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【 ORIGINAL ARTICLE 】

Eltrombopag in Combination with Rabbit Anti-thymocyte Globulin/Cyclosporine A in Immunosuppressive Therapy-naïve Patients with Aplastic Anemia in Japan

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Abstract:

Objective In Japan, immunosuppressive therapy (IST) with anti-thymocyte globulin (ATG), and cyclosporine A (CsA) is the standard of care in patients with aplastic anemia (AA) who are not indicated for stem-cell transplantation, although some patients may experience relapse. This study assessed the efficacy and safety of eltrombopag in combination with rabbit-ATG/CsA in IST-naïve patients with non-severe or severe AA in Japan.

Methods In this non-randomized, open-label, single-arm, phase II study, rabbit-ATG/CsA and eltrombopag were initiated on Days 1 and 15 (±3 days), respectively, and continued for ≥26 weeks; rabbit-ATG was given for 5 days (Days 1 to 5). The primary endpoint was the overall response rate (ORR) at Week 26.

Patients Patients with AA who were IST-naïve and ≤70 years old or between 71 and 75 years old based on the recommendation of the investigator were enrolled in Japan.

Results Of the 11 enrolled patients, 10 started treatment with eltrombopag. The ORRs at Weeks 26 and 52 were 70.0% and 60.0%, respectively. The ORR at Week 26 was 100% (all 3 patients) in patients with non-severe AA and 57.1% (4/7) in patients with severe AA. Among transfusion-dependent patients, 66.7% (4/6) and 62.5% (5/8) became red blood cell- and platelet-transfusion independent, respectively. The most common adverse events were nausea and headache. No deaths or hematologic malignancies were reported. A cytogenetic abnormality was reported in one patient.

Conclusion This study confirmed the clinical benefit of eltrombopag plus rabbit-ATG/CsA in IST-naïve patients with non-severe or severe AA in Japan.

Key words: eltrombopag, aplastic anemia, rabbit-ATG/CsA, Japan

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Introduction

Aplastic anemia (AA) is a bone marrow failure disorder characterized by pancytopenia and hypocellular marrow (1, 2). It is most likely caused by an immune-mediated mechanism through T cells, resulting in a marked reduction in hematopoietic stem cells (3-5). A survey data reported that the incidence of AA was 8.2 per million person-years from 2004 to 2012 (6). In Europe and North America, the

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Table 1. Severity Classification.

Stage	Severity	Criteria
Stage I	Mild	Other than the stages below
Stage II	Moderate	At least 2 of the following conditions are met: Reticulocyte count <60,000/μL Neutrophil count <1,000/μL Platelet count <50,000/μL
Stage III	Moderately severe	At least 2 of the following conditions are met and regular RBC transfusion[a] is required: Reticulocyte count <60,000/μL Neutrophil count <1,000/μL Platelet count <50,000/μL
Stage IV	Severe	At least 2 of the following conditions are met: Reticulocyte count <20,000/μL Neutrophil count <500/μL Platelet count <20,000/μL
Stage V	Very severe	At least 1 of the following condition is met in addition to Neutrophil count <200/μL: Reticulocyte count <20,000/μL Platelet count <20,000/μL

[a]Regular RBC transfusion is defined as a need for transfusion of 2 units or more per month.
RBC: red blood cell

incidence is 2-3 per million per year, which is 2- to 3-fold lower than in East Asia (7).

In Japan and some other countries, the standard treatment for AA is immunosuppressive therapy (IST) with antithymocyte globulin (ATG), and cyclosporine A (CsA) in patients not selected for potentially curative allogeneic hematopoietic stem cell transplantation (allo-HSCT) (8, 9). There are limitations associated with ATG/CsA treatment, mainly a "ceiling" response rate of 60-70%, with one-third relapse rates by 2 years, incomplete responses, and clonal evolution in nearly 15% of patients after long-term treatment (7, 10).

Eltrombopag is an oral, small-molecule thrombopoietin (TPO) mimetic that binds to the TPO receptor myeloproliferative leukemia protein, which leads to the differentiation of hematopoietic stem cells to megakaryocytes (11, 12). A preclinical study showed that eltrombopag promoted multilineage hematopoiesis (12). Previous studies have shown that eltrombopag was effective in patients with AA refractory to immunosuppression (13, 14). Another important study evaluating the addition of eltrombopag to standard IST as the first-line treatment showed that the overall response rate (ORR) at 6 months was about 90% in patients with severe AA (15). The complete response (CR) rate was 44%, which was 27% higher than that historically observed with IST alone. Based on these trial results, eltrombopag was approved in the US in combination with standard IST for the first-line treatment of adult and pediatric patients ≥2 years old with severe AA.

