Research Article

EASL EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER | JOURNAL OF HEPATOLOGY

Phase II study of avatrombopag in thrombocytopenic patients with cirrhosis undergoing an elective procedure

Norah A. Terrault[1,*], Tarek Hassanein[2], Charles D. Howell[3], Shobha Joshi[4], John Lake[5], Linda Sher[6], Hugo Vargas[7], Joe McIntosh[8], Shande Tang[8], Tim M. Jenkins[9]

[1]*University of California San Francisco, San Francisco, CA, United States;* [2]*Southern California Liver Centers, Coronado, CA, United States;* [3]*University of Maryland School of Medicine, Baltimore, MD, United States;* [4]*Tulane University School of Medicine, New Orleans, LA, United States;* [5]*Department of Medicine, University of Minnesota, Minneapolis, MN, United States;* [6]*University of Southern California, Los Angeles, CA, United States;* [7]*Mayo Clinic Hospital, Phoenix, AZ, United States;* [8]*Eisai Corporation of North America, Woodcliff Lake, NJ, United States;* [9]*Eisai Ltd, Hatfield, UK*

See Editorial, pages 1199–1201

Background & Aims: This is a phase II multicentre study to investigate the efficacy and safety of avatrombopag (E5501), an investigational second-generation thrombopoietin receptor agonist, administered one week prior to elective procedures in patients with thrombocytopenia secondary to cirrhosis.

Methods: Adults with cirrhosis and platelet counts $\geqslant$10 to $\leqslant 58 \times 10^9$/L were randomized to placebo or avatrombopag in two sequential cohorts. Cohort A: placebo *vs.* one of 3 different doses (100 mg loading dose followed by 20, 40, or 80 mg/day on days 2–7) of a first-generation avatrombopag formulation. Cohort B: placebo *vs.* one of 2 different doses (80 mg loading dose followed by 10 mg/day for days 2–7, or 20 mg/day for days 2–4) of a second-generation avatrombopag formulation. Primary end point was achievement of a platelet increase of $\geqslant 20 \times 10^9$/L from baseline and $>50 \times 10^9$/L at least once during days 4–8.

Results: A total of 130 patients were randomized: 93 patients (51, cohort A; 42, cohort B) to avatrombopag and 37 (16, cohort A; 21 cohort B) to placebo. The primary end point was achieved by 49.0% of treated patients in cohort A and 47.6% in cohort B compared to 6.3% and 9.5% of controls; a dose response was seen. Each avatrombopag regimen had a higher proportion of responders compared with their respective cohort placebo arms (p <0.01), except for the 100/40 mg group in cohort A (p = 0.17). The most common adverse events were nausea, fatigue, and headache. One patient in the (100/80) avatrombopag group, without a Doppler assessment at screening was diagnosed with portal vein thrombosis during post-treatment follow-up.

Conclusions: In this study avatrombopag was generally well-tolerated and increased platelet counts in patients with cirrhosis undergoing elective invasive procedures.

Introduction

Thrombocytopenia is a frequent finding in patients with cirrhosis [1]. Causes include splenic sequestration, increased destruction (auto-antibodies or low-grade disseminated intravascular coagulation), decreased production of thrombopoietin, and viral- or alcohol-induced myeloid suppression [2,3]. As platelet counts decline, the risk of bleeding in association with trauma or invasive procedures increases [4], although the risk depends upon the severity of thrombocytopenia and type of procedure [5,6]. In addition to a greater risk of bleeding following trauma, cirrhotics are also susceptible to thrombosis due to abnormal coagulation [7], with portal vein thrombosis (PVT) reported in up to 15% of cirrhotic patients in some studies [8]. Prolonged elevations in platelet count ($>200 \times 10^9$/L) can, in certain circumstances, confer risk of thrombosis as shown in a recent study involving the oral thrombopoietin receptor (TPO-R) agonist eltrombopag [9].

In patients with severe thrombocytopenia (platelet count $<50 \times 10^9$/L), platelet transfusions are often utilized for prophylaxis prior to invasive procedures. Platelet transfusions can lead to significant health consequences, including refractoriness to platelet transfusions, transmission of infectious agents, transfusion reactions, and rarely, fatalities [10]. Also, like other blood products, platelets are a relatively precious resource [11]. Avatrombopag (E5501) is an orally administered, investigational, small-molecule TPO-R agonist that is believed to mimic the biological effects of thrombopoietin *in vitro* and *in vivo* [12,13]. Like

