Acta Haematologica Polonica 51(4) • December 2020 • 226–229 • DOI: 10.2478/ahp-2020-0039

sciendo

ORIGINAL RESEARCH ARTICLE

journal homepage: https://content.sciendo.com/ahp

Eltrombopag use in chronic immune thrombocytopenia of childhood: results from nationwide therapeutic program

Article history:
Received: 14.06.2020
Accepted: 19.06.2020

Monika Richert-Przygońska*,
Ewa Demidowicz,
Natalia Bartoszewicz,
Krzysztof Czyżewski,
Mariusz Wysocki,
Jan Styczyński

Department of Pediatric Hematology and Oncology, Collegium Medicum, Nicolaus Copernicus University in Toruń, Jurasz University Hospital 1, Bydgoszcz, Poland

Abstract

Background: Thrombopoietin receptor agonists have been repeatedly confirmed to be safe, efficient, and well tolerated in pediatric patients with chronic immune thrombocytopenia (cITP). Material and methods: In this report, we present data summarizing the Polish experience of the use of eltrombopag in cITP patients, refractory to standard first-line care. Our analysis was based on clinical and epidemiological data from the Nationwide Therapeutic Program 2018–2020. Quality of the response to the eltrombopag treatment was defined according to the International Consensus Guidelines as follows: complete response (CR) defined as platelet count (PLT) ≥100 x 10^9/L and absence of bleeding; response (R) defined as PLT ≥30 x 10^9/L and at least two-fold increase in the baseline count and absence of bleeding. Results: We evaluated 60 patients (33 boys and 27 girls) with chronic and refractory ITP. Median age at beginning of treatment was 9.5 years. Median PLT at the first eltrombopag administration was 30 x 10^9/L. The median follow-up was 7 months (range, 3–22 months). After 1 week of treatment, response (R) was noted in 53.3% (95% confidence interval [CI]: 40.7%–66.0%) patients, and complete response (CR) was seen in 21.6% (95% CI: 11.2%–32.1%). We evaluated the long-term duration of the response and found that it was obtained in 84.4% (95% CI: 71.8%–97.0%) and 88.9% (95% CI: 77.0%–100%) of patients after 6 and 12 months, respectively, of eltrombopag therapy, while CR was reached, respectively, in 46.9% (95% CI: 29.6%–64.2%) and 29.6% (95% CI: 12.4%–46.9%) patients. No serious adverse events were reported. Conclusion: Our data support the safety and efficacy of eltrombopag use in cITP pediatric patients.

Keywords:
chronic immune thrombocytopenia, childhood, eltrombopag

Introduction

Primary immune thrombocytopenia (ITP) is one of the most common hematological disorders in childhood. It is usually a mild, self-limiting disease, without life-threatening bleeding episodes or the need for hospitalization [1, 2]. About 20%–30% of children develop chronic ITP (cITP), defined as thrombocytopenia persisting longer than 12 months [3, 4]. In some situations, treatment of cITP cases is more complex than the use of first-line treatment with steroid cycles or intravenous immunoglobulins (IVIGs). If immunosuppressive therapy fails, other drug groups should be considered. Thrombopoietin receptor agonists (TPO-RAs) stimulate the proliferation and maturation of megakaryocytes due to their interactions with the thrombopoietin receptor, resulting in platelet count increase [4]. It has been proven that TPO-RAs are one of the highly effective alternative treatment options before and after splenectomy and other agents in the adult population [5, 6]. Several studies have confirmed the safety, efficacy, and good tolerance of TPO-RAs in pediatric patients, especially orally administered eltrombopag [7, 8]. Based on these results, since 2018, in Poland, the National Therapeutic Program (NTP) for chronic ITP, as announced by the Ministry of Health and reimbursed by the National Health Fund (NFZ), has allowed the use of eltrombopag in ITP patients refractory to standard first-line care.

In this report, we present the data summarizing the first 2 years' experience of the NTP with eltrombobag in pediatric cITP.

Material and methods

Retrospective analysis of epidemiological and clinical data of pediatric cITP patients was conducted after the first 2-year period of introduction of the NTP. Demographic and baseline ITP data and treatment-related data were obtained from the central monitoring electronic system created for the NTP. The monitoring data base was founded by the NFZ and consulted by the first author of this report as an assigned coordinator. According to the NTP enrollment criteria, all patients were diagnosed with cITP, defined as a platelet count (PLT) <100 x 10^9/L for a period of at least 12 months or longer, who were resistant to previous ITP treatment (IVIGs and steroids) and were in the age range of 1–18 years. After enrollment into the NTP group and final qualification for the eltrombopag treatment, the diagnostic tests were scheduled for each patient as follows: full blood count every week during the first month of treatment and every month later on; biochemistry tests of the liver function enzymes every 2 weeks in the first month and every 3 months in the following phase of treatment (elevated transaminases were defined as 3-fold increase of normal value); and ophthalmological examination every 6 months.

