Eltrombopag enables initiation and completion of pegylated interferon/ribavirin therapy in Japanese HCV-infected patients with chronic liver disease and thrombocytopenia

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Abstract. To investigate the efficacy of eltrombopag for the treatment of thrombocytopenia in patients with chronic hepatitis C, a phase II, single-arm, open-label study with a 9-week pre-antiviral phase was conducted, followed by a 48-week antiviral phase and a 24-week follow-up phase. The proportion of patients who achieved a platelet count threshold, the proportion of patients who maintained a platelet count >50,000/μl, sustained virological response (SVR) rates and safety parameters were evaluated. Of the 45 enrolled patients (median age, 59 years; median platelet count, 63,000/μl; 98% with Child-Pugh class A), 43 (96%) achieved the platelet count threshold during the pre-antiviral phase. A total of 13 patients (29%) experienced ≥1 adverse event (AE), of which headache and vomiting were the most common, and 41 patients (mostly receiving eltrombopag 12.5 mg or 25 mg) entered the antiviral phase, of which 36 (88%) maintained the platelet count threshold; no patient platelet

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Abbreviations: AE, Adverse event; ALT, alanine transaminase; AST, aspartate transaminase; AUC_{0-t}, area under the plasma concentration-time curve up to the last measurable concentration; $AUC_{0-\tau}$, area under the plasma concentration curve to the end of the dosing period; BL, baseline; cEVR, complete early virological response; CI, confidence interval; CLD, chronic liver disease; C_{max}, maximum plasma concentration; DAA, direct-acting antiviral; DAIDS, Division of Acquired Immunodeficiency Syndrome; ETR, end-of-treatment response; EVR, early virological response; FU, follow-up; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; IFN, interferon; ITP, immune thrombocytopenic purpura; LFT, liver function test; MELD, Model for End-Stage Liver Disease; PegIFN, pegylated interferon; RBV, ribavirin; RVR, rapid virological response; SAE, serious adverse event; SVR, sustained virological response; TEE, thromboembolic event; T_{max}, time to maximum plasma concentration; TPO, thrombopoietin; TPO-R, thrombopoietin receptor; ULN, upper limit of normal

Key words: chronic hepatitis C, chronic liver disease, eltrombopag, ethnic difference, pegylated interferon/ribavirin therapy, thrombocytopenia

count decreased below 25,000/μl. Nine patients (22%) achieved an SVR at the 24-week follow-up. Grade ≥3 AEs occurred in 25 patients (61%). A total of 8 serious AEs occurred in five patients (12%). No mortality, thromboembolic events (TEEs), or cataract progression were reported. Eltrombopag increased the platelet count in chronic hepatitis C virus-infected patients with cirrhosis and thrombocytopenia and enabled them to initiate and complete interferon-based antiviral therapy (NCT01636778; first submitted: July 05, 2012).

Introduction

Thrombocytopenia is a frequent complication in cirrhotic patients and its severity correlates with the disease severity (1). In addition to hypersplenism secondary to portal hypertension, impaired production of endogenous thrombopoietin (TPO) in the liver is a major cause of thrombocytopenia (2). Until recently, the combination of pegylated interferon (pegIFN) α and ribavirin (RBV) was the standard treatment for chronic hepatitis C and compensated cirrhosis (3). However, thrombocytopenia interferes with the initiation and continuation of interferon (IFN) therapy owing to its myelosuppressive effects, especially in patients with cirrhosis (2).

The recently developed direct-acting antivirals (DAAs) have revolutionized the treatment of hepatitis C virus (HCV) infections, with highly sustained virological response (SVR) rates and better tolerability than the IFN-based therapy (4,5). Nevertheless, DAAs have several potential limitations, including the issue of resistance-associated variants and their high cost. Furthermore, the long-term effects of DAAs remain unclear. Certain DAAs have been associated with the worsening of dyslipidemia (6,7). Although some recent reports have suggested that an SVR by DAA therapy reduces the risk of developing hepatocellular carcinoma (HCC), the role of DAAs in the recurrence of HCC in patients treated for hepatic decompensation remains controversial, and thus, warrants further elucidation and follow-up in the HCC high-risk group (8). Moreover, DAAs have not been approved worldwide as they have limited access, and their high price creates a barrier, especially in low-income countries with high prevalence of HCV as well as in some developed countries due to payer restrictions on the DAA therapy (3,8). In addition, IFN-based therapy is still one of recommendations for patients with chronic infection of HCV that has multiple drug resistance mutation (9).

For the aforementioned reasons, IFN-based therapy still remains a feasible treatment strategy in countries where DAAs are not accessible or affordable. As thrombocytopenia may restrict the initiation or continuation of IFN-based therapy, its control has clinical importance. The clinical management of thrombocytopenic patients with HCV infection receiving IFN-based therapy primarily depends on IFN dose reductions, which may preclude patients from achieving an SVR.

