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Second-Line Treatments in Children with Immune Thrombocytopenia: Effect on Platelet Count and Patient-Centered Outcomes

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Abstract

Immune thrombocytopenia (ITP) is an autoimmune bleeding disorder with isolated thrombocytopenia and hemorrhagic risk. While many children with ITP can be safely observed, treatments are often needed for various reasons, including to decrease bleeding or improve health related quality of life (HRQoL). There are a number of available second-line treatments, including rituximab, thrombopoietin-receptor agonists, oral immunosuppressive agents, and splenectomy, but data comparing treatment outcomes are lacking. ICON1 is a prospective, multi-center, observational study of 120 children starting second-line treatments for ITP designed to compare treatment outcomes including platelet count, bleeding, and HRQoL utilizing the Kids ITP Tool (KIT). While all treatments resulted in increased platelet counts, romiplostim had the most pronounced effect at 6 months (p=0.04). Only patients on romiplostim and rituximab had a significant reduction in both skin-related (84% to 48%, p=0.01 and 81% to 43%, p=0.004) and non-skin-related bleeding symptoms (58% to 14%, p=0.0001 and 54% to 17%, p=0.0006) after 1 month of treatment. HRQoL significantly improved on all treatments. However, only patients treated with eltrombopag had a median improvement in KIT scores at 1 month that met the minimal important difference (MID). Bleeding, platelet count, and HRQoL improved in each treatment group, but the extent and timing of the effect varied among treatments. These results are hypothesis generating and help to improve our understanding of the effect of each treatment on specific patient outcomes. Combined with future randomized trials, these findings will help clinicians select the optimal second-line treatment for an individual child with ITP.

Clinicaltrials.gov NCT01971684

Keywords

Immune thrombocytopenia; Rituximab; Thrombopoietin Receptor Agonists; quality of life

Introduction

Immune thrombocytopenia (ITP) is an immune-mediated disorder characterized by isolated thrombocytopenia without an identifiable cause.[1] The majority of children with ITP present with platelet counts below 20 $\times 10^9$/L which lead to variable bleeding manifestations, as well

as symptoms and activity restrictions that impact health-related quality of life (HRQoL). Current guidelines for the management of newly diagnosed patients with ITP suggest observation in the absence of bleeding symptoms, or treatment with standard first-line therapies (corticosteroids, anti-RhD immunoglobulin, or intravenous immunoglobulin (IVIG)) for those with bleeding symptoms.[2] In the Pediatric and Adult Registry on Chronic ITP, 38-47% of the children who received upfront treatment required second-line therapies at 6-24 months.[3] Reasons for treating patients with second-line therapies may include refractory disease, bleeding symptoms or risk of bleeding, poor perceived quality of life, need for peri-procedural management, and/or desire to achieve remission.

An International Working Group proposed criteria for assessing outcomes in ITP trials, including specific platelet responses, as well as additional outcomes of bleeding symptoms and HRQoL assessments.[1] Nonetheless, there are limited studies reporting platelet counts, bleeding, and HRQoL outcomes for second-line therapies, and none directly comparing treatments.[4] With an increasing number of available therapies, including the emergence of thrombopoietin-receptor agonists for pediatric use,[5] the selection of the optimal second-line agent remains challenging. Each treatment has differences in cost, mode of administration, time to response, rate of response, monitoring requirements, tolerability, and toxicity, adding to the difficulty in comparison. This highlights major gaps in available evidence to guide clinical decision-making when initiating second-line therapy for pediatric ITP.

ICON1 is a prospective, longitudinal cohort study conducted by the Pediatric ITP Consortium of North America (ICON) that followed pediatric patients starting second-line treatments for ITP. In this report, we describe the results of a comparison of second-line treatments with respect to platelet count, bleeding symptoms, and HRQoL.

Methods

Patients and Treatments:

ICON1 is a longitudinal observational cohort of 120 children with ITP requiring second-line treatments.[6] Participants were enrolled at 21 centers in the United States and Canada between September 2013 and December 2015 following local institutional review board/research ethics board approval. Consent was provided by caregivers and assent by the participants if age appropriate for participation in the study. Enrollment requirements included: age 1-17 years and starting a second-line treatment as monotherapy. Second-line treatments included all treatments except observation, IVIG, corticosteroids, or anti-D immunoglobulin. Patients with secondary ITP were included unless they had Evans syndrome with prior or ongoing autoimmune hemolytic anemia. After consent was obtained, treatment was initiated according to the preferences of the physician and patient.

Data forms were completed at baseline and 1, 6, and 12 months after starting treatment. Baseline and follow-up demographic and clinical characteristics were recorded, including disease duration, bleeding scores, rescue therapy, and platelet counts. Duration of ITP was defined as chronic in those with ITP for ≥12 months, persistent in those with ITP for 3-<12 months, and newly diagnosed in those with ITP for <3 months from initial diagnosis.

Treatments were selected for comparison in this analysis if there were at least 15 evaluable patients in the study cohort. Physicians were asked at each timepoint for their assessment of the patient's adherence to the treatment.

Platelet Response:

Platelet counts were collected as per clinical indications. A complete platelet response (CR) was defined as ≥50% of platelet counts >100 × 10^9/L since the prior study visit. A partial platelet response (PR) was defined as ≥50% of platelet counts >30 × 10^9/L and twice the baseline platelet count. No response (NR) was defined as any platelet count change that did not meet criteria for CR or PR. Using these definitions, the platelet response was compared by the change in response category from the baseline visit. The platelet response was evaluated for individual treatments, as well as compared between treatment groups. The frequency of patients with a single platelet count response of >100 × 10^9/L or >30 × 10^9/L and a doubling from the baseline platelet count was also reported separately for each treatment over the duration of the study. Platelet counts measured ≤30 days after the date of rescue medication were excluded from calculations of platelet response.