* Corresponding author: Monika Richert-Przygońska, Department of Pediatric Hematology and Oncology, Collegium Medicum, Nicolaus Copernicus University in Toruń, Jurasz University Hospital 1, Skłodowskiej-Curie 9, 85-094 Bydgoszcz, Poland, phone: +48 52 5854860, e-mail: monika_richert@yahoo.com

Quality of the response to the eltrombopag treatment was defined according to the International Consensus Guidelines as follows: complete response (CR) was defined as PLT ≥100 x 10^9/L and absence of bleeding; response (R) was defined as PLT ≥30 x 10^9/L and at least two-fold increase in the baseline count and absence of bleeding; no response (NR) as PLT ≤30 x 10^9/L or <2-fold increase of baseline platelet count or bleeding; and duration of response was measured from the achievement of CR or R to the time of loss of CR or R [3].

Statistical analysis

Descriptive analysis was performed, with median and range values. Response and complete response rates at each time point were provided with 95% confidence intervals (95% CIs) [9].

Results

The total number of 62 children was qualified to receive the therapeutic program of therapy with eltrombopag for cITP between March 2018 and March 2020. Two patients did not meet the criteria of cITP and were excluded from this analysis. Among all patients treated with eltrombopag, 33 were boys and 27 girls (Tab. I). The median age at the date of NTP enrollment was 9.5 years (2–17 years). At the beginning of treatment, the median PLT was 30 x 10^9/L (range: 1–98 x 10^9/L). The median follow-up was 7 months (range: 3–22 months).

After the first week of eltrombopag therapy, the median PLT was 51 x 10^9/L, CR was observed in 21.6% (95% CI: 11.2%–32.1%) patients, and R was achieved in 53.3% (95% CI: 40.7%–66.0%) of patients. After the first 4 weeks of therapy, CR was observed in 33.3% (95% CI: 20.4%–46.3%), and R was noted in 72.6% (95% CI: 60.3%–84.8%) patients. Additionally, eltrombopag efficacy and response duration was evaluated in patients with complete laboratory and clinical data at the time points of 6 months and 12 months after beginning of therapy. The long-term duration of the response was assessed, and we found that it was obtained in 84.4% (95% CI: 71.8%–97.0%) and in 88.9% (95% CI: 77.0%–100%) of patients after6 and 12 months, respectively, of eltrombopag therapy, while CR was reached, respectively, in 46.9% (95% CI: 29.6%–64.2%) and 29.6% (95% CI: 12.4%–46.9%) patients (Fig. 1).

No serious adverse effects were observed. In only one patient a transient increase in transaminases level was reported.

Discussion

Data on eltrombopag use in children with cITP are limited and are mostly based on evidence from studies in adults, few clinical randomized trials, or single-center experiences. This observational report is a retrospective evaluation of the first 2 years of Polish experience with eltrombopag use in clinical practice in pediatric patients. So far, eltrombopag is the only available option of TPO-RA reimbursed by the National Health Fund for cITP pediatric patients in Poland. This determines the final results and also limits the final choice of second-line therapy for children and adults with cITP, refractory to previous steroid or IVIGs treatment.

Table I. Data of pediatric patients treated with eltrombopag in NTP in Poland 2018–2020

Characteristics	Value
Gender	
Male, No (%)	33 (55)
Female, No (%)	27 (45)
Age at start of eltrombopag treatment, years	
Median (range)	9.5 (2–17)
Baseline PLT count, 10^9/L	
Median (range)	30 (1–98)
Median starting dose, mg	
Median (range)	50 (25–50)
Eltrombopag efficacy in time	
TW1	
Median PLT count, 10^9/L; median (range)	51 (1–471)
Patients with R; No./TOT (%)	32/60 (53.3)
Patients with CR; No./TOT (%)	13/60 (21.6)
T1	
Median PLT count, 10^9/L; median (range)	67 (1–446)
Patients with R; No./TOT (%)	37/51 (72,6)
Patients with CR; No./TOT (%)	17/51 (33.3)
T3	
Median PLT count, 10^9/L; median (range)	77.5 (5–327)
Patients with R; No./TOT (%)	37/42 (88.1)
Patients with CR; No./TOT (%)	15/42 (35.7)
T6	
Median PLT count, 10^9/L; median (range)	97.5 (1–852)
Patients with R; No./TOT (%)	27/32 (84.4)
Patients with CR; No./TOT (%)	15/32 (46.9)
T12	
Median PLT count, 10^9/L; median (range)	77 (7–339)
Patients with R; No./TOT (%)	24/27 (88.9)
Patients with CR; No./TOT (%)	8/27 (29.6)

