

Long-Term Use of the Thrombopoietin-Mimetic Romiplostim in Children With Severe Chronic Immune Thrombocytopenia (ITP)

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Background. Treatment of chronic severe pediatric ITP is not well studied. In a phase 1/2 12–16-week study, 15/17 romiplostim-treated patients achieved platelet counts $\geq 50 \times 10^9/L$, and romiplostim treatment was well tolerated. In a subsequent open-label extension (≤ 109 weeks), 20/22 patients received romiplostim; all achieved platelet counts $> 50 \times 10^9/L$. Twelve patients continued in a second extension (≤ 127 weeks). Longitudinal data from start of romiplostim treatment through the two extensions were evaluated to investigate the safety and efficacy of long-term romiplostim treatment in chronic severe pediatric ITP. **Procedure.** Patients received weekly subcutaneous romiplostim, adjusted by $1 \mu\text{g}/\text{kg}/\text{week}$ to maintain platelet counts ($50\text{--}200 \times 10^9/L$, maximum dose $10 \mu\text{g}/\text{kg}$). Bone marrow examinations were not required. **Results.** At baseline, patients were median age 10.0 years; median ITP duration 2.4 years; median platelet count $13 \times 10^9/L$; 73% were male; and 36% had prior splenectomy. Median romiplostim treatment duration was 167 weeks

(Q1, Q3: 78,227 weeks), and median average weekly dose was $5.4 \mu\text{g}/\text{kg}$ (Q1, Q3: 4.3, $8.0 \mu\text{g}/\text{kg}$). Seven patients discontinued treatment: four withdrew consent, two were noncompliant, and one received alternative therapy. None withdrew because of adverse events (AEs). After the first 12 weeks, median platelet counts remained $> 50 \times 10^9/L$. Eight (36.4%) patients received rescue medication, and 14 (63.6%) used concurrent ITP therapy. Seven patients (31.8%) reported serious AEs, and two (9.1%) reported life-threatening AEs (both thrombocytopenia); there were no serious AEs attributed to treatment and no fatalities. **Conclusions.** Long-term romiplostim treatment in this small cohort increased and maintained platelet counts for over 4 years in children with ITP with good tolerability and without significant toxicity. *Pediatr Blood Cancer* 2015;62:208–213. © 2014. The Authors. *Pediatr Blood & Cancer* published by Wiley Periodicals, Inc.

Key words: autoimmunity; bleeding; platelets; thrombopoietin

INTRODUCTION

Immune thrombocytopenia (ITP) during childhood is an autoimmune disorder characterized by increased platelet destruction and suboptimal platelet production resulting in thrombocytopenia. The presentation of this disease varies, ranging from severe acute bleeding to mild bruising and purpura to an asymptomatic incidental diagnosis [1–4]. In contrast to adult ITP, treatment options for severe chronic ITP in children are very poorly studied; even single-arm trials are limited. Current therapeutic approaches to managing chronic pediatric ITP rely on data from adult studies further informed by small pilot studies in children and expert opinion, as there is virtually no evidence derived from randomized controlled trials [1].

Two thrombopoietin (TPO) receptor agonists, romiplostim and eltrombopag, have been approved for the treatment of chronic ITP in adults in the United States and elsewhere. Romiplostim, an Fc-peptide fusion protein that stimulates growth and maturation of megakaryocytes thus increasing platelet production, was developed to address the unmet need in the long-term treatment of adults with chronic ITP. In randomized controlled trials, romiplostim consistently demonstrated a high response rate and a good safety and tolerability profile, and reduced the need for splenectomy and use of rescue medication [5–7]. Additionally, adults with ITP who received romiplostim experienced a significant reduction in the rate of moderate and severe bleeding events and reported improved quality of life [5,8,9]. Long-term studies have shown good safety and tolerability profiles in adults over more than 5 years of continuous treatment [10].

The use of romiplostim in pediatric ITP was initially explored in a small randomized, double-blind, placebo-controlled, phase 1/2 study of patients between the ages of 1 and 18 years who had been diagnosed with ITP at least 6 months prior to enrollment [11]. The primary endpoint was the mean percentage of patients who achieved a platelet count $\geq 50 \times 10^9/L$ for 2 consecutive weeks, which was achieved in 15 of 17 patients who received romiplostim compared with none who received placebo ($P = 0.0008$) [11]. Likewise, the

percentage of patients who received rescue medication during the treatment period was lower in the romiplostim-treated group than in the placebo-treated group [11]. Overall, the response of pediatric patients to romiplostim was similar to that of adults observed in two phase 3 studies of romiplostim in patients with ITP [5,11]. In addition, romiplostim was well tolerated and there were no safety issues. Another small study had similar findings, although with a slightly lower response rate [12]. However no data on long-term use of romiplostim in children exist.