Bleeding Response:

Bleeding was characterized by score on the ITP Bleeding scale (IBLS), a validated measure for use to assess bleeding in childhood ITP in clinical trials.[7] The IBLS was used to assess worst bleeding in the week prior to the baseline visit and between the 1, 6 and 12 month visits after starting treatment. The change in bleeding score from baseline to 1 month and between baseline and 6 months were used for the primary analysis while the change in bleeding score between baseline and 12 months was assessed as a secondary analysis. The IBLS scores bleeding at 9 different sites and grades most sites as 0 (no bleeding), 1 (mild to moderate bleeding), or 2 (significant bleeding). For the analysis, the scores were dichotomized into grade 0 versus grade 1 or 2 bleeding and into skin versus non-skin bleeding. The change in bleeding was evaluated on the individual treatments and also compared between treatment groups.

Rescue Treatment:

Response was also characterized by whether treatment with a rescue medication, such as corticosteroids or IVIG, was needed between visits. For the primary analysis, the need for rescue was assessed between 0 and 1 month and between 0 and 6 months. The use of rescue medications was dichotomously analyzed for each treatment and then compared between treatment groups.

Health-Related Quality of Life:

HRQoL was measured at baseline, 1 month, and 12 months after starting treatment using the Kids ITP Tool (KIT), which is scored from 0-100 with higher scores consistent with better quality of life. The KIT is a valid and reliable measure of HRQoL for use in clinical trials of childhood ITP.[8] The child KIT was completed in children ≥7 years and older, and the parent proxy KIT in parents of children ≥2 years of age. For the primary analysis, the change in child KIT score was calculated from baseline to 1 month for each participant. As a

secondary analysis, the change in child KIT score from baseline to 12 months was also evaluated. For those with missing child KIT scores due to age, the parent proxy KIT scores were used (n=24). The correlation between the child KIT score and parent proxy score for patients who had both was r=0.58 (n=71). The minimal important difference (MID) of the KIT has been determined to be a difference of 9 points.[9] The change in KIT score on the individual treatments was evaluated for both statistical significance and to assess if the change surpassed the MID. The change in KIT score was also compared between treatment groups.

Statistical Methods:

The data were collected using REDCap and analyzed with SAS v9.4 (Cary, NC). Primary outcomes were: bleeding (as defined by skin and non-skin bleeding events); the need for rescue medication; platelet response (a 3-level variable: complete, partial, and no response); and change from baseline child KIT scores. Due to patient attrition at the 12 month follow-up, only data from the baseline, 1 month, and 6 month time points were considered in the primary analysis when testing for the effect of the treatment group. The data are analyzed based on the patients remaining on individual treatments at each timepoint. The visit time point was treated as a categorical variable. To take into account the repeated measures nature of the data, Generalized Estimating Equations models were used (SAS Proc Genmod). These models tested for an interaction between treatment group and visit and, when the interaction was not significant, looked for main effects of treatment group. For skin and non-skin bleeding, the models were logistic, with the bleeding outcome collapsed to two categories. The platelet response outcome was multinomial (complete response, partial, and no response). Time to first rescue medication was analyzed with a survival analysis. In a single analysis, when pairwise comparisons were made between the four treatment groups, the Tukey method was used to adjust for chance findings due to multiple comparisons, and adjusted p values<0.05 were considered significant. No adjustment was made for the number of analyses and thus findings should be interpreted as hypothesis-generating.

Results

ICON1 Demographics

One hundred twenty patients were enrolled on ICON1 and started on the following second-line treatments: rituximab (43/120, 36%), romiplostim (31/120, 26%), eltrombopag (20/120, 17%), oral immunosuppressant agents (19/120, 16%), splenectomy (4/120, 3%), and dapsone (3/120, 3%). Oral immunosuppressant agents included 6-mercaptopurine (n=13), azathioprine (n=1), mycophenolate (n=3), and sirolimus (n=2). Children had received a median of 3 prior treatments (range 0-8), with 47 (39%) patients having received at least one prior second-line treatment, including rituximab (n=12, 10%), romiplostim (n=11, 9%), eltrombopag (n=10, 8%), 6-mercaptopurine/azathioprine (n=6, 5%), and/or splenectomy (n=3, 3%). Two patients had not received prior treatments and had been managed with observation alone.

Table 1 shows the demographic and clinical features of the cohort overall, in which 19 (17%) were newly diagnosed, 34 (30%) persistent, and 60 (53%) chronic. Treatment groups

were not different with regard to the number of patients with chronic ITP (p=0.97) or previous treatment with second-line agents (p=0.10, Table 1). There were no differences between the treatment groups at baseline with respect to age, platelet count, bleeding score, or physician's perception of patient adherence to previous medications and/or clinical care.

Patient attrition was seen at all time points post-baseline (Table 1). Patients dropped out of their treatment group for various reasons, including: treatment failure by platelet count or bleeding (n=19), patient lost to follow up (n=8), clinical or laboratory side effects from treatment (n=4), patient preference (n=4), switched to dual therapies (n=3), developed autoimmune hemolytic anemia (n=3), investigator withdrew patient (n=2),and effect waned (n=1). Overall, the rate at which patients left their treatment group was similar among treatments except for oral immunosuppressants, which had the highest rate of attrition (Table 1). Among the patients taking oral immunosuppressants, primary reasons for leaving the treatment were continued bleeding or thrombocytopenia (n=8) and side effects or lab toxicity (n=3).

Treatment Outcomes

Platelet Response—The numbers of platelet assessments between clinical visits varied widely, with a mean number of total platelet assessments of 6 (range 1-15). Romiplostim treated patients had a significantly greater number of platelet counts checked between visits compared with all other treatments (8 vs. 5, p<0.001). The median platelet count significantly increased from baseline in all treatment groups: rituximab, eltrombopag, romiplostim, and oral immunosuppressants (Table 2, Figure 1A). At the one month visit, platelet count response rates did not significantly vary between treatments (p=0.71, Table 2, Supplemental Table). CR rates 1 month after starting treatment ranged from 13% in the group receiving oral immunosuppressants, 19% in the rituximab group, 21% in the romiplostim group, to 30% in the eltrombopag group. Combined CR/PR rates 1 month after starting treatment ranged from 32% in the oral immunosuppressant group, 52% in the romiplostim group, to 55% in both the rituximab and eltrombopag groups (p=0.41).