Keywords: Avatrombopag; Chronic liver disease; Cirrhosis; Elective procedure; Platelet; Thrombocytopenia; Thrombopoietin receptor agonist.
Received 3 March 2014; received in revised form 3 July 2014; accepted 6 July 2014; available online 15 July 2014
☆ DOI of original article: http://dx.doi.org/10.1016/j.jhep.2014.08.051.
* Corresponding author. Address: Division of Gastroenterology, University of California San Francisco, S357, 513 Parnassus Ave, San Francisco, CA 94143-0538, United States. Tel.: +1 415 502 0318.
E-mail address: norah.terrault@ucsf.edu (N.A. Terrault).
Abbreviations: PVT, portal vein thrombosis; TPO-R, thrombopoietin receptor; NASH, non-alcoholic steatohepatitis; MELD, model for end-stage liver disease; PK, pharmacokinetic; PD, pharmacodynamic; EOT, end of treatment; AE, adverse events; BMI, body mass index; CTP, Child-Turcotte-Pugh score; TEAE, treatment-emergent adverse event.

thrombopoietin, avatrombopag is believed to bind to and activate the human TPO-R receptor, inducing signal transduction through a cascade of cellular events involving activation of the JAK-STAT and Shc-Ras-Raf-ERK signalling pathways, and ultimately enhancing megakaryocytic proliferation/differentiation and platelet production. In a phase II, double-blind, placebo-controlled study involving patients with chronic immune thrombocytopenia, 80% of patients who received once-daily avatrombopag 20 mg for 28 days had platelet count $\geqslant 50 \times 10^9$/L [14]. This is the first study to evaluate the safety and efficacy of avatrombopag in patients with cirrhosis scheduled to undergo an elective procedure. A first generation formulation of avatrombopag, used in the chronic immune thrombocytopenia phase II studies, as well as a second generation formulation of avatrombopag, that was much better suited for upscaling tablet production for large clinical trials and subsequent potential clinical use, were evaluated.

Materials and methods

Study design and treatment

This was a phase II, multicentre, randomized, placebo-controlled, double-blind, parallel-group study (study E5501-G000-202; NCT00914927) of patients with chronic liver disease and thrombocytopenia who were scheduled to undergo elective procedures (Supplementary Table 1). The main inclusion criteria were age $\geqslant 18$ years; chronic liver disease secondary to viral hepatitis non-alcoholic steatohepatitis [NASH], or alcoholic liver disease; model for end-stage liver disease (MELD) score $\leqslant 24$; two independent baseline platelet counts ranging from $\geqslant 10$ to $\leqslant 58 \times 10^9$/L, an elective invasive procedure scheduled 1–4 days after the last dose of avatrombopag or placebo; and a life expectancy of $\geqslant 3$ months. Major exclusion criteria were the presence of any primary haematologic disorder, idiopathic thrombocytopenic purpura of any cause, and a history of arterial or venous thrombosis. Additional exclusions criteria are noted in the Supplementary Materials and methods section.

Patients received once-daily oral avatrombopag *vs.* placebo with two formulations of avatrombopag studied sequentially. Cohort A used the first-generation formulation of avatrombopag. Patients were randomized 1:1:1:1 to receive either placebo or avatrombopag at one of three doses: 100 mg loading dose on day 1, followed by 20, 40 or 80 mg/day on days 2–7. Following completion of cohort A, two doses of the second-generation were therefore added to the study to bridge to the first generation formulation doses used in cohort A. Patients in cohort B were randomized 1:1:1 to receive placebo or avatrombopag at one of two doses: 80 mg loading dose on day 1, followed by either 10 mg/day on days 2–7, or 20 mg on days 2–4 and placebo on days 5–7 (Fig. 1). Cohort B doses were chosen to yield similar overall exposures to some of the doses used in cohort A. Dose selection was based on phase I pharmacokinetic data, pharmacokinetic (PK) and pharmacodynamic (PD) data from cohort A and subsequent PK/PD modelling and simulation. In phase I studies, the second-generation formulation produced about 1.6 times the exposure relative to the first-generation formulation. Platelet counts were determined at baseline and at least once during days 4–8, including end of treatment (EOT), on the day of procedure and on days 3, 7, 10, 14, 21, and 30 after the last dose.