Ethnic differences in the pharmacokinetics (PK) of eltrombopag have been reported, with a Japanese population showing approximately 2-fold greater exposure than a non-Japanese population (predominantly Caucasian) (16, 17). Thus, the dose of eltrombopag must be carefully adjusted in Japanese patients compared with Caucasians because of the overlapping liver toxicities of eltrombopag and ATG/CsA.

Considering the ethnic and treatment differences, use of ATG/CsA in the treatment of non-severe AA and the current situation that only rabbit-ATG is available in Japan, we conducted a phase II study to assess the efficacy and safety of eltrombopag in combination with rabbit-ATG/CsA in IST-naïve Japanese patients with non-severe or severe AA.

Materials and Methods

Patients

This study enrolled patients between 18 and 70 years old; patients between 71 and 75 years old, if eligible, were also included based on the recommendation of the investigator. Patients had to have a diagnosis of non-severe (stage II and III) or severe AA (stage IV and V) according to the diagnosis criteria established by the Study Group on Idiopathic Hematopoietic Disorder (Table 1) and had to be considered eligible for treatment with rabbit-ATG and CsA. In addition, patients had to have an Eastern Cooperative Oncology Group performance status of 0 or 1 and an adequate organ function. Patients with congenital AA or cytogenetic abnormalities, who had received prior rabbit- or horse-ATG/antilymphocyte globulin (ALG)-based therapy or steroid pulse therapy for AA, or who had been treated with CsA within six months prior to rabbit-ATG therapy were excluded from the study.

The institutional review board for each center reviewed the study protocol and all amendments, and the study was conducted in accordance with the Declaration of Helsinki. All patients were required to provide their written informed consent.

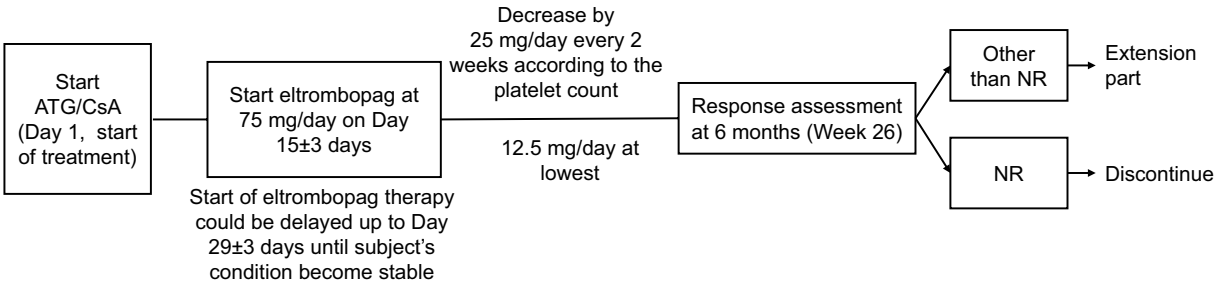

Figure 1. **Study design. AA: aplastic anemia, ATG: anti-thymocyte globulin, CsA: cyclosporine A, NR: no response**

Table 2. **Criteria for Dose Adjustment of Eltrombopag: Weeks 2-26.**

Platelet count	Dose adjustment
Over 200,000/μL	Decrease the dose by 25 mg every 2 weeks to the lowest dose that maintains the platelet count at 50,000-200,000/μL (minimum 12.5 mg/day)[a]
Over 400,000/μL	Interrupt the drug until the platelet count reaches less than 200,000/μL; restart administration at a dose 25 mg/day lower (12.5 mg/day if the dose at interruption was 25 mg/day)[b]

[a]The dose of eltrombopag was to be decreased once the platelet count exceeded 200,000/μL, even within 2 weeks after dose increase, according to the dose adjustment criteria. When the platelet count remained above 200,000/μL after the dose reduction, the dose was to be decreased further, 2 weeks after the dose reduction. Eltrombopag could be decreased up to 12.5 mg/day but was to be interrupted if a further dose reduction to ≤12.5 mg/day became necessary. The modified dose of eltrombopag was to be maintained for 2 weeks or longer.

