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ORIGINAL ARTICLE

An open-label extension study evaluating the safety and efficacy of romiplostim for up to 3.5 years in thrombocytopenic Japanese patients with immune thrombocytopenic purpura (ITP)

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Abstract Long-term use of the thrombopoietin mimetic romiplostim was examined in Japanese patients with chronic immune thrombocytopenic purpura (ITP) in this open-label extension. The starting dose of romiplostim was the previous trial dose or 3 μg/kg/week, which was titrated up to 10 μg/kg/week to maintain platelet counts between 50 and 200 $\times$ 10^9/L. As of April 2010, 44 patients had enrolled; 71 % women, median age 55.5 years, with five patients discontinuing romiplostim due to patient request (2), administrative decision (2), or not achieving study-defined platelet response (1). Median treatment duration was 100 weeks; median average weekly dose was 3.8 μg/kg. Twenty-eight patients (64 %) self-injected romiplostim. The most frequent adverse events were nasopharyngitis and headache. Nine patients (20 %) had a total of 14 serious adverse events (0.31/100 patient-weeks); of these, only oral hemorrhage was considered treatment related. Fifty hemorrhagic adverse events were reported in 20 patients (46 %) (1.12/100 patient-weeks). Ninety-six percent of patients had a platelet response (doubling of baseline platelet count and platelet count $\geq$50 $\times$ 10^9/L). Of the 25 patients receiving concurrent ITP therapy at baseline, all reduced or discontinued the therapy. Eight patients (18 %) received rescue medications. Administration of up to

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3.5 years of romiplostim increased platelet counts and was well tolerated in Japanese patients with chronic ITP.

Keywords Immune thrombocytopenic purpura (ITP) · Romiplostim · Thrombopoietin receptor agonists · Thrombopoietin mimetic

Introduction

Immune thrombocytopenic purpura (ITP) is an autoimmune disorder characterized by isolated thrombocytopenia (i.e., no other hematologic abnormality) with platelet counts below 100×10^9/L, due to both increased platelet destruction and a relatively low level of platelet production [1–5]. Incidence of ITP in Japan is 2.16/100,000/year, with approximately 70 % of cases occurring in patients older than 50 years [6, 7]. Treatment is typically not recommended for patients with platelet counts $>50 \times 10^9$/L [2, 8, 9]. When treatment is necessary, options include corticosteroids and other immunosuppressive agents, splenectomy, and immunoglobulins [8, 9]. However, a significant proportion of ITP patients either will not respond to or will not have a sustained platelet response with these agents, many of which are accompanied by significant side effects [8, 15, 16]. For those ITP patients who have active *Helicobacter pylori* infection, *H. pylori* eradication therapy appears to improve thrombocytopenia in some [6, 10–14].

While, traditionally, options such as those listed above aim to limit platelet destruction, a new class of agents addresses the now understood relative deficiency in platelet production. Romiplostim, a thrombopoietin (TPO) mimetic with no structural overlap with TPO, increases platelet production by a mechanism similar to that of endogenous TPO [5, 17, 18]. Romiplostim, which has been shown to be effective for the treatment of chronic ITP with good tolerability, has been approved in many countries for the treatment of chronic ITP in adult patients with an insufficient response to previous treatments [19]. Specifically, romiplostim (Nplate®) is indicated in the United States for the treatment of thrombocytopenia in patients with chronic ITP who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy [20]. Romiplostim should be used only in patients with ITP whose degree of thrombocytopenia and clinical condition increases the risk for bleeding, but not to normalize platelet counts [20]. In Europe, romiplostim is indicated for the treatment of splenectomized adult chronic ITP patients who are refractory to other treatments and may be considered as second-line treatment for adult non-splenectomized ITP patients for whom surgery is contraindicated [21]. As of January 21, 2011, the Japanese regulatory agency, the Ministry of Health, Labour, and Welfare, approved romiplostim (brand name Romiplate®) for the treatment of thrombocytopenia in adult chronic ITP in patients who have had an inadequate response to or are intolerant of other therapies for ITP [22]. Romiplostim should be used only in those patients with ITP whose degree of thrombocytopenia and clinical condition increase the risk for bleeding [22].

