most of the events were considered to have been due either to the pharmacological action of tolvaptan or to the underlying disease. Adverse events observed in 2 or more subjects during the study are summarized in Table 4. Most of the adverse events were observed following administration at 15 mg, and the incidence of adverse events did not increase with dose titration. The most frequently reported adverse events, occurring in 3 subjects or more, were thirst, pollakiuria, insomnia, and increased blood uric acid. No noteworthy changes in clinical laboratory values (hematocrit and hemoglobin), blood pressure, or ECG were observed. In particular, as shown in Table 5, no increases in blood pressure were observed.

Adverse events judged to be adverse drug reactions (i.e., potentially study-related) were also observed in all 18 subjects who received tolvaptan, for a total of 53 episodes. Four serious adverse events (anal fistula, esophageal varices, hepatic neoplasm malignant, and hepatic encephalopathy) were observed in one subject each, and relationship to tolvaptan could not be denied for the anal fistula observed in one subject during 3-day repeated administration at 60 mg. It was confirmed at the poststudy follow-up assessment that all adverse drug reactions were either recovered or ameliorated. Discontinuation of tolvaptan administration or dose reduction was not required in any subject. No adverse events were attributable to aggravation of the underlying disease by administration of tolvaptan in patients with decompensated liver cirrhosis.

Discussion

Although tolvaptan had previously been shown to improve volume expansion in patients with heart failure [11–13] and to raise serum sodium level in cases of hyponatremia [14], its effects on ascites and edema of the extremities

Table 2 Improvement rates at (a) individual maximum doses and (b) each dose

	Grading				Total	Improvement rate (%)[a]	Two-sided 95% CI
	Markedly Improved	Improved	Unchanged	Worsened			
(a)							
Ascites[b]	–	14	2	0	16	87.5	61.7–98.4
Lower limb edema[c]	5	0	1	0	6	83.3	35.9–99.6
Composite ascites/edema[d]	4	11	2	0	17	88.2	63.6–98.5
(b)							
Ascites[b]							
15 mg Day 3	–	9	7	0	16	56.3	
30 mg Day 6	–	12	3	0	15	80.0	
60 mg Day 9	–	10	1	0	11	90.9	
Lower limb edema[c]							
15 mg Day 3	3	0	3	0	6	50.0	
30 mg Day 6	4	1	0	0	5	100.0	
60 mg Day 9	2	0	1	0	3	66.7	
Composite ascites/edema[d]							
15 mg Day 3	1	10	6	0	17	64.7	38.3–85.8
30 mg Day 6	5	7	3	0	15	80.0	51.9–95.7
60 mg Day 9	2	8	1	0	11	90.9	58.7–99.8

[a] Improvement rate = (number of subjects with grading of improved or markedly improved)/(total number of subjects with corresponding symptom) × 100

[b] Grading criteria for ascites: improved = abdominal circumference decreased by 2 cm or more; unchanged = change in abdominal circumference of less than 2 cm; worsened = abdominal circumference increased by 2 cm or more or emergence of ascites

[c] Grading criteria for lower limb edema: markedly improved = resolution or improvement by 2 grades or more; improved = improvement by one grade; unchanged = symptoms unchanged or no symptoms at baseline; worsened = worsened by one grade or more [severity grades: (1) none = no observable pitting; (2) mild = barely visible pitting; (3) moderate = observable pitting; (4) severe = obvious edema at first sight]

[d] Grading criteria for composite ascites/edema: markedly improved = improved for ascites and markedly improved or improved for lower limb edema; improved = unchanged for ascites and markedly improved or improved for lower limb edema; unchanged = unchanged for both ascites and lower limb edema; worsened = worsened for either ascites or lower limb edema

Table 3 Ascites/edema resolution rate at individual maximum doses

Resolved	Not resolved	Total	Resolution rate (%)	Two-sided 95% CI
7	10	17	41.2	18.4–67.1

Ascites/edema resolution rate = (number of subjects resolved)/(total number of subjects) × 100

Fig. 7 Changes in composite ascites/edema improvement gradings. Composite ascites/edema improvement was assessed by the investigator after the final dosing of 3-day repeated oral administration at each dose (15 mg on days 1 through 3, 30 mg on days 4 through 6, and 60 mg on days 7 through 9). Four of six subjects assessed as "unchanged" at 15 mg/day were assessed as "improved" or "markedly improved" following dose titration to 30 mg/day, and 2 of 3 subjects assessed as "unchanged" at 30 mg/day were assessed as "improved" or "markedly improved" following dose titration to 60 mg/day, with some subjects showing further improvement with each dose titration. *Numbers in parentheses* indicate number of subjects

associated with decompensated liver cirrhosis remained to be explored.

In the present study, we administered tolvaptan as add-on therapy to decompensated liver cirrhosis patients with ascites and/or lower limb edema that was resistant to conventional diuretics. We evaluated efficacy based on changes in body weight, abdominal circumference, daily urine volume, and the severity of lower leg edema, all of which are commonly used parameters for assessing hypervolemia associated with decompensated liver cirrhosis.
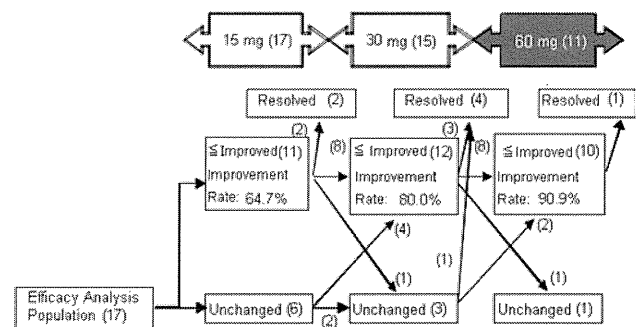
Table 4 Summary of adverse events

Item	Tolvaptan 15–60 mg $(N = 18^a)$ n (%)
Adverse events occurring during study (all causes)	18 (100)
Serious adverse events[b]	4 (22.2)
Adverse drug reactions occurring during study	18 (100)
Serious adverse events judged to be adverse drug reactions[c]	1 (5.6)
Adverse events (all causes) by body system and MedDRA preferred term[d]	
Gastrointestinal disorders	
Constipation	2 (11.1)
Esophageal varices	2 (11.1)
General disorders and administration site conditions	
Thirst	15 (83.3)
Malaise	2 (11.1)
Pyrexia	2 (11.1)
Investigations	
Blood uric acid increased	3 (16.7)
Blood glucose increased	2 (11.1)
Metabolism and nutrition disorders	
Anorexia	2 (11.1)
Psychiatric disorders	
Insomnia	4 (22.2)
Renal and urinary disorders	
Pollakiuria	8 (44.4)
Skin and subcutaneous tissue disorders	
Dry skin	2 (11.1)

[a] All subjects who received at least one dose of the study medication (tolvaptan) were included in safety analysis

[b] All-cause serious adverse events occurring during the study were anal fistula, esophageal varices, hepatic neoplasm malignant, and hepatic encephalopathy in one subject each

[c] The only serious adverse event judged to be an adverse drug reaction (i.e., potentially study-related) was anal fistula in one subject

[d] Adverse events occurring in 2 or more subjects are listed

A marked decrease in body weight accompanying increased urine volume was observed soon after the start of administration of tolvaptan, which has a vasopressin V_2 receptor blocking action. Similar to the effects previously seen in patients with heart failure, in the present study administration of tolvaptan also improved ascites and pitting edema (signs indicating hypervolemia) in patients with decompensated liver cirrhosis.

