Case Report

Quality of Life Improvements Following Eltrombopag Treatment in Children with Chronic Immune Thrombocytopenia: Case Report

Nongnuch Sirachainan MD[1], Pakawan Wongwerawattanakoon BSc[2], Duantida Songdej MD, PhD[1], Ampaiwan Chuansumrit MD[1], Surapong Lertthammakiat MD[1,3]

[1] Department of Pediatrics, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, Thailand

[2] Department of Nursing, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, Thailand

[3] Chakri Naruebodindr Medical Institute, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Samut Prakan, Thailand

The present case series described six chronic immune thrombocytopenia patients (cITP), with a median age of 7.7 (7.0 to 13.0) years and low platelet count at 15,500 (7,000 to 20,000)/uL. They were suffering from bleeding symptoms and side effects of treatment. After enrollment, they were treated with thrombopoietin receptor agonist (eltrombopag). Five patients responded positively, showing a median platelet count of 115,000 (39,000 to 433,000)/uL. The median dose of eltrombopag used was 1.3 (0.8 to 2.2) mg/kg/day. The quality of life (QoL) improved for all patients, with their median overall score using a Pediatric QoL questionnaire showing 25.0% improvement. Median scores also showed improvements in each sphere of life functioning as physical (30.8%), emotional (26.4%), social (16.4%), and school (21.4%). The present report demonstrated that a select group of cITP patients, with low platelet count and bleeding symptoms, benefitted from treatment with eltrombopag, as shown by increased platelet counts and improved QoL.

Keywords: Chronic ITP, Thrombopoietin receptor agonist, Children

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Children with chronic immune thrombocytopenia (cITP) usually suffer from bleeding problems, especially when their platelet count is less than 20,000/uL[(1)]. Treatments with medications, such as high dose steroids and immunosuppressive agents, or splenectomy, can cause unavoidable negative side effects[(1)]. Low platelet count and side effects from medications consequently affect the patients' quality of life (QoL). Most children with cITP cannot attend regular school or participate in normal daily activities. In 2015, thrombopoietin receptor agonist (TPO-RA) was approved by the U.S. Food and Drug Administration (FDA) for treatment of cITP children. The oral preparation of TPO-RA, eltrombopag, has been used in the past with overall negative side effects reported as fewer than with the previously prescribed medications or treatments[(2,3)]. However, because eltrombopag is considerably expensive, its usage is restricted, especially in countries with limited resources. For the benefit of cITP children, the present study aimed to demonstrate the significant QoL improvements and positive outcomes of cITP children with very low platelet count treated with eltrombopag, as well as further understanding on the use of eltrombopag as a treatment for cITP in general.

Correspondence to:

Sirachainan N.

Department of Pediatrics, Faculty of Medicine Ramathibodi Hospital, 270 Rama VI Road, Rachathewi District, Bangkok 10400, Thailand.

Phone: +66-2-2011749, **Fax**: +66-2-2011748

Email: nongnuch.sir@mahidol.ac.th

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Case Report

Children with cITP, 18 years or younger, having a platelet count of 10,000/uL or less or 20,000/uL or less, with a bleeding scale of grade 2 or more according to the World Health Organization (WHO) Bleeding Scale[(4)], were included in the present study. Eltrombopag was started at a dose of 12.5 mg/day and increased every two to four weeks until platelet count increased to at least twice the baseline value and bleeding symptoms improved to grade 0 or 1. Six patients, which included four females and two males with a median age of 7.7 (7.0 to 13.0) years, were enrolled. The patients' median platelet count was 15,500 (7,000 to 20,000)/uL and the median