Disease presentation, pharmacokinetics, pharmacodynamics, and safety may be affected by ethnic background [23, 24]. Therefore, the use of romiplostim in Japanese patients with ITP was assessed in clinical studies in Japanese patients with ITP. Similar to early phase studies in other populations, romiplostim was found to be well tolerated and effective at increasing platelet counts in a dose-dependent manner with good tolerability in Japanese patients with ITP [25–27]. Likewise, romiplostim significantly increased and maintained platelet counts and was well tolerated in a phase 3 study of 34 Japanese patients with ITP, with similar dosing to that seen in non-Asian patients [27, 28]. However, there are few reports of the long-term safety and efficacy of romiplostim in clinical trials. We describe here the results of patients from the phase 2 and phase 3 studies who then continued into an open-label extension study for up to 3.5 years of romiplostim treatment.

Materials and methods

Study design

This was an open-label extension study designed to assess the safety and efficacy of long-term romiplostim dosing in thrombocytopenic Japanese patients with ITP (Fig. 1). If patients entered the extension study within 12 weeks of receiving the last romiplostim dose in the previous study and had shown an increase in platelet counts $\geq 20 \times 10^9$/L from baseline at least once during the 13-week treatment period of the original trial (excluding 4 weeks after rescue medication), they were treated with romiplostim at the same weekly dose last received in the previous study. Otherwise, patients were treated with romiplostim at a starting dose of 3 μg/kg. Romiplostim was administered by subcutaneous (SC) injection once per week. Dose adjustment based on platelet counts was permitted throughout the treatment period to allow patients to maintain platelet counts in the target range of $50–200 \times 10^9$/L, up to a maximum permitted dose of 10 μg/kg. Patients who achieved a stable dose of romiplostim for at least 3 consecutive weeks were allowed to self-inject romiplostim away from the clinic. The study began in October 2006 and is ongoing.

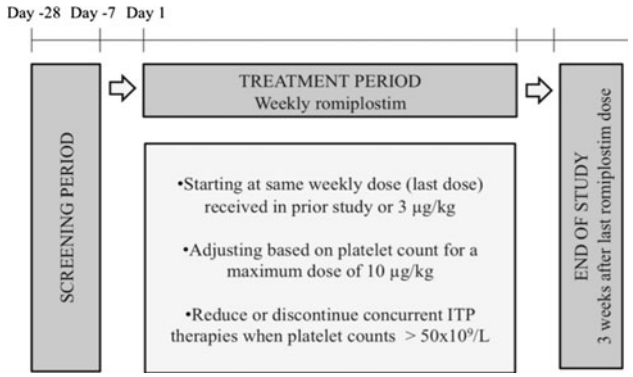

Fig. 1 Study design. This was an open-label extension study of long-term romiplostim dosing in thrombocytopenic Japanese patients with ITP

Eligibility

Patients who had completed any previous romiplostim ITP study in Japan (a phase 2 open-label study and a phase 3 randomized study) were eligible to screen for this study. Additionally, patients were required to provide written informed consent before any study-specific procedures were performed and must have had a platelet count at screening of $<50 \times 10^9$/L. Patients were excluded from the study if they had any significant change in medical history since completion of the previous romiplostim ITP study, including bone marrow stem cell disorders or new active malignancies; tested positive for neutralizing antibodies to romiplostim in the previous romiplostim ITP study; were receiving any treatment for ITP except oral corticosteroids, azathioprine, and/or danazol administered at a constant dose and schedule for at least 4 weeks prior to the screening visit; were pregnant, breastfeeding, or of reproductive potential and not using adequate contraception; had a known severe drug hypersensitivity; or were unlikely to comply with the protocol.

