ARTICLE

Long-term treatment with romiplostim and treatment-free platelet responses in children with chronic immune thrombocytopenia

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ABSTRACT

Children with immune thrombocytopenia for ≥6 months completing a romiplostim study received weekly subcutaneous romiplostim (1-10 μg/kg targeting platelet counts of 50-200x10^9/L) in this extension to examine romiplostim's long-term safety and efficacy. Sixty-five children received romiplostim for a median of 2.6 years (range: 0.1-7.0 years). Median baseline age was 11 years (range: 3-18 years) and platelet count was 28x10^9/L (range: 2-458x10^9/L). No patient discontinued treatment for an adverse event. Median average weekly dose was 4.8 μg/kg (range: 0.1-10 μg/kg); median platelet counts remained >50x10^9/L, starting at week 2. Nearly all patients (94%) had ≥1 platelet response (≥50x10^9/L, no rescue medication in the previous 4 weeks), 72% had responded at ≥75% of visits, and 58% had responded at ≥90% of visits. Treatment-free response (platelets ≥50x10^9/L ≥24 weeks without immune thrombocytopenia treatment) was seen in 15 of 65 patients while withholding romiplostim doses. At onset of treatment-free response, the nine girls and six boys had a median immune thrombocytopenia duration of four years (range: 1-12 years) and had received romiplostim for two years (range: 1-6 years). At last observation, treatment-free responses lasted for a median of one year (range: 0.4-2.1 years), with 14 of 15 patients still in treatment-free response. Younger age at first dose and platelet count >200x10^9/L in the first four weeks were associated with treatment-free responses. In this 7-year open-label extension, three-quarters of the patients responded ≥75% of the time, and romiplostim was well tolerated, with no substantial treatment-related adverse events. Importantly, 23% of children maintained treatment-free platelet responses while withholding romiplostim and all other immune thrombocytopenia medications for ≥6 months. (Registered at *clinicaltrials.gov identifier: 01071954*)

Introduction

Chronic immune thrombocytopenia (ITP) in children is an autoimmune disorder characterized by increased platelet destruction and suboptimal platelet production.[1] Newly diagnosed and persistent ITP in children have high rates of spontaneous remission; only a small minority develop clinically severe chronic disease.[2] However, these children often have very low platelet counts that are very difficult to treat, have an ongoing risk of intracranial hemorrhage and other bleeding, and have an impaired quality of life.[3,4] There are few data on long-term improvement

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beyond two years of disease,[5,6] and all major centers are familiar with patients with very long-term (i.e. of many years' duration) refractory chronic ITP for whom they have no good treatment options.

Thrombopoietin (TPO) receptor agonists are an important second-line option in children with chronic ITP. The overall efficacy, safety, and tolerability profile compares favorably to other treatment options, with the major concern being that treatment may need to be continued indefinitely. While there are two large randomized, placebo-controlled trials of eltrombopag in children with chronic ITP,[7,8] there are no long-term safety and efficacy data of eltrombopag in children with ITP. In phase I/II and III placebo-controlled studies in children with ITP for ≥6 months, the TPO receptor agonist romiplostim increased and maintained platelet counts in most patients.[9,10] Children completing the placebo-controlled romiplostim studies could enroll in the open-label long-term extension study reported here. An interim report described data for 22 patients in the phase I/II study, including 12 who entered this extension study.[11] This report includes final data from all 66 patients in the extension study, including 12 patients from the phase I/II study and 54 patients from the phase III study.

The objectives of this study were to describe the safety and efficacy of long-term use of romiplostim in children with ITP. End points included the occurrence of adverse events (AE), platelet responses, bleeding, reduced use of concurrent ITP medications, and a *post hoc* end point of treatment-free response, defined as maintaining platelet counts ≥50x10^9/L for at least six months with no ITP medications, including romiplostim. As this was not a predicted occurrence, there were no prospective immunological studies to explore markers of treatment-free response.

Methods

Patients were recruited from 28 sites in the US, Canada, Spain, and Australia. The study ran from 30th December 2009 (first patient enrolled) to 12th January 2017 (last visit). Study guidelines for romiplostim dosing and possible reasons for withholding romiplostim doses are summarized in *Online Supplementary Figure S1*. Romiplostim was administered weekly, starting at 1 μg/kg or continuing at the last dose from the previous study. The dose of romiplostim was adjusted to a maximum of 10 μg/kg based on platelet count. If, in the opinion of the investigator, the patient maintained acceptable platelet counts without weekly dosing, romiplostim could be withheld until the platelet count fell to <50x10^9/L. Dose reduction by 1 μg/kg was required for two consecutive weekly platelet counts >200 and <400x10^9/L. If any platelet count was ≥400x10^9/L, romiplostim was withheld until the platelet count was <200x10^9/L, then decreased by 1 μg/kg. If the current dose was 1 μg/kg and a dose reduction was required for elevated platelet counts, then romiplostim was withheld until platelet counts fell to <50x10^9/L, when it was restarted at a dose of 1 μg/kg. Patients could receive other ITP medications at a stable dose and schedule, which could be reduced or withheld for platelet counts ≥50x10^9/L. Patients could receive rescue medications [intravenous immunoglobulin (IVIg), anti-D, platelet transfusions, corticosteroids, or antifibrinolytics] for platelet counts <10x10^9/L, for bleeding/wet purpura, or per investigator (e.g. pre-procedure).