Serum sodium level was also increased following administration of tolvaptan, as was seen in heart-failure patients and cases of hyponatremia. This increase in serum sodium level is considered to be due to an increase in urine volume induced by tolvaptan's vasopressin V_2 receptor antagonist action. As rapid elevation of serum sodium can cause central pontine myelinolysis (CPM), any increase in serum sodium level should not exceed 12 mmol/L within a 24-h period [15, 16]. No complications of CPM or hypernatremia have been observed in clinical studies of tolvaptan.

Although plasma AVP level also increased during administration of tolvaptan, it subsequently decreased after completion of treatment. This increase in plasma AVP was probably due to an increase in plasma osmotic pressure rather than to any decrease in plasma volume, since

hematocrit and hemoglobin values remained unchanged after administration of tolvaptan, indicating that a decrease in plasma volume was unlikely. In addition to promoting the reabsorption of water in the kidney via vasopressin V_2 receptors, AVP also induces vasoconstriction via vasopressin V_1 receptors, resulting in an increase in blood pressure. While increased blood pressure can lead to the rupture of esophageal varices, no variceal bleeding was observed in this study, indicating that tolvaptan would be safe for the treatment of hypervolemia as a complication of decompensated liver cirrhosis. Although thirst is a common adverse drug reaction seen with tolvaptan, in the present study thirst was improved by allowing free access to drinking water.

The results of this study demonstrated that tolvaptan exerted a dose-dependent aquaretic effect in patients with furosemide-resistant intractable ascites and/or edema. Most of the adverse events reported were predictable based on tolvaptan's known pharmacological action, and dose titration to 60 mg was well tolerated, with no discontinuations due to adverse events.

In conclusion, based on current study data, tolvaptan is considered to be a safe and effective agent for the treatment of chronic liver failure patients with ascites and/or pitting

Table 5 Blood pressure values

Item (unit)	Time point	N	Mean	SD
Systolic blood pressure (mmHg)	Day 1 predose	18	110.5	16.6
	2–4 h postdose	17	108.2	12.4
	6–8 h postdose	18	110.2	12.1
	Day 2	17	109.4	13.7
	Day 3	17	108.9	15.2
	Day 4 predose	17	107.3	16.0
	2–4 h postdose	15	109.1	13.9
	6–8 h postdose	16	105.0	15.9
	Day 5	15	109.5	12.7
	Day 6	15	106.7	12.3
	Day 7 predose	15	108.3	14.2
	2–4 h postdose	11	106.6	10.0
	6–8 h postdose	11	105.5	8.2
	Day 8	11	104.8	11.1
	Day 9	11	104.7	14.6
	Day 10	10	105.8	12.1
Diastolic blood pressure (mmHg)	Day 1 predose	18	68.1	7.6
	2–4 h postdose	17	65.3	9.5
	6–8 h postdose	18	67.0	7.3
	Day 2	17	66.4	7.9
	Day 3	17	67.4	4.7
	Day 4 predose	17	68.1	13.0
	2–4 h postdose	15	65.3	9.0
	6–8 h postdose	16	65.6	9.7
	Day 5	15	68.2	8.7
	Day 6	15	67.1	8.1
	Day 7 predose	15	68.4	9.2
	2–4 h postdose	11	69.3	10.5
	6–8 h postdose	11	69.9	6.7
	Day 8	11	66.4	8.9
	Day 9	11	63.4	4.9
	Day 10	10	68.6	5.9

edema that is resistant to powerful diuretics such as furosemide. We also concluded that continued investigation in a parallel-group comparison study is needed to further clarify the drug's efficacy.

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Indications and limitations for aged patients with chronic hepatitis C in pegylated interferon alfa-2b plus ribavirin combination therapy

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Background & Aims: This study investigated the efficacy and adverse effects of pegylated interferon (Peg-IFN) plus ribavirin therapy in aged patients with chronic hepatitis C (CH-C).
Methods: A total of 1040 naïve patients with CH-C (genotype 1, n = 759; genotype 2, n = 281), of whom 240 (23%) over 65 years old (y.o.), were treated with Peg-IFN alfa-2b plus ribavirin and assessed after being classified into five categories, according to age.
Results: The discontinuance rate was higher for patients over 70 y.o. (36%), the most common reason being anemia. In the presence of genotype 1, the SVR rate was similar (42–46%) among patients under 65 y.o. and declined (26–29%) among patients over 65 y.o. For patients over 65 y.o., being male (Odds ratio, OR, 3.5, p = 0.035) and EVR (OR, 83.3, p <0.001) were significant factors for SVR, in multivariate analysis. The Peg-IFN dose was related to EVR, and when EVR was attained, 76–86% of patients over 65 y.o. achieved SVR. SVR was not achieved (0/35, 0/38, respectively) if a 1-log decrease and a 2-log decrease were not attained at week 4 and week 8, respectively. In the presence of genotype 2, the SVR rate was similar (70–71%) among patients under 70 y.o. and declined among patients over 70 y.o. (43%).

Conclusions: Aged patients up to 65 y.o. with genotype 1 and 70 y.o. with genotype 2 can be candidates for Peg-IFN plus ribavirin therapy. The response-guided therapy can be applied for aged patients with genotype 1.

Introduction

Pegylated interferon (Peg-IFN) plus ribavirin combination therapy has led to a marked progress in the treatment of chronic hepatitis C (CH-C) [1–4]. However, in aged patients, problems remain with respect to its anti-viral effect and tolerability [5–9]. Recently, the addition of a protease inhibitor to Peg-IFN plus ribavirin combination therapy has been reported, on the one hand, to improve the anti-viral effect, and, on the other hand, to increase side effects, especially severe anemia [10–11].

Therefore, this new therapy does not solve the problems encountered when treating aged patients.

With aging, the progression of liver fibrosis and the occurrence of hepatocellular carcinoma (HCC) have been shown to be accelerated, especially in patients over 60 y.o. [12–14]. In general, the anti-viral therapy can lead to an improvement in liver fibrosis and thus diminish the risk of HCC and ameliorate the prognosis in patients with CH-C [15–21]. Among aged patients, those results are mainly achievable upon eradication of the hepatitis C virus (HCV) [18,21]. Accordingly, the first goal of treatment of aged patients with a high-risk of HCC should be HCV elimination.

Thus, a treatment strategy, aiming at the improvement of the anti-viral efficacy in aged patients, should be established based on detailed large-scale studies.