Table 1. Data of the chronic immune thrombocytopenia patients

Patient	Age (year)	Sex	Time since diagnosis ITP (year)	Platelet (before) ($\times 10^3$/uL)	Bleeding grade	Eltrombopag (mg/kg)		Time to (year)			Platelet ($\times 10^3$/uL)		FU time (year)
						Initial	Maximum	Response*	Discontinue prednisolone	Discontinue eltrombopag	Maximum	Recent	
1	4.5	F	1.9	20.0	2	1	2	NR	No**	No**	26.0	25.0	0.8
2	10.6	M	3.1	7.0	3	1.5	1.5	0.5	0.4	No**	50.0	24.0	2.8
3	3.5	F	2.3	15.0	2	1.1	1.1	0.1	0.2	0.7	115.0	115.0	0.9
4	8	M	4.7	8.0	3	0.7	2.2	1.9	1.9	No**	39.0	12.0	2.7
5	13.1	F	1	17.0	2	0.9	1.3	0.03	0.6	0.7	433.0	236.0	2.4
6	7.3	F	1	16.0	3	0.8	0.8	0.1	0.3	1.5	148.0	115.0	1.6

F=female; M=male; ITP=immune thrombocytopenia; NR=no response; FU=follow-up

* Response meant platelet count increased to at least twice the baseline value and bleeding symptoms improved to grade 0 or 1, ** Patients continued medications until the end of the study

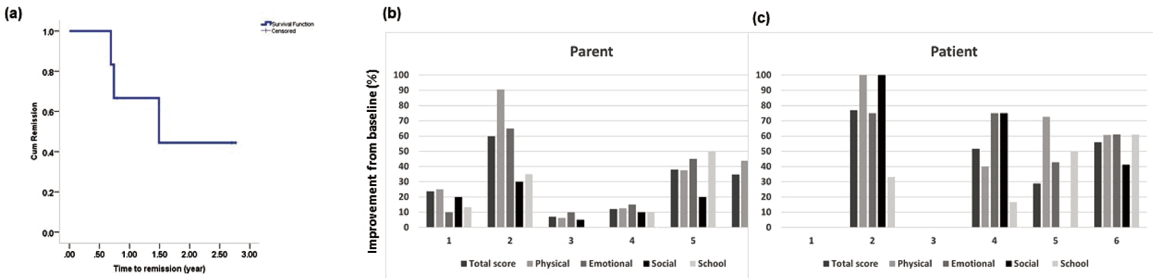

Figure 1. Survival analysis shows time to remission of the three patients (a) and percentages by which quality of life scores, answered by each parent (b) and each patient except patient 1 and 3 whose age <7 years (c).

time from diagnosis to the enrollment was 2.1 (1 to 4.7) years. Three patients had a bleeding scale of grade 3 and three patients had a bleeding scale of grade 2. Before enrollment, all six patients had been receiving different medications and treatments including intravenous immunoglobulin (five patients), dexamethasone (two patients), cyclosporine A (one patient), cyclophosphamide (one patient), and splenectomy (one patient). All six patients had been receiving prednisolone and all had a Cushingoid appearance. One patient had a compression fracture and two had heights below the third percentile as a side effect of steroid use. During the study, five patients responded to eltrombopag without complications. Their median platelet count was 115,000 (39,000 to 433,000)/uL and their median dose of eltrombopag used was 1.3 (0.8 to 2.2) mg/kg/day. The median time of eltrombopag treatment was 1.1 (0.7 to 2.8) years. The total follow-up time was 2.0 (0.8 to 2.8) years. Patient number 1 did not respond to eltrombopag, showing no increment of platelet count, even at the maximum dose of 2 mg/kg/day. Subsequently, she was diagnosed with hypoplastic myelodysplastic syndrome as determined by recent bone marrow findings of hypocellularity and dysplastic of megakrayocytes. Immature platelet fraction (IPF), a parameter of young platelets, in patients responsive to eltrombopag increased 9.5% (5.0 to 10.2) from their baselines. Three patients were in remission with a platelet count of 100,000/uL or greater, within a median time of 0.7 (0.7 to 1.5) years from the beginning of the study, then the medication could be discontinued (Table 1, Figure 1a).

A Thai version of the Pediatric QoL (Ped-QoL) questionnaire[5] was completed by patients older than seven years, or their guardians at the time of enrollment and then at six months after taking eltrombopag. The answers to the questionnaires by parents showed a QoL improvement for each patient overall (25.0% improvement), but also in each sphere of life functioning as physical (30.8%), emotional (26.4%), social (16.4%), and school (21.4%) (Figure 1b). Patient number 3 was not enrolled in school, therefore data for school functioning could not be collected. The improvement of QoL was also observed in the patients (Figure 1c).