NTP – National Therapeutic Program; No – number; M – male; F – female; PLT – platelet count; TW – after 1 week; T1 – after 1 month; T3 – after 3 months; T6 – after 6 months; T12 – after 12 months; CR – complete remission; R – remission; TOT – total number

In all 60 patients, eltrombopag therapy was well tolerated and safe during the observational period of almost 2 years, consistent with the results of prior publications [10]. The overall 3-month, 6-month, and 12-month response rate to eltrombopag in this demonstrated group was over 80%, which is also comparable to the results from previous pediatric international studies [11–14]. Response duration and response quality were satisfactory, and moreover, constantly rising in time. Almost 90% of the followed-up and evaluated patients presented durable response with sustained platelet response (≥30 x 10^9/L). Indirectly, we can assume that this helped not only to improve the platelet count in every single patient but also decreased the need for other ITP therapies and resulted in improvement of quality of life (QoL). Nevertheless, no data are available whether eltrombopag therapy reduced the percentage of patients who required other concomitant drugs or salvage therapies.

Recently, the American Society of Hematology (ASH) published updated recommendations for adult and pediatric patients with ITP, including cITP [1]. The panel of experts agreed on several new diagnostic and management approaches, including the use of TPO-RAs. Regarding the disease-related definitions and the diagnostic routine, these have not been changed since 2011 [15]; current treatment recommendations favor therapies that avoid the side effects of medication and have minimal negative impact on health-related QoL (HRQoL) (Tab. II).

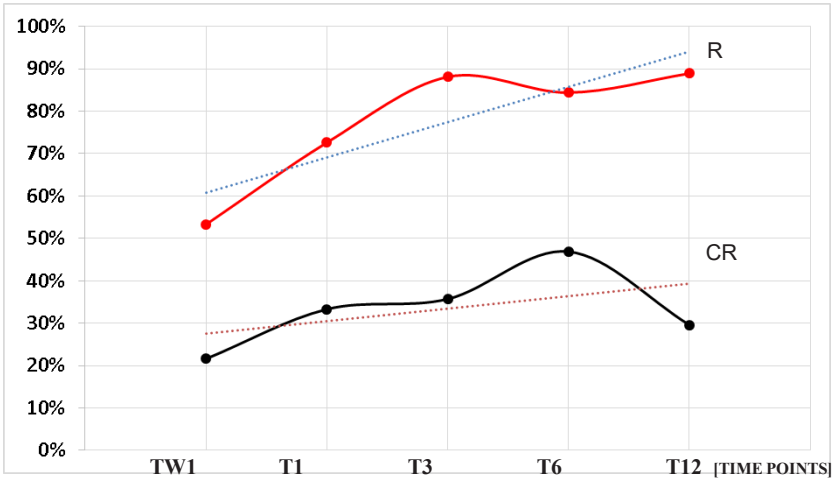

Fig. 1. Time-dependent response to eltrombopag therapy
CR – complete response; R – response; TW1 – after 1 week; T1 – after 1 month; T3 – after 3 months; T6 – after 6 months; T12 – after 12 months; lines of trends are shown

Table II. ASH recommendations for therapy in children with chronic ITP [1]

Management approach	Recommendation
Observation	In children with ndITP who have no or mild bleeding only (skin manifestation), regardless of the platelet count In children with ndITP who have no or minor bleeding preferred over corticosteroids, anti-D, or IVIGs
First-line therapy	In children with ndITP who have non–life-threatening mucosal bleeding and/or diminished HRQoL, corticosteroid courses rather than anti-D or IVIGs - Steroid courses not longer than 7 days - Prednisone preferably - Dosing: **(i) Prednisone** 2-4 mg/kg/day; maximum 120 mg daily; for 5–7 days **(ii) Dexamethasone** 0.6 mg/kg/day; maximum 40 mg/kg/day, for 4 days Anti-D or IVIGs comparatively
Second-line therapy	In children with ITP who have non–life-threatening mucosal bleeding and/or diminished HRQoL and do not respond to first-line treatment: - **TPO-RAs** rather than rituximab - **TPO-RAs** rather than splenectomy - **rituximab** rather than splenectomy

ITP – immune thrombocytopenia; ndITP – newly diagnosed ITP; HRQoL – health-related quality of life; IVIGs – intravenous immunoglobulins; TPO-Ras – thrombopoietin receptor agonists