Eligible patients had completed a placebo-controlled romiplostim ITP study,[9,10] had ITP for ≥6 months (before initial study), and were ≤18 years of age; those turning 18 after enrollment were allowed to stay on study. The studies were conducted in compliance with all regulatory obligations and institutional review board and informed consent regulations at each investigational site and the Declaration of Helsinki. All patients/legal representatives provided written informed consent/assent.

Assessments included platelet count, blood smear, and review of AE (including bleeding) every four weeks; and physical examination, vital signs, complete blood count, and serum chemistries every 12 weeks. Samples for binding antibodies against romiplostim and TPO were tested yearly and at study end; positive samples were tested for neutralizing antibodies. Bone marrow aspirates/biopsies were not required but could be performed at the investigator's discretion.

Efficacy outcomes included platelet counts and platelet response (≥50x10^9/L, no rescue medication use in the previous 4 weeks). Missing data for platelet counts were imputed using the average of neighboring values within ±1 week. Treatment-free response was defined *post hoc* as platelet counts ≥50x10^9/L in the absence of all ITP medications including romiplostim for ≥24 weeks.

Statistical analyses were descriptive. Categorical end points were summarized by the number and percentage of patients in each category. Continuous end points were summarized by number of patients, mean, standard deviation, median, and 25th percentile and 75th percentile, with minimum and maximum values. AE were also summarized as the number of events and rate per 100 patient-years of exposure. Proportional hazards models were used to evaluate factors correlating with time to treatment-free response; patients without treatment-free response were censored at their final platelet count. For the univariate model, each potential factor was considered alone (analogous to a log-rank test). If the assumption of proportional hazards was violated, non-parametric tests (Fisher exact test for categorical variables and Kruskal-Wallis test for continuous variables) were used. For multivariate models, a forward stepwise selection criterion was used with significance levels for entry and exit set at 0.05.

Results

Demographics and disposition

Sixty-six patients gave consent for this extension study; one withdrew before treatment and 65 received romiplostim. Fifteen patients had received placebo previously and this study was their first exposure to romiplostim; patients already receiving romiplostim could enroll without interruption of dosing. At baseline, patient median age was 11 years (range: 3-18 years), 56% (37 of 66) were female, and median platelet count was 28 x10^9/L (range: 2-458x10^9/L) (Table 1). Median ITP duration was 3.0 years (range: 1-13 years), past ITP treatments included IVIg, anti-D, corticosteroids, and rituximab, and 9% (6 of 66) had prior splenectomy (Table 2). There were no notable differences at baseline for patients achieving treatment-free response.

Investigators reported that 37 of 66 patients (56%) completed romiplostim treatment (Figure 1). Reasons for discontinuation of romiplostim treatment (28 of 66, 42%) included consent withdrawn (n=10), required other therapy (n=5), non-compliance (n=4), per protocol (n=3), administrative decision (n=2), AE (n=2), and other (n=2). AE were asthenia, headache, dehydration, and vomiting in one patient and anxiety in the other; investigators did not consider these AE to be treatment-related.

Romiplostim exposure

Median romiplostim treatment duration was 2.6 years (range: 0.1-7.0 years) and total exposure to romiplostim was 182 patient-years. Median average weekly romiplostim dose (i.e. cumulative romiplostim dose divided by duration of treatment) was 4.8 μg/kg (range: 0.1-10 μg/kg). The mean maximum weekly romiplostim dose was 6.9 μg/kg and the median maximum weekly dose was 8.0 μg/kg. Twenty patients started on 1 μg/kg of romiplostim, including the 15 patients who previously received placebo and five patients with >24 weeks since the last dose of romiplostim. The median weekly dose was typically between 4 and 5 μg/kg during the first two years (Figure 2A). The smaller number of patients continuing romiplostim treatment for more than four years complicated median dose calculations at later visits. In a *post hoc* analysis, all 65 patients received their doses per protocol >90% of the time; 21 patients missed ≥1 dose as a result of non-compliance a total of 65 times.

Safety

The most common AE were headache and contusion (Table 3). Fifty-four serious AE occurred in 19 patients (*Online Supplementary Table S1*). One patient had treatment-related concurrent serious AE of grade 4 thrombocytopenia, grade 3 epistaxis, and grade 2 anemia, using investigator-reported severity ratings from the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0. Five patients with serious AE of low platelet counts had fluctuating platelet counts (*Online Supplementary Figure S2*). Bleeding AE occurred in 57 patients; only three of these AE were deemed treatment-related (injection site hemorrhage, injection site bruising, and epistaxis). The most frequent bleeding AE were contusion (51%, 33 of 65), epistaxis (49%, 32 of 65), and petechiae (31%, 20 of 65). There were no cases of intracranial hemorrhage; specific bleeding events included menorrhagia (3 of 65, 5%), hematuria (3 of 65, 5%), rectal hemorrhage (3 of 65, 5%), hematochezia (2 of 65, 3%), hemoptysis (2 of 65, 3%), anal hemorrhage (1 of 65, 2%), and hematemesis (1 of 65, 2%) (Figure 2B). There were seven patients with serious or grade 3 AE of bleeding (*Online Supplementary Table S2*). For one patient, the investigator considered the serious AE of worsening epistaxis (and serious AE of anemia and thrombocytopenia) to be treatment-related; tests for the patient's anti-drug binding antibodies were all negative. No arterial or venous thromboembolic AE were reported. Of note, the contusion rate dropped from 239 to 92 per 100 patient-years when one patient who had 499 AE was excluded from the analysis (Table 3). That patient, a 7-year old boy at baseline, was in the study for 3.4 years and had several serious AE: six of decreased platelet count, and one each of headache, head injury, vomiting, leukopenia, hematoma, pharyngitis streptococcal, and gastroenteritis. His platelet counts ranged from 10 to 872x10^9/L and his dose was increased to 7-10 μg/kg. Seventy percent of his reported AE were non-serious AE of contusion (271 events) or petechiae (78 events). Per the treating investigator, he was a very active child who played multiple sports.