Some points need to be further elucidated when using the Peg-IFN plus ribavirin combination therapy for the treatment of aged patients with CH-C: (i) the characteristics before treatment

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that would lead to the successful elimination of HCV, (ii) the prediction factors of treatment efficacy after the initiation of the therapy, and (iii) the utility of a response-guided therapy established in the treatment.

In the present study, using a large cohort, we aimed at clarifying these points taking into account the patients' age.

Patients and methods

Patients

This study was a retrospective, multicenter trial conducted by the Osaka University Hospital and other institutions participating in the Osaka Liver Forum. A total of 1040 naïve patients with CH-C were enrolled between December 2004 and June 2007. All patients were Japanese, infected with a viral load of more than 10^5 IU/ml, and treated with a combination of Peg-IFN alfa-2b plus ribavirin. Patients were excluded from the study if they had decompensated cirrhosis or other forms of liver disease (alcohol liver disease, autoimmune hepatitis), co-infection with hepatitis B or anti-human immunodeficiency virus. This study was conducted according to the ethical guidelines of the 1975 Declaration of Helsinki and informed consent was obtained from each patient.

Treatment

All patients received Peg-IFN alfa-2b (PEGINTRON; Schering-Plough, Kenilworth, NJ, USA) plus ribavirin (REBETOL; Schering-Plough). Treatment duration was 48 weeks for patients with genotype 1 and 24 weeks for those with genotype 2. As a starting dose, Peg-IFN alfa-2b was given once weekly, at a dosage of 1.5 μg/kg, and ribavirin was given at a total dose of 600–1000 mg/day based on body weight (body weight <60 kg, 600 mg; 60–80 kg, 800 mg; >80 kg, 1000 mg), according to a standard treatment protocol for Japanese patients.

Dose reduction and discontinuance

Dose modification followed, as a rule, the manufacturer's drug information on the intensity of the hematologic adverse effects. The Peg-IFN alfa-2b dose was reduced to 50% of the assigned dose when the white blood cell (WBC) count was below 1500/mm³, the neutrophil count below 750/mm³ or the platelet (Plt) count below 8×10^4/mm³, and was discontinued when the WBC count was below 1000/mm³, the neutrophil count below 500/mm³ or the Plt count below 5×10^4/mm³. Ribavirin was also reduced from 1000 to 600 mg, 800 to 600 mg, or 600 to 400 mg when the hemoglobin (Hb) was below 10 g/dl, and was discontinued when the Hb was below 8.5 g/dl. Peg-IFN alfa-2b and ribavirin had to be both discontinued if there was a need to discontinue either of them. No ferric medicine or hematopoietic growth factors, such as epoetin alpha, or granulocyte–macrophage colony stimulating factor (G-CSF), were administered.

Virologic assessment and definition of virologic response

Serum HCV RNA level was quantified using the COBAS AMPLICOR HCV MONITOR test, version 2.0 (detection range 6–5000 KIU/ml; Roche Diagnostics, Branchburg, NJ) and qualitatively analyzed using the COBAS AMPLICOR HCV test, version 2.0 (lower limit of detection 50 IU/ml; Roche Diagnostics). The rapid virologic response (RVR) was defined as undetectable serum HCV RNA at week 4; the early virologic response (EVR) as undetectable serum HCV RNA at week 12; and the late virologic response (LVR) as detectable serum HCV RNA at week 12 and undetectable serum HCV RNA at week 24. Moreover, the sustained virologic response (SVR) was defined as undetectable serum HCV RNA, 24 weeks after treatment.

According to the protocol, genotype 1 patients, with less than a 2-log decrease in HCV RNA level at week 12 compared to the baseline, or with detectable serum HCV RNA at week 24, had to stop the treatment and were regarded as non-response (NR). Treatment discontinuance was evaluated except for those patients who had discontinued the treatment at up to 24 weeks, due to absence of response. Anti-viral efficacy was evaluated, for all study patients, using the intention-to-treat analysis (ITT analysis) and the per protocol analysis (PP analysis) for patients without treatment discontinuation due to side effects, and was assessed considering the definition of EVR or LVR for genotype 1, and RVR or non-RVR for genotype 2, as previously reported [1].

Assessment of drug exposure

The amounts of Peg-IFN alfa-2b and ribavirin, taken by each patient during the full treatment period, were evaluated by reviewing the medical records. The mean doses of Peg-IFN alfa-2b and ribavirin were calculated individually as averages, on the basis of the body weight at baseline: Peg-IFN alfa-2b expressed as μg/kg/week, ribavirin expressed as mg/kg/day.

Statistical analysis

Patients' baseline data are expressed as means ± SD or median values. To analyze the difference between baseline data, ANOVA or Mantel–Haenszel Chi-square test were performed. Factors associated with the viral response were assessed by univariate analysis using the Mann–Whitney U test or Chi-square test and multivariate analysis using logistic regression analysis. A two-tailed p value <0.05 was considered significant. The analysis was conducted with SPSS version 15.0J (SPSS Inc., Chicago, IL).

Results

Patient's profile

Baseline characteristics of the patients categorized by age are shown in Table 1.

Genotype 1 patients ($n = 759$) were distributed into five categories: 266 patients were under 55 y.o. (group 1A), 159 were 55–59 y.o. (group 1B), 149 were 60–64 y.o. (group 1C), 134 were 65–69 y.o. (group 1D), and 51 were 70 y.o. or older (group 1E). With advancing age, the male-to-female ratio and peripheral blood cell count (WBC, neutrophil count, Red blood cell (RBC), Hb, Plt) decreased significantly. Patients with a progression of liver fibrosis (METAVIR fibrosis score 3 or 4) significantly increased with age (Table 1A).

Genotype 2 patients ($n = 281$) were also distributed into five categories: 145 patients were under 55 y.o. (group 2A), 43 were 55–59 y.o. (group 2B), 38 were 60–64 y.o. (group 2C), 41 were 65–69 y.o. (group 2D), and 14 were 70 y.o. or older (group 2E). As observed in genotype 1 patients, the peripheral blood cell count decreased and the ratio of advanced fibrosis (score 3–4) increased significantly with age (Table 1B). For both genotypes, the initial doses of Peg-IFN in patients over 70 y.o. were lower than in those under 70 y.o., this was not the case for the ribavirin doses.

Dose reduction and discontinuance for adverse event

The overall discontinuance rate of treatment was 15% (140/919); 18% (112/639) for genotype 1 and 10% (28/280) for genotype 2, respectively. Table 2 shows the reason for and the rate of treatment discontinuance according to age. The discontinuance rate increased with age, being 10% (36/363) for patients under 55 y.o., 15% (27/182) for patients with 55–59 y.o., 17% (28/169) for patients with 60–64 y.o., 19% (28/147) for patients with 65–70 y.o., and significantly higher, 36%, (21/58) for patients over 70 y.o. The discontinuance of treatment due to hemolytic anemia was significantly higher for patients over 70 y.o. as compared to those under 70 y.o. (<70 y.o., 1% (9/861) vs. ⩾70 y.o., 16% (9/58), p <0.0001).