Response to treatment varied significantly among treatments at 6 months (p=0.04), at which time, patients treated with romiplostim had the highest CR/PR (83%) compared to the other treatments with CR/PR of oral immunosuppressants 38%, eltrombopag 67%, and rituximab 79%. Patients treated with rituximab and romiplostim also had a statistically significant increase in CR/PR from 1 to 6 months (p=.0003, p=.0001, respectively). Therefore, many patients who had not had a CR/PR by 1 month on rituximab and romiplostim went on to respond between 1 and 6 months after starting treatment whereas CR/PR rate was stable between 1 and 6 months in those receiving eltrombopag and oral immunosuppressants.

A single platelet count response >100 × 10^9/L occurred by 1 month for 45% on rituximab (77% at 6 months), 65% on eltrombopag (67% at 6 months), 48% on romiplostim (88% at 6 months), and 27% on oral immunosuppressants (38% at 6 months). A single platelet count response >30 × 10^9/L and a doubling from the baseline platelet count occurred by 1 month for 60% on rituximab (90% at 6 months), 75% on eltrombopag (80% at 6 months), 62% on romiplostim (92% at 6 months), and 40% on oral immunosuppressants (40% at 6 months). Differences in response were statistically significant at 6 months using either criteria of

platelet response (>100 × 10^9/L or >30 × 10^9/L, p=0.04 and p=0.007, respectively); in each case, platelet response to oral immunosuppressants was only about half that of other treatments.

Bleeding Outcome—Grade 2 skin-related bleeding occurred in 47 (42%) patients at baseline and 12 (11%) patients at 1 month, 5 (6%) at 6 months, and 3 (5%) at 12 months. Grades 1 and 2 skin-related bleeding symptoms improved over time in all treatments (p<0.001, Table 3, Figure 1b). Comparing treatments, there was no significant difference in skin-related bleeding at any of the time points (p=0.98 at baseline, p=0.41 at 1 month, p=0.29 at 6 months, and p=0.27 at 12 months). In patients treated with romiplostim, rituximab, and oral immunosuppressants, grades 1 and 2 skin-related bleeding significantly improved from baseline to the 1 month visit (p=0.01, p=0.0004,and p=0.04, respectively). However, from baseline to 6 months, skin-related bleeding symptoms were significantly improved only in those patients receiving romiplostim and rituximab (p=0.02 and p=<0.001, respectively).

Grade 2 non-skin bleeding occurred in 29 (26%) of patients at baseline and 11 (10%) at 1 month, 6 (8%) at 6 months, and 2 (3%) at 12 months. Grades 1 and 2 non-skin bleeding symptoms improved over time in all treatments (p<0.001, Table 3, Figure 1b). Comparing between treatments, there was no significant difference in the degree of non-skin bleeding (p=0.95 at baseline, p=0.54 at 1 month, p=0.17 at 6 months, and p=0.28 at 12 months). In patients taking romiplostim and rituximab only, grades 1 and 2 non-skin bleeding significantly improved from baseline to the 1 month visit (p=0.0001 and p=0.0006, respectively). Only patients on rituximab had a significant improvement in non-skin bleeding from baseline to 6 months (p=0.003, Table 3).

Rescue Therapy—The use of rescue therapy was similar among treatments between baseline and 1 month (16-25%, p=0.88) and between baseline and 6 months (21-44%, p=0.22). There was no difference among treatments with regard to the time until a rescue therapy was used. However, between 1 and 6 months, the patients treated with rituximab and romiplostim used significantly less rescue therapy, 6.1% and 12.5% respectively, as compared with those treated with oral immunosuppressants or eltrombopag, 37.5% and 40%, respectively (p=0.0099).

Health-Related Quality of Life—The baseline report of HRQoL was different between the treatment groups with children receiving rituximab reporting significantly lower pre-treatment KIT scores (p=0.02). At 1 month, the mean KIT scores, adjusted for baseline, were not different among treatments (p=0.32). This was also true at 12 months (p=0.43).

From baseline to 1 month, KIT scores significantly improved for rituximab (p=0.0001), romiplostim (p=0.0003), eltrombopag (p=0.0008), and oral immunosuppressants (p=0.0006, Table 4). At the 12 month time point, the KIT score was also significantly improved over the baseline time-point for all treatment groups (Table 4).

The median improvement from baseline to 1 month met the threshold for the MID for eltrombopag (median change = + 10.9), whereas the median changes in score for the other

treatment groups were below this threshold. However, the percent of patients who had an individual change in KIT scores that met the threshold for the MID was not different between the treatment groups at 1 month (37-55% of each treatment group, p=0.61). At the 12 month time-point, the rituximab and eltrombopag treatment groups had significantly more patients whose change in KIT scores met the MID (80% and 70% respectively) as compared with the oral immunosuppressant and romiplostim groups (25% and 21% respectively, p=0.001).

Discussion

Children with ITP are treated with second-line therapy for a variety of reasons including bleeding, risk of bleeding, fatigue, activity restrictions, and poor quality of life, among others. Given this diversity of reasons for which second-line treatment is initiated, providers need to understand the effect of each treatment on these outcomes to select the best treatment for an individual patient. Currently, selecting a specific treatment is challenging because there are no randomized controlled trials directly comparing the available treatments and no existing algorithms to follow. Furthermore, in single arm studies, outcomes beyond platelet count are often not well-described. This prospective, longitudinal observational study is the first to evaluate and compare the efficacy of various second-line therapies for ITP in children with a focus on important patient related outcomes including bleeding, platelet count, and HRQoL.