[b]Eltrombopag was to be interrupted once the platelet count exceeded 400,000/μL, even within 2 weeks after dose increase, according to the dose adjustment criteria.

Study design

This multicenter, non-randomized, open-label, phase II study evaluated the efficacy and safety of eltrombopag in combination with rabbit-ATG/CsA in Japanese patients who had non-severe or severe AA and had not been treated with ATG/ALG-based IST. Patients received intravenous rabbit-ATG (2.5-3.75 mg/kg/day per local practice) from Days 1 to 5 and oral CsA (3 mg/kg) twice per day on Day 1 until Week 26. Eltrombopag 75 mg was initiated on Day 15 (Fig. 1). All doses were administered in a fasting state. The criteria for dose adjustments from Weeks 2 to 26 are shown in Table 2.

Patients were monitored for the platelet count or hematologic response criteria weekly for the first four weeks and then every two weeks until Week 26. Patients in whom the treatment was assessed as effective [achieved complete response (CR)/partial response (PR) or showed a trend of hematological improvement] at Week 26 entered the extension phase to continue treatment until the product became commercially available. The criteria for dose adjustments in the extension part are provided in Table 3. Supportive therapy was permitted throughout the study when required and included granulocyte colony-stimulating factor (G-CSF), iron chelation, or platelet transfusion (if the count was <10,000/μL with apparent bleeding tendency or <20,000/μL with pyrexia) and red blood cell (RBC) transfusion (if hemoglobin was <7 g/dL or in the presence of relevant signs and symptoms, such as exertional dyspnea).

Endpoints and assessments

The primary efficacy endpoint was the ORR at six months after the start of treatment (Week 26), which was defined as the proportion of patients who achieved either CR or PR. The response was assessed based on the established response criteria, and the details are described in Table 4. PR was determined in cases achieving transfusion independence from RBCs and platelets with a diagnosis improving from severe AA in those who had initially had severe AA. In patients with non-severe AA who were transfusion-dependent at the study entry and achieved transfusion independence, an improvement in the hemoglobin level or neutrophil or platelet count according to the predefined criteria (Table 4) or doubling or normalization of at least 1 blood cell lineage was considered to indicate PR. In patients with both severe and non-severe AA, CR was determined in cases achieving transfusion independence, a hemoglobin level ≥12 g/dL for women and ≥13 g/dL for men, an absolute neutrophil count ≥1,500/μL, and a platelet count ≥ 150,000/μL.

The secondary efficacy endpoints were the ORR at Weeks 14 and 52; the CR rate at Week 26 based on the modified response criteria, as used in the study by Townsley et al. (15); the blood counts (platelets, hemoglobin, neutrophils, and reticulocytes); and the time to the onset and duration of CR and PR. The PK of eltrombopag were also determined. In addition, the incidence of adverse events (AEs), with their severity assessed using the Common Terminology

Table 3. Criteria for Dose Adjustment in the Extension Part.

Platelet count	Dose adjustment
Less than 50,000/μL, or the amount required for platelet transfusion does not decrease	Increase the dose by 25 mg every 2 weeks to a maximum of 75 mg/day
Between 50,000/μL and 100,000/μL	Maintain the dose
Over 100,000/μL	Decrease the dose by 25 mg every 2 weeks until the platelet count can be maintained between 50,000/μL and 100,000/μL. However, maintaining the dose without reduction is acceptable for the following subjects: - patients who achieved CR at Week 26 - patients who are expected to achieve CR in the extension part - patients who have achieved CR in the extension part
Over 200,000/μL	Interrupt the drug until the platelet count decreases to lower than 50,000/μL; restart administration at a dose 25 mg/day lower (12.5 mg/day if the dose at interruption was 25 mg/day)

When all of the hematologic responses remained fulfilled for >8 weeks during the extension part: the dose of eltrombopag was decreased by half and further modified as below.