The rate without dose reduction of both drugs decreased with age (<55 y.o., 41% (171/411); 55–59 y.o., 20% (40/202); 60–64 y.o., 26% (48/187); 65–69 y.o., 23% (41/175); ⩾70 y.o., 18% (12/65)). In the presence of genotype 1, the mean dose of Peg-IFN

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Table 1. Baseline characteristics of patients.

Patients with genotype 1

Factor		<55 y.o.	55 - 59 y.o.	60 - 64 y.o.	65 - 69 y.o.	≥70 y.o.	p value
Number		266	159	149	134	51	
Age (y.o.)		44.4 ± 8.1	56.9 ± 1.4	62.0 ± 1.4	66.8 ± 1.4	71.4 ± 1.7	<0.001
Sex: male / female		160 / 106	64 / 95	57 / 92	54 / 80	23 / 28	<0.001
Body weight (kg)		64.6 ± 11.7	58.3 ± 9.4	58.1 ± 9.6	56.3 ± 9.3	56.3 ± 9.2	<0.001
White blood cells (/mm^3)		5608 ± 1668	4901 ± 1664	4888 ± 1488	5113 ± 1426	4883 ± 1511	<0.001
Neutrophils (/mm^3)		2923 ± 1214	2425 ± 1031	2559 ± 1155	2535 ± 1017	2599 ± 1149	<0.001
Red blood cells (×10^4/mm^3)		454 ± 47	432 ± 38	427 ± 40	424 ± 37	424 ± 46	<0.001
Hemoglobin (g/dl)		14.4 ± 1.5	13.8 ± 1.2	13.7 ± 1.3	13.6 ± 1.2	13.7 ± 1.4	<0.001
Platelets (×10^4/mm^3)		18.6 ± 6.2	16.3 ± 5.7	15.4 ± 5.3	15.1 ± 5.0	14.4 ± 4.2	<0.001
AST (IU/L)		62 ± 50	62 ± 45	64 ± 46	72 ± 45	64 ± 40	0.295
ALT (IU/L)		79 ± 68	76 ± 64	73 ± 63	77 ± 58	65 ± 41	0.657
Serum HCV RNA (KIU/ml)*		1800	1600	1700	1700	1700	0.691
Histology (METAVIR)†	Fibrosis, 0 - 2 / 3 - 4	177 / 19	99 / 20	90 / 19	76 / 28	21 / 9	0.001
	Activity, 0 - 1 / 2 - 3	117 / 79	63 / 56	59 / 50	47 / 57	13 / 16	0.146
Peg-IFN dose (μg/kg/week)¶		1.47 ± 0.14	1.47 ± 0.16	1.46 ± 0.18	1.44 ± 0.18	1.36 ± 0.24	<0.001
Ribavirin dose (mg/kg/day)¶		11.5 ± 1.1	11.5 ± 1.4	11.5 ± 1.4	11.5 ± 1.7	11.2 ± 2.2	0.65

Patients with genotype 2

Factor		<55 y.o.	55 - 59 y.o.	60 - 64 y.o.	65 - 69 y.o.	≥70 y.o.	p value
Number		145	43	38	41	14	
Age (y.o.)		40.9 ± 8.9	56.7 ± 1.3	62.3 ± 1.4	66.7 ± 1.5	71.8 ± 1.8	<0.001
Sex: male / female		78 / 67	17 / 26	17 / 21	18 / 23	6 / 8	0.441
Body weight (kg)		63.4 ± 12.0	59.5 ± 11.5	58.6 ± 11.7	58.5 ± 9.8	55.9 ± 6.8	0.783
White blood cells (/mm^3)		6011 ± 1965	4874 ± 1346	4982 ± 1210	5079 ± 1877	4414 ± 871	<0.001
Neutrophils (/mm^3)		3214 ± 1511	2468 ± 971	2576 ± 950	2492 ± 1119	2521 ± 683	0.001
Red blood cells (×10^4/mm^3)		454 ± 48	430 ± 42	432 ± 50	430 ± 43	408 ± 48	<0.001
Hemoglobin (g/dl)		14.3 ± 1.6	13.5 ± 1.3	13.9 ± 1.4	13.9 ± 1.3	13.3 ± 1.2	0.001
Platelets (×10^4/mm^3)		21.3 ± 5.4	18.3 ± 6.1	17.0 ± 5.2	15.8 ± 5.4	13.9 ± 4.7	<0.001
AST (IU/L)		53 ± 59	57 ± 45	55 ± 38	83 ± 48	68 ± 29	0.029
ALT (IU/L)		65 ± 59	73 ± 70	68 ± 62	105 ± 62	78 ± 43	0.008
Serum HCV RNA (KIU/ml)*		1700	1100	900	1100	500	0.008
Histology (METAVIR)‡	Fibrosis, 0 - 2 / 3 - 4	102 / 0	25 / 3	29 / 2	21 / 9	7 / 1	<0.001
	Activity, 0 - 1 / 2 - 3	68 / 34	18 / 10	18 / 13	9 / 21	5 / 3	0.01
Peg-IFN dose (μg/kg/week)¶		1.48 ± 0.16	1.48 ± 0.14	1.45 ± 0.18	1.46 ± 0.15	1.28 ± 0.26	0.001
Ribavirin dose (mg/kg/day)¶		11.5 ± 1.1	11.4 ± 1.2	11.5 ± 1.4	11.3 ± 1.6	11.0 ± 1.4	0.55

*, Data shown are median values.
†, 201 Missing.
‡, 82 Missing.
¶, Initial doses.

during the whole treatment period was lower (1.1 ± 0.3 μg/kg/week) for patients over 70 y.o. than for those under 70 y.o. (1.3 ± 0.3 μg/kg/week) and that of ribavirin decreased with age (<55 y.o., 10.3 ± 1.9 mg/kg/day; 55–59 y.o., 9.8 ± 1.9 mg/kg/day; 60–64 y.o., 9.3 ± 2.3 mg/kg/day; 65–69 y.o., 9.2 ± 2.3 mg/kg/day; ≥70 y.o., 8.5 ± 2.5 mg/kg/day). The same tendency was observed with genotype 2.

Sustained virologic response

In genotype 1 patients, the overall SVR rate was 40% (305/759), being 46% (123/266) for group 1A, 44% (70/159) for group 1B, 42% (62/149) for group 1C, 26% (35/134) for group 1D, and 29% (15/51) for group 1E, following ITT analysis. The same tendency was observed using the PP analysis (n = 647). The SVR rates for patients over 65 y.o. were significantly lower than those for patients under 65 y.o. (ITT analysis: ≥65 y.o., 27% vs. <65 y.o.,

44%, p <0.0001; PP analysis: ≥65 y.o., 31% vs. <65 y.o., 50%, p <0.0001) (Fig. 1A). Among genotype 1 patients over 65 y.o., the SVR rate was significantly lower for female patients than for male patients (ITT analysis: male, 40% (31/77) vs. female, 18% (19/108), p <0.001; PP analysis: male, 49% (27/55) vs. female, 20% (18/90), p <0.001).

