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ORIGINAL RESEARCH ARTICLE

VIA MEDICA

Eltrombopag and high-dose dexamethasone as first-line treatment in children with newly diagnosed primary immune thrombocytopenia

Monika Richert-Przygońska*, Dominika Kołuda, Mariusz Wysocki

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

Abstract

Introduction: Novel treatment strategies for newly diagnosed immune thrombocytopenia (ndITP) pediatric patients are required.

Material and methods: The aim of this study was to analyze the safety and efficacy of eltrombopag and dexamethasone when used as the first-line treatment in children with ndITP. Inclusion criteria: age 5–18 years, and ndITP with bleeding manifestation. Treatment course: 28 days of eltrombopag with oral dexamethasone in three repeated courses.

Results: A complete response was achieved in 90% of patients after the first week of treatment, and in all patients after the end of the treatment course. Durable and sustained platelet response was observed in 90% of patients after 12 months of follow-up.

Conclusions: Our finding support safety and efficacy of eltrombopag and dexamethasone as combined first-line therapy of ndITP in children.

Keywords: eltrombopag, dexamethasone, children, immune thrombocytopenia

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Introduction

Primary immune thrombocytopenia (ITP) is one of the most common hematological disorders in childhood. Due to the duration of the disease, ITP can be qualified as newly diagnosed (ndITP), which defines all cases at diagnosis, or persistent ITP (pITP) — lasting 3–12 months from diagnosis, or chronic ITP (cITP) lasting for more than 12 months. ITP is usually a self-limiting and mild disease, without life-threatening bleeding episodes or the need for hospitalization or treatment intervention [1, 2]. Although most children with ndITP achieve remission spontaneously, others require therapy for minor or moderate bleedings and improvements in their health related quality of life [3, 4]. The first-line treatment for ndITP includes corticosteroids, intravenous immunoglobulin, and anti-D globulin [1, 3, 5].

However, 10–20% of children with ITP do not respond to the recommended first-line therapies, going on to develop pITP or cITP. In addition, some patients become steroid-dependent or refractory, and this leads to adverse events and challenges in logistical and economic terms [4].

In recent years, several treatment modalities such as mycophenolate mofetil, rituximab and thrombopoietin

*Address for correspondence: Monika Richert-Przygońska, Department of Pediatric Hematology and Oncology, *Collegium Medicum*, Nicolaus Copernicus University in Toruń, Jurasz University Hospital 1, Marii Skłodowskiej-Curie 9, 85–094 Bydgoszcz, Poland, e-mail: monika_richert@yahoo.com

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receptor agonists have been explored for cITP pediatric patients, with the aim of establishing a durable platelet response and minimizing the bleeding risk or splenectomy qualification [6–17]. Even so, there remains a gap in the availability of novel treatment strategies for ndITP patients which may result in durable platelet response.

PINES is an ongoing phase III prospective randomized trial of eltrombopag's use in the management of ndITP in children [4]. Moreover, there has been convincing data from adult cohort studies suggesting that early aggressive and combined treatment protocols may be a good first-line therapeutic strategy for ndITP, resulting in sustained response rates [18, 19].

The aim of our study was to analyze the safety and efficacy of the use of eltrombopag and high-dose dexamethasone as the first-line treatment in children with ndITP.

Material and methods

Study design

Based on prior results from an adult study [18], we designed and performed an open-label, single-arm, observational, single-center study in pediatric patients with newly diagnosed ITP. Eligible patients were aged 5–18 years, with bleeding manifestation of ndITP scored according to the Buchanan bleeding scale [20, 21].

The study was conducted in accordance with the Declaration of Helsinki. The local Bioethical Committee approved the study, and all patients' legal caregivers gave written consent before enrollment (KB 695/2019).

The treatment course consisted of 50 mg of eltrombopag given orally from the day of ITP diagnosis for 28 days, and oral dexamethasone 28 mg/m^2/day, divided into three doses (maximum 40 mg/day), given as four-day courses, repeated three times alongside the eltrombopag ongoing therapy on days 1–4, 15–18, and 29–32. If the platelet count exceeded ≥400 × 10^9/L, eltrombopag was stopped.

Response assessment

Complete blood count assessment was performed at baseline, on days 7, 14, 32 and 46, and every three months until the end of the 12-month observation period.

Quality of response to the applied treatment was defined according to the International Consensus Guidelines: complete response (CR) was defined as platelet count ≥100 × 10^9/L and absence of bleeding; response (R) was defined as platelet count ≥30 × 10^9/L and at least a 2-fold increase in the baseline count and absence of bleeding; and no response (NR) was defined as platelet count ≤30 × 10^9/L or less than a 2-fold increase of baseline platelet count or bleeding. The duration of response was measured from the achievement of CR or R to the loss of CR or R [2].

Statistical analysis

Descriptive analysis was performed, with median and range values. Response and complete response rates at each timepoint were provided with 95% confidence intervals (95% CI). Duration of the response included the entire period of the follow up with any responses achieved (CR or R).