Eltrombopag is an orally bioavailable, small molecule thrombopoietin receptor (TPO-R) agonist that has been approved for the treatment of chronic immune thrombocytopenic purpura (ITP). It significantly increases the platelet counts in a dose-dependent manner in thrombocytopenic patients with chronic hepatitis C [Eltrombopag to initiate and maintain interferon antiviral treatment to benefit subjects with hepatitis C-related liver disease (ENABLE)-1 and ENABLE-2 studies] (10), as well as in those with chronic ITP. However, eltrombopag has been associated with an increased risk of thrombosis in patients with chronic liver disease (CLD) (11-13), there are reports of portal vein thrombosis associated with the use of eltrombopag (14). In this study, we assessed the ability of eltrombopag in increasing the platelet counts in HCV-infected patients with thrombocytopenia to a sufficient level to initiate and maintain pegIFN/RBV therapy without dose modifications of pegIFN and development of thrombosis.

Patients and methods

Study design. This was a phase II, single-arm, open-label study comprising three phases: A pre-antiviral phase (up to 9 weeks), an antiviral phase (48 weeks, with possible extension to 72 weeks in slow or late responders), and a 24-week follow-up phase (Fig. 1). The study was approved by the National Hospital Organization Central Review Board of four national hospitals and institutional review boards of 12 other participating centers; the study was performed in accordance with the Declaration of Helsinki, Good Clinical Practice guidelines, and local laws and regulations. All participating patients provided written informed consent prior to their inclusion in the study. This study is registered at ClinicalTrials.gov (NCT01636778; July 05, 2012).

Patients who achieved the required platelet count threshold (≥100,000/μl) in the pre-antiviral phase entered the antiviral phase and received antiviral therapy in combination with eltrombopag for 48 weeks. Extended treatment with pegIFN/RBV for up to 72 weeks was allowed based on the investigator's judgment; however, the duration of treatment with eltrombopag was limited to 48 weeks. During the follow-up period, the SVR was also evaluated in addition to monitoring the safety of eltrombopag at 4, 12, and 24 weeks after the treatment.

Evaluations. The primary endpoints included the proportion of patients who achieved a platelet count >100,000/μl during the pre-antiviral phase and those who maintained a platelet count >50,000/μl throughout the antiviral phase.

Secondary efficacy endpoints included the median platelet counts throughout the study, the proportion of patients who had to undergo dose reductions or discontinuation of pegIFN and/or RBV, and the SVR rate. The SVR rate was defined as the proportion of patients with undetectable HCV RNA at the end of the treatment and all subsequent planned visits up to 24 weeks after completing the treatment. Rapid virological response (RVR), early virological response (EVR), complete EVR (cEVR), and end-of-treatment response (ETR) were also assessed at weeks 4, 12, and 48, respectively.

Adverse events (AEs) and their severity and causality were assessed by the individual investigator and summarized by incidence and severity. Since one of major complications of eltrombopag is portal vein thrombosis, doppler ultrasound of abdomen was performed at screening or baseline and every 6 months thereafter to assess portal vein thrombosis. In addition, abdominal image (e.g., CT, MRI) was performed whenever any symptoms of portal vein thrombosis are observed. The severity of AEs was graded using the Division of Acquired Immunodeficiency Syndrome (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events (version 1.9, dated December 2004).