Doppler ultrasound assessment of the portal vein was not used in cohort A. As information regarding a potential association between thrombopoietin agonists and PVT was emerging from other studies, a protocol amendment coinciding with

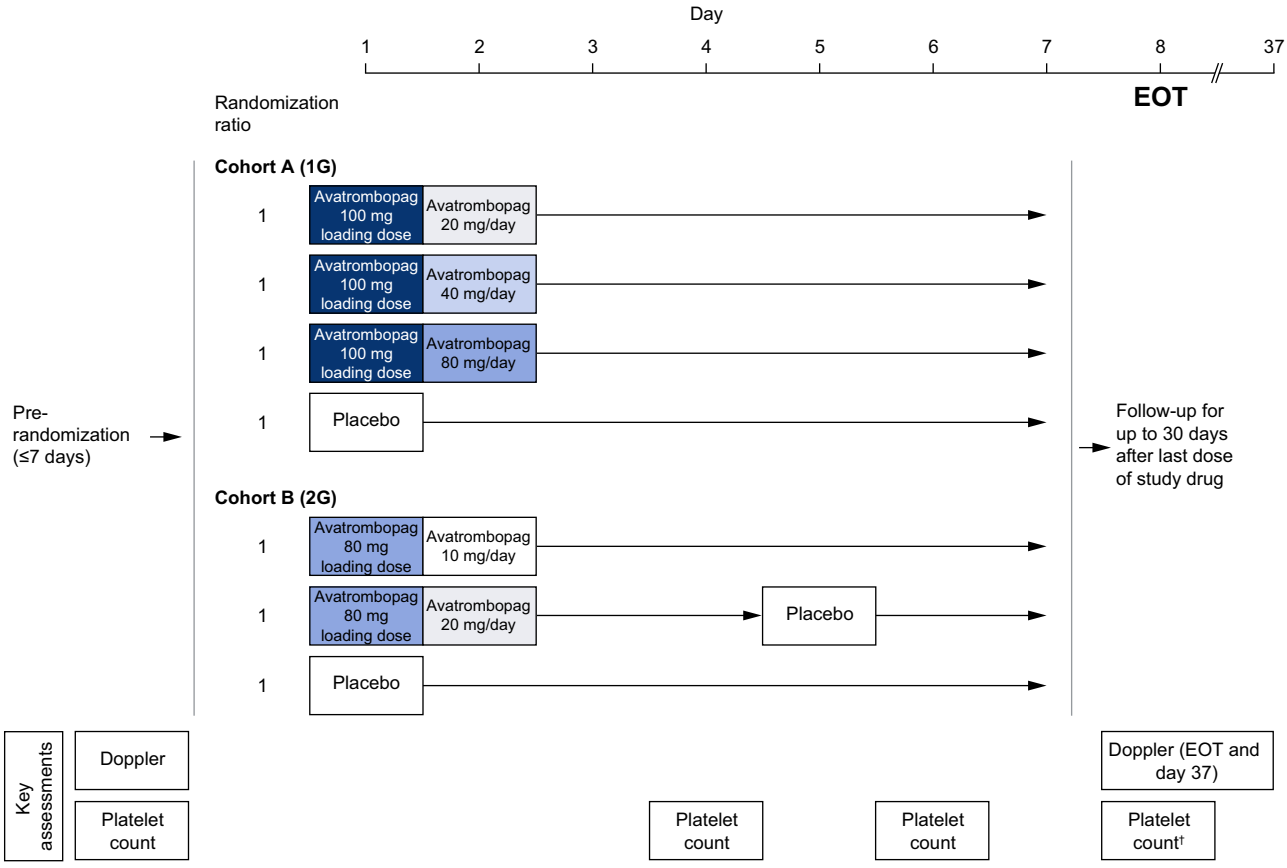

Fig. 1. Avatrombopag study E5501-G000-202 design. †Additional platelet counts where taken on days 10, 14, 17, 21, 28, and 37 (i.e., days 3, 7, 10, 14, 21, and 30 after the last dose).

cohort B enrolment was made to include baseline Doppler ultrasound evaluation. All protocol amendments are listed in the Supplementary Materials and methods section.

All patients provided written informed consent and local institutional review boards and ethics committees approved the protocol. The study was conducted in accordance with the principles of the Declaration of Helsinki, the International Conference for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, and FDA regulations on good clinical practice.

Study end points

Efficacy

The primary efficacy end point was an increase in platelet count $\geqslant 20 \times 10^9$/L above baseline and at least one platelet count $>50 \times 10^9$/L from days 4–8. A exploratory efficacy end point included the proportion of patients achieving a platelet count $>75 \times 10^9$/L or $>100 \times 10^9$/L at least once from days 4–8.

Safety

Patients were monitored for tolerability and adverse events (AEs) with physical examinations, medical updates, haematology and chemistry parameters obtained at baseline and day 8. Also electrocardiograms were obtained at baseline and day 8. In cohort B, Doppler ultrasounds were obtained at baseline, on day 8 and day 37 (i.e. 30 days after last dose). The number of patients receiving platelet transfusions prior to the procedure was recorded.

