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A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study to Determine the Effect of Romiplostim on Health-Related Quality of Life in Children with Primary Immune Thrombocytopenia and Associated Burden in Their Parents

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Background. Chronic immune thrombocytopenia (ITP) in children can negatively impact their health-related quality of life (HRQoL) and impose a burden on their parents. This study sought to examine the effect of romiplostim on HRQoL and parental burden in children with primary ITP. ***Procedure.*** This was a phase 3, randomized, double-blind, placebo-controlled study. Children aged <18 years with ITP ≥6 months were randomly assigned to receive romiplostim or placebo for 24 weeks. The Kids' ITP Tool (KIT) was used to measure HRQoL and was administered to patients and/or their parents at baseline and weeks 8, 16, and 25. Mean KIT scores at each assessment and mean changes in KIT scores from baseline were calculated overall by treatment group and platelet response status. Psychometric properties of the KIT were evaluated and the minimally important difference (MID) was estimated for different KIT versions. ***Results.*** Sixty-two patients (42 romiplostim and 20 placebo) were enrolled. Changes in KIT scores by treatment group showed numerically greater and more often statistically significant improvements from baseline to each assessment for children receiving romiplostim versus placebo. Mixed-effects analysis demonstrated statistically significantly greater reduction in parental burden from baseline in the romiplostim group versus placebo. Ranges for the MID were estimated as 9–13 points for the Child Self-Report version and 11–13 points for the Parent Impact version. ***Conclusions.*** The treatment with romiplostim may be associated with improved HRQoL in children with primary ITP and reduced burden to their parents. Pediatr Blood Cancer 2016;63:1232–1237. © 2016 The Authors. *Pediatric Blood & Cancer*, published by Wiley Periodicals, Inc.

Key words: health-related quality of life; kids' ITP tools; minimally important difference; parental burden; pediatric immune thrombocytopenia; romiplostim

INTRODUCTION

Immune thrombocytopenia (ITP) is an autoimmune disorder characterized by low platelet counts.[1] In children, ITP is typically a benign, self-limiting disorder that occurs following an infectious illness and recovers spontaneously and completely within weeks to months of the onset of illness, irrespective of any platelet-enhancing therapies that are given.[2] Persistence of thrombocytopenia below 100,000 per microliter for greater than 1 year defines the chronic form of the disorder;[3] approximately 5% of children (< 18 years of age) with typical primary ITP will have persistence of clinically severe thrombocytopenia, characterized by a circulating platelet count of < 20,000 per microliter at 12–18 months following the onset of ITP[4] and will require ongoing platelet-enhancing therapies for management of clinically significant thrombocytopenia. Studies from Germany, UK, and Scandinavia between 2001 and 2010 estimated the incidence of ITP in children to be between 2.2 and 5.3 per 100,000.[5–8] Incidence of ITP tends to be higher for younger males[5,6] and most commonly occurs between 5 and 6 years of age.[9] The likelihood of ITP can increase after receipt of the measles, mumps, and rubella vaccine.[10,11]

Childhood ITP can have a negative impact on patients' health-related quality of life (HRQoL)[12] and imposes a burden on their parents. It has been shown that HRQoL improves in patients (and their parents) who recover compared with those with persistent ITP.[13] The goal of treatment of ITP is to maintain a safe platelet count while minimizing the potential for adverse events.[9] Traditional treatments have included corticosteroids, intravenous immunoglobulin, and anti-D immune globulin. Immunosuppressive agents, used singly or in combination, and splenectomy are typically second-line therapies in children with primary, chronic ITP.[9,14,15] The treatment with immunoglobulins is more common in children (including among those hospitalized with newly diagnosed ITP[16]), while corticosteroids are used more frequently in adults.[17]

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Abbreviations: HRQoL, health-related quality of life; ITP, immune thrombocytopenia; KIT, Kids' ITP Tools; MDC, minimal detectable change; MID, minimally important difference; SD, standard deviation; SES, standardized effect size