Hematologic value	Dose adjustment
The following levels are kept for longer than 8 weeks: - platelet count of >50,000/μL and - hemoglobin of >10 g/dL and - neutrophil count of >1,000/μL	Decrease the dose by 50% (12.5 mg/day at the lowest)
Values remain fulfilling the above criteria at the 50% dose for additional 8 weeks	Interrupt the administration
Values decreased to the following levels at the 50% dose: - platelet count of <30,000/μL or - hemoglobin of <9 g/dL or - neutrophil count of <500/μL	Permitted to increase the dose by 12.5 mg every 2 weeks to a maximum of 75 mg/day[a]
Values decreased to below the above levels after dose interruption	Permitted to resume the treatment at the dose at interruption

[a]Increasing the dose by 25 mg up to 75 mg was acceptable at the discretion of the investigator (or sub-investigator). However, consultation with the Sponsor's medical advisor was required before increasing the dose to a level higher than the dose before reduction. Even when the hematologic values remained below the criteria, maintaining the dose without increase was acceptable at the discretion of the investigator (or sub-investigator).

CR: complete response

Table 4. Response Criteria.

Response	Subjects with severe/very severe AA	Subjects with moderate/moderately severe AA
NR	Aggravated or remains severe/very severe	Aggravated/not meeting the criteria mentioned for PR and CR
PR	Transfusion independent (RBC and platelet) and not meeting the criteria for severe AA	Transfusion independent (RBC and platelet) (when dependent at baseline), or doubling from baseline or normalization of at least 1 blood cell lineage, or increase of baseline hemoglobin of >3 g/dL (when <6 g/dL at baseline), or increase of baseline neutrophil count of >500/μL (when <500/μL at baseline), or increase of baseline platelet count of >20,000/μL (when <20,000/μL at baseline)
CR	Transfusion independence and hemoglobin ≥12 g/dL for female/≥13 g/dL for male and absolute neutrophil count ≥1,500/μL and platelet count ≥150,000/μL	

Hematologic values were assessed in the state with no influence of transfusion (platelet and RBC) or G-CSF.

AA: aplastic anemia, CR: complete response, G-CSF: granulocyte colony-stimulating factor, NR: no response, PR: partial response, RBC: red blood cell

Criteria for Adverse Events (CTCAE) version 4.0, and their relationship with the study drug were monitored and reported.

PK

Pre-dose blood samples were collected 15 days after starting 75, 50, or 25 mg eltrombopag to determine the plasma