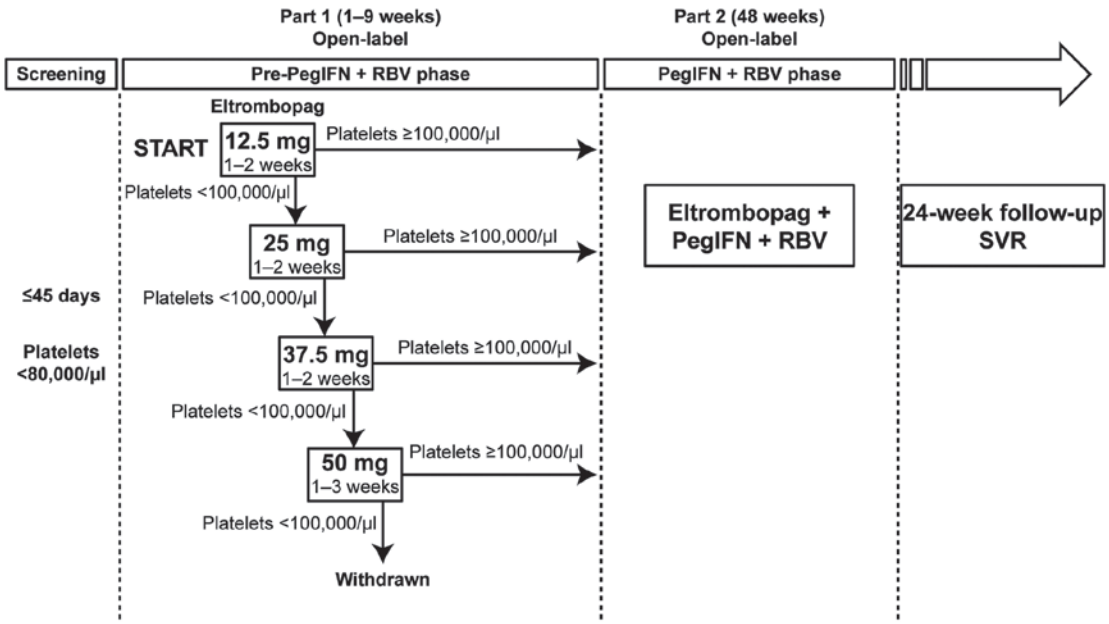

Figure 1. Study design. In the first phase of the study after screening, open-label eltrombopag was administered for up to 9 weeks until the platelet count increased sufficiently to enable initiation of the antiviral (pegIFN + RBV) treatment. In the second phase, eltrombopag was administered together with the antiviral treatment for a period of 48 weeks. The antiviral treatment consisted of either pegIFN α-2a/RBV or pegIFN α-2b/RBV; the treatment regimen was selected by the investigator. PegIFN, pegylated interferon; RBV, ribavirin; SVR, sustained virologic response.

Patients. Patients aged between 20 and 75 years who were diagnosed with hepatitis C or compensated liver cirrhosis and thrombocytopenia (baseline platelet count, <80,000/μl) were eligible.

Patients who had a Child-Pugh score of 6 or less (Child-Pugh class A) without hepatic encephalopathy or ascites and adequate hepatic, renal, and hematologic function to receive antiviral therapy were appropriate candidates for the pegIFN/RBV therapy. Those who had received prior treatment with pegIFN/RBV but had stopped the treatment because of disease- or treatment-related thrombocytopenia were also eligible.

The exclusion criteria were based on the ENABLE studies (10). In brief, patients who did not respond to previous pegIFN/RBV therapy for reasons other than thrombocytopenia or had decompensated liver disease, serious medical complications (including serious cardiac, cerebrovascular, or pulmonary disease, a history of arterial or venous thrombosis, hepatitis B virus or human immunodeficiency virus infection, or platelet aggregation abnormalities), active bleeding, or a history of clinically significant bleeding from esophageal or gastric varices were excluded from the study. Patients with HCC or a history of previous HCC within 5 years before enrollment were also excluded.

Treatment. In view of the differences in the pharmacokinetics of eltrombopag caused by inter-ethnic differences, lower doses of eltrombopag (12.5 mg as the starting dose and 50 mg as the maximum dose) were used compared with those used in the ENABLE studies (10). All doses were administered orally once daily in the fasting state.

During the pre-antiviral phase, all patients initially received 12.5 mg of eltrombopag. The dose was increased by 12.5 mg every 2 weeks up to 50 mg until the platelet count increased to the required threshold (≥100,000/μl) to initiate antiviral therapy. Patients who did not achieve the platelet count threshold after 3 weeks of treatment with eltrombopag at 50 mg once daily discontinued the treatment and entered the 24-week follow-up phase. Patients achieving the platelet count threshold initiated antiviral therapy (pegIFN α-2a/RBV or pegIFN α-2b/RBV; the treatment regimen was selected by the investigator) in combination with eltrombopag per the package insert of each drug (15-18).

During the antiviral phase, dose adjustments of eltrombopag were based on individual platelet response to maintain the platelet counts between 50,000/μl and 150,000/μl, which was a lower threshold (more cautious on platelet increases) than that applied in the ENABLE studies (50,000-200,000/μl) (10). Patients showing a trend toward greater increases in platelet counts were allowed a dose reduction of eltrombopag per the investigator's decision, even if their platelet counts were lesser than 150,000/μl. The platelet counts were monitored weekly until week 8 of treatment and every 4 weeks thereafter.

Pharmacokinetics. Serial blood samples were collected prior to dose administration (prior to the morning administration of eltrombopag on day 14) and at 1, 2, 4, 6, 8, and 24 h after the dose administration in five patients who received 12.5 mg of eltrombopag. Pharmacokinetic parameters [maximum plasma concentration (C_{max}), time to maximum plasma concentration (T_{max}), area under the plasma concentration-time curve up to the last measurable concentration ($AUC_{0\text{-}t}$), and area under the plasma concentration curve to the end of the dosing period ($AUC_{0\text{-}\tau}$)] were calculated at actual sampling timings using non-compartmental analysis. Summary statistics were used to summarize the pharmacokinetic parameters. If patients withdrew from the study because of abnormal liver function tests (LFTs), plasma eltrombopag concentrations were to be measured within 3 days after withdrawal.