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After completing the initial first-in-children phase 1/2 study [11], patients were offered the option of entering an extension study. At the end of this first extension study, patients who were still aged <18 years could choose to enter a second extension study. Twenty of 22 patients from the 12–16 week phase 1/2 study received romiplostim in the first open-label extension study (≤ 109 weeks); all achieved platelet counts $>50 \times 10^9/L$. Twelve patients continued in a second extension study (≤ 127 weeks). This report presents the results of up to 4.7 years of romiplostim treatment of pediatric patients with ITP who received romiplostim or placebo in the randomized study [11] through the first or the first and second extension studies. The objective of these post hoc analyses was to describe the safety and efficacy of long-term use of romiplostim in children with severe, chronic ITP.

METHODS

Study Design and Treatment

Study design for the initial 12–16 week phase 1/2 study [11] and first open-label extension study [13,14] has been described elsewhere. Briefly, children aged 1–18 years who had been diagnosed with ITP per American Society of Hematology guidelines [15] 6 or more months before screening were eligible to enter the initial study if the mean of two platelet counts taken within 3 weeks before enrollment was $\leq 30 \times 10^9/L$, with no individual platelet count exceeding $35 \times 10^9/L$. Exclusion criteria included having undergone splenectomy within 8 weeks of screening, ongoing stable treatment for ITP besides corticosteroids, and receiving rituximab within 14 weeks before the screening visit. Patients with a history of a bone marrow stem cell disorder, venous or arterial thrombotic or thromboembolic event, systemic lupus erythematosus, or Evans syndrome or other known secondary causes of thrombocytopenia were also excluded.

Patients who completed the initial phase 1/2 study were eligible to enter the first open-label extension study; the second open-label extension study was restricted so that only patients aged <18 years were able to enter. In the open-label extension studies, all patients were to receive subcutaneous romiplostim once weekly, with a starting dose of $1 \mu\text{g}/\text{kg}$. Doses were adjusted by $1 \mu\text{g}/\text{kg}$ per week as needed to maintain platelet counts of $50\text{--}200 \times 10^9/L$ to a maximum dose of $10 \mu\text{g}/\text{kg}$, as in adults. Patients who had received romiplostim in the initial study entered the extension study at the same romiplostim dose last received in the initial study, unless more than 24 weeks had elapsed since the patient's last dose of romiplostim, in which case treatment was initiated at $1 \mu\text{g}/\text{kg}$ per week. Patients who had received placebo in the initial study started romiplostim at a dose of $1 \mu\text{g}/\text{kg}$ per week in the first extension study. Patients could continue to receive other ITP treatments (e.g., corticosteroids, danazol, or azathioprine) that had been administered at a constant dose and schedule prior to the study start. These additional treatments could be reduced or discontinued at any time after platelet counts reached $50 \times 10^9/L$. Patients could also receive rescue treatments when platelet counts were below $10 \times 10^9/L$, when there was bleeding or wet purpura, or when deemed medically necessary by the investigator. Rescue treatment was defined as any treatment administered to increase the platelet count. Permitted rescue treatments included intravenous immunoglobulin G (IVIG), anti-D, platelet transfusions, steroids, and antifibrinolytics. The studies were conducted in compliance with all regulatory obligations and institutional review board and

informed consent regulations at each investigational site. Data are summarized from three sequential studies, ClinicalTrials.gov Identifiers NCT00116688, NCT00515203, and NCT01071954.

Assessments, Outcomes, and Statistics

Platelet counts, concurrent treatments, and adverse events were assessed at each designated visit. During the extension studies, samples were collected for complete blood counts and blood chemistry determinations every 4 weeks, and physical examinations were performed at week 1 and every 12 weeks thereafter. Efficacy outcomes included the platelet counts at each visit and the platelet response (platelet count $\geq 50 \times 10^9/L$ without rescue medication use in the past 4 weeks). Platelet counts of individuals who received rescue medication within the previous 4 weeks were excluded from the analyses. Missing platelet counts were imputed using last observation carried forward (LOCF) during each study. Other efficacy assessments included the proportion of patients using other ITP treatments and the proportion of patients who required rescue treatment.