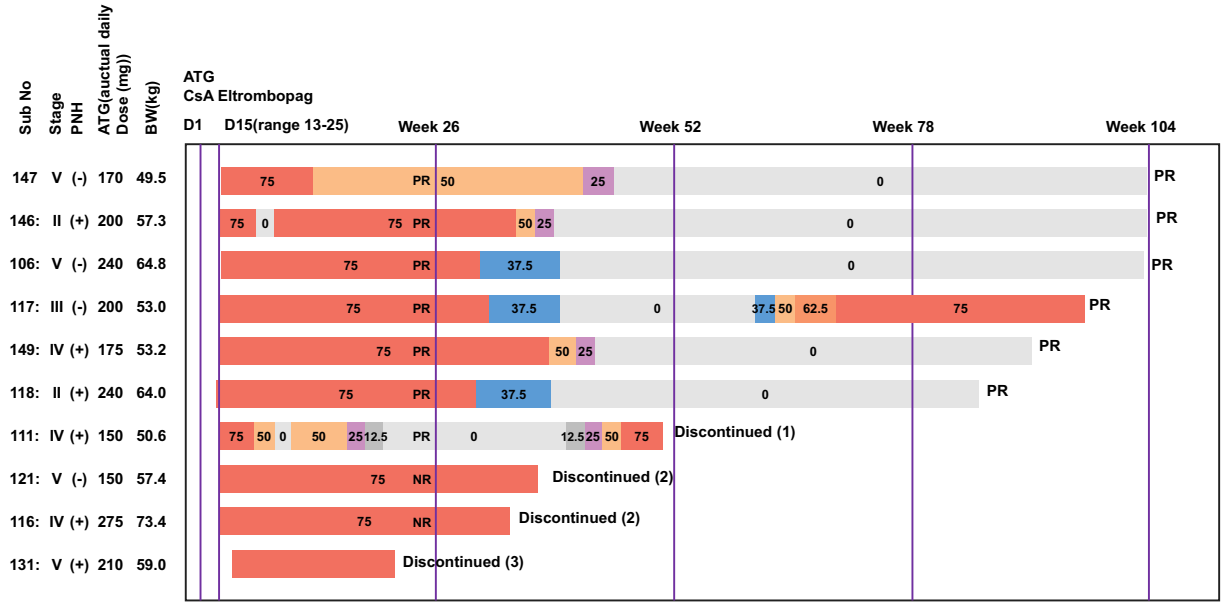

Figure 2. **Clinical courses of all patients. The numbers in the bar graph indicate the dose of eltrombopag. (1) Restarted eltrombopag after interruption based on the dose adjustment criteria but discontinued the treatment because of a lack of efficacy later. (2) Continued eltrombopag treatment even though they did not achieve PR because of hematologic improvement but discontinued the treatment because of lack of efficacy later. (3) Discontinued eltrombopag because of prolonged QT on an electrocardiogram, but this event was considered to be unrelated to any study treatment. ATG: antithymocyte globulin, CsA: cyclosporine A, NR: no response, PNH: paroxysmal nocturnal hemoglobinuria, PR: partial response, Sub: subject**

trough concentrations. For the 75-mg dose, blood samples were also collected 4 hours after administration. The plasma concentrations were measured using liquid chromatography-tandem mass spectrometry, with a lower quantitation limit of 100 ng/mL.

Statistical analyses

Ten patients were planned for inclusion based on study feasibility. Given the study design, the analysis was descriptive. A point estimate and the exact 2-sided 95% confidence intervals were determined for the ORR, CR rate, and PR rate at Weeks 26 (primary endpoint) and 52. For the other endpoints, summary statistics were provided.

Results

Patient characteristics

Between May 2015 and January 2016, 12 patients were screened for eligibility; 11 were enrolled and received rabbit-ATG/CsA. Of these 11 patients, 10 initiated eltrombopag, and 1 was withdrawn from the study before the initiation of eltrombopag due to not meeting the eligibility criteria. Of the 10 patients, 4 withdrew from the study treatment: 3 because of lack of efficacy and 1 on reaching the protocol-defined criteria for stopping the treatment (QT prolongation). Among the remaining six patients, one completed the treatment until the study end, and five interrupted eltrombopag treatment based on the dose adjustment criteria (Table 2, 3) for efficacy. The clinical course of all patients throughout the study is shown in Fig. 2.

The baseline demographics and clinical characteristics are provided in Table 5. The median age was 55.5 years old, and majority of the patients were women (n=7). The median time since the diagnosis of AA was 17.7 days; 3 patients (30%) had non-severe AA (stage II and III), and 7 (70%) had severe AA (stage IV and V). Six patients were transfused with RBCs within eight weeks before starting rabbit-ATG/CsA, and eight were transfused with platelets within four weeks before starting rabbit-ATG/CsA.

PK

The mean trough eltrombopag concentrations measured 15 days after the administration of eltrombopag at 25 mg (n =1), 50 mg (n=2), and 75 mg (n=10) were 6,070 ng/mL, 20,800 ng/mL, and 21,800 ng/mL, respectively. The mean trough concentrations numerically increased with the increase in the eltrombopag dose (Table 6). The mean eltrombopag concentration measured 4 hours after the administration of eltrombopag at 75 mg was 28,400 ng/mL.

Efficacy and relapse

The ORR was 70.0% (7/10) and 60.0% at Weeks 26 and 52, respectively (Table 7). All responders had PR, and no additional response was observed after Week 26.

The median duration of observation of patients was 88.36

Table 5. Patient Demographics and Baseline Characteristics.

	Eltrombopag+ATG/CsA (N=10)
Characteristic	
Age (years)	
Median	55.5
Range	39-67
Age group (years), n (%)	
<18	0
18-64	9 (90)
65-74	1 (10)
≥75	0
Race, n (%)	
Asian-Japanese	10 (100)
Sex, n (%)	
Female	7 (70)
Male	3 (30)
Time since diagnosis, days	
Median	17.7
Range	3-102
Stage at screening, n (%)	
II	2 (20)
III	1 (10)
IV	3 (30)
V	4 (40)
Transfusion RBC, n (%)	
Independence	4 (40)
Dependence	6 (60)
Transfusion platelet, n (%)	
Independence	2 (20)
Dependence	8 (80)
PNH, n (%)	
Positive	6 (60)
Negative	4 (40)
Laboratory parameters	
Platelets (cells/μL)	
Median	14,250
Range	3,000-31,000
Hemoglobin (g/dL)	
Median	7.8
Range	7.1-8.5
Neutrophils (cells/μL)	
Median	262.4
Range	30-1,122
Reticulocytes (cells/μL)	
Median	10,000
Range	2,380-66,330
TPO (ng/L)	
Median	419.72
Range	215.6-1,354.7
MCV (fL)	
Median	90.15
Range	86.5-107

ATG: anti-thymocyte globulin, CsA: cyclosporine A, MCV: mean corpuscular volume, PNH: paroxysmal nocturnal hemoglobinuria, RBC: red blood cell, TPO: thrombopoietin

months (range, 22.0-104.1 months). In the responders, the median time to response was 3.75 months (range, 2.5-4.8 months). The median duration of response was 17.28 months for 7 patients who responded at least once by the end of the study.