Prior studies of ITP treatments have focused on the platelet count as the primary measure of efficacy. In this study, the platelet count generally increased from baseline with all treatments. The primary analysis used a durable platelet count measure which is clinically relevant but more stringent than a number of other reports of second-line treatment which used single platelet count measures. While the effect of treatment on the platelet count was significant according to all measures, the findings were more pronounced when non-durable platelet reponse criteria were used. By 6 months after starting treatment, romiplostim and rituximab had the most robust platelet response rate, both in terms of median platelet count and durable platelet response. In this observational study, the role of observed adherence may have contributed to the efficacy of romiplostim and rituximab, given that both are administered in the hospital setting, and dietary interactions with eltrombopag were not rigorously monitored. Many patients who had not responded by 1 month, responded to romiplostim and rituximab by 6 months, whereas patients who responded to eltrombopag and oral immunosuppressants generally did so by 1 month after treatment initiation. For all treatments, the platelet response rates did not significantly change between 6 and 12 months. These findings may help guide physicians about when patience and continued treatment are appropriate and when a change in therapy should be considered.

Overall rates of grade 2 non-skin bleeding once treatment was started were low. Both skin and non-skin related bleeding symptoms improved over time on all treatments with the most significant reduction in bleeding in patients on rituximab and romiplostim. Furthermore, patients treated with rituximab and romiplostim received significantly less rescue therapy as compared with the other treatments.

HRQoL improved in patients on all treatments, but the greatest effect was seen in both the eltrombopag and rituximab groups, although these groups had the lowest baseline KIT scores. Clinicians may be more likely to select rituximab as a second-line agent in patients with a greater impact from ITP on everyday life due to the upfront nature of dosing and the longer effect of the treatment, if successful, on the patient's platelet count.[10,11] Rituximab is typically administered intravenously for a total of four weekly doses with no medication administration between the 1 and 6 month timepoints. Given this schedule of administration and the effect on platelet count and bleeding, the HRQoL improvement is not surprising. The positive effect of eltrombopag on HRQoL may be due to the combination of the oral administration and its improvement in platelet count and bleeding.

This analysis did not systematically address additional outcomes of interest, such as potential side effects and cost. An earlier cost per response analysis slightly favors romiplostim over eltrombopag in adults with ITP.[12] Eltrombopag and romiplostim appear to be equivalent in terms of safety in a systematic review including nine randomized trials in 786 adults, using an indirect comparison design.[13] The side effect profile and cost of rituximab and oral immunosuppressants have not been directly compared to the thrombopoietin-receptor agonists in a meaningful way. The mechanisms of action and the routes of administration are also considerations in the selection of these agents. Specific treatments are often selected by parent and/or patient preference which may be why patients showed an increase in HRQoL across treatments.[6] If patients and families engage in the selection of their treatment, it will increase the likelihood that the therapy will match their lifestyles and goals, ultimately increasing HRQoL.

Though splenectomy can offer a durable response rate of approximately 70%, the response cannot be predicted in a given patient, and there are associated risks.[14,15] Providers enrolling in the ICON1 study reported that they chose splenectomy for its curative potential; however, very few were performed during the several years of this study.[16] Splenectomy rates have been consistently declining over time with the increased use of pharmacologic therapies.[17] Only 4 patients in this cohort underwent splenectomy during this study, consistent with this trend. Immunosuppressive agents were among the earliest therapies for steroid refractory ITP, but given the relatively low efficacy and potential for significant toxicity, their use is limited.[18] These data support that physicians are choosing these therapies less frequently, and these agents clearly resulted in less improvement in platelet count, bleeding, and HRQoL than the other treatments.

Due to the real world nature of the study cohort, there was patient attrition at each study time point after baseline for a variety of reasons including lack of efficacy, side effects, remission, and lack of follow up. With this attrition, the cohort at 6 and 12 months is likely over-representative of responders. To partially account for this limitation, the 12 month time-point was used as a secondary analysis while the 1 and 6 month time points were used in the primary analysis. An additional limitation of this observational study is that medications may not have been dosed or titrated similarly among centers or patients, even though dosing regimens are standardized for these treatments. Additionally, platelet count surveillance was variable among centers and providers. Platelet counts were collected as per clinical indications; thus, the numbers of platelet assessments between clinical visits varied between

centers. We combined grade 1 and 2 bleeding in the assessment of change in bleeding over time due to the low rate of grade 2 bleeding. This combination of bleeding grades may not give an accurate assessment of change in the most severe bleeding. Lastly, because physician-patient teams determined optimal treatment independently, several treatment options did not have enough patients to meaningfully analyze outcomes. For this reason, the group of oral immunosuppressants represents a more heterogenous treatment group, which may have impacted the overall outcomes. Many of these factors also contribute to the difficulties of designing randomized trials to compare these treatments. In the absence of any randomized trials, this study provides hypothesis-generating findings for future studies and randomized trials. Despite these limitations, this study's approach has allowed for an assessment of second-line treatments in pediatric ITP with regard to the efficacy of individual treatments and comparisons between treatments.