Moreover, for genotype 2 patients, the overall SVR rate was 78% (220/281), being 88% (128/145) for group 2A, 70% (30/43) for group 2B, 71% (27/38) for group 2C, 71% (29/41) for group 2D, and 43% (6/14) for group 2E, following ITT analysis. The same tendency was observed with the PP analysis (n = 253). The SVR rates for patients over 70 y.o. were significantly lower than those for patients under 70 y.o. (ITT analysis: ≥70 y.o., 43% vs. <70 y.o., 80%, p <0.0001; PP analysis: ≥70 y.o., 56% vs. <70 y.o., 85%, p <0.05) (Fig. 1B). Among patients over 70 y.o. with genotype 2, the difference according to gender was not clear because of the small sample.

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Table 2. Reasons for treatment discontinuation.

Factor	<55 y.o. (n = 363)	55 - 59 y.o. (n = 182)	60 - 64 y.o. (n = 169)	65 - 69 y.o. (n = 147)	≥70 y.o. (n = 58)	Total (n = 919)
Neutropenia	2	3	0	0	0	5
Thrombopenia	1	0	1	1	0	3
Anemia	0	4	3	2	9	18
Fatigue	1	1	3	3	1	9
Gastrointestinal disorder	2	1	0	0	1	4
Cough, Dyspnea	1	0	3	0	0	4
Vertigo	1	0	0	0	3	4
Psychosis (depression)	7 (3)	7 (3)	4 (4)	3 (3)	2 (2)	23
Rash	5	2	5	7	1	20
Thyroid dysfunction	2	0	2	0	0	4
Fundal hemorrhage	0	2	0	2	0	4
Drug-induced hepatitis	3	1	0	0	0	4
Interstitial pneumonia	0	1	0	1	1	3
Cerebral hemorrhage, infarction	2	0	0	1	0	3
Others	9	5	7	8	3	32
Total	36 (10%)	27 (15%)	28 (17%)	28 (19%)	21 (36%)	140 (15%)

A

B
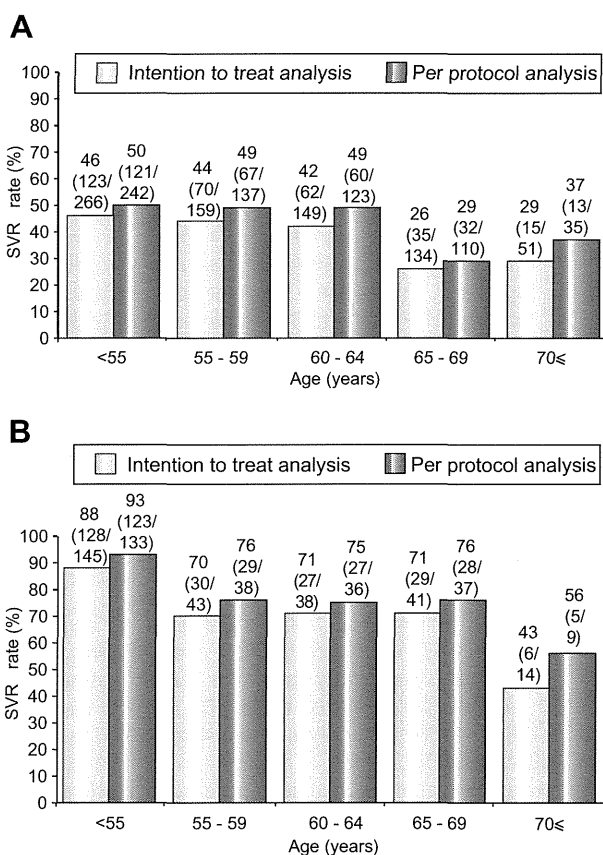
Fig. 1. SVR rate according to age. (A) Genotype 1. (B) Genotype 2.

Fig. 2. Antiviral effect during treatment according to age. (A) <55 y.o. (B) 55–59 y.o. (C) 60–64 y.o. (D) 65–69 y.o. (E) ≥70 y.o.

Timing of HCV RNA negativation for genotype 1, according to age

Treatment responses distributing EVR, LVR, and NR according to age are shown in Fig. 2. The rates of NR were similar in patient groups under 65 y.o. (30–36%), but increased in almost half of
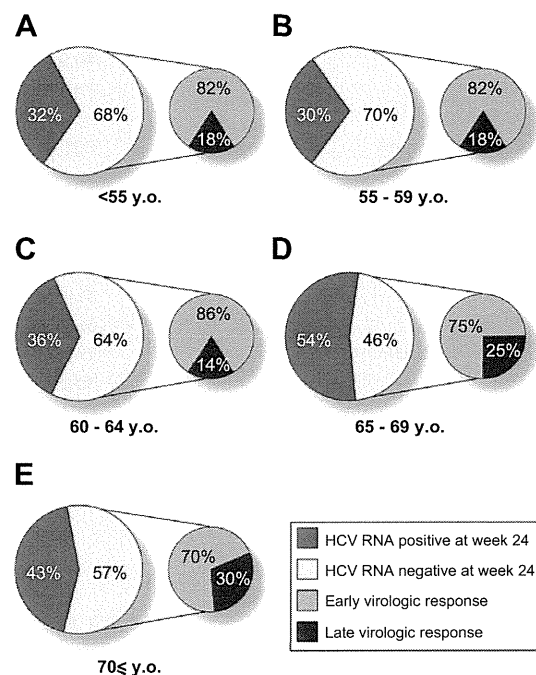
the patients over 65 y.o. (p <0.0001). Moreover, among the virologic responders, the proportion of LVR tended to increase in patients over 65 y.o. (25–30%) compared to patients under 65 y.o. (14–18%) (p = 0.06).

SVR rate according to the timing of HCV RNA negativation

SVR rates according to EVR or LVR in genotype 1, and RVR or non-RVR in genotype 2 are summarized in Table 3. Genotype 1 patients with EVR achieved high SVR rates regardless of age; in particular, if EVR had been attained, 76% of patients with 65–69

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Table 3. SVR rate according to genotype and viral response in patients responding to PEG-IFN plus ribavirin combination therapy.

Factor	<55 y.o.	55 - 59 y.o.	60 - 64 y.o.	65 - 69 y.o.	≥70 y.o.
Genotype 1					
with EVR, % (n)	85 (114/134)	79 (62/79)	81 (55/68)	76 (29/38)	86 (12/14)
with LVR, % (n)	23 (7/30)	29 (5/17)	46 (5/11)	23 (3/13)	17 (1/6)
Genotype 2					
with RVR, % (n)	93 (57/61)	82 (14/17)	85 (17/20)	92 (11/12)	100 (4/4)
without RVR*, % (n)	96 (22/23)	60 (6/10)	57 (4/7)	50 (4/8)	0 (0/3)

RVR, rapid virologic response.
EVR, early virologic response.
LVR, late virologic response.
*, Serum HCV RNA was detectable at week 4, but undetectable at week 24.