The response rate according to the subgroup analysis of sex, age, disease severity, and presence/absence of paroxysmal nocturnal hemoglobinuria (PNH) clones at Week 26 is shown in Table 8. Overall, five of seven women and two of three men achieved the ORR. In patients <65 years old, 7 of 9 responded, while no patients ≥65 years old responded. All patients with non-severe AA responded, while only four of seven patients with severe AA achieved PR. There were three responders (one with stage III disease at screening and two with stage V at screening) among the four PNH-negative patients and four responders (two with stage II disease at screening and two with stage IV at screening) among the six PNH-positive patients. Of these seven responders, five showed PR until the end of study; one patient relapsed after interrupting eltrombopag and could not achieve a response even after resuming eltrombopag, while the other relapsed patient achieved PR by the end of the study after resuming eltrombopag (Fig. 2).

Of the six RBC transfusion-dependent patients at baseline, four had been transfusion-independent for at least eight weeks after starting treatment with rabbit-ATG/CsA, three remained independent until Week 52, and one resumed RBC transfusion because of a lack of efficacy during the extension phase. Of the eight platelet transfusion-dependent patients at baseline, five had been transfusion-independent at least for four weeks after starting treatment with rabbit-ATG/CsA. Of these five patients, four remained platelet transfusion-independent until Week 52. Nine patients received at least 1 dose (range, 1-8 doses) of G-CSF as supportive therapy during the study. Overall, the median platelet count, hemoglobin, neutrophil count, and reticulocyte count at Week 52 were 89,000/μL, 11.0 g/dL, 1,729.6/μL, and 59,755/μL, respectively.

Safety

The median actual treatment duration of eltrombopag therapy excluding days of interruption was 251 days (range, 125-518 days) as of the final analysis. The median modified average daily dose of eltrombopag excluding days of interruption was 69.4 mg/day (range, 49-75 mg/day). The dose of eltrombopag was reduced and interrupted in most patients (seven of nine) in the extension phase. The reasons for dose interruption/reduction other than the dose adjustment criteria were nausea, vomiting, increased bilirubin, alanine aminotransferase (ALT), gamma-glutamyltransferase, and epigastric distress. The median average dose of CsA was 114.3 mg/day (range, 71-217 mg/day), and the median duration of CsA was 618.5 days (range, 302-729 days).

All patients treated with eltrombopag experienced at least one AE on treatment. Eltrombopag was interrupted in seven patients at least once during the study.

Table 6. Plasma Trough Concentrations of Eltrombopag.

Eltrombopag dose, n	Sample time point	Concentration, ng/mL Mean (SD)	CV% Mean
25 mg (n=1)	0 h pre-dose	6,070 (-)	
50 mg (n=2)	0 h pre-dose	20,800 (7,920)	38.1
75 mg (n=10)	0 h pre-dose	21,800 (7,370)	33.9
75 mg (n=10)	4 h post-dose	28,400 (8,960)	31.6

CV%=coefficient of variation (%)=SD/Mean×100.

CV: coefficient of variation

Table 7. Efficacy of Eltrombopag at Weeks 26 and 52.

ORR	At 3 months	At 6 months	At 12 months
Patients, n	10	10	10
Response, n [% (95% CI)]			
ORR (PR+CR)	7 [70 (34.8–93.3)]	7 [70 (34.8–93.3)]	6 [60 (26.2–87.8)]
PR	7 [70 (34.8–93.3)]	7 [70 (34.8–93.3)]	6 [60 (26.2–87.8)]
CR	0	0	0

CI: confidence interval, CR: complete response, ORR: overall response rate, PR: partial response

Table 8. Response by Subgroups at Week 26.