Post-dosing antibodies were assayed annually in 60 patients; data covered >200 patient-years of exposure (including parent studies). One girl had anti-romiplostim neutralizing antibody detected upon leaving the study to receive other therapy; the neutralizing antibody was absent on retesting three and six months later. She received multiple additional therapies and was stable on mycophenolate mofetil. No patients developed anti-TPO neutralizing antibody.

Bone marrow biopsies were performed in two patients with additional cytopenias; both were found to have iron-deficiency anemia and no abnormal cellularity, fibrosis, or malignancy. The first was a 17-year old girl who underwent a bone marrow biopsy after two years on study to evaluate her persistent anemia. With regular supplemental iron intake and lighter menstrual bleeding, her anemia improved. The second bone marrow biopsy, performed after six weeks on study, was in an 11-year old girl who developed neutropenia and anemia; she received iron for

Table 1. Baseline demographics.

	All patients enrolled N=66	Patients with treatment-free response N=15
Female, n (%)	37 (56)	9 (60)
Race/ethnicity, n (%)		
White	40 (61)	10 (67)
African American	9 (14)	3 (20)
Hispanic/Latino	9 (14)	1 (7)
Asian	6 (9)	1 (7)
Other	2 (3)	0 (0)
Age, years, median (range)	11 (3-18)	8 (4-18)
Age group, years, n (%)		
≥1 to <6	12 (18)	2 (13)
≥6 to <12	25 (38)	8 (53)
≥12	29 (44)	5 (33)
Baseline platelet count, x10^9/L, median (range)	28 (2-458)*	14 (1-44)†

*For extension study described in this paper (i.e. not parent studies); 19 of 21 patients with baseline platelet count >50x10^9/L had previous romiplostim treatment; only one had rescue medication use right before baseline. †At start of parent study.

Table 2. Patient immune thrombocytopenia (ITP) medication history.

	All patients enrolled N=66 n (%)	Patients with treatment-free response N=15 n (%)
ITP duration, median (range), years	3.0 (1-13)	4 (1-12)
Number of prior ITP treatments		
1	7 (11)	2 (13)
2	17 (26)	4 (27)
3	15 (23)	3 (20)
>3	26 (39)	6 (40)
Prior splenectomy	6 (9)	0 (0)
Received specific therapies in the past		
IVIg	60 (91)	15 (100)
Corticosteroid	54 (82)	12 (80)
Anti-D antibody	24 (36)	5 (33)
Rituximab	24 (36)	5 (33)
Vincristine/vinblastine	4 (6)	0 (0)
Danazol	4 (6)	1 (7)
Azathioprine	4 (6)	0 (0)
Other*	26 (39)	5 (33)

IVIg: intravenous immunoglobulin. *Other includes aminocaproic acid, cyclosporine, dapsone, mercaptopurine, mycophenolate mofetil, platelets, sirolimus, and tranexamic acid. Designation of platelet transfusion as a rescue medication was per investigator.

the anemia and had pre-existing intermittent neutropenia, which eventually resolved.

Efficacy

Median platelet counts remained >50x10^9/L from week 2 on and >100x10^9/L from weeks 24 to 260 (Figure 2C). Nearly all patients (94%) had ≥1 platelet response (platelet counts ≥50x10^9/L, excluding counts ≤4 weeks after rescue medication). Most patients (72%) had a platelet response ≥75% of the time and over half (58%) had a platelet response ≥90% of the time. Fifty-nine patients (91%) or their caregivers self-administered romiplostim at least once (i.e. administered at home, not at the clinic). In a *post hoc* analysis, self-administration started at a median study week of 7 (1-162) for a total duration of 112 weeks (range: 3-362 weeks). After patients started self-administration, they remained on self-administration (i.e. they did not interrupt it to receive romiplostim in the clinic for ≥4 weeks) for a median of 92% (range: 8-100%) of the time. Most subjects (45 of 59, 76%) remained on self-administration to the last non-zero dose of romiplostim. Twenty-three of 65 patients (35%) received rescue medications (*Online Supplementary Table S3*); usage was highest in the first few months of the study (*Online Supplementary Figure S3A*). At baseline, five patients were taking other ITP medications: aminocaproic acid, prednisolone, prednisone, and tranexamic acid. The rate of ITP medication use decreased during the study (*Online Supplementary Figure S3B*).

Treatment-free responses

Per the study dosing guidelines (*Online Supplementary Figure S1*), romiplostim doses were withheld if consecutive platelet counts were >200x10^9/L but <400x10^9/L and the current dose was 1 μg/kg/week; if the platelet count was ≥400x10^9/L at any dose of romiplostim; or if, in the investigator's opinion, the patient could maintain acceptable platelet counts of ≥50x10^9/L without weekly romiplostim treatment. Fifteen patients (23%) achieved a treatment-free response when romiplostim was withheld, and maintained platelet counts ≥50x10^9/L with no ITP medications for ≥24 weeks (Table 4). All 15 patients also maintained platelet counts >100x10^9/L for ≥24 weeks and the median time having platelet counts >100x10^9/L was 46 weeks (range: 25-109 weeks).

