Pediatr Blood Cancer 2012;58:395–398

Pilot Study of the Effect of Romiplostim on Child Health-Related Quality of Life (HRQoL) and Parental Burden in Immune Thrombocytopenia (ITP)

Robert J. Klaassen, MD,[1]* Susan D. Mathias, MPH,[2] George Buchanan, MD,[3] James Bussel, MD,[4] Robert Deuson, PhD,[5] Nancy L. Young, PhD,[6] Anderson Collier, MD,[7] Lisa Bomgaars, MD,[8] and Victor Blanchette, MD[9]

Background. Childhood ITP can have a negative impact on the child and his/her family even though it is typically a benign disorder with low risk of serious bleeding. In adults and now children, romiplostim increases the platelet count without significant adverse effects. In this study, the impact of romiplostim treatment on the HRQoL of children with chronic ITP was assessed using the Kid's ITP Tools (KIT). ***Procedure.*** Subjects 1–18 years old, with chronic ITP (>6 months), were enrolled in a multi-center, randomized, double-blind, placebo-controlled phase 1/2 treatment study with romiplostim (reported elsewhere). Subjects and/or proxies completed the KIT at baseline, week 5, and week 13. Scores were computed for child self-report (children >7 years), proxy-report, and parent impact. Changes in mean scores from baseline to week 13 were computed. ***Results.*** Twenty-two children (17 receiving romiplostim, 5 placebo) and/or their parents provided data. Change in mean scores demonstrated significant improvement in HRQoL for romiplostim versus placebo for parent impact (24 ± 17 vs. -6 ± 8; $P = 0.008$). Change scores for child self-report trended toward improvement with romiplostim and decreased with placebo (5 ± 10 vs. -7 ± 17; $P = 0.29$). Romiplostim proxy-report mean change scores were 6 points higher than placebo (8 ± 16 vs. 2 ± 12; $P = 0.50$). ***Conclusions.*** Romiplostim significantly reduced parental burden in this study. Whether the same and/or additional improvements in HRQoL would be demonstrated by a larger, longer study of romiplostim-treated children with ITP remains to be determined. Pediatr Blood Cancer 2012;58:395–398.

Key words: idiopathic; parents; purpura; quality of life; questionnaires; thrombocytopenic

INTRODUCTION

Immune thrombocytopenia (ITP) is an autoimmune disorder characterized by thrombocytopenia (platelet count $< 150 \times 10^9$/L) due to accelerated platelet destruction and suboptimal platelet production [1]. ITP has an incidence of 4–5 cases per 100,000 children per year [2]. It typically presents in a previously healthy child with a sudden onset of petechiae and bruising and occasionally mucosal bleeding, usually causing great concern for families [3]. Children are more likely to have the acute, spontaneously resolving form of ITP; however, chronic ITP, previously defined as thrombocytopenia persisting for >6 months, develops in 20–40% of cases [4,5].

Romiplostim is an Fc-peptide fusion protein (peptibody) that increases platelet production by binding to and activating the thrombopoietin (TPO) receptor; other agents such as eltrombopag and AKR501 (EE501) also increase the platelet count in patients with ITP by a similar mechanism. Eltrombopag is administered orally, while AKR501 is not yet approved for use. Romiplostim is currently approved (with restrictions) for the treatment of adult chronic ITP in North America, Europe, and Australia. Long-term treatment has been shown to significantly increase the platelet count (to $\geq 50 \times 10^9$/L and double the baseline value) in up to 87% of adult patients [6–9]. Further, data have also shown adults with chronic ITP were often able to reduce or discontinue use of other ITP medications while receiving treatment with romiplostim and required less emergency treatment for low platelet counts or bleeding. The main pediatric study, of which this HRQoL study is a part, demonstrated responses in 15 of 17 children in the treatment group and none in placebo group; all efficacy endpoints were met [10].

Even though childhood ITP is typically a benign disorder with low risk of serious bleeding, it can have a negative impact on the child and his/her family. Because of this impact, HRQoL is an important consideration when determining whether to use active treatment [5] and, if so, which options to choose.