Safety

Safety assessments included review of adverse events, physical examination, vital signs, serum chemistries, complete blood count, platelet count, and antibody status. Medically significant adverse events considered to be treatment-related by the investigator were followed until they resolved or were considered stable. The investigator assigned the following attributes: description; dates of onset and resolution; severity; assessment of relatedness to treatment, other suspect drug, or device; and action taken. The severity of toxicities was assessed on the following scale with appropriate clinical definitions: 1 = mild, 2 = moderate, 3 = severe, 4 = life-threatening, and 5 = fatal. Serious adverse events included any adverse events that were fatal, were life threatening, required inpatient hospitalization, or prolonged existing hospitalization. Standard Common Terminology Criteria for Adverse Events (CTCAE) grading of adverse events was used. Thromboembolic events were assessed as part of the overall adverse event evaluation, not as a separate assessment. Bone marrow biopsies were not required at study entry or at any time, but could be performed at the investigator's discretion; a biopsy was recommended if there were abnormalities in the peripheral blood smear (e.g., nucleated red blood cells) or if a loss of response to romiplostim occurred despite increasing doses. Blood samples for assays for antibodies to TPO and romiplostim were collected at week 1, week 52, then annually thereafter, and also at the end of the study.

Data Analyses

All analyses performed for this study were post hoc. Statistical analyses were descriptive. Categorical endpoints were summarized by the number and percentage of patients in each category. Continuous endpoints were summarized by number of patients, mean, standard deviation, median, and 25th percentile (Q1) and 75th percentile (Q3), with minimum and maximum values.

RESULTS

Demographics and Disposition

Baseline characteristics when the 22 patients enrolled in the initial phase 1/2 study were median age, 10.0 years; median duration

of ITP, 2.4 years; median platelet count, $13 \times 10^9/L$; 73% male; and 36% with prior splenectomy (Table I). All 22 patients completed the phase 1/2 study, 21 of whom entered the first extension study; one of these 21 patients did not receive study drug. The 20 treated patients received up to 109 weeks of romiplostim in this first extension study; four patients withdrew (two due to withdrawal of consent, one due to noncompliance, and one due to requirement for alternative therapy), leaving 17 patients (of the 21) who completed the first extension study. Of these 17 patients, three were not eligible for the second extension study (two because they were over 18 years of age). Twelve of the 14 eligible patients chose to enter the second extension study, three of whom later withdrew (two due to consent withdrawal and one due to noncompliance). In this second extension study, patients received up to 127 weeks of romiplostim.

Dose and Exposure

The median romiplostim treatment duration for all three studies combined was 167 weeks (Q1, Q3: 78, 227 weeks; range: 12–242 weeks or nearly 5 years) (Fig. 1). The total duration of treatment was 63.3 patient-years for these three consecutive studies. The median average weekly dose was $5.4 \mu\text{g}/\text{kg}$ (Q1, Q3: 4.3, $8.0 \mu\text{g}/\text{kg}$); the median average weekly dose increased over time until Weeks 85–96 and then fell (Fig. 2). Excluding the first 12 weeks of dose finding in the first study, patients received doses within $2 \mu\text{g}/\text{kg}$ of their most frequent dose 52% of the time.

At the time of these analyses, nine children remained in the study. The median cumulative duration of treatment in these nine children was 234 weeks (range: 193–242 weeks) and the median average weekly dose was $6.0 \mu\text{g}/\text{kg}$ (range: $3.1\text{--}9.7 \mu\text{g}/\text{kg}$). However, the median last dose was only $3.0 \mu\text{g}/\text{kg}$ (range: $0\text{--}10 \mu\text{g}/\text{kg}$).

Efficacy

Over the course of the three studies, 21 of the 22 (95.5%) children treated had a peak platelet count $\geq 150 \times 10^9/L$, and 11 (50%) had a peak platelet count $\geq 400 \times 10^9/L$. After the first 12 weeks, median platelet counts stayed above $50 \times 10^9/L$ (Fig. 2).