Platelet counts and romiplostim doses are shown in *Online Supplementary Figure S4* for each patient with a treatment-free response. Among these patients, median platelet counts were 14 (1-44)x10^9/L at baseline and 299x10^9/L (range: 217-730x10^9/L) in the last few months before romiplostim was first withheld.

At the onset of treatment-free response (i.e. when romiplostim was first withheld), these nine girls and six boys had had ITP for a median of 4 years (range: 1-12 years) and had received romiplostim for two years (range: 1-6 years) (Figure 3A). Three were from the phase I/II study and 12 were from the phase III study. Eleven received romiplostim throughout and four received placebo in the phase III parent study. No patient with a treatment-free response

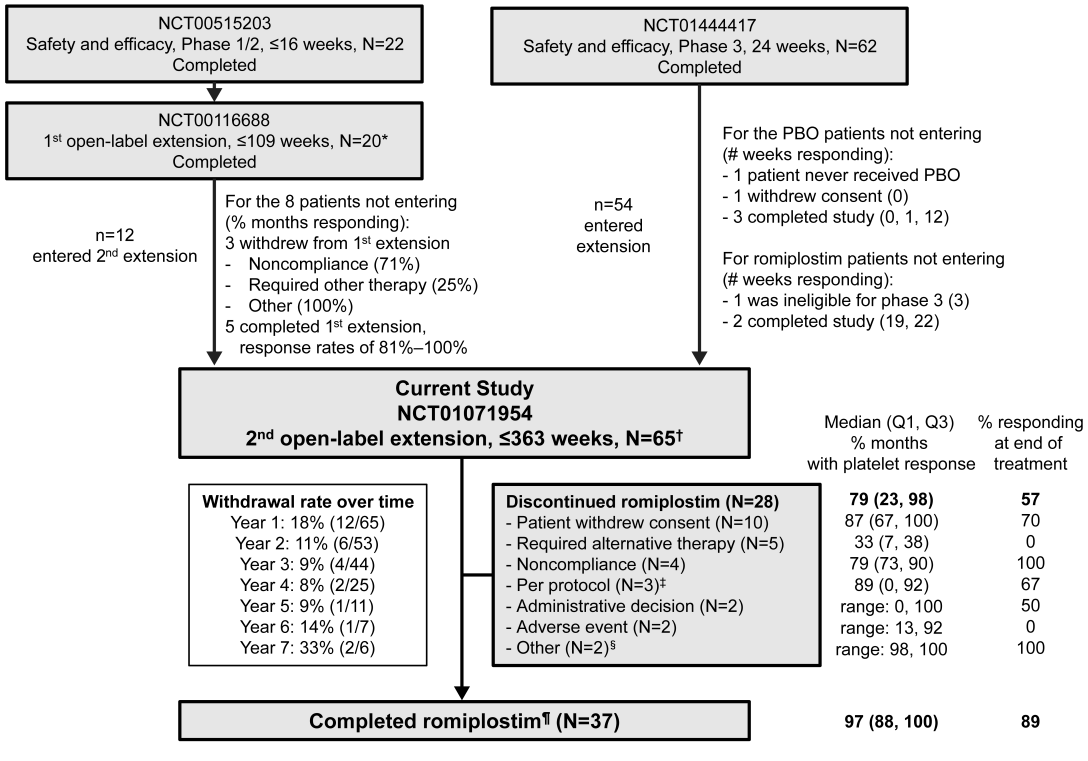

Figure 1. Study flow and patient disposition. Reasons for discontinuing romiplostim are provided. *Of the 21 patients who entered the first extension, one withdrew consent before treatment. †Of the 66 patients who enrolled on the second extension, one withdrew consent before treatment. ‡Of these three patients, two had treatment-free response and one had platelet counts <30x10^9/L despite ten weeks on 10 μg/kg. §Other reasons were that the study ended and treatment-free response. ¶Received romiplostim until study end January 2017 (12 months after the last patient enrolled). #: number of; PBO: placebo; Q1, Q3: 25th and 75th percentiles.

had prior splenectomy; of those without treatment-free response, six had prior splenectomy (Table 2).

Treatment-free responses lasted for a median of one year (range: 0.4-2.1 year). Fourteen patients maintained a treatment-free response without restarting romiplostim by study end. The 15th patient, a 4-year old boy, achieved a treatment-free response while withholding romiplostim in weeks 36 to 67; he received romiplostim again in weeks 68 to 96, then was off all ITP treatments again in weeks 97 to 99 per the dosing rules (he had consecutive platelet counts of 397x10^9/L and 343x10^9/L).