To most appropriately assess HRQoL in this population, a disease-specific HRQoL measure is required since generic tools may not adequately address the issues in this population [11]. The Kids' ITP Tools (KIT) was developed based on data from interviews involving 88 children and 90 parents [12]. It was subsequently shown to be valid, reliable and responsive to change in a North American study of 41 children with newly diagnosed ITP and 49 with chronic ITP [13]. The KIT has three different components: a child self-report version that can be completed by children 7 years of age and older; a proxy-report version that is completed by a caregiver (usually a parent) on behalf of children

[1]Children's Hospital of Eastern Ontario, University of Ottawa, Ottawa, Ontario, Canada; [2]Health Outcomes Solutions, Winter Park, Florida; [3]University of Texas Southwestern Medical Center at Dallas, Dallas, Texas; [4]New York Presbyterian Hospital, Weill Medical College of Cornell University, New York, New York; [5]Amgen Inc., Thousand Oaks, California; [6]Laurentian University, Sudbury, Ontario, Canada; [7]Lehigh Valley Hospital, Bethlehem, Pennsylvania; [8]Texas Children's Cancer Center, Baylor College of Medicine, Houston, Texas; [9]Division of Hematology/Oncology, Hospital for Sick Children and Department of Pediatrics, University of Toronto, Toronto, Ontario, Canada

Conflict of Interest: Robert Klaassen has received research funding support from Cangene Corp. and Novartis, Canada. James B. Bussel has received research support from Amgen Inc., Eisai Inc, Shionogi, Sysmex, Ligand, Immunomedics, GlaxoSmithKline, Cangene, and Genzyme; has served on an advisory board for Amgen Inc., Ligand and GlaxoSmithKline, Shionogi, Eisai Inc.; and holds equity in Amgen Inc. and GlaxoSmithKline. Nancy Young is supported by a Canada Research Chair from the Canadian Institutes of Health Research.

*Correspondence to: Robert J. Klaassen, MD, Children's Hospital of Eastern Ontario, 401 Smyth Road, Ottawa, ON, Canada K1H 8L1. E-mail: rklaassen@cheo.on.ca

Received 31 May 2011; Accepted 25 July 2011

DOI 10.1002/pbc.23312
Published online 9 September 2011 in Wiley Online Library (wileyonlinelibrary.com).

2–18 years of age; and a parent impact version that is completed by parents to assess the parental burden of caring for a child with ITP.

The purpose of this study was to assess the effect of romiplostim versus placebo on child HRQoL and parental burden using the three components of the KIT, embedded as part of a randomized placebo-controlled trial of romiplostim in the treatment of children with chronic ITP.

METHODS

Study Design

Patients between 12 months and up to 18 years of age diagnosed with chronic ITP (thrombocytopenia for $\geq$6 months) according to the 1996 American Society of Hematology (ASH) Guidelines [14] were enrolled in a 12 week, multi-center, randomized, double-blind, placebo-controlled, phase 1/2 study of romiplostim to determine the safety, tolerability, and efficacy of romiplostim. Patients were eligible to participate if they had persistent severe thrombocytopenia defined as two platelet counts $\leq 30 \times 10^9$/L with no single count $>35 \times 10^9$/L within 28 days of the enrollment visit. They were excluded if they were receiving any treatment for ITP other than corticosteroids. Potential subjects were stratified by age (12 months to <3 years; 3 to <12 years; 12 to <18 years) and randomized 3:1 to each treatment group (romiplostim:placebo) at a starting dose of 1 mcg/kg. Individual dose adjustments could be made in 2 mcg/kg increments every 2 weeks based on platelet counts to a maximum dose of 10 mcg/kg. Rescue medications were permitted at any time during the study at the discretion of the investigator, and a reduction in concurrent corticosteroids was acceptable when the platelet count was $>50 \times 10^9$/L. The results of the clinical study have been reported [10].

All subjects and/or their parents completed the KIT at baseline (week 1), and weeks 5 and 13. Data from two subjects who completed the child self-report version were excluded because it was determined that they were too young (<7 years of age) to reliably complete a self-administered questionnaire.

Overview of the KIT Assessment

The KIT is comprised of a child self-report component, a parent-proxy component, and a parent-impact component and is relevant to newly diagnosed, persistent, and chronic ITP patients. Each component consists of 26 items and is aggregated into a single overall score ranging from 0 (worst) to 100 (best). A higher score represents better HRQoL for the child or, with the parent impact version, less burden. The questionnaire is designed to be completed independently by children 7 years or older (self-report version), or can be proxy-completed by parents of children as young as 2 years up to 18 years (parent-proxy version).The KIT has proven to be a valid and reliable measure of HRQOL for use in clinical trials of childhood ITP [13].

Statistical Analysis

Mean overall scores were analyzed at each time point (weeks 1, 5, and 13) by treatment group for the child self-report, proxy-report, and parent impact measures. The change in scores for each component of the KIT was also computed at each time point for both treatment groups. Because of the small sample size, Mann–Whitney non-parametric tests of statistical significance (based on a two-tailed exact method) were used to assess differences between the drug and placebo groups. Test–retest reliability was evaluated for all 3 components of the KIT using the intra-class correlation coefficient (ICC) with data from the screening and baseline assessments.