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New platelet-enhancing therapies include thrombopoietin receptor agents, romiplostim and eltrombopag, which have both been shown to be efficacious in increasing platelet counts in patients with ITP.[18,19] Efficacious treatment with minimal side effects could have a positive impact on the HRQoL for children with primary ITP as well as the parents who care for them. The treatment of ITP with romiplostim in pediatric patients in a pilot study has previously been shown to reduce parental burden[20] as measured by the Kids' ITP Tools (KIT).[12,21] The current study utilizes data from a clinical trial for which the primary goal was to investigate platelet response associated with romiplostim in pediatric subjects with ITP. Efficacy results, in terms of platelet response, showed romiplostim to be effective in inducing high rates of durable and overall platelet responses.[22] Specifically, we performed an exploratory analysis of the impact of treatment with romiplostim on the HRQoL of patients in this trial and their parents, as measured by KIT scores. Additionally, this study attempted to evaluate the psychometric properties and estimate the minimally important difference (MID) of the KIT, even though the study was not designed or powered for these outcomes.

METHODS

Study Design and Patient Selection

This was a phase 3, randomized, double-blind, placebo-controlled study on the efficacy and safety of romiplostim conducted from January of 2012 to February of 2015.[23] Children aged <18 years with ITP ≥6 months as defined by 1996 ASH guidelines[24] were recruited from 27 sites in the United States, Canada, and Australia. Patients were excluded if they had a medical history of bone marrow stem cell disorder, active or prior malignancy, congenital thrombocytopenia, venous thromboembolism, or thrombotic events, or if they had received rituximab ≤14 weeks before the screening visit. Also excluded were those who had undergone a splenectomy ≤4 weeks before screening. Once enrolled and consented, patients were randomly assigned to receive romiplostim or placebo for 24 weeks. An institutional review board at each site approved study procedures, and all patients or their legal representatives provided written informed consent (ClinicalTrials.gov identifier, NCT01444417).

Measures

While the primary outcome of the trial was platelet response, data on HRQoL were also collected as an exploratory endpoint using the KIT tool,[12,21] a psychometrically validated disease-specific HRQoL instrument. When designing the trial, it was hypothesized that improvement in platelet response with minimal side effects would translate into better HRQoL for the children suffering from ITP and greater reduction in burden for their parents. The KIT questionnaires were self-administered to patients and/or their parents at baseline and weeks 8, 16, and 25. Each questionnaire was completed at the clinic visit before the patient was seen by the clinician and/or undergoing any procedures. All three KIT versions were used in this study: the Child Self-Report version was used for children ≥7 years, while KIT scores for children <7 years were obtained via the Parent Proxy version; the Parent Impact version was used for parents of children of all ages to assess the impact of children's ITP on parental burden. Each KIT version contains 26 items, summarized in a single score ranging from 0 to 100. Higher KIT scores in the Child Self-Report or Parent Proxy versions reflect better HRQoL of a child with ITP, and higher Parent Impact scores reflect less parental burden.

The primary outcome of platelet response was measured per the protocol definition. *Overall platelet response* was defined as achieving a weekly platelet response (platelet count ≥ 50×10^9/l) for ≥4 weeks during weeks 2–25, and *durable platelet response* was defined as achieving a weekly platelet response for ≥6 weeks during weeks 18 through 25. For purposes of comparing HRQoL changes by platelet response, patients were classified as "responders" and "nonresponders" based on either the overall or durable platelet response criteria, and then KIT scores were compared between groups.

Statistical Analysis

Descriptive statistics for demographic and baseline characteristics were summarized for all randomized patients. For categorical variables, the number and percentage of patients in each category were summarized. Continuous variables were summarized by number, mean, and standard deviation (SD). Mean (SD) KIT scores and mean (SD) change from baseline were calculated for each KIT version at each assessment by treatment group and platelet response status. A mixed-effects repeated measures analysis was conducted to estimate the difference in changes in KIT scores between treatment group, controlling for baseline score, the child's age, race, and gender.