TABLE I. Baseline Demographics

	N = 22
Age group in years, n (%)	
1–2	4 (18.2)
3–11	10 (45.5)
12–17	8 (36.4)
Age (years), median (range)	10 (1–17)
Male, n (%)	16 (72.7)
Race, n (%)	
White or Caucasian	13 (59.1)
Black or African American	5 (22.7)
Hispanic or Latino	3 (13.6)
Other	1 (4.5)
Splenectomy, n (%)	8 (36.4)
Baseline concurrent ITP therapy, n (%)	3 (13.6)
Duration of ITP (years), median (range)	2.4 (1–14)
Platelet count $\times 10^9/L$, median (range)	13 (2–29)

Except for baseline platelet counts (which were from the start of the initial study), other demographic characteristics were as of initiating romiplostim.

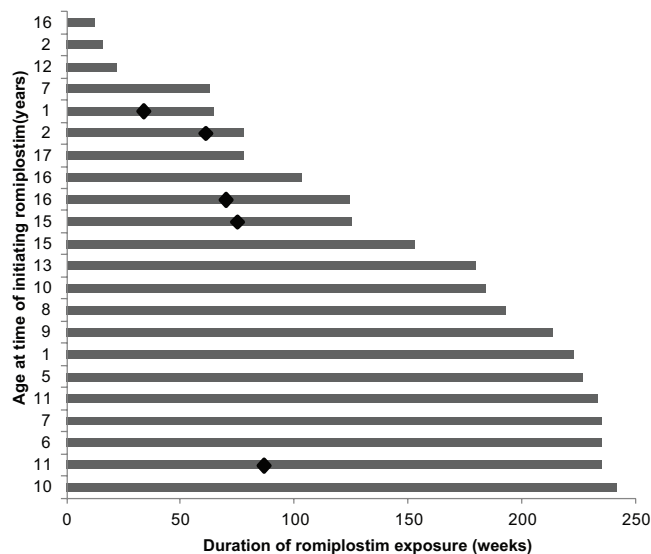


Fig. 1. The total duration of romiplostim treatment for individual children. Diamonds indicate duration of romiplostim treatment when bone biopsies were performed.

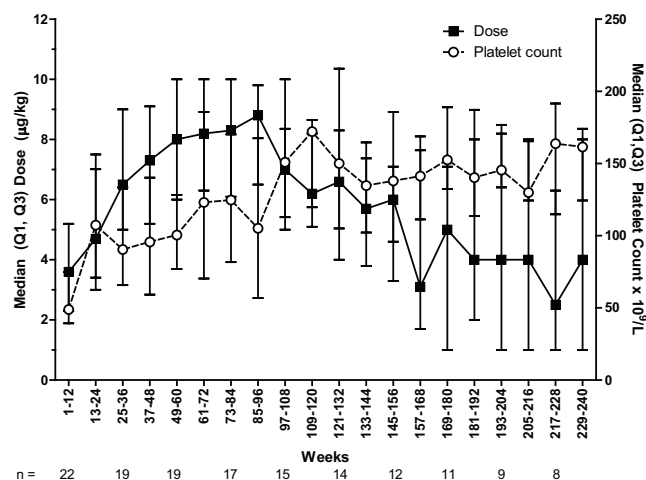


Fig. 2. Median (Q1, Q3) average weekly romiplostim dose (left y-axis) and median (Q1, Q3) platelet counts (right y-axis) are presented over time by 12-week intervals with the number of patients with available data underneath the x-axis.

The median percentage of weeks that these 21 patients had a platelet response was 84.3% (Q1, Q3: 69.9%, 90.8%). Of the three patients who had baseline concurrent ITP therapy, two discontinued these therapies. Fourteen (63.6%) patients used concurrent ITP therapy during the study (Table II); the proportion of patients using concurrent ITP medications decreased gradually over time. Concurrent ITP therapy included those medications continued from baseline as well as any medications added or increased in dose to increase platelet count, with the added/increased medications considered rescue therapy. Of the 14 patients receiving concurrent ITP therapy, eight (36.4%) received rescue medication, including one platelet transfusion (Table II). Rescue medication use was low

TABLE II. Concurrent and Rescue ITP Medications

	N = 22, n (%)
Concurrent medications	
All	14 (63.6)
Corticosteroids	10 (45.4)
Prednisone	6 (27.3)
Dexamethasone	3 (13.6)
Hydrocortisone	2 (9.1)
Methylprednisolone sodium succinate	1 (4.5)
Immunoglobulin	5 (22.7)
Aminocaproic acid	1 (4.5)
Dapsone	1 (4.5)
Immunoglobulin anti-Rh (anti-D)	1 (4.5)
Vincristine	1 (4.5)
Rescue medications	
All	8 (36.4)
Immunoglobulin	5 (22.7)
Dexamethasone	2 (9.1)
Immunoglobulin anti-Rh (anti-D)	1 (4.5)
Platelets	1 (4.5)
Prednisone	1 (4.5)
Vincristine	1 (4.5)

throughout romiplostim treatment—for example, rescue medication was not administered in most 12-week time periods.