RESULTS

Twenty-two subjects (16 boys, 6 girls; age 9.5 $\pm$ 5.1 years) with median baseline platelet counts of 13×10^9/L (romiplostim) and 9×10^9/L (placebo) (range, 2–29 $\times 10^9$/L) and their parents were enrolled. Child self-report data were available for 4 of 5 subjects in the placebo group and 12 of 17 subjects in the romiplostim group. Parent proxy-report and parental impact data were available for all enrolled patients. Missing data from the questionnaire version were minimal, as only 1 subject omitted 1 item from the 26 items contained in the child self-report questionnaire. The children and parents were generally aware of the results of the baseline and often the follow up platelet counts when completing the questionnaires.

Demographic and clinical characteristics for the study subjects at week 1 are shown in Table I. There were no significant differences at baseline between the romiplostim and placebo groups.

Parent Impact Report

Figure 1 shows the summary results of the impact, or burden, of the child's condition on the parent. In the romiplostim group, improvements in parental impact were seen at week 5 (39 $\pm$ 18–48.9 $\pm$ 17.5), with further improvements at week 13 (61.8 $\pm$ 21). In the placebo group, parental impact remained stable from week 1 to week 5 (35.9 $\pm$ 6.5–35.4 $\pm$ 25.9), with a trend to increased impact, or burden at week 13 (29.8 $\pm$ 1.9). The analysis of the change in scores highlights these results, with improvements in the romiplostim group versus a decline in the placebo group at week 5 (12.5 $\pm$ 19.2 vs. -3.0 ± 23.5, $P = 0.221$) and further improvements for romiplostim versus placebo at week 13

TABLE I. Demographic and Clinical Characteristics

	Placebo (N = 5)	Romiplostim (N = 17)
Median age, n (range)	11 (2–14)	9 (1–17)
<2 years (%)	0 (0)	2 (12)
2 to <7 years (%)	1 (20)	3 (18)
7 to <18 years (%)	4 (80)	12 (71)
Sex – male, n (%)	3 (60)	13 (76)
Baseline platelet count $\times 10^9$/L, median (range)	9 (8–29)	13 (2–27)
Time since ITP diagnosis, years, median (range)	4.1 (0.6–8.6)	2.4 (0.8–14.0)
Splenectomy, n (%)	2 (40)	6 (35)
Received prior ITP treatment, n (%)	5 (100)	16 (94)

There were no significant differences at baseline between the romiplostim and placebo groups.

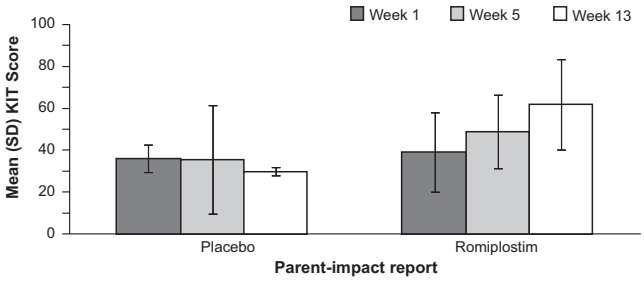

Fig. 1. Mean KIT scores of the parent-impact report. Quality of life is represented for both the placebo and the romiplostim groups at weeks 1, 5, and 13.

(24.0 ± 17.1 vs. -6.1 ± 8.4, $P = 0.008$). Specific items demonstrating the most improvement related to activity limitations (e.g., did your child's ITP change your usual activities or family plans?).

Child Self-Report of Quality of Life

Figure 2 shows summary results for child self-report of HRQoL by visit. Subjects in the romiplostim group remained fairly stable at all time points (81.2 ± 13.3), and were not statistically different from baseline or from placebo (75.5 ± 21.1; $P = 0.573$). Items that showed the most improvement in the romiplostim group included questions about general anxiety and limitation in activities as well as being bothered by venipuncture.

Parent Proxy-Report of Child's Quality of Life

Figure 2 also shows summary results of the parent report of the child's HRQoL by visit. Parents of children in the romiplostim group reported a mean 9 point increase in child HRQoL by week 5 (81.6 ± 14.0), which remained stable through week 13 (81.3 ± 14.2) whereas the placebo group did not change. However, the changes did not reach statistical significance. Again the items that improved the most related to limitations in activities.

Test–Retest Reliability

Test–retest reliability was evaluated using the intra-class correlation coefficient (ICC) with data from the screening and baseline assessments. The ICC was >0.70 for all 3 components of the KIT (ICC = 0.75 for the child self-report of HRQoL, 0.82 for the parent report of child's HRQoL, and 0.72 for the parent impact report of HRQoL), indicating acceptable test–retest reliability [15].