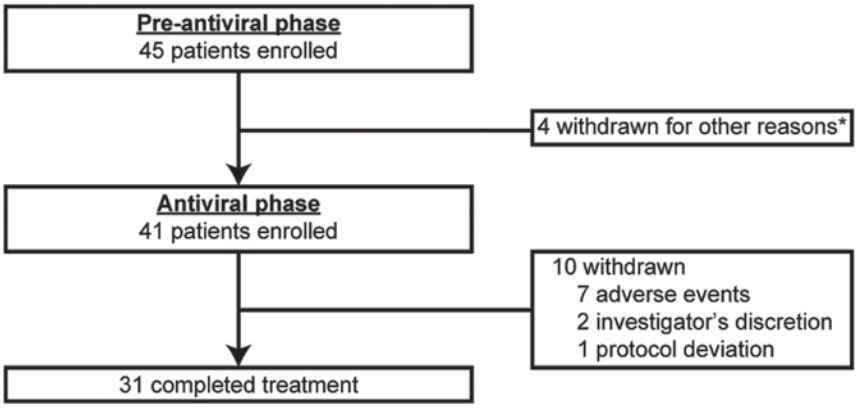

Figure 2. Patient disposition. *Four patients were withdrawn in the pre-antiviral phase, three because of violation of the eligibility criteria and one due to lack of achievement of the pre-defined platelet count threshold.

Statistical analysis. The proportion of patients who maintained the platelet counts at >50,000/μl during the antiviral phase was assumed to be 70% on the basis of the results [68.9%, 95% confidence interval (CI): 64.4-73.1] of a previous phase III study (unpublished data). Based on the analysis of binomial distribution, 50 evaluable patients were needed to provide 95% or more power to detect a response rate of at least 60%. Considering the proportion of patients who would not complete the pre-antiviral phase, the planned sample size for this study was 52 evaluable patients. However, the study was terminated early by the sponsor because of introduction of DAAs and low recruitment rates.

Continuous variables were summarized using descriptive statistics and categorical variables were summarized using frequency counts and percentages. The primary endpoints for the pre-antiviral and antiviral phases were analyzed using point estimates and two-sided 95% CI. For analysis of the SVR and other virologic endpoints, a patient with missing HCV RNA data at the assessment for any reason was regarded as a non-responder. A patient with missing data due to early discontinuation of the antiviral therapy and being treated with antiviral therapy beyond 48 weeks was regarded as a non-responder for all subsequent assessments.

Results

Pre-antiviral phase

Patient demographic and baseline characteristics. A total of 45 patients with HCV infection were enrolled from 16 centers in Japan between July 2012 and April 2014. Of these, four patients were withdrawn in the pre-antiviral phase, three because of violation of the eligibility criteria and one due to lack of achievement of the pre-defined platelet count threshold (Fig. 2). The baseline patient demographic and disease characteristics in the pre-antiviral phase are shown in Table I.

At baseline, the median age of patients was 59 years (range, 31-72 years), and 67% of the patients were female. The median platelet count at baseline was 63,000/μl. In total, 98% of the patients had Child-Pugh class A and 73% had genotype b HCV infection with high viral load (≥5 log IU/ml). Approximately half of the patients (24 patients, 53%) had undergone antiviral therapy at least once and 71% (17 patients) of them had experienced treatment failure.

Efficacy and safety. Of the 45 enrolled patients, 43 (96%) achieved a platelet count ≥100,000/μl, which was the platelet count threshold required to initiate the antiviral combination therapy with pegIFN α/RBV. The median time to response was 2.14 weeks (range, 1.0-9.6 weeks), and 36 patients (84%) achieved the threshold within 4 weeks after starting eltrombopag. A total of 41 patients, almost all of whom were receiving 12.5 mg or 25 mg of eltrombopag, entered the antiviral phase (Fig. 2). The remaining two responders did not meet the eligibility criteria after starting eltrombopag and were withdrawn from the study in the pre-antiviral phase.

During the pre-antiviral phase, two patients did not achieve platelet counts ≥100,000/μl. One patient withdrew from the study 1 week after starting eltrombopag because the severity of liver cirrhosis was re-classified as Child-Pugh class B. The other patient withdrew for lack of achievement of the platelet count threshold at week 9 despite dose escalation to the maximum dose of eltrombopag (50 mg).

Thirteen patients (29%) experienced at least one AE during the pre-antiviral phase. All AEs reported were grade 1 in severity. Headache and vomiting were the most common AEs and occurred in two patients each. AEs considered to be drug related were reported by four patients (9%); no serious AEs (SAEs) were reported during the pre-antiviral phase (Table II).

Antiviral phase

Patient demographic and baseline disease characteristics. A total of 41 patients who achieved the platelet count threshold entered the antiviral phase. The patient demographic and baseline disease characteristics are consistent with those in the pre-antiviral phase (Table III).

Efficacy. During the antiviral phase, eltrombopag doses were adjusted to maintain platelet counts ≥50,000/μl, which exceeded the threshold for dose reductions/interruptions of pegIFN. Of the 41 patients who entered the antiviral phase, 36 (88%) maintained the platelet count threshold throughout the antiviral phase. Although the five remaining patients experienced a transient decrease in platelet counts (<50,000/μl), no patient had a platelet count <25,000/μl (threshold for dose discontinuation of pegIFN) during the antiviral phase. Following the initiation of the antiviral combination therapy, the median platelet

Table I. Patient demographics and baseline disease characteristics during the pre-antiviral phase.