Overall, bleeding, platelet count, and HRQoL all improved in each treatment group. Nevertheless, there were important differences among the treatments, with certain treatments having a greater effect on bleeding and the platelet count and others having a greater effect on HRQoL. Given these findings, it is clear that clinicians should weigh and balance the reasons for treatment when choosing among therapies, as treatments do not necessarily lead to the same outcomes. If a child needs a rapid response within the first month, eltrombopag may be appropriate. If a child is being primarily treated due to the impact of ITP on their daily life, rituximab or eltrombopag may provide the greatest benefit, whereas if a child is being treated due to recurrent bleeding, romiplostim or rituximab may be most efficacious. With an improved understanding of the effect of each treatment on different outcomes in ITP, clinicians and families can select the optimal second-line treatment for an individual child using a shared-decision making approach.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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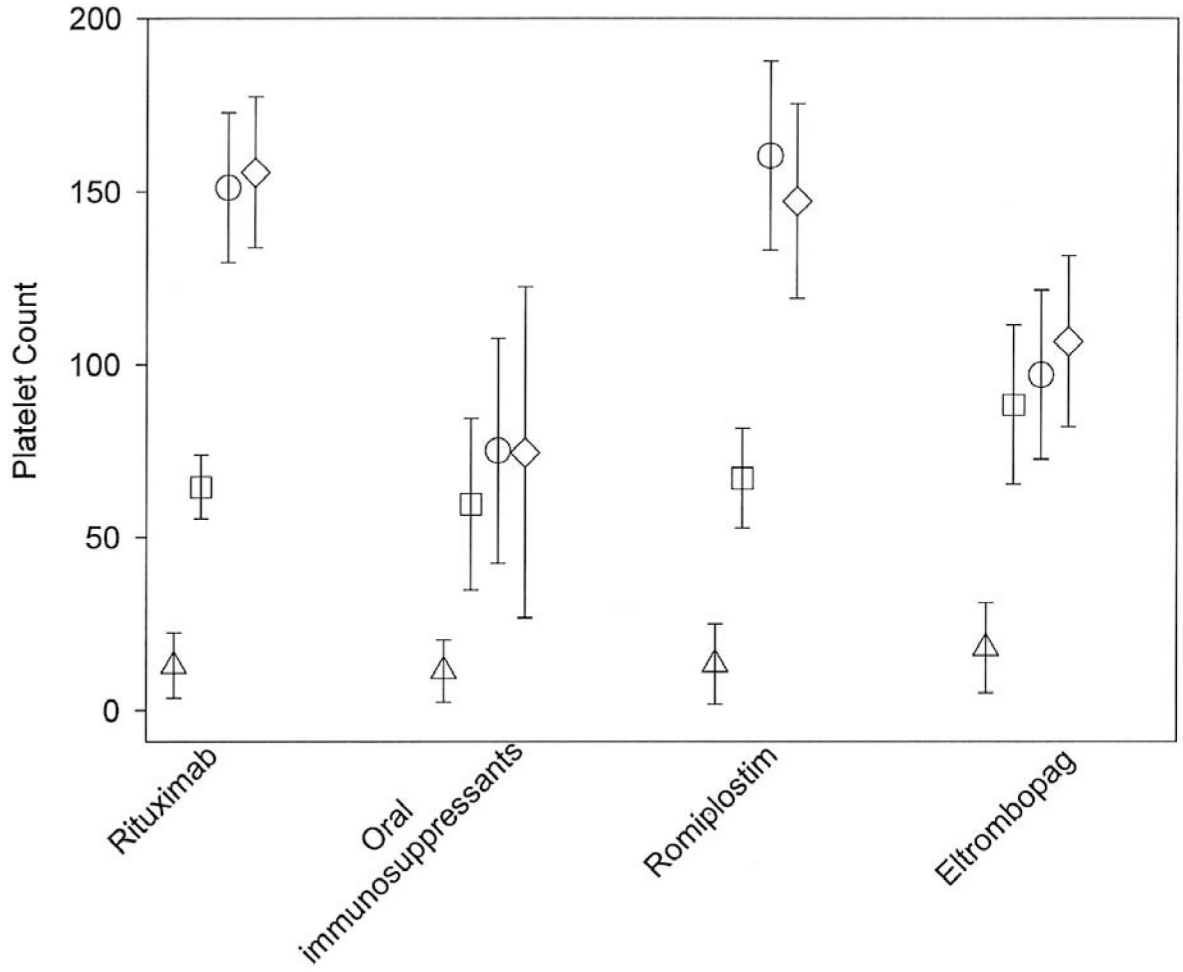
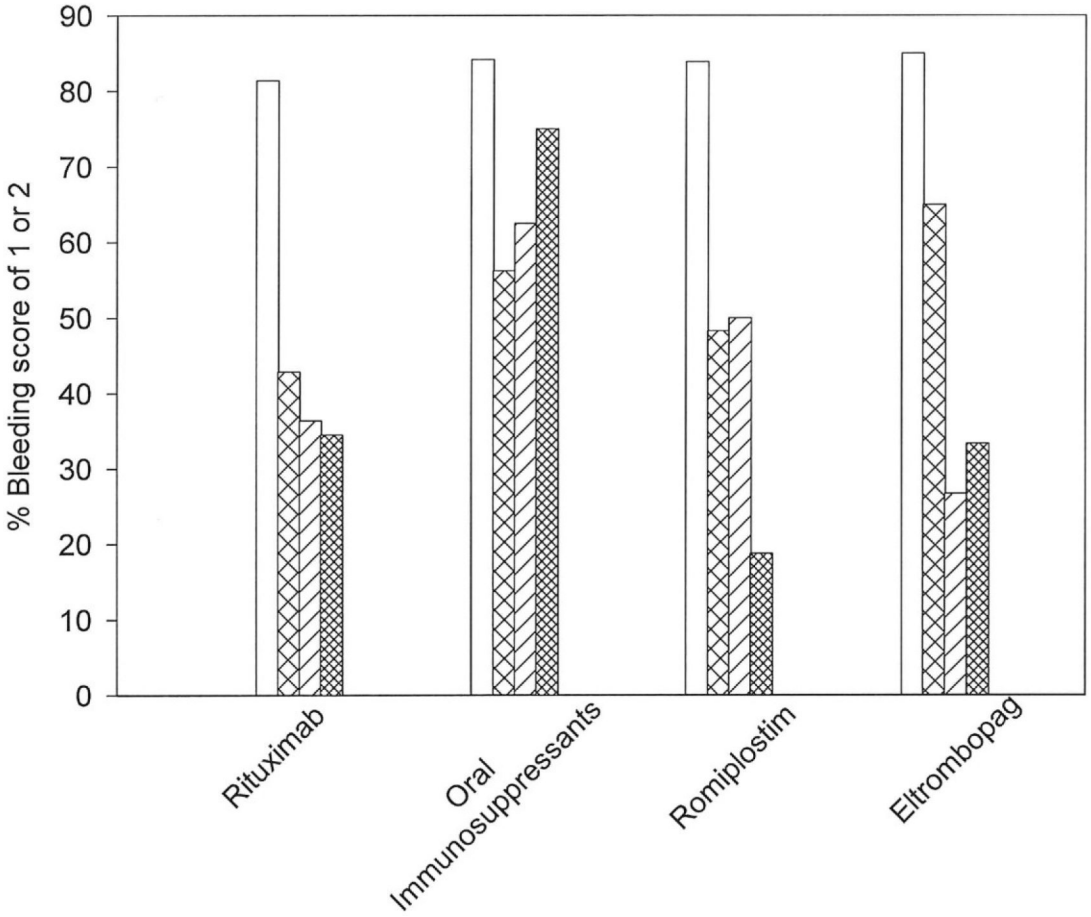
References