Table 4. Multivariate analysis for the factors associated with SVR among all patients.

Factor	Category	Odds ratio	95% CI	p
Age (y.o.)	<65 / ≥65	0.485	0.295 - 0.799	0.005
Sex	male / female	0.524	0.353 - 0.777	0.001
Platelets (×10⁴/mm³)	<12 / ≥12	1.780	1.039 - 3.049	0.040
Serum HCV RNA (KIU/ml)	<2000 / ≥2000	0.599	0.401 - 0.896	0.010
Histology (METAVIR): Fibrosis	0 - 2 / 3 - 4	0.599	0.333 - 1.076	0.090

y.o. and 86% of patients over 70 y.o. achieved SVR, and these SVR rates compared favorably with those of younger patients. On the other hand, the SVR rates for patients with LVR ranged from 17% to 46%, which were lower than those for EVR patients in each age group, and no significant differences of SVR rates were found among LVR patients by age.

With genotype 2, patients with RVR achieved high SVR rates ranging from 82% to 100% regardless of age. Even for patients without RVR, 96% of those under 55 y.o. attained SVR, a rate that was significantly higher than that for patients over 55 y.o. (50%, 14/28) (p <0.001).

Factors associated with SVR for genotype 1

The factors associated with SVR were assessed for the variables shown in Table 1. The factors selected as significant by the univariate analysis: age, gender, WBC, neutrophils, RBC, Hb, Plt, aspartate aminotransferase, serum HCV RNA level, the degree of liver fibrosis, and the initial dose of Peg-IFN, were evaluated by multivariate logistic regression analysis. The factor of age over 65 y.o. was the independent factor for SVR (p = 0.005), apart from the gender (p = 0.001), Plt value (p <0.05), and serum HCV RNA level (p = 0.01) (Table 4).

Factors associated with EVR and SVR for patients over 65 y.o. with genotype 1

The results of univariate analysis for EVR among patients over 65 y.o. are shown in Table 5A. Gender, Plt value, and mean dose of Peg-IFN during the first 12 weeks were factors significantly associated with EVR. In multivariate analysis, the mean dose of Peg-IFN during the first 12 weeks was the independent factor for EVR (p = 0.03), apart from gender (p = 0.002) (Table 5B). The EVR rates were 41% (41/101) in patients who received ≥1.2 μg/kg/week on average during the first 12 weeks, and declined to 36% (8/22) in patients given 0.9-1.2 μg/kg/week of Peg-IFN, and

to 14% (3/22) in patients administered with <0.9 μg/kg/week of Peg-IFN.

The baseline and on-treatment factors, which are correlated with the SVR among the patients over 65 y.o., were assessed by univariate and multivariate analyses. Univariate analysis showed that factors significantly associated with SVR were gender and virologic response (Table 6A), and they were also selected as significant independent factors in multivariate analysis (p = 0.035, p <0.001) (Table 6B).

Negative prediction of SVR for patients over 65 y.o. with genotype 1

We tried positive and negative predictions of SVR for aged patients, focusing on the decrease of HCV RNA at treatment week 4 and 8. The SVR rate was 47% (29/62) for patients with more than a 1-log decrease in HCV RNA level at week 4, while no patients with less than a 1-log decrease at week 4 attained SVR (0/35) (p <0.0001). Similarly, 55% (35/64) of patients with more than a 2-log decrease at week 8 attained SVR, whereas no patients with less than a 2-log decrease at week 8 attained SVR (0/38) (p <0.0001).

Discussion

Peg-IFN plus ribavirin combination therapy can improve anti-viral efficacy and is presently recommended as first-line therapy [1–4]. However, with respect to aged patients with CH-C, there have been only a few small-scale cohort studies which reported poor anti-viral effect and poor tolerability in comparison with non-aged patients [5–9]. The problem in the treatment of aged patients with CH-C is most serious in Japan, because HCV carriers in Japan are 10–20 years older than those in the United States and European countries [22]. Therefore, in the present study, we examined the efficacy and prevalence of side effects with a focus on patient's age using a large-scale cohort.

Table 5. Factors associated with EVR among patients over 65 y.o.

Univariate analysis

Factor		EVR	Non-EVR	p value
Number		52	93	
Age (y.o.)		67.9 ± 2.3	67.8 ± 2.5	0.66
Sex: male / female		28 / 24	27 / 66	0.003
White blood cells (/mm³)		5063 ± 1474	5001 ± 1422	0.76
Neutrophils (/mm³)		2566 ±1110	2551 ± 1071	0.87
Red blood cells (×10⁴/mm³)		426 ± 36	421 ± 38	0.64
Hemoglobin (g/dl)		13.7 ± 1.2	13.5 ± 1.2	0.21
Platelets (×10⁴/mm³)		16.5 ± 5.5	14.0 ± 4.6	0.009
AST (IU/L)		70 ± 51	70 ± 40	0.49
ALT (IU/L)		76 ± 58	70 ± 41	0.80
Serum HCV RNA (KIU/ml)*		1700	1900	0.62
Histology (METAVIR)†	Fibrosis, 0 - 2 / 3 - 4	25 / 10	47 / 20	0.54
	Activity, 0 - 1 / 2 - 3	16 / 19	29 / 37	0.52
Peg-IFN dose (µg/kg/week)‡		1.35 ± 0.24	1.25 ± 0.31	0.03
Ribavirin dose (mg/kg/day)‡		10.0 ± 2.2	9.6 ± 2.3	0.40

Multivariate analysis

Factor	Category	Odds ratio	95% CI	p value
Sex	male / female	0.309	0.149 - 0.644	0.002
Platelets (×10⁴/mm³)	<12 / ≥12	-	-	N.S
Peg-IFN dose (µg/kg/week)‡	<1.2 / ≥1.2	2.481	1.079 - 5.705	0.03

*, Data shown are median values.
†, 43 Missing.
‡, Mean doses during 0 to 12 weeks.
N.S., not statistically significant.

Table 6. Factors associated with SVR among patients over 65 y.o.