Results

A total of 10 children were enrolled in the study between February 2020 and January 2022. All patients met the criterion of newly diagnosed primary immune thrombocytopenia. Of the 10 patients, six were boys, and four were girls (Table I). Median age at the start of the combined eltrombopag/dexamethasone treatment protocol was 9.5 years (range 6–16). At the beginning of treatment, median platelet count was 7 × 10^9/L (range 1–30 × 10^9/L). The median follow-up was 23 months (range 14–37).

After the first week of eltrombopag/dexamethasone therapy, median platelet count was 315 × 10^9/L. Response was observed in 90% of patients, and 80% of patients achieved CR. In two patients, eltrombopag was stopped due to the platelet count being ≥400 × 10^9/L, and no relapse was noted. At the end of the therapy protocol (day 32), CR was observed in all patients. A long-term duration of response was obtained in all patients after six months, and in 90% of patients after 12 months, of follow-up (Figure 1). One patient relapsed 12 months after the initial eltrombopag/dexamethasone treatment, and received intravenous immunoglobulin rescue.

No serious adverse effects were observed during the study.

Discussion

It has been proven that thrombopoietin receptor agonists (TPO-RAs) are one of the most effective alternative treatment options for patients with cITP [22–24]. Several studies have so far confirmed the safety and efficacy of TPO-RAs in pediatric patients, with special regard to orally administered eltrombopag in cITP [7, 13, 14]. Although there has been no data regarding eltrombopag use in newly diagnosed ITP patients, we can expect that with its mechanism of action i.e. stimulating the proliferation and maturation of megakaryocytes due to interactions with thrombopoietin receptor, eltrombopag use may result in significant platelet count increase [25]. Eltrombopag, indirectly increasing T-regulator cell activity, may play a significant role in modulating the natural history of ITP.

It is known from other studies that both newly diagnosed and chronic patients can achieve remission with high-dose dexamethasone courses (HDD). HDD can be effective in about 45% of pediatric severe cITP patients [8].

Table I. Patient characteristics and treatment results

Patient	Age/sex	Bleeding score	Baseline PLT	D7/PLT	D14	D32	3 months	6 months	12 months	Follow-up/ months
1	9/M	2	7	325	CR	CR	CR	CR	CR	37
2	14/M	3	30	261	NR	CR	R	R	R	36
3	15/F	2	12	191	R	CR	R	R	R	26
4	6/M	2	8	323	NR	CR	CR	CR	CR	26
5	16/M	2	2	372	CR	CR	CR	CR	CR	23
6	11/M	1	12	308	R	CR	CR	CR	NR	26
7	8/M	2	3	10	R	CR	CR	CR	CR	21
8	6/F	2	7	661	CR	CR	CR	CR	CR	20
9	14/F	2	2	86	NR	CR	NR	CR	CR	19
10	10/F	1	1	859	CR	CR	CR	CR	CR	14

M – male; F – female; PLT – number of platelets; CR – complete response; R – response; NR – no response; D7 – day 7; D14 – day 14; D32 – day 32

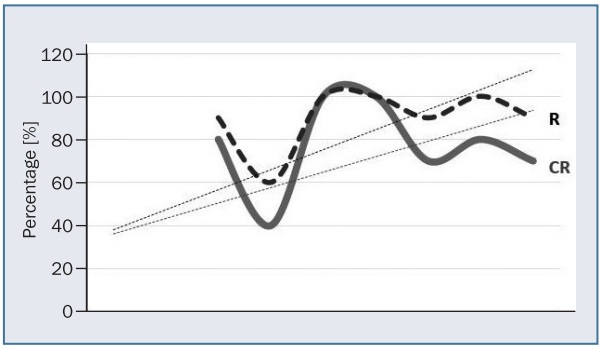

Figure 1. Time-dependent response (R) to eltrombopag/dexamethasone combined therapy; CR – complete response

Other authors have concluded that HDD courses may be preferable in terms of bringing about rapid platelet count increases, but not in terms of improved durable platelet count responses, compared to standard-dose prednisone [26].

Conclusions

Our study confirms that combined eltrombopag/HDD therapy may lead to a quick initial response in newly diagnosed ITP pediatric patients. We found that early escalated therapy determined high CR rates as well as sustained and long-lasting remissions. In all patients, an early escalated and short course of eltrombopag/HDD therapy was well tolerated and safe during the observation period. Response duration and response quality were satisfactory, and, moreover, constantly rising. Almost all of the evaluated patients presented durable response with sustained platelet response after a single course of combined treatment within their first episode of ITP.

Our data supports the safety and efficacy of eltrombopag and high-dose dexamethasone as first-line therapy for newly diagnosed ITP in children.

Article information and declarations

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Authors contributions

MRP, MW – design of study; MRP, DK – provision of clinical data; MRP – writing manuscript, editing manuscript; all authors – analysis of clinical data, critical revision and final approval.

Conflict of interests

MRP and MW received lecture fees from, and participated in meetings organized by, Novartis.

Data availability statement

All data underlying the results is available as part of the article, and no additional source data is required.

Ethics statement

The study was conducted in accordance with the Declaration of Helsinki. The local Bioethical Committee approved the study and all patients' legal caregivers gave written consent before enrollment (KB 695/2019).

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Supplementary material

None.

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