1. Rodeghiero F, Stasi R, Gernsheimer T, et al. Standardization of terminology, definitions and outcome criteria in immune thrombocytopenic purpura of adults and children: report from an international working group. Blood. 2009;113(11):2386–2393. [PubMed: 19005182]
2. Neunert C, Lim W, Crowther M, et al. The American Society of Hematology 2011 evidence-based practice guideline for immune thrombocytopenia. Blood. 2011;117(16):4190–4207. [PubMed: 21325604]
3. Schifferli A, Holbro A, Chitlur M, et al. A comparative prospective observational study of children and adults with immune thrombocytopenia: 2-year follow-up. American journal of hematology. 2018;93(6):751–759. [PubMed: 29516627]
4. Grace RF, Neunert C. Second-line therapies in immune thrombocytopenia. Hematology Am Soc Hematol Educ Program. 2016;2016(1):698–706. [PubMed: 27913549]

5. Neunert C, Despotovic J, Haley K, et al. Thrombopoietin Receptor Agonist Use in Children: Data From the Pediatric ITP Consortium of North America ICON2 Study. Pediatr Blood Cancer. 2016;63(8):1407–1413. [PubMed: 27135461]
6. Grace RF, Despotovic JM, Bennett CM, et al. Physician decision making in selection of second-line treatments in immune thrombocytopenia in children. Am J Hematol. 2018;93(7):882–888. [PubMed: 29659042]
7. Page LK, Psaila B, Provan D, et al. The immune thrombocytopenic purpura (ITP) bleeding score: assessment of bleeding in patients with ITP. British journal of haematology. 2007;138(2):245–248. [PubMed: 17542983]
8. 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. The Journal of pediatrics. 2007;150(5):510–515, 515 e511. [PubMed: 17452226]
9. Mathias SD, Li X, Eisen M, Carpenter N, Crosby RD, Blanchette VS. 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. Pediatric blood & cancer. 2016;63(7):1232–1237. [PubMed: 27037553]
10. Arnold DM, Dentali F, Crowther MA, et al. Systematic review: efficacy and safety of rituximab for adults with idiopathic thrombocytopenic purpura. Annals of internal medicine. 2007;146(1):25–33. [PubMed: 17200219]
11. Cuker A, Neunert CE. How I treat refractory immune thrombocytopenia. Blood. 2016.
12. Fust K, Parthan A, Li X, et al. Cost per response analysis of strategies for chronic immune thrombocytopenia. The American journal of managed care. 2018;24(8 Spec No):SP294–SP302. [PubMed: 30020741]
13. Zhang J, Liang Y, Ai Y, et al. Eltrombopag versus romiplostim in treatment of adult patients with immune thrombocytopenia: A systematic review incorporating an indirect-comparison meta-analysis. PloS one. 2018;13(6):e0198504. [PubMed: 29856837]
14. Kojouri K, Vesely SK, Terrell DR, George JN. Splenectomy for adult patients with idiopathic thrombocytopenic purpura: a systematic review to assess long-term platelet count responses, prediction of response, and surgical complications. Blood. 2004;104(9):2623–2634. [PubMed: 15217831]
15. Wang KK, Charles C, Heddle NM, Arnold E, Molnar L, Arnold DM. Understanding why patients with immune thrombocytopenia are deeply divided on splenectomy. Health expectations : an international journal of public participation in health care and health policy. 2012.
16. Grace RF, Despotovic JM, Bennett CM, et al. Physician decision making in selection of second-line treatments in immune thrombocytopenia in children. American journal of hematology. 2018.
17. Bhatt NS, Bhatt P, Donda K, et al. Temporal trends of splenectomy in pediatric hospitalizations with immune thrombocytopenia. Pediatric blood & cancer. 2018;65(7):e27072. [PubMed: 29637697]
18. Godeau B, Provan D, Bussel J. Immune thrombocytopenic purpura in adults. Current opinion in hematology. 2007;14(5):535–556. [PubMed: 17934364]