An independent Data Monitoring Safety Board reviewed all adverse events (AEs), from the day of signed informed consent through 30 days after a patient's last dose of study medication. All AEs were graded on a 5-point scale according to reported common terminology criteria for adverse events (NCI-CTC, version 3.0). Additional safety assessments included monitoring haematology and blood chemistry parameters, vital signs, physical examination and electrocardiogram.

Statistical methods

The planned enrolment was ~20 per treatment arm. However the final sample sizes for cohorts A (4 treatment arms) and B (3 treatment arms) were 67 and 63, respectively. Assuming that 10% of patients enrolled would not be evaluable and a placebo response rate of 20%, cohort A was predicted to generate a 79% power to detect a $\geqslant$50% absolute difference in the proportion of treated *vs.* placebo patients with a platelet response (with a 2-sided type-1 error of 0.05). For cohort B, using the same assumptions the power was predicted to be 83%.

All randomized patients who received $\geqslant$1 dose of study drug were included in the efficacy analysis (intent-to-treat [ITT] population). All randomized patients who received $\geqslant$1 dose of study drug and who had a post-baseline safety assessment were included in the safety analysis. Pooled avatrombopag-treated patients from cohorts A and B were compared to pooled placebo-treated patients (Fisher's exact test; two-sided significance level of 0.05). Responder counts and percentages were summarized by treatment group for each cohort with 95% exact confidence intervals. A prespecified sensitivity analysis that excluded patients who met inclusion criteria but whose platelet count was $>50 \times 10^9$/L on the treatment start date was performed.

Results

Study population

In total, 197 patients were screened and 130 randomized across 27 U.S. sites. Of these, 93 patients, including 51 in cohort A and 42 in cohort B, received $\geqslant$1 dose of avatrombopag (Fig. 2). Baseline demographics of the avatrombopag- and placebo-treated patients combined by cohort are shown in Table 1. Groups were similar except that HCC was more frequent among avatrombopag-treated patients compared to placebo-treated patients.

Efficacy

Proportion of responders

For the ITT population, the proportion of responders among all avatrombopag-treated patients was 48.4% *vs.* 8.1% in the combined placebo group (p <0.0001). Dose-dependent responses were evident across cohorts for avatrombopag-treated patients (Table 2). The primary end point (increase in platelet count $\geqslant 20 \times 10^9$/L above baseline and at least one platelet count $>50 \times 10^9$/L from days 4–8) was achieved by 49% of treated patients in cohort A and 47.6% in cohort B compared to 6.3% and 9.5% of controls. The proportion of patients achieving the treatment end point increased from 38.9% in the 100/20 mg arm to 76.6% in 100/80 mg arm in cohort A, and from 42.9% in the 80/10 mg arm to 52.4% in the 80/20 mg arm of cohort B (Table 2). Each avatrombopag regimen had a higher proportion of responders compared with their respective cohort placebo arms (p <0.01), except for the 100/40 mg group in cohort A (p = 0.17).

Sensitivity analysis

Sixteen patients (13 in the avatrombopag group and 3 in the placebo group) had a baseline platelet count $>50 \times 10^9$/L. With exclusion of these patients, the overall rate of platelet response was similar to that of the overall ITT population (Supplementary Table 2). The proportion of combined avatrombopag-treated patients with baseline platelet count $<50 \times 10^9$/L) who achieved the treatment end point was 47.5% *vs.* 8.8% in the combined pla-

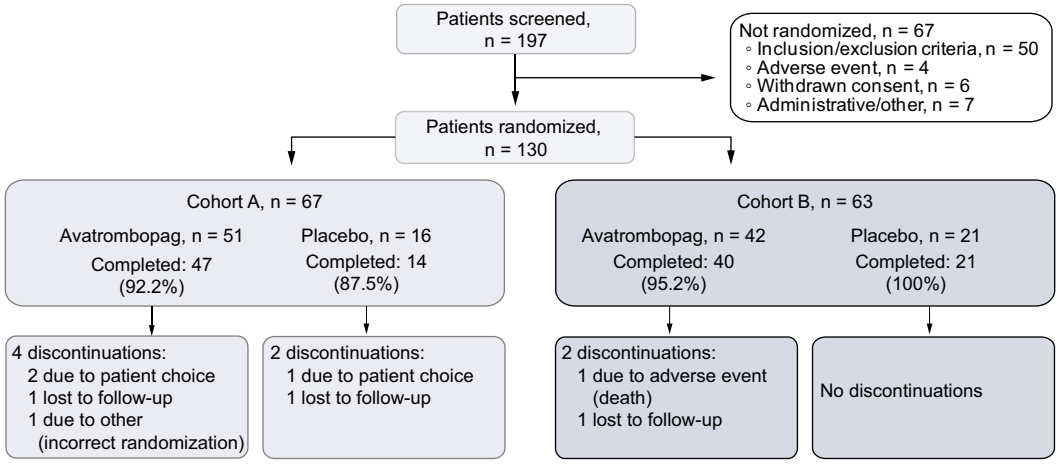

Fig. 2. Avatrombopag phase II study E5501-G000-202 patient flow.