Univariate analysis

Factor		SVR	Non-SVR	p value
Number		45	100	
Age (y.o.)		68.0 ± 2.4	67.7 ± 2.5	0.45
Sex: male / female		27 / 18	28 / 72	<0.001
White blood cells (/mm³)		5006 ± 1516	5030 ± 1409	0.81
Neutrophils (/mm³)		2575 ±1130	2548 ± 1063	0.96
Red blood cells (×10⁴/mm³)		427 ± 40	421 ± 36	0.53
Hemoglobin (g/dl)		13.8 ± 1.3	13.5 ± 1.2	0.14
Platelets (×10⁴/mm³)		16.1 ± 5.6	14.3 ± 4.7	0.09
AST (IU/L)		71 ± 54	69 ± 40	0.47
ALT (IU/L)		76 ± 56	70 ± 43	0.77
Serum HCV RNA (KIU/ml)*		1700	2000	0.51
Histology (METAVIR)†	Fibrosis, 0 - 2 / 3 - 4	21 / 8	51 / 22	1.00
	Activity, 0 - 1 / 2 - 3	14 / 15	31 / 41	0.66
Peg-IFN dose (µg/kg/week)‡		1.27 ± 0.28	1.23 ± 0.33	0.31
Ribavirin dose (mg/kg/day)‡		8.8 ± 2.1	9.1 ± 2.5	0.38
Virologic response: EVR / non-EVR		41 / 4	11 / 89	<0.001

Multivariate analysis

Factor	Category	Odds ratio	95% CI	p value
Sex	male / female	0.283	0.088 - 0.914	0.035
Virologic response	EVR / non-EVR	0.012	0.004 - 0.043	<0.001

*, Data shown are median values.
†, 43 Missing.
‡, Mean doses during treatment.

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With respect to the side effects and discontinuance rate of treatment in aged patients with CH-C, treated with Peg-IFN plus ribavirin combination therapy, Reddy et al. reported that there was no difference related to the incidence and reason for side effects between non-aged and aged patients [6]. Another paper reported that the incidence of side effects was more frequent in aged patients [5]. In our study, not only the continuance rate without reduction of both drug decreased with age, but also the discontinuance rate of treatment increased with age, with a third of the patients over 70 y.o. discontinuing the treatment. The discrepancy, existing between our results and those reported in the former study cited above, is due to the difference in the number of aged patients enrolled; Reddy's study analyzed a small cohort including only a few cases of patients over 65 y.o. and classified all those over 50 y.o. as aged patients.

Discontinuance of treatment due to progression of anemia was significantly higher in patients over 70 y.o., accounting for 43% (9/21) of the discontinuance in this group. Although the ratio of advanced fibrosis (score 3-4) increased with age, the high discontinuance rate due to anemia among patients over 70 y.o. was similar regardless of the progression of fibrosis (F0-2: <70 y.o., 1% (6/559) vs. ⩾70 y.o., 21% (6/28), p <0.0001; F3-4: <70 y.o., 0% (0/ 83) vs. ⩾70 y.o., 22% (2/9), p <0.0001). It is possible that poor hematopoietic function and renal function led to the progression of anemia in aged patients. For patients who develop severe anemia, using epoetin alpha or taribavirin, which are ribavirin prodrugs, has been shown to result in a lower incidence of anemia, although no significant increase of SVR has been reported so far, even with the addition of taribavirin to Peg-IFN [23-24].

With genotype 1 patients, the SVR rates were almost equal up to 65 y.o. (49-50%), but decreased to 31% (45/145) among the patients that were over 65 y.o., and even for those who completed the entire treatment schedule in this study. Since the degree of liver fibrosis and drug exposure have been shown to be associated with anti-viral efficacy, the progression of liver fibrosis or decrease of drug exposure with age could account for the reduction of SVR rate among the aged patients. However, the stratified analysis, according to the progression of liver fibrosis and drug exposure, revealed that older patients still yielded low a SVR rate (F0-2, Peg-IFN during the first 12 weeks ⩾1.2 μg/kg/week:<65 y.o., 55% (143/261) vs. ⩾65 y.o., 33% (15/ 46), p <0.0001; F0-2, Peg-IFN during the first 12 weeks <1.2 μg/ kg/week:<65 y.o., 43% (26/60) vs. ⩾65 y.o., 23% (6/26), p = 0.07), which means that older patients would be difficult to treat. From our results showing a low SVR rate and a high discontinuance rate for patients over 65 y.o., the genotype 1 patients under 65 y.o were those who benefited the most from Peg-IFN plus ribavirin combination therapy. The high prevalence of treatment failure (non-SVR) among the aged patients seems to be due to the high populations of NR and LVR (Fig. 2). A high population of LVR is considered to lead to a higher transient response rate among aged patients, since those over 65 y.o. with LVR showed a much higher relapse rate (79%, 15/19) than those with EVR (21%, 11/52) (p <0.0001), as can be seen from Table 3.

In this study, multivariate analysis for SVR, in patients over 65 y.o., showed that the factors associated with SVR were EVR and gender. This indicates that better SVR can be expected even with older patients if EVR is attained and response-guided therapy guidelines can be useful for aged patients. A low SVR rate among aged female patients was as previously reported [7], although the

mechanism remains unclear. This finding suggests that female patients should be treated before 65 y.o.

The next question is how aged patients should be treated in order to attain EVR. We have examined the impact of drug exposure on treatment efficacy [25-26] and reported that Peg-IFN is dose-dependently correlated with EVR [25]. In this study, the dose-dependent efficacy of Peg-IFN for EVR was also revealed in aged patients over 65 y.o., with less than 0.9 μg/kg/week of Peg-IFN leading to a low EVR rate for aged patients. If patients are difficult to treat with more than 1.2 μg/kg/week of Peg-IFN, using as much Peg-IFN as possible is desirable, in order to attain higher EVR rates. Accordingly, a reduction of Peg-IFN to 80% may need to be considered, although the manufacturer's drug information recommends reducing the dose of Peg-IFN to 50% of the assigned one. Since reduction of Peg-IFN has been reported to not affect the SVR rate after HCV RNA disappearance [26], using G-CSF for aged patients who develop severe neutropenia can be beneficial, especially in the first 12 weeks.

We also examined the negative prediction of SVR, i.e. an HCV RNA decrease at an earlier point of treatment than the usual prediction at treatment week 12 of a 2-log decrease, among aged patients with CH-C treated by Peg-IFN plus ribavirin combination therapy. We found that none of the patients without a 1-log decrease at week 4 or a 2-log decrease at week 8 could attain SVR, even if the complete treatment duration was given, the negative predictive value (NPV) for SVR equaled 100%. This earlier prediction is applied just as well to aged patients as to non-aged patients in order to avoid additional adverse effects. Recently, a genetic polymorphism near the *IL28B* gene has been reported to be associated with non-response to Peg-IFN plus ribavirin combination therapy [27-29], which is beneficial to patients. Nevertheless, even in the presence of this genetic polymorphism, NPV for SVR remains at 57-87%; 100% accuracy is not guaranteed. Thus, in addition to the pretreatment prediction, an earlier negative prediction for SVR during treatment is also considered to be useful.