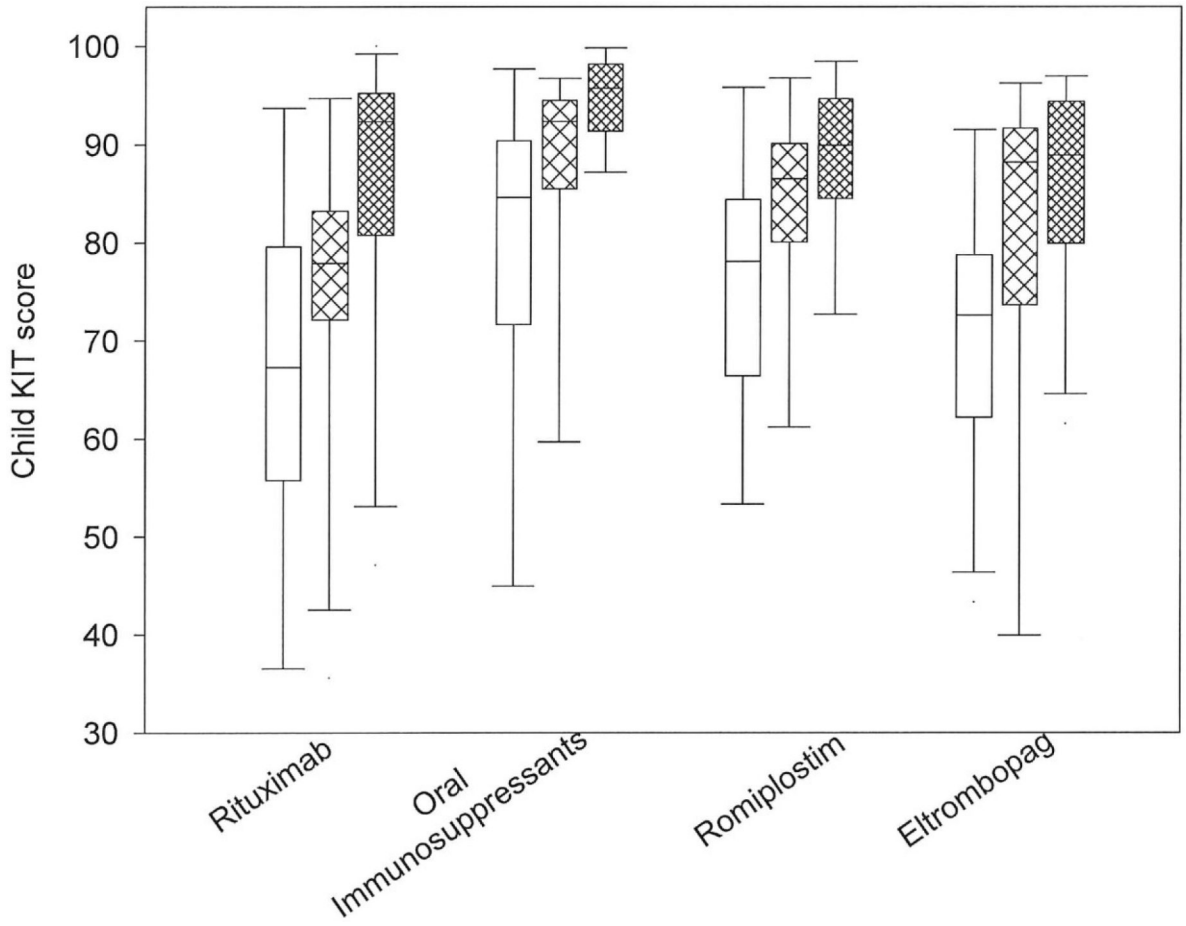


Figure 1. Outcomes by Treatment Group

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Table 1.

Baseline characteristics overall and by treatment group

	Overall cohort	Rituximab	Oral immunosuppressants	Romiplostim	Eltrombopag	p value*
N	113	43	19	31	20	n/a
Mean Age, years (range)	11.0 (1.7-17.8)	12.2 (5.3-17.6)	10.7 (1.7-17.3)	9.8 (1.2-17.8)	11.5 (4.6-16.7)	0.08
Gender, n (%) Male	44 (39%)	16 (37%)	7 (37%)	13 (42%)	8 (40%)	0.98
ITP Phase (%)						
New Diagnosed	19 (17%)	8 (19%)	2 (11%)	6 (19%)	3 (15%)	0.98
Persistent	34 (30%)	12 (28%)	7 (37%)	9 (29%)	6 (30%)	
Chronic**	60 (53%)	23 (53%)	10 (53%)	16 (52%)	11 (55%)	
ITP Type						
Primary	95 (84%)	34 (79%)	17 (89%)	27 (87%)	17 (85%)	0.77
Secondary***	18 (16%)	9 (21%)	2 (11%)	4 (13%)	3 (15%)	
Baseline Platelet Count						
$<10 \times 10^9$/L	58 (51%)	21 (49%)	11 (58%)	18 (58%)	8 (40%)	0.73
10-19 $\times 10^9$/L	26 (23%)	12 (28%)	5 (26%)	5 (16%)	4 (20%)	
20-29 $\times 10^9$/L	13 (12%)	6 (14%)	2 (11%)	3 (10%)	2 (10%)	
$\geq 30 \times 10^9$/L	12 (10%)	3 (7%)	1 (5%)	4 (13%)	4 (20%)	
Unknown	4 (4%)	1 (2%)	0	1 (3%)	2 (10%)	
Baseline Bleeding Score# 1 or 2 (%)						
Grade 1 Skin	42%	42%	58%	26%	50%	0.33
Grade 2 Skin	42%	40%	26%	58%	35%	
Grade 1 Non-Skin	28%	30%	16%	29%	35%	0.73
Grade 2 Non-Skin	26%	23%	37%	29%	15%	
Physician Assessment of Patient Adherence (% nearly perfect)##	66%	75%	69%	66%	53%	0.27
Number of Patients at study timepoints###						
Baseline	113	43	19	31	20	0.0006
1 month	107	42	16	29	20	
6 months	80	33	8	24	15	

	Overall cohort	Rituximab	Oral immunosuppressants	Romiplostim	Eltrombopag	p value*
12 months	63	31	4	16	12	

* p value compares baseline characteristics between treatment groups

** Chronic ITP defined as ≥12 months

*** Secondary ITP diagnoses: Evans syndrome (n=9), underlying immunodeficiencies (n=5), rheumatologic conditions (n=3), and inflammatory bowel disease (n=1)

ITP Bleeding Score determined by clinician at the baseline visit

Clinician's assessment of patient adherence with clinical care, medication, and monitoring in general prior to starting treatment.