Patient demographics	Pre-antiviral treatment phase N=45
Age (years), median (range)	59 (31-72)
Sex, n (%)	
Female	30 (67)
Male	15 (33)
Body mass index (kg/m^2), mean ± SD	23.3±3.5
Diagnosis, n (%)	23/22 (51/49)
Chronic hepatitis C	23 (51)
Cirrhosis	22 (49)
HCV genotype, n (%)	
1a	0
1b	33 (73)
2a	6 (13)
2b	5 (11)
Other[a]	1 (2)
Child-Pugh classification, n (%)	
A (score 5-6)	44 (98)
B (score 7-9)	1 (2)
Platelet count, median (range)	63,000 (34,000-78,000)
HCV RNA (Log IU/ml), mean ± SD	6.4±0.7
ALT (U/l), mean ± SD	78.2±47.8

[a]This patient was infected with HCV serogroup 2. ALT, alanine aminotransferase; HCV, hepatitis C virus; SD, standard deviation.

Table II. AEs during the pre-antiviral phase.

AEs	Antiviral phase N=45
AEs occurring in ≥2 patients, n (%)	4 (8%)
Vomiting	2 (4%)
Headache	2 (4%)
Grade ≥3 adverse events, n (%)	0
Serious adverse events, n (%)	0

Adverse events during the pre-antiviral phase. The severity of adverse events was graded using the Division of AIDS Table for grading the Severity of Adult and Pediatric Adverse Events (version 1.9, dated December 2004). AE, adverse event.

counts gradually decreased by 4 weeks and remained at around 80,000/μl thereafter (Fig. 3).

No dose reductions of pegIFN were required in approximately half of the patients (20 patients, 48%) while administering eltrombopag in addition to the pegIFN therapy, 25% with pegIFN α-2a and 64% with pegIFN α-2b. However, one or no dose reductions of pegIFN were required in 63 and 72% of patients, respectively.

Table III. Patient demographic and baseline disease characteristics during the antiviral phase.

Patient demographics	Antiviral phase N=41
Age (years), median (range)	61 (31-72)
Sex, n (%)	
Female	28 (68)
Male	13 (32)
Body mass index (kg/m^2), mean ± SD	23.2±3.6
Diagnosis, n (%)	
Chronic hepatitis	22 (54)
Cirrhosis	19 (46)
HCV genotype, n (%)	
1a	0
1b	31 (76)
2a	6 (15)
2b	3 (7)
Other[a]	1 (2)
Child-Pugh classification	
A (score 5-6)	40 (98)
B (Score 7-9)	1 (2)
Baseline platelet counts, median (range)	63,000 (37,000-78,000)
HCV RNA (Log IU/ml), mean ± SD	6.4±0.7
ALT (IU/l), mean ± SD	82.0±48.0

[a]This patient was infected with HCV serogroup 2. ALT, alanine transaminase; HCV, hepatitis c virus; SD, standard deviation.

Overall, eight patients (20%) discontinued the pegIFN therapy prematurely because of AEs (six patients) and insufficient antiviral response (two patients). The proportions of patients who achieved the RVR, EVR, and ETR were 15% (six patients), 68% (28 patients), and 46% (19 patients), respectively. Nine patients (22%) achieved an SVR at the 24-week follow-up, 25% with pegIFN α-2a and 20% with pegIFN α-2b. Patients with non-genotype 1 HCV infection had a higher SVR rate compared with those having the genotype 1 HCV (60% vs. 10%, respectively). Patients aged <65 years had a higher SVR rate compared with those aged ≥65 years (27% vs. 9%, respectively). Viral breakthrough during the pegIFN/RBV therapy and relapse after the end of therapy were observed in two and eight patients (42% of patients achieving the ETR), respectively.

Safety. During the antiviral phase, all 41 patients experienced at least one AE or drug-related AE, with the majority being grade 2 or grade 3 in severity. The most common AEs were pyrexia, anemia, neutropenia, alopecia, pruritus, headache, and rash, which occurred in at least 30% of patients.

Grade 3 or higher AEs occurred in 25 patients (61%) during the treatment. Only four patients discontinued eltrombopag because of these AEs.

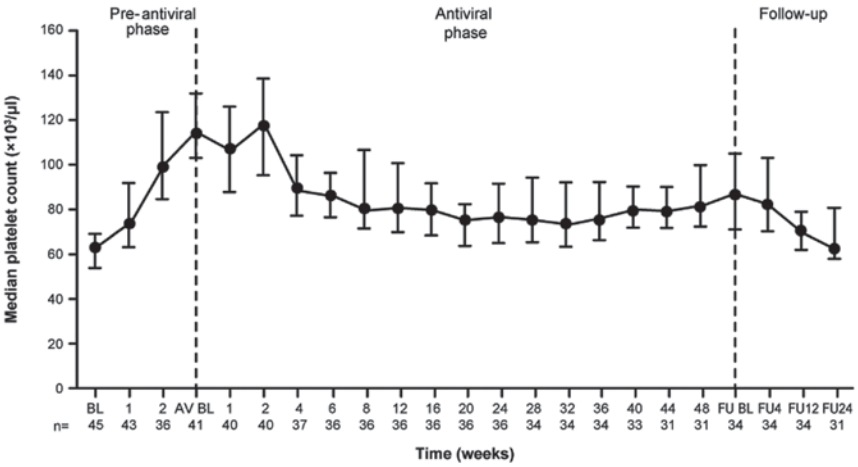

Figure 3. Median platelet counts during the study. AV BL, anti-viral baseline; BL, baseline; FU, follow-up.