In children with newly diagnosed ITP (ndITP) who have no or mild bleeding only, regardless of the platelet count, the ASH guideline panel suggests outpatient treatment rather than hospital admission. Similarly, observation is preferred rather than steroid, IVIGs, or anti-D therapy in ndITP children with no bleeding or skin bleeding manifestation only. In children with ndITP with no life-threatening bleeding or no diminished HRQoL, the ASH panel suggest steroids as the first-line ITP therapy preferably over IVIGs or anti-D. In children who do not have response to first-line treatment, it is recommended to use TPO-RAs rather than rituximab or splenectomy. The expert panel recognized the use of TPO-RAs as being beneficial with reference to durable response and reduction or discontinuation of steroid use.

Conclusion

These initial data of the Polish Therapeutic Program support the safety and efficacy of eltrombopag use in chronic ITP pediatric patients, with almost 90% response in 12-month follow-up.

Acknowledgments

The authors thank the Head Office of the NFZ for providing access to the data of patients qualified to enroll in the Therapeutic Program.

Authors' contributions

MRP, JS – study design and statistical analysis. MRP – data analysis, interpretation, manuscript writing, and administrative support. All authors – provision of important clinical data, data checkup, and final approval.

Conflict of interest

MRP is a coordinator assigned by the NFZ to consult with the therapeutic program on eltrombopag use in children with chronic ITP. JS is a National Consultant in Pediatric Hematology and Oncology. All other authors declare no conflicts of interest related to this study.

Financial support

None.

Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; Uniform requirements for manuscripts submitted to biomedical journals.

References

[1] Neunert C, Terrell DR, Arnold DM, et al. American Society of Hematology 2019 guidelines for immune thrombocytopenia. Blood Adv 2019;3:3829–66.

[2] Giordano P, Lassandro G, Barone A, et al. Use of eltrombopag in children with chronic immune thrombocytopenia (ITP): a real life retrospective multicenter experience of the Italian Association of Pediatric Hematology and Oncology (AIEOP). Front Med 2020;7:66.

[3] 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 international working group. Blood 2009;113:2386–93.

[4] Kuter DJ. The biology of thrombopoietin receptor agonists. Int J Hematol 2013;98:10–23.

[5] Bussel JB, Provan D, Shamsi T, et al. Effect of eltrombopag on platelet counts and bleeding during treatment of chronic idiopathic thrombocytopenic purpura: a randomised, double-blind, placebo-controlled trial. Lancet 2009;373:641–8.

[6] Ghanima W, Godeau B, Cines DB, Bussel JB. How I treat immune thrombocytopenia: the choice between splenectomy or a medical therapy as a second-line treatment. Blood 2012;120:960–9.

[7] Bussel JB, de Miguel PG, Despotovic JM, et al. Eltrombopag for the treatment of children with persistent and chronic immune thrombocytopenia (PETIT): a randomised, multicentre, placebo-controlled study. Lancet Haematol 2015;2:e315–25.

[8] 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.

[9] Andrasiak I, Wróbel T. Statistics in hematological practice. Acta Haematol Pol 2018;49: 121–7.

[10] Grainger JD, Locatelli F, Chotsampancharoen T, et al. Eltrombopag for children with chronic immune thrombocytopenia (PETIT2): a randomised, multicentre, placebo-controlled trial. Lancet 2015;386:1649–58.

[11] Cekdemir D, Guvenc S, Ozdemirkiran F, et al. A multi-center study on the efficacy of eltrombopag in management of refractory chronic immune thrombocytopenia: a real-life experience. Turk J Haematol 2019;36:230–7.

[12] Gonzalez-Lopez TJ, Alvarez-Roman MT, Pascual C, et al. Eltrombopag safety and efficacy for primary chronic immune thrombocytopenia in clinical practice. Eur J Haematol 2016;97:297–302.

[13] Mazza P, Minoia C, Melpignano A, et al. The use of thrombopoietin-receptor agonists (TPO-RAs) in immune thrombocytopenia (ITP): a "real life" retrospective multicenter experience of the Rete Ematologica Pugliese (REP). Ann Hematol 2016;95:239–44.

[14] Wong RSM, Saleh MN, Khelif A, et al. Safety and efficacy of long-term treatment of chronic/persistent ITP with eltrombopag: final results of the EXTEND study. Blood 2017;130:2527–36.

[15] Neunert C, Lim W, Crowther M, et al. The American Society of Hematology 2011 evidence-based practice guideline for immune thrombocytopenia. Blood 2011;117:4190–207.