Several aspects of reliability and validity of the KIT tool were assessed. The details of these analyses, including measures of internal consistency reliability, known-groups validity, and construct validity, can be found in the Supplementary Material. The responsiveness of the KIT tool was assessed by calculating three different parameters (see Supplementary Material) and also evaluating changes in KIT scores from baseline to the end of treatment by durable and overall platelet response status.

In order to provide guidance to clinicians and researchers regarding what constitutes a relevant change in KIT scores, we sought to estimate the MID, the smallest change that can be considered to be clinically meaningful. KIT scores at multiple assessment periods were used to estimate the MID using a combination of distribution- and anchor-based methods. Distribution-based methods are based on measures of spread of the data observed (e.g., the SD) and therefore consider the variability of the change in KIT scores to identify the amount of change that is clinically meaningful. These measures include the standardized effect size (SES), also known as Cohen's D,[25] the responsiveness statistic,[26] and the standard error of the mean. For the SES and the responsiveness statistic, it is necessary to set thresholds for their magnitude; common choices for these thresholds based on published literature are 0.20 (small), 0.50 (medium), and 0.80 (large).[27] Anchor-based methods utilize external criteria such as patients' judgment of how much their health status has changed. In the current study, patients were asked at the end of treatment to rate the change in the severity of their symptoms and change in HRQoL using response options ranging from "a very great deal better/worse" to "minimally better/worse" and including "no change" as an option. Then, mean changes in KIT scores from baseline to the end of treatment were calculated among patients who indicated only

TABLE I. Baseline Characteristics

	Placebo (N = 20)	Romiplostim (n = 42)	Total (n = 62)
Age (years), mean (SD)	9.4 (4.7)	9.7 (4.1)	9.6 (4.3)
Sex, n (%)			
Male	9 (45)	18 (42.9)	27 (43.5)
Female	11 (55)	24 (57.1)	35 (56.5)
Race, n (%)			
Asian	2 (10)	3 (7.1)	5 (8.1)
Black or African American	2 (10)	6 (14.3)	8 (12.9)
Multiple	0 (0)	1 (2.4)	1 (1.6)
Black or African American, White	0 (0)	1 (2.4)	1 (1.6)
Native Hawaiian or other Pacific Islander	0 (0)	1 (2.4)	1 (1.6)
Other	1 (5)	5 (11.9)	6 (9.7)
White	15 (75)	26 (61.9)	41 (66.1)
Baseline platelet count (10^9/l), mean (SD)	19.9 (19.3)	17.5 (10.7)	18.3 (13.9)
Time since ITP diagnosis[a] (years), mean (SD)	3.0 (2.3)	3.0 (2.8)	3.0 (2.6)
Splenectomized, n (%)	1 (5.0)	1 (2.4)	2 (3.2)
Number of prior ITP treatments received, n (%)			
1	6 (30)	8 (19.0)	14 (22.6)
2	3 (15)	18 (42.9)	21 (33.9)
3	6 (30)	8 (19.0)	14 (22.6)
>3	5 (25)	8 (19.0)	13 (21.0)

[a]Years are calculated as (randomization date – ITP diagnosis/splenectomy date)/365.25. Partial dates of ITP diagnosis/splenectomy with missing day only are imputed at 15, partial dates with missing month and day are imputed as July 1. SD, standard deviation; ITP, immune thrombocytopenia.

"minimal" or "no change" in health status to identify how much KIT scores could be expected to vary when patients experience only slight changes in health status. The establishment of the MID then involved combining information obtained from both the distribution- and anchor-based methods.

RESULTS

This study included a total of 62 patients; 42 were randomly assigned to receive romiplostim and 20 to receive placebo. The mean age of the study population was 9.6 years (range: 3–17 years); there were 16 patients younger than 7 years of age (Table I). Fifty-seven percent of patients were female and 66% were Caucasian.