Study endpoints

The primary endpoint of this study was to determine the safety of romiplostim as a long-term treatment in thrombocytopenic Japanese patients with ITP, as measured by the incidence of adverse events, including clinically significant changes in laboratory values. Additional endpoints included incidence of anti-romiplostim antibody formation, incidence of platelet response (doubling of the baseline platelet count at study entry of the previous study and platelet counts $\geq 50 \times 10^9$/L), and proportion of patients able to reduce or discontinue their concurrent ITP therapies (for patients who were receiving oral corticosteroids at a constant dose and schedule at the screening visit). Anti-romiplostim antibodies were assayed at week 1, every 12 weeks during the study and at end of study. Specifically, two validated assays were used: a Biacore 3000 (Biacore International, AB, Uppsala, Sweden) immunoassay and a cell-based bioassay to detect neutralizing or inhibitory effects in vitro [29–31]. If a sample was positive in both assays, a subject was defined as positive for neutralizing antibodies. Throughout the study, investigators could perform a bone marrow biopsy when deemed medically appropriate.

Statistics

The statistical analyses in this open-label extension study were descriptive in nature. Categorical endpoints were summarized by the number and percentage of patients in each category. Continuous endpoints were summarized by number in an eligible subset (n), mean, standard deviation, median, Q1 (25th percentile), Q3 (75th percentile), and minimum and maximum values.

Results

Patient characteristics, disposition, and exposure

As of April 2010, 44 patients who had previously completed either a phase 2 or phase 3 study in Japan [25, 27] enrolled in this open-label extension study. These patients had baseline characteristics of 71 % women, median age 55.5 years (ranging from 25 to 81 years), and median (Q1, Q3) platelet count of 16.5 (6.0, 23.0) $\times 10^9$/L (Table 1). Past treatments included corticosteroids (98 %), IVIg (57 %), *H. pylori* eradication (48 %), splenectomy (39 %), azathioprine (25 %), danazol (23 %), cyclophosphamide (11 %), vincristine/vinblastine (7 %), and rituximab (7 %). Two patients had a past medical history of hepatitis B virus (HBV), three of hepatitis C virus (HCV), and one of HBV and HCV. As of this data cutoff, 5 patients (11 %) discontinued romiplostim due to patient request (2, after 85 and 183 days of treatment, respectively), administrative decision secondary to platelet counts $>200 \times 10^9$/L (2, after 281 and 583 days of treatment, respectively) and platelet counts $\leq 20 \times 10^9$/L after 4 weeks of dosing with 10 μg/kg (1, after 247 days of treatment). The patients who discontinued romiplostim completed an end of study visit 3 weeks after the last administration of romiplostim. All patients received at least one dose of romiplostim, with the mean (SD) treatment duration being 102 (47) weeks (ranging from 12 to 184 weeks) and the mean (SD) average weekly dose being 4.3 (2.7) μg/kg (ranging from 0 to 10 μg/kg). The overall mean weekly dose increase around week 150 corresponds to when the study population consisted of patients from the phase 2 study only (i.e., none

Table 1 Baseline characteristics

	Phase 2 ($N = 11$)	Phase 3 ($N = 33$)	Total ($N = 44$)
Age (years)			
Mean ± SD	55.5 ± 9.8	54.7 ± 13.9	54.9 ± 12.9
Median (min, max)	62.0 (32, 63)	54.0 (25, 81)	55.5 (25, 81)
Sex, *n* (%)			
Female	7 (63.6)	24 (72.7)	31 (70.5)
Male	4 (36.4)	9 (27.3)	13 (29.5)
Baseline platelet count ($\times 10^9$/L)[a]			
Mean ± SD	11.5 ± 10.1	17.7 ± 8.5	16.1 ± 9.2
Median (min, max)	5.5 (3, 31)	19.5 (3, 32)	16.5 (3, 32)
Platelet count prior to the treatment of this study ($\times 10^9$/L)[b]			
Mean ± SD	10.7 ± 8.6	16.3 ± 11.9	14.9 ± 11.3
Median (min, max)	6.0 (3, 25)	11.0 (3, 53)	11.0 (3, 53)

[a] Baseline platelet count in this study was baseline platelet count obtained in the previous study

[b] Platelet count of week 1 or pre-treatment platelet count closest to the first dose of romiplostim in this study if platelet count of week 1 was missing