In *post hoc* analyses, baseline characteristics and out-

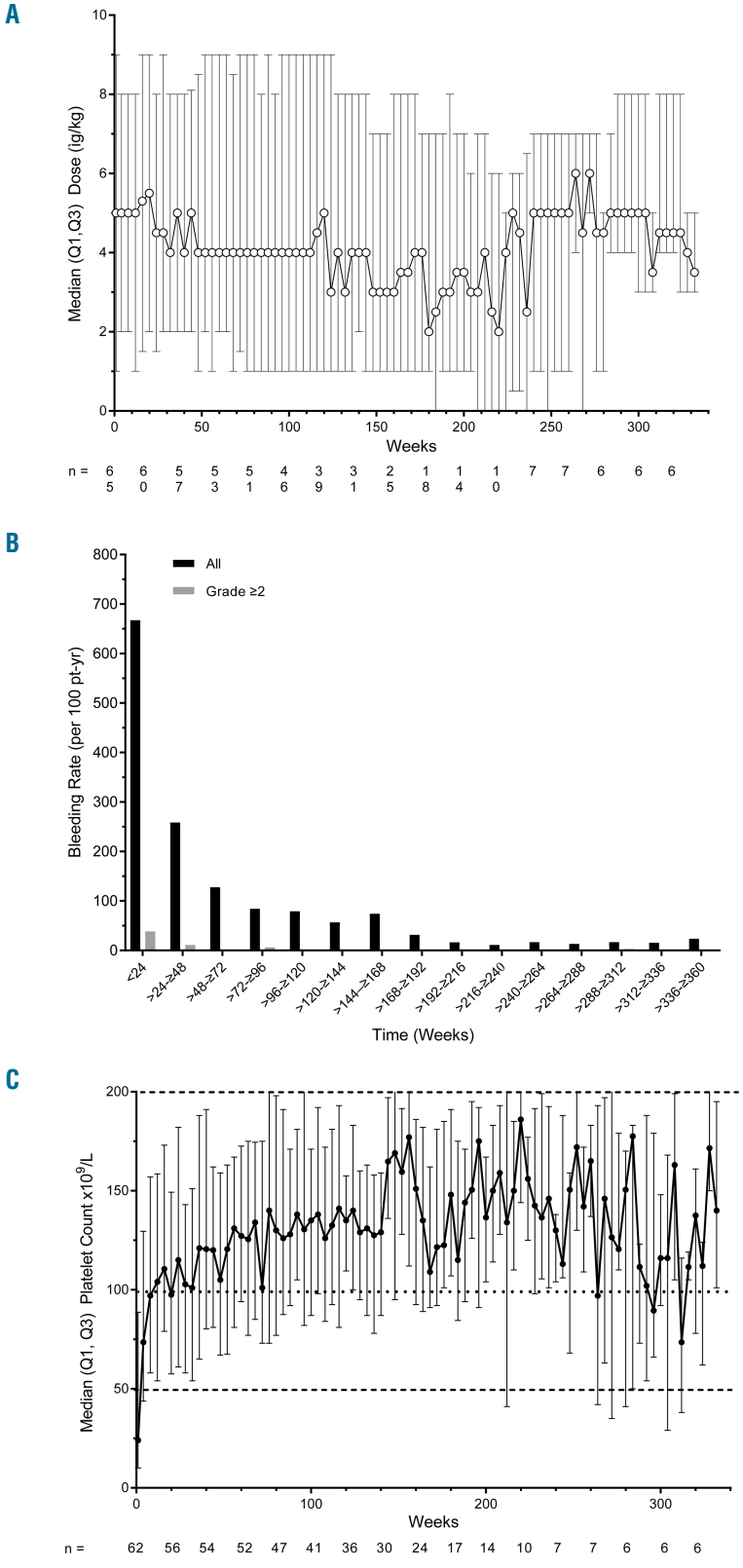

Figure 2. Dose, bleeding adverse events, and platelet counts over time. Shown are median dose (A), rate of bleeding adverse events per 100 patient-year (all and grade ≥2) (B), and median platelet counts (C) over time. (C) The area marked by the dotted lines indicates the target platelet count of 50-200x10^9/L. Patients received weekly subcutaneous romiplostim, starting with the same dose as the final dose in the parent study or 1 μg/kg [if previously on placebo (n=15) or >24 weeks since the last dose (n=5)]. The dose was adjusted weekly by 1 μg/kg from 1-10 μg/kg to target platelet counts of 50-200x10^9/L. Bleeding was assessed per Common Terminology Criteria for Adverse Events version 3.0 grading of adverse events: 1, mild; 2, moderate; 3, severe; 4, life - threatening; 5, fatal. pt-yr: patient-years; Q1, Q3: 25th and 75th percentiles.

comes such as ITP duration, past ITP treatments, and platelet counts in the first four weeks on study were evaluated for their ability to predict treatment-free response. In the univariate model, younger age at diagnosis, younger age at first dose, platelets >200x10^9/L in the first four weeks, and higher mean platelet count in the first four weeks were each associated with developing a treatment-free response (Table 5). In the multivariate model, age at first dose (P=0.0012) and platelet counts >200x10^9/L in the first four weeks (P=0.0035) continued to correlate with treatment-free response (Figure 3B).

Discussion

The data from up to seven years of treatment in this open-label extension study in children with ITP demonstrated that romiplostim was well tolerated and generally maintained its efficacy. There were no complications of thrombotic events, fatalities, or new safety concerns, despite 182 patient-years of exposure to romiplostim (>200 patient-years including parent studies) in 65 patients, half of whom were 11 years of age or less at study baseline. Approximately one-third of patients had serious AE in this trial in which patients were on study for a median of 2.6 years, but only one patient had an episode of concurrent treatment-related serious AE: thrombocytopenia, epistaxis, and anemia. One patient developed neutralizing anti-romiplostim antibodies, discovered when she discontinued the study due to needing other treatments, but neither she nor any other patient developed neutralizing antibody to TPO. This finding in 1 of 60 children is consistent with data from adults treated with romiplostim for ITP. In an integrated database of romiplostim ITP trials, anti-romiplostim neutralizing antibodies were found in 4 of 1,046 adult patients with a total exposure of 1,832 patient-years.[12]