Table 1. Baseline and procedural characteristics of the study population.

	Avatrombopag cohort A - combined (n = 51)	Placebo - cohort A (n = 16)	Avatrombopag cohort B - combined (n = 42)	Placebo - cohort B (n = 21)
Age, median (yr)	55.0	52.5	56.0	56.0
Males (%)	74.5	68.8	59.5	66.7
Caucasian (%)	90.2	87.5	81.0	90.5
BMI, median (kg/m^2)	29.8	30.48	30.4	30.1
MELD (median)	13	12	12	13
CTP (median)	7	7	7	7
CTP A (%)	37.3	43.8	42.9	38.1
CTP B (%)	45.1	43.8	40.5	52.4
CTP C (%)	17.6	12.5	14.3	9.5
Disease etiology				
Viral (%)	76.5	75.1	81.0	85.7
Alcohol (%)	3.9	6.3	4.8	4.8
NASH (%)	19.6	18.5	14.3	9.5
HCC (%)	23.5	0	16.7	14.3
Baseline platelet count (median, range)*	40.0 (18, 55[a])	38.0 (18, 52)	42.0 (18, 57)	38 (20,55)
Baseline platelet count ≤50 K (%)*	88.2	93.8	83.3	90.5
Invasive procedure performed				
Dental procedure	3	1	1	3
Liver biopsy	1	1	0	1
Vascular catheterization	0	0	0	0
Paracentesis	3	0	1	2
Endoscopy	10	7	12	5
Bronchoscopy	0	0	0	0
TIPS	0	0	0	0
Umbilical hernia repair	1	0	0	0
Pleurocentesis/pleural biopsy	0	0	0	0
Other[b]	33	7	27	10

[a]One patient was mistakenly randomized at a high platelet count of 107 × 10^9/L; this patient, randomized to the 100/20 mg arm of cohort A, was discontinued from the study.
[b]Procedures within the "Other" category include the following: colonoscopy, colonoscopy with polypectomy/polyp removal, esophagogastroduodenoscopy (EGD), EGD with banding, endoscopy with possible esophageal banding, periodontal scaling and root planing, endoscopy with banding, colonoscopy and endoscopy, transcatheter arterial chemoembolization, right heart catheterization, radiofrequency ablation, upper GI endoscopy, and chemoembolization.
*Based on local results.
BMI, body mass index; CTP, Child-Turcotte-Pugh score; HCC, hepatocellular carcinoma; MELD, model for end-stage liver disease.

cebo group. Each avatrombopag regimen had a higher proportion of responders *vs.* their respective cohort placebo arms.

Change in platelet count over time

The change from baseline in median platelet count over time is shown in Fig. 3. The maximum median platelet count increase from baseline in all avatrombopag-treated patients occurred within 10–13 days. The proportion of patients with a platelet count >75 × 10^9/L prior to procedure ranged from 22.2% to 41.2% for cohort A avatrombopag-treated patients *vs.* 6.3% for placebo-treated patients and 14.3–33.3% with cohort B avatrombopag-treated patients *vs.* 0% with placebo-treated patients. A platelet count >100 × 10^9/L prior to procedure occurred in 0–17.6% of patients treated with avatrombopag, and in no placebo patient. Two cohort A 100/80 mg patients achieved a platelet count >200 × 10^9/L, with maximum platelet counts of 204 × 10^9/L and 256 × 10^9/L. No thrombotic complications were observed in either patient. The median platelet counts by treatment group, following the last dose of study drug, are shown in Supplementary Table 3.

Safety

The overall incidence of AEs was similar for both the avatrombopag-treated and placebo groups (Table 3). Treatment-related adverse events (TEAEs) considered by investigator to be possibly or probably related to study drug, or TEAEs with missing causality, occurred in 29.0% and 29.7% of patients in the combined avatrombopag and placebo groups, respectively, and similarly in the individual avatrombopag formulation cohorts (Supplementary Table 4).