For the 16 patients who were younger than 7 years (11 treatment and five placebo), the Parent Proxy version of the KIT was completed since the child was too young to be able to self-administer the Child Self-Report version. However, inadequate sample sizes at each assessment period did not allow for meaningful comparisons by the treatment group or platelet response; therefore, results from the Parent Proxy versions are not presented here, except when it was possible to combine them with those from the Child Self-Report versions. The remaining 46 patients (31 treatment and 15 placebo) were old enough and able to self-administer the Child Self-Report version. The Parent Impact version was completed by all parents, regardless of the child's age. Changes in KIT scores by the treatment group showed numerically greater and more often statistically significant improvements from baseline to each assessment for children receiving romiplostim versus placebo (Table II).

In the mixed-effects analysis, changes in child KIT scores (combined from the Child Self-Report and Parent Proxy versions) were not significantly different by treatment group, age, gender, or race. In fact, only the baseline KIT score was significantly associated with changes in child KIT scores. However, for the Parent Impact scores, the mixed-effects analysis demonstrated greater reduction in parental burden from baseline in the romiplostim group versus the placebo group ($P = 0.015$), and significantly greater improvements (across both groups) at weeks 16 ($P = 0.020$), and 25 ($P = 0.030$), compared with week 8. Age, gender, and race were not associated with significantly different changes in Parent Impact scores (data not shown).

Results of the assessment of psychometric properties of the KIT provided moderate evidence of its reliability and validity within this study sample, although this study was not designed or powered for this purpose. As evidenced by Cronbach's alpha coefficients at each assessment, the Child Self-Report and Parent Impact versions demonstrated excellent internal consistency reliability. When using questionnaires with at least 75% of the responses answered, missing scores were imputed and alpha values ranged from 0.88 to 0.96. When patients were stratified by platelet count to assess known-groups validity, KIT scores did not significantly differ across platelet count category, and when assessing construct validity, correlations between KIT scores from the Child and Parent Impact versions tended to be at or below 0.50. More details of these results can be found in the Supplementary Material.

The responsiveness of the Child and Parent Impact versions was measured by examining and comparing the KIT change scores between platelet responders (overall and durable response) and nonresponders. Results were similar for both response groups, but in general, changes in mean KIT scores by response status showed numerically greater and more often statistically significant improvements from baseline to each assessment for responders versus nonresponders. In the Child Self-Report version, small differences were evident, with responders producing mean changes between 11 and 16 and nonresponders producing mean changes ranging from 3 to 10. For the Par-

TABLE II. Mean Changes in KIT Scores by Treatment Group

	Placebo		Romiplostim	
	Weekly KIT Score	Change from Baseline	Weekly KIT score	Change from baseline
Child self-report				
Baseline	68.9 (16.8) n = 12	–	66.8 (16.0) n = 28	–
Week 8	77.2 (17.4) n = 13	9.1 (12.8)[a] N = 11	76.3 (14.8) n = 30	9.4 (13.9)[a] n = 28
Week 16	76.9 (17.3) n = 12	8.4 (15.6) n = 10	78.1 (14.4) n = 29	10.7 (14.3)[a] n = 27
Week 25 (end of study)	78.0 (18.9) n = 13	9.8 (15.7) n = 11	80.2 (14.8) n = 30	13.7 (16.7)[a] n = 28
Between group difference in mean change from baseline[b] (*P*-value)		N.S.		
Parent impact				
Baseline	35.5 (17.0) n = 18	–	34.4 (19.0) n = 40	–
Week 8	39.2 (20.7) n = 17	3.6 (17.3) n = 16	48.3 (22.5) n = 42	13.3 (11.7)[a] n = 40
Week 16	48.3 (18.9) n = 18	12.3 (15.4)[a] n = 17	50.1 (22.9) n = 41	15.4 (16.4)[a] n = 39
Week 25 (end of study)	49.4 (18.2) n = 17	12.8 (16.3)[a] n = 16	53.7 (25.4) n = 39	17.5 (16.7)[a] n = 37
Between group difference in mean change from baseline[b] (*P*-value)		$P = 0.015$		