A 64-year-old man experienced a hepatic function abnormality on day 56 (42 days after starting the antiviral treatment): Increase in alanine aminotransaminase (ALT) concentration to >5 times the upper limit of normal (ULN) (417 U/l) and aspartate transaminase (AST) concentration to >3 times the ULN (301 U/l), in conjunction with a total bilirubin concentration two times the ULN (2.4 mg/dl). The patient withdrew from the study based on the pre-defined criteria. Treatment with pegIFN and eltrombopag was discontinued on day 50 and 57, respectively. Although the abnormality seemed to improve with treatment discontinuation and use of conservative therapy, he was hospitalized due to grade 3 acute liver injury on day 63 (6 days after discontinuation of eltrombopag). The event was considered to be related to all three study treatments (eltrombopag, pegIFN, and RBV). On day 70, he developed mild hepatic encephalopathy due to hepatic failure. His platelet count began to increase after discontinuation of pegIFN and eltrombopag and reached the peak level (646,000/μl) on day 89; this was reported as a drug-related SAE (thrombocytosis). However, this patient did not present with a TEE. Using conservative therapy, the liver injury associated with the study treatment improved by day 152.

Another 37-year-old man experienced a liver disorder (grade 3 AE) on day 64 (29 days after starting the antiviral treatment), which manifested as increased ALT concentration to >5 times the ULN (363 U/l) and AST concentration to >3 times the ULN (308 U/l), in conjunction with a total bilirubin concentration two times the ULN (3.8 mg/dl). He was withdrawn from the study based on the pre-defined liver stopping criteria. The event was considered to be related to the study treatment and it resolved by day 99 (36 days after the discontinuation of the study treatment) without any treatment.

A 53-year-old woman experienced an increase in the percentage of myeloblasts (grade 3 SAE) on day 78 (3 days after starting the antiviral treatment), which was considered to be related to the antiviral treatment as it developed immediately after treatment initiation. Although eltrombopag was discontinued on day 80, the abnormality remained thereafter. The possibility of fibrosis was excluded based on a bone marrow biopsy performed on day 81.

Another 67-year-old woman experienced a decrease in body weight (grade 4 AE) by day 56 (41 days after starting the antiviral treatment), which was considered to be related to the study treatment. Although her weight decreased from 48.2 kg at baseline to 45.0 kg on day 56, the study treatment was continued thereafter. By day 323, her weight decreased to 37.8 kg and the treatment was discontinued. The decrease in body weight did not subside with treatment discontinuation.

During the antiviral phase, 20 patients (49%) experienced hepatobiliary AEs, with the majority being grade 1 or grade 2 in severity. Other than the above grade 3 hepatobiliary AEs (liver injury and liver disorder), one case of hyperbilirubinemia was reported as a grade 3 AE that resolved without dose modifications of the study drug. Only one patient presented with hepatic decompensation (grade 1 ascites) during the antiviral phase, and there was one case of hepatic encephalopathy during the follow-up phase. No deaths, TEEs, or cataract progression occurred in this study.

A total of eight SAEs were seen in five patients (12%) during the study (Table IV). In addition to the three SAEs (liver injury and thrombocytosis in the same patient and increase in the percentage of myeloblasts in another) described above, five other SAEs were reported in five patients, including the three patients with HCC and one patient each with herpes zoster and trigeminal neuralgia. None of these events were considered to be related to eltrombopag treatment. All of these other SAEs except one case of HCC resolved/recovered during the study.

Pharmacokinetics. The geometric mean C_{max} was 2.23 μg/ml (95% CI, 1.56-3.22) for the 12.5 mg dose of eltrombopag at approximately 5 h [T_{max}, 4.94 (95% CI, 3.38-7.24)] after drug administration and the geometric mean of the $AUC_{0-\tau}$ was 44.54 μg h/ml (95% CI, 26.2-67.6). In this study, two patients withdrew from the study because of hepatobiliary AEs; their plasma eltrombopag concentrations were 11.8 and 10.1 μg/ml at 14.5 and 12.5 h after the last dose (25 mg doses) of eltrombopag, respectively.

Discussion

The present study demonstrated that eltrombopag treatment ameliorates thrombocytopenia in Japanese patients with HCV-related cirrhosis and facilitates the initiation and subsequent maintenance of the pegIFN-based antiviral therapy for

Table IV. AEs during the antiviral treatment phase.