Nausea, fatigue, and headache were among the most commonly reported AEs (occurring in >2 patients in any treatment group) in patients receiving avatrombopag or placebo. An overview of TEAEs and serious AEs (SAEs; safety population) is presented in Supplementary Table 4. Investigator assessments of TEAEs that were "possibly" or probably" related to study drug

Table 2. Proportion of patients achieving platelet count response* (ITT population).

Cohort A	Placebo	Avatrombopag			
	(n = 16)	20 mg (n = 18)	40 mg (n = 16)	80 mg (n = 17)	Total (n = 51)
Response, n (%) 95% CI	1 (6.3) 0.2, 30.2	7 (38.9) 17.3, 64.3	5 (31.3) 11.0, 58.7	13 (76.5) 50.1, 93.2	25 (49.0) 34.8, 63.4
vs. placebo		0.0425	0.1719	<0.0001	0.0005#

Cohort B	Placebo	Avatrombopag		
	(n = 21)	10 mg (n = 21)	20 mg (n = 21)	Total (n = 42)
Response, n (%) 95% CI	2 (9.5) 1.2, 30.4	9 (42.9) 21.8, 66.0	11 (52.4) 29.8, 74.3	20 (47.6) 32.0, 63.6
vs. placebo		0.0325	0.0063	0.0093#

*Defined as an increase in platelet count from baseline of $\geqslant 20 \times 10^9$/L and at least one platelet count $>50 \times 10^9$/L.
Percentages are based on the total number of patients in relevant treatment group; 2-sided exact 95% CI.
#Global test using Chi-square test.

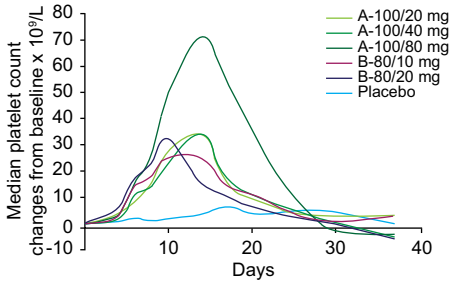

Fig. 3. Change from baseline in median platelet count over time for all patients receiving avatrombopag. (This figure appears in colour on the web.)

occurred in 29.0% and 29.7% of patients in the combined avatrombopag and placebo groups, respectively. Sixteen (17.2%) avatrombopag-treated patients had SAEs and 4 (10.8%) placebo patients. Most SAEs were consistent with complications of cirrhosis. There was one discontinuation due to AEs (NCI-CTC grade 1) in a cohort A (100/80 mg arm) patient with mild nausea and vomiting, two days after the first dose of avatrombopag.

Serious adverse events occurred in 10.8% of placebo and 17.9% of avatrombopag-treated patients ($p = 0.36$). The most frequently observed serious adverse events, reflected complications of underlying cirrhosis, including, ascites, hepatic encephalopathy, gastrointestinal bleeding and infections. Bleeds, reported as serious treatment-emergent adverse events, occurred rarely; only a

Table 3. Treatment-emergent adverse events occurring in >2 patients in any treatment group in study E5501-G000-202, shown in order of overall frequency with avatrombopag (safety population).

MedDRA preferred term	Cohort A					Cohort B			
	Placebo (n = 16) n (%)	20 mg (n = 18) n (%)	40 mg (n = 16) n (%)	80 mg (n = 17) n (%)	Avatrombopag - combined (n = 51) n (%)	Placebo (n = 21) n (%)	10 mg (n = 21) n (%)	20 mg (n = 21) n (%)	Avatrombopag - combined (n = 42) n (%)
Any TEAE	12 (75.0)	17 (94.4)	13 (81.3)	13 (76.5)	43 (84.3)	16 (76.2)	17 (81.0)	18 (85.7)	35 (83.3)
Nausea	2 (12.5)	1 (5.6)	2 (12.5)	2 (11.8)	5 (9.8)	3 (14.3)	5 (23.8)	2 (9.5)	7 (16.7)
Fatigue	1 (6.3)	4 (22.2)	1 (6.3)	0	5 (9.8)	4 (19.0)	2 (9.5)	2 (9.5)	4 (9.5)
Headache	2 (12.5)	2 (11.1)	2 (12.5)	1 (5.9)	5 (9.8)	3 (14.3)	1 (4.8)	3 (14.3)	4 (9.5)
Portal hypertensive gastropathy	0	4 (22.2)	2 (12.5)	0	6 (11.8)	2 (9.5)	3 (14.3)	0	3 (7.1)
Abdominal pain	0	4 (22.2)	1 (6.3)	1 (5.9)	6 (11.8)	3 (14.3)	2 (9.5)	0	2 (4.8)
Vomiting	0	1 (5.6)	2 (12.5)	3 (17.6)	6 (11.8)	1 (4.8)	0	1 (4.8)	1 (2.4)
Diarrhea	0	2 (11.1)	1 (6.3)	1 (5.9)	4 (7.8)	2 (9.5)	0	3 (14.3)	3 (7.1)
Dizziness	1 (6.3)	2 (11.1)	0	1 (5.9)	3 (5.9)	1 (4.8)	3 (14.3)	1 (4.8)	4 (9.5)
Pyrexia	2 (12.5)	0	0	2 (11.8)	2 (3.9)	3 (14.3)	1 (4.8)	0	1 (2.4)
Rectal hemorrhage	0	0	0	0	0	0	3 (14.3)	0	3 (7.1)
Any TEAE leading to study drug d/c	0	0	0	1 (2.0)	1 (2.0)	0	0	0	0
Serious TEAEs	1 (6.3)	3 (16.7)	2 (12.5)	3 (17.6)	8 (15.7)	3 (14.3)	5 (23.8)	3 (14.3)	8 (19.0)
Deaths	0	0	0	0	0	0	1 (4.8)	0	1 (4.8)

MedDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent adverse event.

total of 4 subjects reported such bleeds among the 130 enrolled subjects in this study (i.e. incidence of 3%). All of these reported bleeds were gastrointestinal bleeds (3 upper gastrointestinal bleeds and 1 haemorrhoidal bleed).

There was one death after an operative procedure, deemed possibly related to study drug, in a cohort B (80/10 mg arm) patient with pre-existing cardiopulmonary disease (Child-Turcotte-Pugh [CTP] grade C [score 10] cirrhosis and a MELD score of 20). The patient had an unwitnessed cardiopulmonary arrest two days after biopsy of a head and neck tumour, and expired prior to arrival at the hospital. SAEs in this patient were hemoptysis, acute respiratory failure, metabolic acidosis, renal failure, and cardiopulmonary arrest. There had been no elevation in platelet count from baseline in this patient; a platelet transfusion was given prior to an endoscopy procedure performed eight days after randomization.

Use of platelet transfusions was not standardized across sites. In cohort A, 7 (14.9%) patients in the avatrombopag arm and none in the placebo arm received platelet transfusions ($p = 0.18$) and in cohort B, 2 (5.3%) avatrombopag-treated *vs.* 7 (35%) placebo-treated patients received transfusions ($p = 0.006$).

A PVT was identified in a cohort A (100/80 mg arm) patient with a CTP grade C (score 10) cirrhosis and a MELD score of 19, and no hepatocellular carcinoma and a prior ultrasound (3 months before study entry) demonstrating low portal vein flow (~5 cm/s). The PVT was diagnosed on study day 34 and was treated successfully with warfarin and portal vein thrombectomy. The patient's baseline platelet count was 53×10^9/L, and 102×10^9/L at EOT. At the time of PVT diagnosis, platelet count was 55×10^9/L, having decreased from a peak platelet count of 199×10^9/L observed on day 17.

Discussion

In this phase II study of a new investigational thrombopoietin-receptor agonist, avatrombopag, we found avatrombopag elevated platelet counts in a generally dose-dependent manner in patients with cirrhosis and thrombocytopenia. Avatrombopag was generally well tolerated; the most commonly reported AEs were nausea, fatigue and headache, all similar to placebo. These results support to further study avatrombopag as a potential treatment for thrombocytopenia in patients with advanced chronic liver disease undergoing elective invasive procedures.

The risk of thrombotic events in the context of using thrombopoietin-receptor agonists is a concern. A prior study of eltrombopag in patients with cirrhosis undergoing invasive procedures suggested an association between platelet counts $>200 \times 10^9$/L and PVT events [9]. In that study, >25% of patients on eltrombopag attained a platelet count $>200 \times 10^9$/L; of the six patients on eltrombopag who developed PVT, five had a platelet count $>200 \times 10^9$/L. In the current study, a platelet count $>200 \times 10^9$/L occurred in two of 93 (2.15%) patients in cohort A without the occurrence of PVT. One case of PVT developed in a patient in cohort A whose peak platelet count reached 199×10^9/L, with a platelet count at time of diagnosis of 55×10^9/L. A Doppler sonography scan performed three months prior to study entry demonstrated evidence of a very low portal vein flow (5 cm/s). Thus, Doppler ultrasound with diminished portal vein velocity appears important for identifying patients at risk of thrombotic events during treatment with thrombopoietin-receptor agonists. We hypothesize that appropriate dose selection and duration of dosing, producing a less aggressive rise in platelet count, might be the reason for the very low incidence (1.1%) of observed PVT in the current study. In addition, introduction of Doppler scans and/or MRI and CT imaging in cohort B removed patients with PVT at screening.