All cell values are mean (SD) and sample size. Change from baseline only includes patients who provided responses at both time points. Note that change from baseline was calculated only using data for those with complete assessments at baseline and the follow-up assessment period of interest. [a]Indicates that confidence interval for mean change from baseline does not include zero, indicating statistical significance [b]A mixed-effects repeated measures analysis was conducted to estimate the difference between treatment groups in mean changes in KIT scores pooled using follow-up data from weeks 8, 16, and 25, controlling for baseline score, the child's age, race, and gender. N.S., not statistically significant.

ent Impact version, at most assessments the mean change for responders was slightly higher than for nonresponders, but at week 16 those with an overall platelet response had a slightly lower mean change than nonresponders (Table III). When the responsiveness statistic was analyzed by treatment group, moderate differences between romiplostim and placebo groups were seen for the Child Self-Report version, and the Parent Impact version produced mixed results (Supplementary Material).

Results of distribution-based methods indicated that lower bounds of the MID for the two KIT versions with adequate sample sizes ranged from 7 to 8 for the Child Self-Report version and from 8 to 9 for the Parent Impact version. With the anchor-based analyses, the mean (SD) changes in Child Self-Report KIT scores among those whose symptoms were rated as having no change ranged from 2.5 (10.13) to 11.7 (12.10), while mean changes in scores among those whose symptoms were rated as "minimally" different (better or worse) ranged from –0.6 to 13.1. For the Parent Impact version, the mean (SD) change in KIT score when symptoms were rated as having either no change or minimal change ranged from 7.2 (13.07) to 26.8 (11.57), but the mean was frequently between 10 and 13 points. When distribution- and anchor-based measures were considered together, the final MID ranges for the Child Self-Report version and the Parent Impact version were 9–13 points and 11–13 points, respectively.

DISCUSSION

This study sought to perform an exploratory analysis of the impact of romiplostim on the HRQoL of pediatric subjects with ITP using data from a clinical trial for which the primary outcome was platelet response. HRQoL was measured using versions of the KIT, a tool developed using data from interviews with 88 children with acute or chronic ITP and their parents,[21] although limited sample sizes among those completing the Parent Proxy version limited the ability to examine these results. The current study, while not powered or designed to measure the impact of romiplostim on changes in HRQoL, found that KIT scores from baseline to the end of the study were numerically greater and more often statistically significant in patients treated with romiplostim versus those receiving a placebo. Mixed-effects analysis revealed that the romiplostim group had statistically significantly more improvement (versus placebo) in the KIT score of the Parent Impact version, but not in the KIT score of the Child Self-Report version.

Responsiveness of the Child Self-Report version was low, while the Parent Impact version produced mixed results. Through the integration of distribution- and anchor-based analyses, the range for the MID for the Child Self-Report version was estimated to be 9–13 points, while for the Parent Impact version the range was estimated to be 11–13 points.