AEs	N=41
AEs in ≥20% of patients, n (%)	41 (100)
Pyrexia	24 (59)
Anemia	22 (54)
Neutropenia	17 (41)
Alopecia	16 (39)
Pruritus	14 (34)
Headache	13 (32)
Rash	13 (32)
Stomatitis	12 (29)
Malaise	11 (27)
Arthralgia	9 (22)
Decreased appetite	9 (22)
Nasopharyngitis	9 (22)
Thrombocytopenia	8 (20)
Grade ≥3 AEs in ≥2 patients, n (%)	25 (61)
Neutropenia	10 (24)
Anemia	4 (10)
Weight decreased	4 (10)
Hemoglobin level decreased	3 (7)
Neutrophil count decreased	3 (7)
WBC decreased	3 (7)
Leucopenia	2 (5)
Thrombocytopenia	2 (5)
Serious AEs, n (%)	5 (12)
Liver injury	1[a] (2)
Myeloblast percentage increased	1 (2)
Hepatocellular carcinoma	3[a,b] (2)
Thrombocytosis	1[a] (2)
Herpes zoster	1[b] (2)
Trigeminal neuralgia	1 (2)

The data include adverse events observed on treatment and all serious adverse events experienced during the study. [a]One patient experienced liver injury during the antiviral treatment phase, and hepatocellular carcinoma and thrombocytosis during the follow-up period. [b]One patient experienced hepatocellular carcinoma during the antiviral treatment phase and herpes zoster thereafter during the follow-up period. WBC, white blood cells; AE, adverse event.

subjects who would otherwise be ineligible or poor candidates for the pegIFN-based antiviral therapy.

Although the median age of patients enrolled was relatively higher compared with the age in the ENABLE studies, our results show that eltrombopag in combination with the antiviral therapy enabled 22% of cirrhotic Japanese patients to achieve a clinically meaningful SVR, which was consistent with the previous findings of ENABLE-1 and ENABLE-2 (23 and 19%, respectively) (10).

In the present study, owing to the effect of inter-ethnic differences on the pharmacokinetics of eltrombopag, a lower starting dose of 12.5 mg, ie, half the daily dose in the ENABLE studies and a more cautious dose titration regimen, was chosen. However, the $AUC_{0-\tau}$ in Japanese patients with HCV receiving 12.5 mg eltrombopag once daily was estimated to be 44.54 μg h/ml, which was unexpectedly lower than that in patients receiving 25 mg eltrombopag once daily in the ENABLE studies (118 μg h/ml) (19). In addition, the mean daily dose of eltrombopag during the antiviral phase was 22 mg/day, which was much lower than the dose used in the ENABLE studies (data not shown). Despite the lower dose, the magnitude of platelet response observed in the pre-antiviral and antiviral phases was similar to that observed in the ENABLE studies. Furthermore, the ability of this lower mean daily dose of eltrombopag has also been confirmed in this population, as observed in previous Japanese ITP studies (20,21). Consistent with this platelet response, the proportion of patients who did not require dose reduction of pegIFN in this study was similar to that found in the pooled analysis from the ENABLE studies (49 and 58%, respectively) (19).

The primary goal of treatment in chronic hepatitis C patients is to achieve an SVR and prevent progression to HCC. Although the SVR rate of 22% may seem low, this finding is in line with the observation in Japanese cirrhotic patients receiving pegIFN/RBV (22). Furthermore, it is clinically meaningful that eltrombopag treatment could facilitate the complete eradication of HCV, as these patients had no other available treatment options. At the time of initiation of this study, triple therapies, consisting of protease inhibitors (telaprevir or simeprevir) plus pegIFN/RBV therapy, were approved in Japan, and this treatment option showed a considerable improvement in the SVR rates in genotype 1 HCV patients (23-26). Further evaluation of the appropriate use of eltrombopag in combination with triple therapy will help in improving the SVR rates in cirrhotic patients with thrombocytopenia.

In this study, eltrombopag was generally well tolerated in patients with HCV infection and thrombocytopenia and the findings were similar to those observed in the previous ENABLE studies (10). TEEs are a frequent complication in patients with CLD, especially liver cirrhosis (2). In the recent studies, the incidence of portal vein thrombosis in patients with cirrhosis was reported to be 4.5-16.4% (27). In a post hoc analysis of a previous eltrombopag study in patients with CLD, it was found that increased platelet counts (>200,000/μl) were associated with the development of TEEs (18). In our study, a lower platelet count threshold for dose reduction than that in the ENABLE studies was considered in order to minimize the risk of thrombosis; the threshold used in this study was 150,000/μl compared with 200,000/μl in the ENABLE studies (10). If any symptoms or ultrasound findings of portal vein thrombosis were observed, abdominal scanning (e.g., CT, MRI) was performed. No TEEs were observed in the present study, whereas a higher incidence of TEEs was observed in the eltrombopag-treated group compared with the placebo-treated group in the antiviral phase of the ENABLE studies (10). However, a low baseline albumin level of ≤35 g/l or patient age >60 years, rather than high platelet counts, has been reported to be associated with the development of TEEs (19). Nevertheless, we recommend maintaining the platelet counts between 50,000 and 150,000/μl in Japanese HCV patients with thrombocytopenia based on the following findings: the platelet response was similar to that observed in the ENABLE studies (10) despite the different platelet count threshold; the increased risk of TEEs by platelets