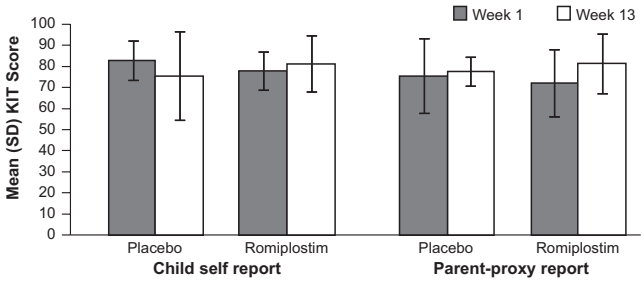

Fig. 2. Mean KIT scores of the child self report and the parent-proxy report. Quality of life is represented for both the placebo and the romiplostim groups at weeks 1 and 13.

DISCUSSION

This study was the first randomized treatment study of childhood ITP that included a disease-specific quality of life tool and a small, but essential, placebo group. This study was designed as a phase 1/2 study to determine the safety, tolerability, and efficacy of romiplostim on the platelet count in children with chronic ITP and was not powered to adequately examine HRQoL given the very small number of patients. In addition, because of the (slow) dose escalation schedule, a number of responders had not yet responded as of week 5. The patient cohort spanned a wide variety of ages and disease duration, which could not be separated out in such a small sample. In spite of these limitations, several findings are evident.

The impact of ITP on parents is often not fully appreciated by health care providers. We were able to specifically target this area since the KIT includes a measure of parental impact with a scale of up to 100 (no burden). A 2007 study of 49 parents of children with chronic ITP found an average KIT parent impact score of 52. This result indicates less impact than on the parents in the current study population, likely due to the fact the 2007 study included patients with higher platelet counts and milder disease, but still indicating significant burden [13]. Parents clearly experience significant worry in spite of reassurance by the health care team that ITP is a benign disorder.

Romiplostim is a TPO receptor agonist that is administered subcutaneously once a week. Clinical data from this study showed that romiplostim was well-tolerated in children with ITP and that it increased platelet counts above 50×10^9/L for >2 weeks, the primary endpoint, in 15 of the 17 romiplostim-treated patients with no change in the platelet count of patients in the placebo group [10]. The weekly injections required in both the romiplostim and placebo groups would be expected to diminish a child's HRQoL, whether by parental proxy report or directly by the child, and the weekly travel to clinic to receive treatment would be expected to increase parent impact. The scores for parental burden increased by more than 25 points (indicating less burden), whereas scores for those in the placebo group showed a decline (more burden). This difference in burden is statistically significant ($P = 0.008$) and is larger than the difference in impact scores previously reported between parents of children with newly diagnosed and chronic ITP (34 vs. 52), which would be considered by most clinicians to be more than a minimally important difference [13]. This substantial reduction in the parental burden of disease seen in this study with romiplostim needs to be considered when weighing therapeutic options in children with difficult-to-treat, chronic ITP.

The data on the child's HRQoL are not as clear. The five children receiving placebo had a seven-point decrease in their self-reported KIT scores, likely related to the frequent follow-up, weekly subcutaneous injections, and their persistently very low counts. Yet for these reasons, their participation was valuable when interpreting the results of the treatment group. Children receiving romiplostim reported a 4.5-point increase in scores.

This improvement from baseline was not statistically significant, representing an 11-point incremental difference compared to the placebo group, similar to the disparity in child self-reported KIT scores between newly diagnosed ITP and chronic ITP [13]. Similarly parent-completed proxy scores increase by 14 in the romiplostim group whereas it remained stable in the placebo group. The parallel change in scores between the parent proxy-report and child-report assessments support that a change might be seen in a larger sample size. The items most responsive to change demonstrating improvement for children receiving romiplostim in all three components consistently centered around reduced limitations in activities.

This study confirmed the test–retest reliability of the KIT with correlations higher than those reported previously [13].

It is becoming increasingly clear within the ITP community that parents and hematologists should not rely on only the platelet count when assessing the effects of treatment in patients [16]. Other outcomes such as bleeding scores, measures of HRQoL, and parental burden need to be included in future studies, in particular phase three trials. A good example of the benefits of this approach can be seen in two placebo-controlled randomized trials of romiplostim in adult patients with ITP. The ITP-PAQ, a disease-specific adult ITP measure, was used in both studies and showed that romiplostim significantly improved scores in the domains of symptoms, physical health, activity, fear, social activity and women's reproductive health [17]. A 6-month randomized study of eltrombopag, an oral, small-molecule, nonpeptide thrombopoietin-receptor agonist, comparable to other recent studies of romiplostim, also showed such a difference [18]. The fact that the 6-week eltrombopag trials did not show such a difference suggests that some time between 6 and 24 weeks is required to demonstrate a change in HRQoL when treating patients with chronic ITP with a thrombopoietic agent such as romiplostim. Therefore in addition to the small sample size of the study, greater benefits in terms of HRQoL might have been seen if the study had been of a longer duration (i.e., 24 weeks instead of 12).