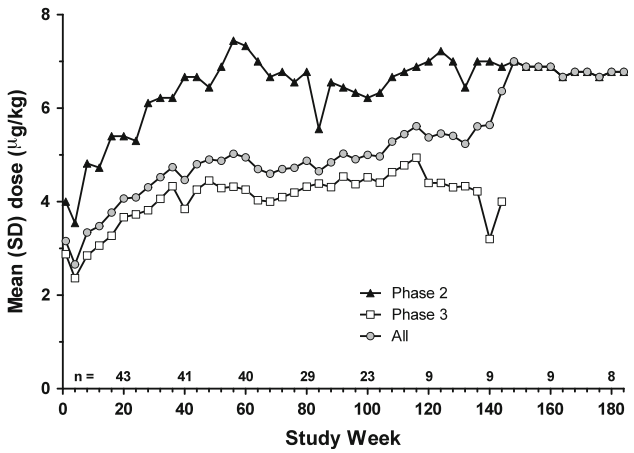

Fig. 2 Mean dose over time. Mean doses for all of the patients, as well as for those who were originally from the phase 2 trial or the phase 3 trial prior to entering the extension, are shown

from the phase 3 study) (Fig. 2). The patients in the phase 2 study had received higher doses throughout this extension. Twenty-eight patients (64 %) received romiplostim by self-injection, beginning after a median (Q1, Q3) of 21 (8.5, 29.0) weeks on study and continuing self-injection for a median (Q1, Q3) duration of 60.0 (28.5, 87.5) weeks. The median (Q1, Q3) percent of weeks these patients were self-injecting was 65 % (42, 81 %). Twelve of these 28 patients (43 %) discontinued self-injection.

Safety

All patients reported at least 1 adverse event after beginning treatment with romiplostim, with 27 patients (61 %) reporting adverse events that were considered by the investigator to be related to the treatment with romiplostim (Table 2). The most frequent adverse events were nasopharyngitis (2.1/100 patient-weeks), headache (0.7/100 patient-weeks), back pain (0.3/100 patient-weeks), contusion (0.3/100 patient-weeks), and malaise (0.3/100 patient-weeks). All nasopharyngitis cases were considered by investigators to not be related to romiplostim, and they were generally mild common upper respiratory tract infections; 6 cases (of 101) were rated as moderate in severity. The most frequently reported treatment-related adverse events were headache (0.52/100 patient-weeks), back pain (0.13/100 patient-weeks), malaise (0.13/100 patient-weeks), and vertigo (0.09/100 patient-weeks).

Nine patients (20 %) reported serious adverse events (duration-adjusted rate of 0.31/100 patient-weeks), with one serious adverse event, mouth hemorrhage, considered by the investigator to be related to the treatment with romiplostim. Other reported serious adverse events included one event each of hemorrhagic anemia, thrombocytopenia, appendicitis, grand mal convulsion, transient ischemic attack, epistaxis, intracranial aneurysm, lumbar spinal stenosis, allergic transfusion reaction, melena, mouth hemorrhage, subcutaneous hematoma, wound, and spinal compression fracture (Table 3). The event of mouth hemorrhage occurred 17 months after initiation of romiplostim in this study. Platelet counts in this patient during romiplostim treatment fluctuated greatly, and thus the dose was frequently adjusted. During one of the times of low platelet counts, the mouth hemorrhage occurred, thus the investigator indicated that there was a reasonable possibility that the hemorrhage was due to romiplostim. As the investigator judged the romiplostim as being effective, treatment with romiplostim was continued. The event of transient ischemic attack occurred 59 days after initiation of romiplostim in this study. The patient had a history of paroxysmal atrial fibrillation, hyperlipidemia, and hyperbilirubinemia. Three days prior to the event, the platelet count was 206×10^9/L. The patient went to the emergency room, where the platelet count was measured at 135×10^9/L. He was not hospitalized, returned home, and the event resolved the next day. Platelet count 4 days after the event was 70×10^9/L. As the investigator judged that the event was caused by transient cerebral hypoperfusion and cerebrovascular spasm, it was considered to not be due to romiplostim, and romiplostim treatment continued. Each of these serious adverse events occurred at a rate of 0.02/100 patient-weeks. There were