or platelet-amplified inflammation cannot be ruled out (28); more cautious criteria (dose reduction if platelet counts >100,000/μl) were recommended in the European Union Summary of Product Characteristics of eltrombopag (29). Following the discontinuation of eltrombopag and pegIFN therapy, one patient developed thrombocytosis. Elevation of platelet counts following discontinuation of eltrombopag was observed in this study, similar to other studies of eltrombopag in patients with CLD and thrombocytopenia (18,30). The increased risk of TEEs should therefore be carefully evaluated, and platelet counts should be closely monitored during and after treatment with eltrombopag.

PegIFN therapy, as well as eltrombopag, has been associated with hepatobiliary laboratory abnormalities. Adjunctive treatment with eltrombopag can help avoid dose reduction or interruption of pegIFN, resulting in a greater exposure to pegIFN, which may contribute to an increased risk of pegIFN-related side effects. In our study, approximately half of the patients experienced hepatobiliary AEs. The majority of the events were grade 1 or 2 in severity and only one patient presented with hepatic decompensation (grade 1 ascites) during the antiviral phase, except for one hepatic encephalopathy during the follow-up phase. However, the plasma eltrombopag concentrations in two patients who withdrew from the study because of abnormal LFTs were 2.2- and 2.6-fold higher than those estimated from the C_{max} and T_{max} values after administration of the 12.5 mg dose in five patients without abnormal LFTs. Furthermore, it has recently been reported that a higher incidence of hepatic decompensation was observed in patients receiving the pegIFN therapy with eltrombopag compared with those receiving placebo (10), and a low baseline albumin level of ≤ 35 g/l or Model for End-Stage Liver Disease (MELD) score ≥10 was found to be associated with a higher risk of hepatic decompensation (18). Thus, hepatic enzymes should be carefully monitored during the treatment, and eltrombopag treatment should be administered with caution in patients with advanced liver disease.

The TPO-R is expressed not only on megakaryocytes but also on hepatic progenitor cells and hepatic sinusoidal endothelial cells, which plays a crucial role in HCC development and progression. TPO accelerates the proliferation of these cell types (31,32). Theoretically, there is a possibility that eltrombopag may increase the risk of HCC. In the present study, the incidence of HCC was 7% (three of 41 patients), similar to the annual rate in Japanese cirrhotic patients with HCV infection (33). A recent report of a randomized open-label study indicated that short-term eltrombopag treatment does not accelerate the progression of HCC in HCV-infected patients with cirrhosis (30). Furthermore, it has been found that the level of TPO-R expression in hematoma cell lines was lower than that in hepatocytes (34) and that TPO does not accelerate the proliferation of Huh7 cells both *in vitro* and *in vivo* (35). Thus, treatment with eltrombopag may not accelerate tumor progression in HCV-infected patients with liver cirrhosis.

Our study lacked a direct comparison with placebo and this could be considered a limitation of the study. However, a lower starting dose (12.5 mg) and a lower platelet count threshold (150,000/μl) for dose adjustment of eltrombopag than those used in the ENABLE studies were helpful to determine the minimum effective dose of eltrombopag without clinically important complications (hepatic decompensation and HCC progression).

In conclusion, eltrombopag (at doses of 12.5-50 mg) increased the platelet counts in chronic HCV-infected patients and enabled these patients to initiate and complete the IFN-based antiviral therapy. Thus, eltrombopag could be useful in the treatment of HCV-infected patients with thrombocytopenia who would be ineligible or poor candidates for the pegIFN-based antiviral therapy.

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Availability of data and materials

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

TK, AK, KF, SN, MK, HT, YT, KN, EM, HN, MSh, KT, and MSa helped in the recruitment of patients in the clinical study and interpreted the clinical data. MSa, TH, and KK contributed to the design of the clinical study. TK and TH wrote and edited the manuscript. TH contributed to the data analysis. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The study was approved by the National Hospital Organization Central Review Board of four national hospitals and institutional review boards of 12 other participating centers. It was performed in accordance with the Declaration of Helsinki, Good Clinical Practice guidelines, and local laws and regulations. All participating patients provided written informed consent prior to their inclusion in the study.

Patient consent for publication

Not applicable.

Competing interests

KT received lecture fees from Bristol-Myers Squibb K.K. (Japan), Abbvie (Japan), and AstraZeneca K.K (Japan). TH is currently an employee of Novartis Pharma K.K. and was an employee of GSK (Japan) during the conduct of the study. TK received lecture fees from Mitsubishi Tanabe Pharma Corporation (Japan), MSD K.K. Japan and Otsuka Pharmaceuticals Co., Ltd.

(Japan). All other authors declare that they have no competing interests.

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