The most common reasons for discontinuation of study treatment were withdrawal of consent (n=10) and required alternative therapy (n=5). Over 90% of patients had a peak platelet count of >50x10^9/L without rescue medication at least once and approximately three-quarters of patients had ≥75% of their platelet counts >50x10^9/L, suggesting a very high rate of efficacy of romiplostim in these children with chronic ITP with a median ITP duration of three years at the start of therapy. Furthermore, median platelet counts were maintained in the desired range (50-200x10^9/L) from week 2 on and at >100x10^9/L from weeks 24 to 260 despite a median dose of 4-5 μg/kg, the same median dose as in the phase III study.[10]

Overall, 15 of 65 children (23%) achieved a treatment-free response, which was defined as platelet counts of ≥50x10^9/L for at least 24 weeks while withholding romi-

Table 3. Adverse events.

Category AE	Patient incidence All treated patients N=65 n (%)	Duration-adjusted events per 100 pt-yr All treated patients 182 pt-yr # (rate)	Duration-adjusted events per 100 pt-yr Excluding 1 patient with 499 AE* 178 pt-yr # (rate)
Most common AE			
Headache	38 (59)	151 (83)	126 (71)
Contusion	33 (51)	435 (239)	164 (92)
Epistaxis	32 (49)	103 (57)	98 (55)
Upper respiratory tract infection	32 (49)	101 (56)	101 (57)
Most common serious AE†			
Any	19 (29)	54 (30)	41 (23)
Thrombocytopenia	4 (6)	6 (3)	6 (3)
Pyrexia	3 (5)	3 (2)	3 (2)
Epistaxis	2 (3)	2 (1)	2 (1)
Headache	2 (3)	2 (1)	1 (0.6)
Vomiting	2 (3)	2 (1)	1 (0.6)

AE: adverse event; pt-yr: patient-years. *See text for a description of the AE in this patient. †A full list of serious AE is provided in *Online Supplementary Table S1*.

Table 4. Patients achieving treatment-free response (defined as a treatment-free period of ≥24 weeks with platelet counts ≥50x10^9/L).

Parent study	Phase I/II			Phase III											
Patient number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Age at treatment-free response start, y	16	6	10	8	6	12	18	7	6	9	4	5	6	16	14
Sex	F	M	M	F	F	F	F	M	M	F	M	F	F	M	F
Race/ethnicity	W	B	W	W	W	W	W	W	B	A	W	B	H	W	W
Parent study treatment	Rom	Rom	Rom	Rom	Rom	Rom	Pbo	Rom	Rom	Pbo	Pbo	Pbo	Rom	Rom	Rom
Baseline platelet count, x10^9/L*	12	5	9	18	7	44	15	26	28	28	25	1	11	4	14
Number of past ITP therapies*	3	6	4	2	2	3	4	5	2	1	2	1	4	3	4
ITP duration, years†	7	6	5	1	4	11	12	3	1	2	3	4	3	3	5
Rituximab use, years†	4	5	5	–	–	–	–	–	–	–	–	–	2	–	5
Romiplostim use, years‡	7	6	5	2	3	5	4	3	3	2	2	2	3	1	3
Maximum romiplostim dose, μg/kg	10	8	9	5	10	2	2	1	3	1	2	1	9	10	4
ITP treatment-free response, year	1.1	2.1	1.1	1.6	1.0	0.8	0.9	1.7	2.1	1.1	0.6‡	0.6	0.8	0.4§	0.6

Data are integrated over parent study and extension study. –: no rituximab use; A: Asian; B: black; F: female; H: Hispanic/Latino; ITP: immune thrombocytopenia; M: male; Pbo: placebo; Rom: romiplostim; W: white. *At start of parent study. †Before treatment-free response. ‡Treatment-free response ended before study end. §This patient met treatment-free response criteria for 0.4 years on study and ≥0.5 years post-study.

plostim and all other ITP treatments. There were two parent studies for this long-term extension.[9,10] Treatment-free response rates were similar for children from the earlier phase I/II study (3 of 12, 25%) and the phase III study (12 of 54, 22%). The three patients entering treatment-free response from the earlier study had received romiplostim longer (5-7 years *vs.* 1-5 years), but their age, ITP duration, number of past ITP therapies, and other characteristics were not particularly different from the patients from the phase III study.

Which children were more likely to enter treatment-free response? In a *post hoc* multivariate analysis of this study, younger age at first dose and platelet count increasing to ≥200x10^9/L in the first four weeks were both independently associated with developing treatment-free response. However, this dataset may not have been large enough to detect additional factors that may also play a role in treatment-free response. Factors found in other studies to be predictive of spontaneous treatment-free response in children with ITP include higher platelet count at diagnosis (>60x10^9/L),[6] younger age,[13-18] recent onset (<2 weeks) of bleeding symptoms,[17,18] decreased bleeding in the first six months,[19] higher bleeding grade at diagnosis,[14] and treatment with IVIg and corticosteroids at diagnosis.[14] Of note, these studies generally considered children with relatively newly diagnosed, persistent, and chronic ITP all together (as definitions changed over time),[20] whereas the treatment-free response in this study occurred in children who had chronic ITP for a median of three years.