TABLE III. Mean Changes in KIT Scores by Platelet Response Group

KIT version	Assessment week	Mean change (95% CI) for responders	Mean change (95% CI) for nonresponders
By overall platelet response[a]			
Child self-report	8	11.1 (4.3, 18.0) n = 23	3.5 (–4.6, 11.6) n = 17
	16	11.2 (4.3, 18.1) n = 22	7.8 (0.9, 14.7) n = 16
	25	15.9 (8.3, 23.6) n = 23	7.9 (0.9, 14.9) n = 16
Parent impact	8	10.7 (7.4, 14.0) n = 30	10.3 (2.8, 17.8) n = 26
	16	13.8 (7.3, 20.3) n = 30	15.2 (9.4, 21.1) n = 26
	25	17.3 (10.3, 24.3) n = 29	14.7 (8.7, 20.7) n = 24
By durable platelet response[b]			
Child self-report	8	11.0 (3.0, 19.0) n = 19	5.1 (–1.9, 12.1) n = 21
	16	11.5 (3.6, 19.3) n = 18	8.3 (2.1, 14.5) n = 20
	25	15.1 (5.9, 24.2) n = 19	10.3 (4.1, 16.5) n = 20
Parent impact	8	12.6 (8.7, 16.4) n = 23	9.1 (3.2, 15.0) n = 33
	16	15.1 (7.6, 22.6) n = 23	14.0 (8.6, 19.4) n = 33
	25	22.2 (14.1, 30.3) n = 22	11.8 (6.7, 16.9) n = 31

[a]Defined as achieving a weekly platelet response (platelet count $\geq 50 \times 10^9$/l) for ≥4 weeks during weeks 2–25 [b]defined as achieving a weekly platelet response for ≥6 weeks during weeks 18 through 25. CI, confidence interval.

A previous study of 22 children with ITP reported that romiplostim (17 children) was associated with a significantly improved Parental Impact KIT scores compared with those receiving placebo (five children). While improvements in child HRQoL (measured by KIT scores) trended toward improvement in those receiving romiplostim, the improvement was not statistically significant.[20] These results are similar to the findings in the current study, a larger follow-up prospective clinical trial. In a study on the effects of eltrombopag on HRQoL among children with ITP, patients and their guardians completed KIT versions at baseline, after 6 and 12 weeks of treatment, and at the end of the study (or withdrawal). The authors reported that patients receiving eltrombopag demonstrated small improvements in KIT scores, but improvements did not exceed what the authors referred to as minimally important differences (estimates for MID are not referenced).[28]

Prior studies on the psychometric properties of the KIT tool with larger sample sizes have confirmed its validity and reliability. A study of 90 patients with ITP aged 2–18 years reported that the KIT was moderately correlated with the Pediatric Quality of Life Inventory (PedsQL), with the KIT demonstrating comparable reliability and better responsiveness.[12] The international version of the KIT (adapted for France, Germany, the United Kingdom, and Uruguay) has also been found to be valid and reliable, and to have moderate correlations with the PedsQL and the KINDL.[29] The current study, while not powered to replicate the assessments of these prior studies, adds to the literature surrounding the KIT tool by providing estimates of the MID for both the Child Self-Report and Parent Impact versions.

The current study has several limitations to consider. To begin, the small sample sizes for the Parent Proxy version did not allow for examination of the results of this version or an estimation of its MID, and for the Child Self-Report version, small sample sizes at some assessments may provide limited precision of estimates. Furthermore, since the primary outcome of the trial was to assess the efficacy and safety of romiplostim, the study was not specifically designed or powered to measure the impact of romiplostim on HRQoL. Additionally, it was not possible to calculate the test–retest reliability because the interval available for these measures was too long. Finally, since patients and their parents were required to visit the clinic for laboratory tests and assessments with a higher frequency than is typically necessary for care of ITP; it is possible that this increased frequency of hospital visits, including venipuncture for blood sampling, could have bothered some children and resulted in worse Child Self-Report scores than would be seen among children with ITP receiving usual care.

Despite these limitations, the results of this study suggest that treatment with romiplostim may be associated with improved HRQoL in children with primary ITP and reduced burden to their parents. This study also provides additional support, albeit limited, of the measurement properties of the KIT. Finally,

MID estimates for both the Child Self-Report and Parent Impact versions of the KIT provide clinicians and researchers with thresholds for what constitutes clinically meaningful change in KIT scores. Future prospective studies with larger sample sizes are warranted to follow-up on the interesting observations from this prelicensure, multicenter, randomized clinical trial comparing romiplostim with placebo in children with ITP with long-term follow up for safety issues.

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