	Gender		Age group		Stage at screening[a]		PNH	
	Female N=7	Male N=3	<65 N=9	≥65 N=1	Non-severe N=3	Severe N=7	Negative N=4	Positive N=6
Overall response – n (%)								
CR+PR (95% CI)[b]	5 (71.4) (29.0-96.3)	2 (66.7) (9.4-99.2)	7 (77.8) (40.0-97.2)	0 (0.0-97.5)	3 (100) (29.2-100.0)	4 (57.1) (18.4-90.1)	3 (75.0) (19.4-99.4)	4 (66.7) (22.3-95.7)
Response – n (%)								
CR (95% CI)[b]	0 (0.0-41.0)	0 (0.0-70.8)	0 (0.0-33.6)	0 (0.0-97.5)	0 (0.0-70.8)	0 (0.0-41.0)	0 (0.0-60.2)	0 (0.0-45.9)
PR (95% CI)[b]	5 (71.4) (29.0-96.3)	2 (66.7) (9.4-99.2)	7 (77.8) (40.0-97.2)	0 (0.0-97.5)	3 (100) (29.2-100.0)	4 (57.1) (18.4-90.1)	3 (75.0) (19.4-99.4)	4 (66.7) (22.3-95.7)
NR	2 (28.6)	1 (33.3)	2 (22.2)	1 (100)	0	3 (42.9)	1 (25.0)	2 (33.3)

[a]Severe AA was defined as severe or very severe AA. Non severe AA was defined as moderate or moderately severe AA.

[b]Exact 95% CI based on binomial distribution.

AA: aplastic anemia, CI: confidence interval, CR: complete response, PR: partial response, NR: no response

Overall, 8 patients (80.0%) had 51 AEs related to any study treatment. Of these, 17 AEs suspected to be related to eltrombopag were reported in 5 patients (50.0%) (Table 9). Majority of the AEs related to eltrombopag therapy were abnormality in liver function tests and myalgia.

Overall, 15 AEs of Grade 3 or 4 severity were reported in 8 patients, but none except for 1 (Grade 4 lymphocyte count decrease considered to be related to rabbit-ATG) was related to the study treatment.

Ten hepatobiliary AEs were reported in 7 patients before Week 26, but none were reported after Week 26. The most common hepatobiliary AEs were increased ALT and blood bilirubin levels [n=3 (30%), for both]. All hepatobiliary events were Grade 1 or 2 in severity.

No AEs leading to study discontinuation or dose reduction or interruption of eltrombopag were reported after the clinical cut-off point at Week 26.

Clonal evolution

No mortality or hematologic malignancies, including myelodysplastic syndrome or acute myeloid leukemia, were reported at the end of the study. Fluorescent *in situ* hybridization did not detect the loss of chromosome 7. A cytogenetic abnormality [46,XX,del(6)(q?)[2]/46,XX[18]] was detected in one patient at Week 52; however, this event was not reported as an AE by the investigator.

Discussion

This was the first prospective study to confirm the efficacy and safety of eltrombopag in combination with rabbit-ATG/CsA in IST-naïve Japanese patients with non-severe or

Table 9. Adverse Events Related to Eltrombopag (Safety Population).

Preferred term	Eltrombopag+ATG/CsA (N=10)
Any event, n (%)	**5 (50.0)**
Myalgia	3 (30.0)
Blood bilirubin increased	2 (20.0)
Nausea	2 (20.0)
Acne	1 (10.0)
Alanine aminotransferase increased	1 (10.0)
Amylase increased	1 (10.0)
Blood alkaline phosphatase increased	1 (10.0)
Gamma-glutamyltransferase increased	1 (10.0)
Headache	1 (10.0)
Impetigo	1 (10.0)
Pneumonia	1 (10.0)
Sebaceous hyperplasia	1 (10.0)

PTs are sorted in the order of descending frequency.

A patient with multiple occurrence of a PT is counted only once in that PT.

A patient with multiple AEs is counted only once in the total row.

Only AEs occurring from the start date of ATG administration to 30 days of the end date of eltrombopag administration are reported.

AE: adverse event, ATG: anti-thymocyte globulin, CsA: cyclosporine A, PT: preferred term

severe AA. Overall, at the end of 26 weeks, 70% of the patients had achieved a response; among patients with non-severe or severe AA, 100% and 57.1% achieved a response, respectively. The clinically relevant response rates observed in this study highlight the efficacy of the combination, regardless of the severity of the disease.