The ongoing development of treatment-free response in children with chronic, difficult-to-treat ITP with continuing romiplostim treatment could be explained either by patients improving spontaneously years after their diagnosis of ITP, or by a sustained effect of romiplostim on ITP in certain patients. The correlation of treatment-free response with early very good response in the first four weeks of romiplostim treatment suggests either that these patients were uniquely sensitive to romiplostim or possibly that they just had milder disease. Arguing against the latter hypothesis was the absence of other clinical factors related to treatment-free response (e.g. relatively few previous treatments, short duration of ITP). There is remarkably little published data describing children such as these (i.e. with chronic ITP and median ITP duration of 3 years). Further studies will be needed to distinguish between the long-term effects of romiplostim and the natural history of chronic ITP in childhood.

Definitions of response, remission, and sustained response can vary considerably. Here, we chose platelet counts ≥50x10^9/L for response and platelet counts ≥50x10^9/L for ≥6 months with no ITP medications for treatment-free response. Other studies have used different platelet thresholds for response and treatment-free periods, such as response per the International Working Group criteria,[20] in which thresholds of 30x10^9/L and 100x10^9/L were used for response and complete response, both in the absence of bleeding, or treatment-free periods of at least a year, as in a long-term rituximab study.[21] Nonetheless, six months of no treatment in this study, with treatment-free response in 15 patients and platelet counts mostly over 100x10^9/L, clearly defines a substantial change between the pre-romiplostim experience and on-study experience of these children.

Several studies have suggested pathways by which romiplostim could affect disease progression. These include, but are not limited to, induction of T-regulatory cells and alteration of FcgRs in favor of FcgRIIb, the inhibitory FcgR.[22-26] Overall, the lack of toxicity despite long-term treatment indicates that romiplostim does not overly impair patients' immunity to an extent that there is a predisposition to infections. To our knowledge, other than a few cases in a retrospective case review,[27] this is the

Table 5. Univariate model for predictors of treatment-free response.

Characteristic	Patients with treatment free response N=15	Patients without treatment free response N=50	HR	95% CI	*P*
Sex, female, n (%)	9 (60)	27 (54)	1.19	0.42, 3.41	0.74
Race, white, n (%)	10 (67)	30 (60)	1.05	0.36, 3.09	0.93
Age at first dose*	6.5 (4.0)	10.6 (4.0)	0.81	0.71, 0.93	0.0019
Age at ITP diagnosis*	4.8 (3.6)	7.5 (3.4)	0.83	0.70, 0.98	0.031
Baseline ITP duration	2.3 (2.4)	3.6 (2.7)	0.79	0.61, 1.03	0.080
Baseline platelet count†	16.5 (11.8)	15.9 (9.5)	1.09	0.66, 1.80	0.74
# Prior therapies	3.1 (1.4)	3.3 (1.9)	0.77	0.56, 1.07	0.12
Prior rituximab, n (%)	5 (33)	19 (38)	NA	NA	1.0
Splenectomized, n (%)	0 (0)	6 (12)	NA	NA	0.32
Dose at first response, µg/kg	3.1 (2.9)	4.1 (3.0)	0.87	0.71, 1.07	0.19
Platelet count >200x10^9/L in first 4 weeks, n (%)	4 (27)	3 (6)	5.48	1.63, 18.42	0.0059
Platelet counts in first 4 weeks†	128 (149)	57.5 (42.9)	1.09	1.04, 1.13	<0.0001
Grade ≥2 bleeding in first 6 months, n (%)	4 (27)	8 (16)	1.44	0.46, 4.53	0.53
Rescue meds in first 6 months	4 (27)	20 (40)	0.65	0.21, 2.04	0.46

Data are mean (standard deviation) unless indicated otherwise. NA for HR and 95% CI when proportional hazards assumption in model was violated and model results are not reliable. *P*-value calculated using Fisher exact test (categorical variables) or Kruskal-Wallis test (continuous variables). #: number of; CI: confidence interval; HR: hazard ratio; ITP: immune thrombocytopenia; meds: medications; NA: not applicable. *Per year of age. †Indicates per 1x10^9/L.

first such report of children entering treatment-free response after treatment with a TPO receptor agonist, although this has been observed in adults.[28-30]

Only 2 of 66 patients discontinued romiplostim due to AE. However, investigators reported that 42% (28 of 66) of patients stopped romiplostim treatment early. It is unknown how many of these patients changed to commercially available romiplostim to avoid the constraints of protocol-required study visits. The withdrawal rate is comparable to the romiplostim ITP extension study in adults (31% withdrawal rate in a 7-year study)[31] and the eltrombopag ITP extension study in adults (55% in an 8-year study).[32]

The lack of a control group in this study limits the interpretation of the results. However, even without a control group, the low number of treatment-related serious AE, lack of new types of AE, and the absence of bone marrow or thromboembolic findings are reassuring. The international nature of this study may have increased the degree of patient and previous treatment heterogeneity but at the same time increased generalizability of the results. The requirement for regular clinic visits and platelet count measurements/dose modifications could have presented a deterrent both for patients to enter and to continue the study; dose modifications required weekly visits again for a short period. A number of children left the study without obvious explanation, suggesting that even when self-administration is an option, a few patients will discontinue treatment despite responding, and are not leaving due to AE or loss of treatment effect. There were no quality-of-life assessments, which could also have indicated how increased platelet counts and decreased use of other ITP medications, and also the requirements of the study itself, affected quality of life.