Attrition reason by treatment: Rituximab (continued bleeding/thrombocytopenia (n=5), patient/parent preference (n=1), lost to follow up (n=4), switched to dual therapies (n=1), enrolled on another trial (n=1)); oral immunosuppressants (continued bleeding/thrombocytopenia (n=8), side effects/toxicity (n=3), patient/parent preference (n=1), lost to follow up (n=1), development of autoimmune hemolytic anemia (n=1), unknown (n=1)); romiplostim (continued bleeding/thrombocytopenia (n=5), investigator decision (n=2), lost to follow up (n=1), developed autoimmune hemolytic anemia (n=2), switched to dual therapies (n=1), unknown (n=4)); eltrombopag (continued bleeding/thrombocytopenia (n=1), side effects/toxicity (n=1), effect waned (n=1), lost to follow up (n=2), switched to dual therapies (n=1), patient/parent preference (n=2))

Table 2.

Platelet Response by Treatment Group at 1, 6 and 12 months after starting treatment

	n**	Median platelet count, × 10^9/L (range)	Complete response*	Partial Response	No Response
Rituximab					
1 month	42	65 (4-230)	8 (19%)	15 (36%)	19 (45%)
6 months	33	151 (3-412)	17 (52%)	9 (27%)	7 (21%)
12 months	31	156 (4-408)	17 (55%)	8 (26%)	6 (19%)
Oral Immunosuppressants					
1 month	16	60 (1-327)	2 (13%)	3 (19%)	11 (69%)
6 months	8	75 (11-261)	2 (25%)	1 (13%)	5 (63%)
12 months	4	75 (10-216)	1 (25%)	1 (25%)	2 (50%)
Romiplostim					
1 month	29	67 (1-357)	6 (21%)	9 (31%)	14 (48%)
6 months	24	160 (6-598)	17 (71%)	3 (15%)	4 (17%)
12 months	16	147 (29-408)	9 (56%)	4 (25%)	3 (19%)
Eltrombopag					
1 month	20	89 (10-402)	6 (30%)	5 (25%)	9 (45%)
6 months	15	97 (6-301)	4 (27%)	6 (40%)	5 (33%)
12 months	12	106(15-300)	5 (42%)	4 (33%)	3 (25%)

Complete platelet response defined as ≥50% of platelet counts >100 × 10^9/L since the prior study visit. A partial platelet response defined as ≥50% of platelet counts >30 × 10^9/L and twice the baseline platelet count. No response was defined as any platelet count change that did not meet criteria for CR or PR.

*The platelet response did not significantly vary between treatments at 1 month (p=0.44). At 6 months, the platelet response varied significantly vary between treatments (p=0.04) with romiplostim showing the highest rate of complete response.

**Patient attrition was seen at all time-points post-baseline. Due to patient attrition, the 12 month time-point was not considered in the primary analysis. Patients dropped out of their treatment group for various reasons (see Results).

Table 3.

Skin and Non-Skin Bleeding Response by Treatment Group at 1, 6, and 12 months after starting treatment

	n	Skin Bleeding			Non-Skin Bleeding		
		Grade 1 or 2 Skin Bleeding	p value baseline to 1 month for Skin Bleeding	p value baseline to 6 months for Skin Bleeding	Grade 1 or 2 Non-Skin Bleeding	p value baseline to 1 month Non-Skin Bleeding	p value baseline to 6 months for Non-Skin Bleeding
Rituximab							
Baseline	43	81.4%	0.0004	<0.0001	53.5%	0.0006	0.003
1 month	42	42.9%			16.7%		
6 months	33	36.4%			15.2%		
12 months	29	34.5%			24.1%		
Oral Immunosuppressants							
Baseline	19	84.2%	0.04	0.21	52.6%	0.23	0.99
1 month	16	56.3%			31.3%		
6 months	8	62.5%			50.0%		
12 months	4	75%			50.0%		
Romiplostim							
Baseline	31	83.9%	0.011	0.024	58.1%	0.0001	0.264
1 month	29	48.3%			13.8%		
6 months	24	50%			33.3%		
12 months	16	18.8%			6.3%		
Eltrombopag							
Baseline	20	85%	0.33	0.005	50.0%	0.067	0.276
1 month	20	65%			20.0%		
6 months	15	26.7%			20.0%		
12 months	12	33.3%			16.7%		

Grades 1 and 2 skin-related bleeding symptoms improved over time in all treatment groups ($p<0.001$).

Severe (Grade 2) non-skin bleeding (n) by treatment: Rituximab: baseline (n=10), 1 month (n=2), 6 months (n=1); oral immunosuppressants: baseline (n=7), 1 month (n=5), 6 months (n=2); Romiplostim: baseline (n=9), 1 month (n=2), 6 months (n=2); Eltrombopag: baseline (n=3), 1 month (n=2); 6 months (n=1)

Table 4.

Health Related Quality of Life as reported by child self or proxy-reported KIT scores by Treatment Group at baseline, 1 month, and 12 months after starting treatment

	n	Median KIT scores	Range	p value (baseline to 1 mo)	p value (baseline to 12 mo)
Rituximab					
Baseline	43	66.7	32.7-96.2	0.0001	<0.0001
1 month	42	75.2	35.6-97.1		
12 months	31	85.2	47.1-100		
Oral Immunosuppressants					
Baseline	19	79.1	39.4-99.0	0.0006	<0.0001
1 month	16	87.1	53.8-97.1		
12 months	4	94.5	86.5-100		
Romiplostim					
Baseline	31	75.6	51.0-98.1	0.0003	0.0001
1 month	29	83.7	57.0-98.1		
12 months	16	87.5	70.2-99.0		
Eltrombopag					
Baseline	20	69.9	43.3-94.2	0.0008	0.0003
1 month	20	80.8	32.7-97.1		
12 months	12	85.0	61.5-97.1		

KIT: Kids ITP Tool