Horse-ATG, used for the treatment of AA in Japan and other Asian countries, has been out of production, and only rabbit-ATG is currently available. As rabbit-ATG is more immunosuppressive than horse-ATG, a higher response rate and improved survival were anticipated. However, some reports showed that the response rate with rabbit-ATG was lower than that with horse-ATG (18-22). Attempts have also been made to improve the response rate beyond the ATG and CsA combination using various drugs, including methenolone enanthate (23), cyclophosphamide (24), high-dose methylprednisolone (25), danazol (26), and mycophenolate mofetil (27); however, none have been successful in clinical trials.

A study by Townsley et al. demonstrated an improvement in the hematologic response when eltrombopag was added to ATG/CsA as the first-line treatment (15). In two non-randomized studies involving patients with refractory AA, eltrombopag monotherapy was shown to improve blood counts and achieve platelet and RBC transfusion independence (13, 14). This implies that eltrombopag monotherapy or in combination with IST can be effective in patients with severe AA. In a previous prospective study, the ORR was about 90% in patients receiving eltrombopag plus horse-ATG/CsA at Week 26 (15). In a recent phase II study in newly diagnosed patients with severe AA, the ORR was 76.0% with eltrombopag plus IST at 2 years of follow-up, which is similar to that in the current study (28). In another study from China in newly diagnosed patients with AA, the ORR was 90% at Week 12, and the responses were maintained in all responders at 47 weeks with eltrombopag as a first-line therapy (29). However, of note, the aforementioned studies had different regimens of IST/ATG, with different types or dosing schedules. In the current study, the ORR was 60% at Week 52, indicating the long-term efficacy of eltrombopag.

The response rates of rabbit-ATG versus horse-ATG were reported to be similar in Asian populations (13, 30, 31). Of the 2 retrospective studies with rabbit-ATG/CsA in Japanese patients with AA, 1 study (moderate AA, n=6; severe AA, n =6) reported ORRs at 3 and 6 months of 50% and 75%, respectively (30). The ORR with rabbit-ATG was 64.6%, and that with horse-ATG was 56.0% at 6 months in the other study (non-severe AA, n=2; severe AA, n=20) (31). These findings suggest that the ORRs in rabbit-ATG are similar to those in horse-ATG in a Japanese population. However, the small sample size hampered the performance of an accurate evaluation of the ORR in Japanese patients with AA.

Because of PK ethnic difference (16, 17), the dose of eltrombopag needs to be carefully adjusted in Japanese patients compared with Caucasians due to overlapping liver toxicities of eltrombopag and ATG/CsA. Ethnic differences in eltrombopag PK and AA as a disease may affect the evaluation of how eltrombopag is performing in combination with rabbit-ATG/CsA. Eltrombopag is initiated at a 50% lower dose in patients with severe AA of East Asian origin than in the US. However, whether or not this difference in the dose of eltrombopag also influences the response with rabbit-ATG/CsA/eltrombopag in patients with AA is unclear.

No AEs of Grade ≥3 related to any study treatment were observed except for a decrease in the lymphocyte count (Grade 4) in 1 patient, potentially due to rabbit-ATG therapy. However, other new safety issues requiring eltrombopag dose reduction were identified. In the current study, eltrombopag was initiated on Day 15 to avoid any potential overlapping liver toxicities with ATG/CsA; however, the highest ORR was reported in patients receiving eltrombopag on Day 1 concurrently with IST (15), suggesting that eltrombopag can be initiated on Day 1.

Clonal evolution or cytogenetic abnormality associated with dysplasia, including the loss of chromosome 7, was not observed in our study. A recent meta-analysis involving 11 studies indicated clonal evolution at the karyotype abnormality level in 8% of IST-naïve patients treated with eltrombopag plus IST (32). In another study, the rates of clonal evolution among patients with severe AA treated with eltrombopag and horse-ATG/CsA were similar to those of their historical cohorts at a median follow-up of 2 years; the role of eltrombopag in clonal evolution is therefore unclear (15). A large, randomized, placebo-controlled trial (RACE: NCT02099747; estimated enrollment: 200 participants) is ongoing and expected to provide additional data on

clonal evolution.

This study confirmed the clinical benefit of eltrombopag in combination with rabbit-ATG/CsA treatment in IST-naïve Japanese patients with non-severe or severe AA at Week 26 and demonstrated a risk-benefit profile favorable for long-term treatment in Japanese participants. The overall tolerability was acceptable and consistent with the previously reported safety profile of eltrombopag.

Author's disclosure of potential Conflicts of Interest (COI).

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