Limited guidelines exist on the use of platelet transfusion in this patient population but there is a general agreement that they should be considered as a pre-procedure treatment for those patients with platelet counts $<50 \times 10^9$/L and who are considered to be at risk for bleeding. This is supported by robust prospective data indicating the potential for a 10-fold increase in bleeding risk, in this patient population, when platelets counts are below this threshold [6]. There is less agreement, however, concerning the treatment of patients with platelet counts between 50 and 75×10^9/L who require an invasive procedure. In cohort B, the transfusion rate was lower in avatrombopag-treated compared to placebo-treated patients but because the use of platelet transfusions was not standardized, these data are difficult to interpret. Nonetheless, the frequency of platelet transfusion would appear to be a clinically meaningful end point to be used in pivotal studies, once information concerning the ability of a thrombopoietin receptor agonist to elevate platelet counts has been obtained in phase II studies.

In summary, avatrombopag achieved significant increases in platelet counts 3–7 days after treatment in approximately 50% of patients, and in up to 75% of those receiving the highest dose. Avatrombopag was generally well tolerated and the rate of PVT was very low. Phase III studies will utilize the rate of platelet transfusion as a primary end point in order to confirm and extend this finding.

Conflict of interest

This study was funded by Eisai Inc. Minor editorial assistance was provided by Complete Medical Communications and was supported by Eisai Inc.

Acknowledgements

We thank all the patients, study coordinators and investigators who participated in this study. The complete list of study investigators can be found in the Supplementary data section.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jhep.2014.07.007.

References

[1] Bashour FN, Teran JC, Mullen KD. Prevalence of peripheral blood cytopenias (hypersplenism) in patients with nonalcoholic chronic liver disease. Am J Gastroenterol 2000;95:2936–2939.
[2] Violi F, Basili S, Raparelli V, Chowdary P, Gatt A, Burroughs AK. Patients with liver cirrhosis suffer from primary haemostatic defects? Fact or fiction? J Hepatol 2011;55:1415–1427.
[3] Stasi R. Pathophysiology and therapeutic options in primary immune thrombocytopenia. Blood Transfus 2011;9:262–273.

[4] Afdhal N, McHutchison J, Brown R, et al. Thrombocytopenia associated with chronic liver disease. J Hepatol 2008;48:1000–1007.
[5] Giannini EG, Greco A, Marenco S, Andorno E, Valente U, Savarino V. Incidence of bleeding following invasive procedures in patients with thrombocytopenia and advanced liver disease. Clin Gastroenterol Hepatol 2010;8:899–902.
[6] Seeff LB, Everson GT, Morgan TR, et al. Complication rate of percutaneous liver biopsies among persons with advanced chronic liver disease in the HALT-C trial. Clin Gastroenterol Hepatol 2010;8:877–883.
[7] Ponziani FR, Zocco MA, Campanale C, et al. Portal vein thrombosis: insight into physiopathology, diagnosis, and treatment. World J Gastroenterol 2010;16:143–155.
[8] Amitrano L, Guardascione MA. Management of portal vein thrombosis in cirrhotic patients. Mediterr J Hematol Infect Dis 2009;1:e2009014.
[9] Afdhal NH, Giannini EG, Tayyab G, et al. Eltrombopag before procedures in patients with cirrhosis and thrombocytopenia. N Engl J Med 2012;367:716–724.
[10] McClelland B, Contreras M. Appropriateness and safety of blood transfusion. BMJ 2005;330:104–105.
[11] Shah NL, Northup PG, Caldwell SH. A clinical survey of bleeding, thrombosis, and blood product use in decompensated cirrhosis patients. Ann Hepatol 2012;11:686–690.
[12] Fukushima-Shintani M, Suzuki K, Iwatsuki Y, et al. AKR-501 (YM477) in combination with thrombopoietin enhances human megakaryocytopoiesis. Exp Hematol 2008;36:1337–1342.
[13] Fukushima-Shintani M, Suzuki K, Iwatsuki Y, et al. AKR-501 (YM477) a novel orally-active thrombopoietin receptor agonist. Eur J Haematol 2009;82:247–254.
[14] Bussel JB, Zhang J, Tang S, McIntosh J, Kuter DJ. A randomized, double-blind, placebo-controlled phase II trial on the efficacy, safety and tolerability of E5501 (AKR501) in subjects with chronic immune thrombocytopenia (ITP). Blood 2010;116:A71.