Despite the small sample size, the results indicate that romiplostim significantly reduces parental burden. A larger study is needed to determine whether such treatment also improves child HRQoL.

ACKNOWLEDGMENT

We thank James O'Kelly, an employee of Amgen Inc, for providing editorial and formatting assistance with the manuscript.

REFERENCES

1. Nugent D, McMillan R, Nichol JL, et al. Pathogenesis of chronic immune thrombocytopenia: Increased platelet destruction and/or decreased platelet production. Br J Haematol 2009;146:585–596.
2. Yong M, Schoonen WM, Li L, et al. Epidemiology of paediatric immune thrombocytopenia in the General Practice Research Database. Br J Haematol 2010;149:855–864.
3. Buchanan GR. Thrombocytopenia during childhood: What the pediatrician needs to know. Pediatr Rev 2005;26:401–409.
4. Kuhne T, Buchanan GR, Zimmerman S, et al. A prospective comparative study of 2540 infants and children with newly diagnosed idiopathic thrombocytopenic purpura (ITP) from the Intercontinental Childhood ITP Study Group. J Pediatr 2003;143:605–608.
5. Kuhne T, Imbach P, Bolton-Maggs PH, et al. Newly diagnosed idiopathic thrombocytopenic purpura in childhood: An observational study. Lancet 2001;358:2122–2125.
6. Bussel JB, Kuter DJ, George JN, et al. AMG 531, a thrombopoiesis-stimulating protein, for chronic ITP. N Engl J Med 2006;355:1672–1681.
7. Bussel JB, Kuter DJ, Pullarkat V, et al. Safety and efficacy of long-term treatment with romiplostim in thrombocytopenic patients with chronic ITP. Blood 2009;113:2161–2171.
8. Kuter DJ, Bussel JB, Lyons RM, et al. Efficacy of romiplostim in patients with chronic immune thrombocytopenic purpura: A double-blind randomised controlled trial. Lancet 2008;371:395–403.
9. Newland A, Caulier MT, Kappers-Klunne M, et al. An open-label, unit dose-finding study of AMG 531, a novel thrombopoiesis-stimulating peptibody, in patients with immune thrombocytopenic purpura. Br J Haematol 2006;135:547–553.
10. Bussel JB, Buchanan GR, Nugent DJ, et al. A randomized, double-blind study of romiplostim to determine its safety and efficacy in children with immune thrombocytopenia. Blood 2011;118:28–36.
11. Klaassen R. Acute immune thrombocytopenic purpura: What do we do when things go well? Paediatr Child Health 2002;7:384–385.
12. Barnard D, Woloski M, Feeny D, et al. Development of disease-specific health-related quality-of-life instruments for children with immune thrombocytopenic purpura and their parents. J Pediatr Hematol Oncol 2003;25:56–62.
13. Klaassen RJ, Blanchette VS, Barnard D, et al. Validity, reliability, and responsiveness of a new measure of health-related quality of life in children with immune thrombocytopenic purpura: The Kids' ITP Tools. J Pediatr 2007;150:510–515 5 e1.
14. George JN, Woolf SH, Raskob GE, et al. Idiopathic thrombocytopenic purpura: A practice guideline developed by explicit methods for the American Society of Hematology. Blood 1996;88:3–40.
15. Aaronson N, Alonso J, Burnam A, et al. Assessing health status and quality-of-life instruments: Attributes and review criteria. Qual Life Res 2002;11:193–205.
16. Tamary HRJ, Chitlur M, Nugent DJ. Consensus Paper-ICIS Expert Meeting Basel 2009 treatment milestones in immune thrombocytopenia. Ann Hematol 2010;89:S5–S10.
17. George JN, Mathias SD, Go RS, et al. Improved quality of life for romiplostim-treated patients with chronic immune thrombocytopenic purpura: Results from two randomized, placebo-controlled trials. Br J Haematol 2009;144:409–415.
18. Cheng G, Saleh MN, Marcher C, et al. Eltrombopag for management of chronic immune thrombocytopenia (RAISE): A 6-month, randomised, phase 3 study. Lancet 2011;377:393–402.