Table 2 Overall summary of safety

	N (%)	Rate
Any adverse events (AE)	44 (100)	11.15
Serious AE (SAE)	9 (21)	0.31
Any treatment-related AE	27 (61)	1.70
Any treatment-related SAE	1 (2)	0.02
Death	0 (0)	0
Withdrawal due to AE	0 (0)	0

Rate events per 100 patient-weeks

Table 3 Serious adverse events (SAE)

	N (rate)
All SAE	14 (0.31)
Hemorrhagic anemia	1 (0.02)
Thrombocytopenia	1 (0.02)
Appendicitis	1 (0.02)
Grand mal convulsion	1 (0.02)
Transient ischemic attack	1 (0.02)
Epistaxis	1 (0.02)
Intracranial aneurysm	1 (0.02)
Lumbar spinal stenosis	1 (0.02)
Allergic transfusion reaction	1 (0.02)
Melena	1 (0.02)
Mouth hemorrhage[a]	1 (0.02)
Subcutaneous hematoma	1 (0.02)
Wound	1 (0.02)
Spinal compression fraction	1 (0.02)

Rate events per 100 patient-weeks

[a] Considered by the investigator to be related to romiplostim

no life-threatening adverse events, and no patients died or withdrew from the study.

A total of 50 hemorrhagic adverse events were reported in 20 patients (46 %), with a duration-adjusted rate of 1.12/100 patient-weeks. The most common hemorrhagic adverse events were contusion (0.29/100 patient-weeks), epistaxis (0.16/100 patient-weeks), purpura (0.11/100 patient-weeks), and conjunctival hemorrhage (0.09/100 patient-weeks). Three patients (7 %) had a total of 5 serious hemorrhagic adverse events; one with epistaxis and hemorrhagic anemia, one with melena and subcutaneous hematoma, and one with mouth hemorrhage.

Regarding adverse events of interest, no cases were reported of hematopoietic malignancy, myelodysplastic syndrome, thrombocytosis, or bone marrow reticulin/collagen fibrosis (bone marrow biopsies were performed at investigator discretion). A total of 14 biopsies were performed on 8 patients over a wide range of time, from before the study (1), within the first year (8), to more than 1 year up to over 2 years (5). All biopsies were negative for reticulin and collagen. However, after this data cutoff (on study day 735), one patient experienced a mild non-serious adverse event of increased reticulin that was considered by the investigator to be related to treatment with romiplostim. The only thromboembolic event was a serious adverse event of transient ischemic attack. Additionally, no patients tested positive for neutralizing antibodies to romiplostim or TPO in the antibody assays that were performed every 12 weeks.

Efficacy

Overall, 96 % of patients had a platelet response (doubling of the baseline platelet count at study entry of the previous study and platelet counts $\geq 50 \times 10^9$/L) (response rate over time shown in Fig. 3). Median platelet counts stayed above 50×10^9/L each week from week 2 onward (Fig. 4). Of the 25 patients receiving concurrent ITP therapy at baseline, all were able to reduce or discontinue that therapy: 11 (44 %) had a >25 % reduction in at least 1 concurrent therapy, 5 (20 %) had a >50 % reduction in at least 1 concurrent therapy, and 9 (36 %) discontinued all concurrent therapies. There was an overall decrease over time in the proportion of patients with bleeding events (Fig. 5). Eight patients (18 %) received rescue medications for ITP at some point during the study. These included prednisolone (6 patients), platelet transfusion (5 patients), immunoglobulins (3 patients), dexamethasone and red blood cell transfusion (each 1 patient). Details on individual patients are provided in Table 4.

Discussion

Results of this study indicate that romiplostim administration for up to 3.5 years was well tolerated in Japanese patients with ITP. The reported incidence of adverse events did not increase over time during long-term exposure to romiplostim and were similar to those seen in other romiplostim studies, such as the long-term open-label extension in ITP patients of other ethnic origins ($N = 292$) [32]. In addition, both studies had similar proportions of patients having a platelet response (96 % in this study, 95 % in the other), similar median doses (3.8 vs. 4.0 μg/kg), and a majority of patients initiating self-injection (64 vs. 82 %). In this study, the safety and tolerability of romiplostim self-injection was generally satisfactory; however, please note that self-injection of romiplostim is not approved in Japan. During self-injection, patients continued to have regular platelet count assessments, and, if platelet counts were greater than the target range (50–200 $\times 10^9$/L), romiplostim was discontinued. This discontinuation rule applied to those who received romiplostim from a healthcare provider