Safety

All patients reported adverse events. Seven patients (31.8%) reported serious adverse events, for a duration-adjusted rate of 0.43 for 100 patient-weeks. The serious adverse events were influenza (in two patients), asthma, epistaxis, hemangioma, hypotension, idiopathic thrombocytopenic purpura, lymphadenitis, pharyngitis streptococcal, pyrexia, sepsis, thrombocytopenia, and transfusion reaction (all in one patient each). There were two life-threatening adverse events (9.1%, 0.06/100 patient-weeks), which were thrombocytopenia in both cases. There were no fatalities. There were no serious adverse events attributed to treatment, and no patients withdrew from treatment due to adverse events (Table III). There were no reports of thrombotic events. Five bone marrow biopsies were performed between 34 and 87 weeks (median: 70 weeks) after the start of treatment, all in the first extension study (Fig. 1); no bone marrow reticulin or fibrosis was observed. There were no reports of neutralizing antibodies to TPO or romiplostim. The most common adverse events were headache, upper respiratory tract infection, and pyrexia (Table IV).

Bleeding adverse events occurred in 17 (77.3%) patients. The most common bleeding adverse events were petechiae (11 patients, 50.0%), epistaxis (10 patients, 45.5%), gingival bleeding (seven patients, 31.8%), and mouth hemorrhage (six patients, 27.3%). Bleeding adverse events of grade 3 or above occurred in two patients and were epistaxis in both cases.

DISCUSSION

Children with chronic ITP by definition have low, but variable, platelet counts; typically those patients with pronounced thrombo-

TABLE III. Summary of Adverse Events

	N = 22, n (%)	3,292 patient-weeks, n (rate ^a)
Patients reporting any adverse events (AE)	22 (100)	745 (22.63)
Patients reporting any severe AE	9 (40.9)	20 (0.61)
Patients reporting any serious AE	7 (31.8)	14 (0.43)
Patients reporting any treatment-related AE	6 (27.3)	37 (1.12)
Patients reporting any serious treatment-related AE	0 (0)	0 (0)
Fatal AE	0 (0)	0 (0)
Patients who withdrew from study or romiplostim due to AE	0 (0)	0 (0)
AEs of interest		
Bone marrow fibrosis	0 (0)	0 (0)
Thrombotic events	0 (0)	0 (0)
Antibodies to romiplostim or TPO	0 (0)	0 (0)

^aRate is exposure-adjusted incidence for 100 patient-weeks.

TABLE IV. Incidence of Overall Adverse Events in Descending Order of Frequency ($\geq 25\%$)

Preferred term	N = 22 (n (%))
Headache	14 (63.6)
Upper respiratory tract infection	14 (63.6)
Pyrexia	12 (54.5)
Oropharyngeal pain	11 (50.0)
Petechiae	11 (50.0)
Cough	10 (45.5)
Epistaxis	10 (45.5)
Contusion	9 (40.9)
Fatigue	9 (40.9)
Nasal congestion	9 (40.9)
Rhinorrhoea	9 (40.9)
Vomiting	9 (40.9)
Nausea	8 (36.4)
Gingival bleeding	7 (31.8)
Nasopharyngitis	7 (31.8)
Rash	7 (31.8)
Arthralgia	6 (27.3)
Mouth hemorrhage	6 (27.3)
Pain	6 (27.3)

cytopenia have the greatest risk for major bleeding [16]. Unfortunately, there are no randomized controlled clinical trials that clearly establish whether any of the common treatment options for ITP is preferable to another in children, or even in adults [1]. Specifically, long-term corticosteroid regimens have considerable toxicity and many patients who respond to steroids require a high dose. Splenectomy, with response rates of approximately 70% in children with chronic ITP, carries a risk of sepsis [1,17,18], which may be increased if an underlying immune deficiency disorder contributes to the persistence and/or severity of ITP. Rituximab therapy is reported to result in long-term remission in only 20–25% of patients [19]; with optimization of rituximab regimens not yet

evaluated in children [20]. Danazol may impact sexual development and shorten final height in pre-pubertal children [21]. Finally, response rates to immunosuppressive agents, such as azathioprine or mycophenolate mofetil or cyclosporin, are not well defined and do not appear to be high in children with chronic ITP, and it may take months for a therapeutic effect to be seen.