We have shown in this study that, in the presence of genotype 2, HCV was easily eliminated even among aged patients; the SVR rates were over 75% for patients who had completed the treatment, and these rates were similar up to 70 y.o. The SVR rate of genotype 2 patients over 70 y.o. was 43%, however, the age limitation of the treatment among patients over 70 y.o. remains unclear, because of the small number of patients enrolled in this study. We have reported that the reduction of treatment drugs had little effect on anti-viral efficacy for patients with genotype 2, meaning that SVR can be attained even with aged patients who are usually given lower drug doses than non-aged patients [30]. Patients under 70 y.o. with genotype 2 should, at least, benefit from this therapy. The SVR rate was maintained among genotype 2 patients being 65-69 y.o., compared to genotype 1 patients. The higher efficacy with shorter treatment duration in genotype 2 aged patients can account for it.

In conclusion, the strategy of a response-guided therapy and an earlier negative prediction for SVR may be beneficial for aged patients, especially those with genotype 1. At present, aged patients up to 65-70 y.o. with CH-C can be candidates for Peg-IFN plus ribavirin combination therapy, if its efficacy and adverse effects are fully taken into account. At the same time, there is an urgent need to establish new treatment procedures, such as combination therapy with protease inhibitor plus polymerase inhibitor without Peg-IFN or ribavirin, for non-responders or patients

with poor tolerability for Peg-IFN plus ribavirin combination therapy among aged patients.

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ORIGINAL ARTICLE—LIVER, PANCREAS, AND BILIARY TRACT

Efficacy of re-treatment with pegylated interferon plus ribavirin combination therapy for patients with chronic hepatitis C in Japan

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Abstract

Background It is still not known which patients with chronic hepatitis C who failed to respond to previous pegylated interferon (Peg-IFN) plus ribavirin therapy can benefit from re-treatment.

Methods Seventy-four patients (HCV genotype 1, $n = 56$, genotype 2, $n = 18$) were re-treated with Peg-IFN plus ribavirin.

Results On re-treatment, the sustained virologic response (SVR) rate was 41% for genotype 1 and 56% for genotype 2. With genotype 1, the factors associated with an SVR were previous treatment response and the serum hepatitis C virus (HCV) RNA level at the start of re-treatment. Patients with a ≥ 2-log decrease in HCV RNA at week 12 (partial early virologic response, p-EVR) in previous treatment had significantly higher SVR rates than those without these

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decreases ($p < 0.001$); no patient without a p-EVR in the previous treatment attained an SVR with re-treatment (0/16). All patients with $<5 \log_{10}$ IU/ml of HCV RNA at the start of re-treatment attained an SVR (6/6), while only 33% (15/45) of those patients with $\geq 5 \log_{10}$ IU/ml of HCV RNA attained an SVR ($p < 0.01$). Among the patients with relapse in the previous treatment, those who attained an SVR on re-treatment required a longer duration of re-treatment than the duration of the previous treatment (re-treatment, 63.8 ± 13.0 weeks vs. previous treatment, 53.9 ± 13.5 weeks, $p = 0.01$).

Conclusions Re-treatment of genotype 1 patients should be limited to patients with a p-EVR in the previous treatment and a low HCV RNA level at the start of re-treatment. In re-treatment with Peg-IFN plus ribavirin, longer treatment duration can contribute to increasing the anti-viral effect.

Keywords Chronic hepatitis C · Pegylated interferon and ribavirin combination therapy · Re-treatment

Introduction

Pegylated interferon (Peg-IFN) plus ribavirin combination therapy can improve anti-viral efficacy and is currently recommended as first-line therapy for chronic hepatitis C. However, hepatitis C virus (HCV) still persists in approximately half of the genotype 1 patients treated with Peg-IFN plus ribavirin [1–4], and the number of patients who fail to achieve a sustained virologic response (SVR) consequently increases over time.

Recently, the addition of a protease inhibitor to Peg-IFN plus ribavirin combination therapy has been reported to improve the anti-viral effect, but this triple therapy increases side effects, especially severe anemia [5–7]. In Japan, HCV carriers are 10–20 years older than those in the United States and European countries, and patients who are ineligible for triple therapy exist in large numbers due to their potential tendency of having anemia. On the other hand, re-treatment with Peg-IFN plus ribavirin is a possible choice, until triple therapy becomes commercially available, for patients who have failed to show an SVR to previous anti-viral therapy, and for patients who are ineligible for triple therapy. As for re-treatment with Peg-IFN plus ribavirin, there have been only a few studies of patients who failed to show an SVR to previous Peg-IFN plus ribavirin [8–11]. Although re-treatment with Peg-IFN plus ribavirin for patients who failed to respond to previous Peg-IFN plus ribavirin is not recommended in the practice guidelines of the American Association for the Study of the Liver (AASLD) [1], there are some patients who respond to re-treatment. However, it remains obscure in which patients eradication of HCV can be successfully attained by re-treatment with Peg-IFN plus ribavirin.

In the present study, we tried to determine which patients could benefit from re-treatment and to identify the factors associated with an SVR in re-treatment.

Patients and methods

Patients

The present study was a retrospective, multicenter trial conducted by Osaka University Hospital and other institutions participating in the Osaka Liver Forum. This study was conducted with 74 chronic hepatitis C patients (genotype 1, $n = 56$, genotype 2, $n = 18$) who had previously completed Peg-IFN α-2b plus ribavirin combination therapy but had failed to attain an SVR. Patients were excluded from this study if they had decompensated cirrhosis or other forms of liver disease (alcoholic liver disease, autoimmune hepatitis), or coinfection with hepatitis B or anti-human immunodeficiency virus. This study was conducted according to the ethical guidelines of the Declaration of Helsinki amended in 2008, and informed consent was obtained from each patient.

Treatment

For the previous treatment, Peg-IFN α-2b (Pegintron; Schering-Plough, Kenilworth, NJ, USA) plus ribavirin (Rebetol; Schering-Plough) was started between December 2004 and January 2008. For re-treatment with Peg-IFN plus ribavirin, Peg-IFN α-2a (Pegasys; Roche, Basel, Switzerland) plus ribavirin (Copegus; Roche) or Peg-IFN α-2b plus ribavirin was started between February 2006 and January 2009. In principle, as a starting dose, Peg-IFN was given once weekly at a dose of 180 μg of Peg-IFN α-2a and 1.5 μg/kg of Peg-IFN α-2b, and ribavirin was given at a total dose of 600–1000 mg/day based on body weight (for genotype 1, body weight <60 kg, 600 mg; 60–80 kg, 800 mg; >80 kg, 1000 mg; for genotype 2, body weight <60 kg, 600 mg; >60 kg, 800 mg), according to a standard treatment protocol for Japanese patients.

Dose reduction and discontinuance

Dose modification followed, as a rule, the manufacturer's drug information on the intensity of the hematologic adverse effects. The Peg-IFN α-2a and α-2b doses were reduced to 50% of the assigned dose when the neutrophil count fell below 750/mm^3 or the platelet (Plt) count fell below 8×10^4/mm^3, and the agent was discontinued when the neutrophil count fell below 500/mm^3 or the Plt count fell below 5×10^4/mm^3. Ribavirin was also reduced from 1000 to 600, 800 to 600, or 600 to 400 mg when the