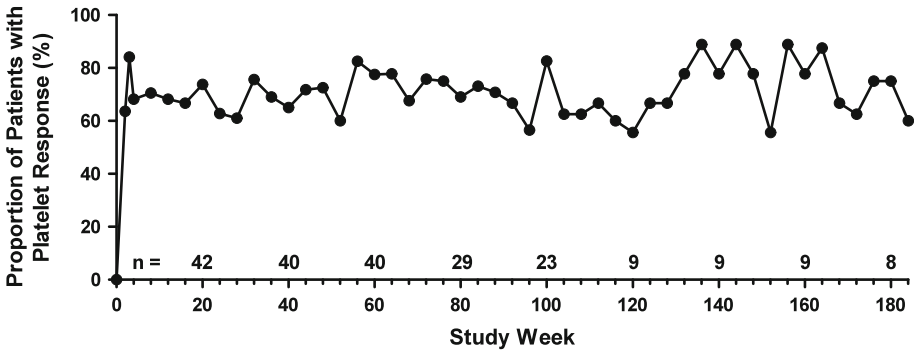

Fig. 3 Platelet response over time

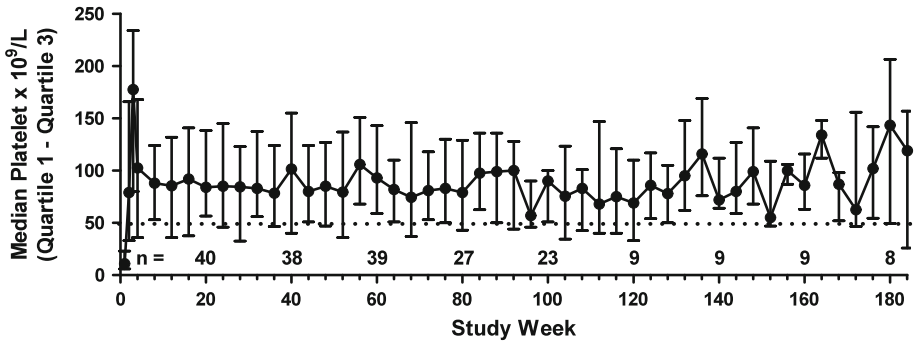

Fig. 4 Platelet count over time

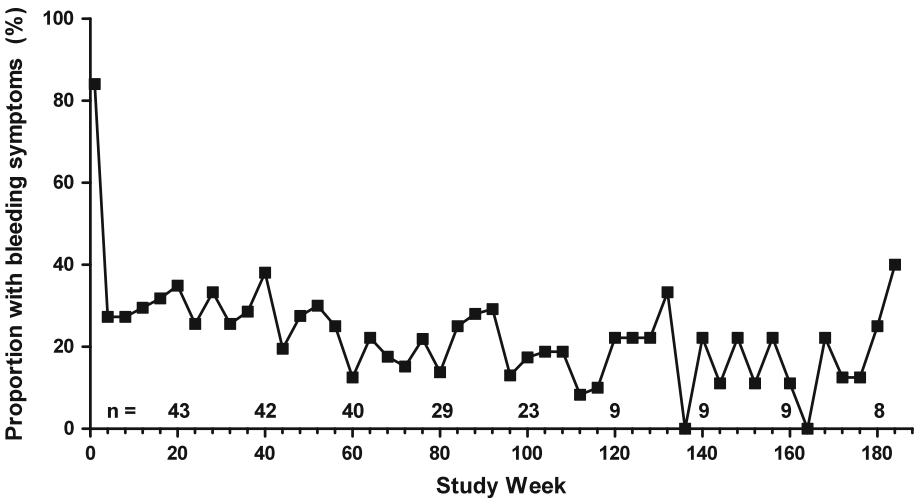

Fig. 5 Bleeding symptoms over time

as well. Concurrent ITP medications at baseline were reduced or discontinued in most patients in both studies (100 vs. 81 %). Overall, the efficacy and safety profile is consistent in these two study populations [28, 33, 34].