The TPO-agent romiplostim has been associated with a relatively low incidence of side effects combined with a high, stable response rate in adults with ITP [13,14]. In the long-term TPO-agent study described here, romiplostim treatment consistently increased platelet counts for over 4 years in a small cohort of children with severe chronic ITP. All but one of the initial 22 patients had peak platelet counts $\geq 150 \times 10^9/L$ in response to treatment and, after the first 12 weeks of treatment, median platelet counts remained consistently above $50 \times 10^9/L$. Romiplostim was well tolerated and without significant toxicity in this small cohort. Toward the end of the greater than 4 years of treatment, the median romiplostim dose decreased from 6 to 4 $\mu g/kg$ while maintaining the platelet response. This may represent slow improvement of the disease with time; no data have clearly demonstrated improvement as a result of TPO-agent treatment.

The primary limitation of this series of consecutive studies is the small sample size, which was further reduced by patient withdrawals, lack of eligibility in three patients, and certain patients' discontinuing treatment over time due to improvement of ITP. In addition, the study protocol did not require specific evaluation of toxicities such as thromboembolic events and bone marrow reticulocytosis, although neither was seen (Table III). The lack of bone marrow findings is encouraging, as grade 1 reticulocytosis may be seen in normal bone marrow (without any treatment). Romiplostim dosing in this study was designed to lessen the development of thrombocytosis, but, because of the nature of pediatric ITP and concurrent viral infections, it was not possible to avoid thrombocytosis and half of the 22 children developed platelet counts over $400 \times 10^9/L$ at least once. However, even in adults, thrombocytosis is not associated with thrombosis [13,14,22], and the transient nature of the thrombocytosis renders it a minor issue. Of note, as most patients were receiving romiplostim through home administration, and thus had monthly rather than weekly assessments, the true extent of platelet fluctuations is unknown. The possibility of infection-related platelet count fluctuations seems to be greater in children, meaning that the dosing schedule may require closer monitoring and that in certain settings of clinical use, dose adjustments may need to be minimized as a result. Finally, one concern about the use of romiplostim in both children and adults with ITP is that it will need to be used for many months or years, if not indefinitely. This concern is compounded by the lack of long-term data in children. In this study of long-term romiplostim use for up to 4.7 years, several children were able to discontinue romiplostim treatment. As to how and when treatment can be discontinued, studies to address these issues are ongoing in adults.

Use of romiplostim in children with chronic ITP offers several possible advantages to other options, notwithstanding the limitations discussed above. Quality-of-life data from the original phase 1/2 study suggest that parental burden is decreased with romiplostim treatment [23]; this has not been addressed with other treatments. While romiplostim requires a weekly subcutaneous injection, it can potentially be given at home, a strategy approved in Europe although not in the United States at the time of writing. Based on data in adults and very limited data in children, the

concern of bone marrow fibrosis due to treatment with romiplostim appears to be low [24]. There is no concern about hepatotoxicity with romiplostim and no restrictive dietary requirements, as opposed to those with eltrombopag [25], although platelet counts may fluctuate more [26], an issue that was seen in this study. No episodes of thromboembolic phenomena have been seen in children. There may be less thrombosis in children than that seen in adults; however, the data here are from only 63 patient-years of exposure to romiplostim, whereas for adults, data from up to 922 patient-years have been published [10]. Compared with adults, there is very little concern about myelodysplastic syndrome masquerading as ITP, resulting in treatment with romiplostim, possibly inducing leukemia. Finally, romiplostim increased platelet counts in children with chronic ITP in this study and in adults with ITP, bleeding is substantially reduced when the platelet count increases.

In conclusion, the data described here suggest that long-term romiplostim treatment in children with chronic ITP provides adverse event and platelet response outcomes similar to those seen in adults. Evaluation of patients enrolled in the ongoing phase 3 study of romiplostim in children with ITP (ClinicalTrials.gov NCT01444417, estimated enrolment of 60) will provide further data as to its safety and efficacy.

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