In conclusion, romiplostim was a highly successful maintenance therapy even in children with ITP ≥6 months' duration not responsive to other therapies, a majority of whom (62%) had received three or more past ITP treatments. Romiplostim treatment demonstrated consistent safety and efficacy over the course of this long-term study. Patients staying on study were able to

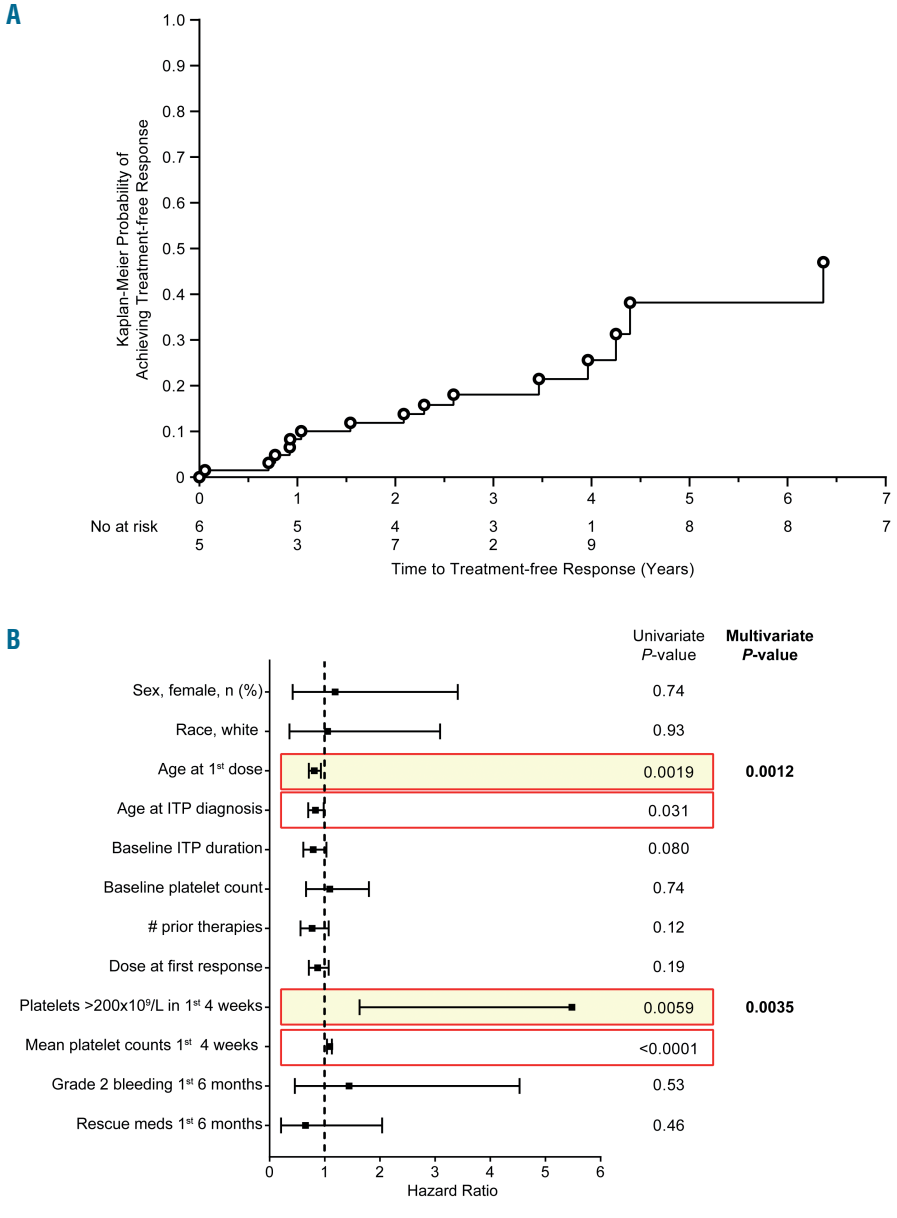

Figure 3. Treatment-free response for at least six months. Shown are time to onset (A) and modeling of characteristics associated with treatment-free response (B). If, in the opinion of the investigator, the patient maintained acceptable platelet counts without weekly dosing, romiplostim could be withheld until the platelet count fell to $<50x10^9$/L. If the platelet count was >200 to $<400x10^9$/L for two consecutive weeks, the dose was reduced by 1 μg/kg at the next scheduled dose. If the platelet count was $\geq400x10^9$/L, the dose was withheld and reduced on the next scheduled day of dosing when the platelet count was $<200x10^9$/L. Red boxes indicate factors significant in the univariate analyses; yellow highlighting indicates those significant in the multivariate analyses. Hazard ratios for age at first dose and age at immune thrombocytopenia (ITP) diagnosis are per year of age, the hazard ratio for baseline platelet count is per $1x10^9$/L, and the hazard ratio for mean platelet count in the first four weeks is per $10x10^9$/L. Hazard ratios greater than 1 indicate an increased likelihood of developing treatment-free response. Note: the univariate models for prior rituximab use (P=1.0) and prior splenectomy (P=0.32) had non-proportional hazards, hence neither factor has a hazard ratio. #: number of; meds: medications.

maintain platelet counts in a hemostatic range, with median platelets >50-100x10^9/L; very few patients left the study because of AE or treatment failure. Development of treatment-free response in almost one-quarter of patients suggests that maintenance with romiplostim in children will not always be a "life-long treatment." The continued, steady development of treatment-free response in patients treated for three or more years is encouraging as well. Additional studies in larger numbers of patients may further clarify some of the issues discussed in this study.

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