During the study, one thromboembolic event of transient ischemic attack was reported. The event occurred in a patient who had a history of paroxysmal atrial fibrillation, hyperlipidemia, and hyperbilirubinemia. Although the transient ischemic attack was not judged to be related to romiplostim by the investigator based on the patient's medical history, this kind of thromboembolic event should be noted and followed carefully during romiplostim treatment. Thus, the benefit:risk ratio of romiplostim should be carefully considered in patients with significant risk factors for thromboembolic events, and platelet counts should be closely monitored. Other reported serious adverse events were mouth hemorrhage, hemorrhagic anemia, thrombocytopenia, appendicitis, grand mal convulsion, epistaxis, intracranial aneurysm, lumbar spinal stenosis, allergic transfusion reaction, melena, mouth hemorrhage, subcutaneous hematoma, wound, and spinal compression fracture, each occurring at a rate of 0.02/100 patient-weeks. Eight patients received rescue medications for ITP, including prednisolone, platelet transfusion,

Table 4 Rescue medication use

Patient	Rescue medication	Number of incidents	Notes[a]
1	Prednisolone	1	
2	Platelet transfusion	2	
3	Prednisolone	3	
4	Prednisolone	2	
	IVIg	1	
5	Dexamethasone	1	
	IVIG	2	GI hemorrhage leading to anemia
	Platelet transfusion	7	One was due to epistaxis, the other 6 due to GI hemorrhage leading to anemia
	Prednisolone	2	
6	Platelet transfusion	1	Mouth hemorrhage
	Prednisolone	5	
	IVIg	3	1 was due to mouth hemorrhage
7	Platelet transfusion	22	2 were due to subcutaneous hematoma
	RBC transfusion	11	All were due to anemia
	Prednisolone	3	
8	Platelet transfusion	4	

GI gastrointestinal

[a] Unless otherwise indicated, use was for thrombocytopenia, not any other specific cause

immunoglobulin, dexamethasone and red blood cell transfusion. There were no deaths and no neutralizing antibodies to romiplostim or TPO. A total of 14 bone marrow biopsies were performed on 8 patients over a wide range of time, with no findings of bone marrow reticulin or collagen as of this data cutoff. Subsequently, there was a mild nonserious adverse event of increased reticulin considered related to romiplostim (study day 735).

A higher romiplostim dose was consistently seen with patients originally from the phase 2 study as compared with those from the phase 3 study. It was thought that this may reflect that the patients from the phase 2 study had a longer history of ITP (median 11.8 vs. 5.8 years for the phase 3 study), and hence likely more advanced disease. To explore this possibility, we performed a post hoc analysis and found that higher romiplostim doses were related to lower platelet count at study entry ($p = 0.0003$)(i.e., inversely related) and inversely related to *H. pylori* eradication prior to study start ($p < 0.0001$), and positively associated with starting dose in this extension study ($p = 0.006$). Of note, the association of ITP duration with romiplostim dose was not statistically significant ($p = 0.1$). Rather, the higher dose in patients originally in the phase 2 study was due to lower platelet count at study entry ($p = 0.01$) and higher starting dose ($p = 0.02$) compared with the phase 3 study, as per study design.

One limitation of this study is the relatively small size (44 patients). Therefore, it is difficult to make conclusions regarding different patient subgroups (such as splenectomized vs. non-splenectomized, etc.). As of this data cutoff, there have been 86 patient-years of romiplostim exposure in this extension study; as this study is ongoing, analyses at future dates will be based on longer exposure time. Another possible limitation is self-selection, as often patients who respond to a medication are more likely to enter an extension study. As a high proportion of patients from earlier studies (44/46, or 96 %) enrolled into this study, it is unlikely that selection bias influenced the results of this extension trial.

In conclusion, similarly to non-Japanese patients, long-term administration of romiplostim was well tolerated in Japanese patients with ITP, with the vast majority of patients achieving a platelet response and no new safety concerns. With the approval of romiplostim in Japan, Japanese patients with ITP will now have access to another option for second-line therapy.

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