Discussion

The present report showed the outcomes of six enrolled cITP children who had extremely low platelet counts of 10,000/uL or less, or 20,000/uL or less with significant bleeding. These six patients were unresponsive to second line treatment and were suffering from the negative side effects of their medications. The findings in the study demonstrate the effective response of almost all patients to eltrombopag, determined by a platelet increment of at least twice the individual patients' baseline levels. Although, it has been previously shown that approximately 20%, 38%, and 48% of cITP children enter spontaneous remission within 1, 2, and 5 years, respectively, after a cITP diagnosis[6,7], the present study suggests that treatment with eltrombopag increases the incidence of remission while also decrease the number of years required to attain the remission stage. In the present report, three patients (50%) went into remission, two within the first year and the other one at 1.5 years. The remission of cITP after discontinuation of eltrombopag was also reported in a previous adult study[8]. The study reported around 40% to 50% of patients had sustained response during the follow-up time of two years. It has been suggested that the mechanisms of the increased incidence of sustained remission in cITP patients, as well as the decrease in time before remission, may be related to the immunomodulator effect of eltrombopag or increased immune tolerance from increased exposure to platelet antigens[8]. The adverse events from eltrombopag use, namely infection and increased liver enzymes, were reported in 8% of patients of the adult study, however, such events were not found in the present report.

All patients in the present report showed improved Ped-QoL scores across all areas. The one exception was patient number 3 that school functioning could not be ascertained because the patient did not attend school. The highest improvements in patients were in physical functioning, followed by emotional functioning. Although patient number 1 did not respond according to the definition in the present report, she did show an increase in IPF from 23.3% to 32.8%. Patients with higher IPF have been reported as having a lower bleeding risk than ITP patients with lower IPF[9]. The increase in IPF of the patients in the present study, resulting in lower bleeding risk, is likely a key factor in patients' improvement of QoL. A study on the QoL of cITP patients treated with eltrombopag was previously reported but the results did not demonstrate significant QoL changes[10]. The difference in results between this previous study and the current study may be due to the inclusion criteria of the enrolled patients. The previous study admitted patients with a higher platelet count with 50% at 15,000/uL or less and 50% with less than 30,000/uL compared to the current study at 7,000 to 20,000/uL. Additionally, only 20% of patients in the previous study had significant bleeding compared to 100% of patients in the current study with significant bleeding, grades 3 and 2[2]. Bleeding symptoms were likely affecting patients' level of functioning in normal activities, including physical, social, and school activities, as well as contributing to any emotional distress related to having a chronic illness. After initiating treatment with eltrombopag, the reduction and subsequent cessation of steroid treatment was possible in all patients except patient number 1. Patient number 1 did not respond to eltrombopag as strongly as other patients but was still able to reduce the dosage of the prednisolone.

Although the number of patients enrolled was small, the present report did demonstrate a positive platelet response in almost all enrolled cITP patients. These patients had previously been on other second line medications without improvement. Even more significant than the increase in the patients' platelet counts, was the improvement to their QoL after treatment. The present report has shown that, in a country with limited resources, such as Thailand, eltrombopag could be an effective treatment option, if the selection criteria for patients who are the offered treatment is well-defined and robust.

Conclusion

Eltrombopag, a TPO-RA, demonstrated an effective response and improved QoL in cITP children who had extremely low platelet count. A future research, such as a case-control study to verify the improvement of QoL after TPO-RA is suggested.

What is already known on this topic?

TPO-RA is approved for the treatment of cITP.

What this study adds?

In limited resource countries, cITP children with extremely low platelet count, having bleeding symptoms and who do not respond to immunosuppressive drugs, should be the selective group for TPO-RA treatment.

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Authors' contributions

Sirachainan N designed the study. Wongwerawattanakoon P, Songdej D, Chuansumrit A, and Lertthammakiat S collected data. Sirachainan N wrote the manuscript. All the authors have read and approved the final manuscript.

Ethical approval and consent to participate

The present report was approved by the Ethics Committee of the Faculty of Medicine, Ramathibodi Hospital (ID 11-61-05). All patients and parents gave informed consents.

Conflicts of interest

The authors declare no conflict of interest.

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