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Efficacy and Safety of Eltrombopag for the Treatment of Chronic Idiopathic Thrombocytopenic Purpura in Children and Adolescents

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ABSTRACT

Background: Chronic ITP is a very common disease in children. Most treatment options have focused on slowing platelet destruction like corticosteroids and IVIG. These treatments are not always effective, or have only a transient effect, and treatment related adverse events often restrict further use. Impaired platelet production has been evolved as a potential disease mechanism for ITP. As a result, growth factor and growth factor analogue stimulation of megakaryopoiesis has also been investigated.

Objective: is to evaluate the efficacy and safety of eltrombopag for the treatment of children and adolescents with chronic ITP.

Subjects and methods: It was a prospective cohort study which was conducted on forty patients (22 males and 18 females) with chronic ITP. They were treated with eltrombopag for a period ranged from 6 months to 2 years after failure of first line of treatment (steroids, IVIG or both). Patients started eltrombopag with mean initial platelet count 14.4 X 10^3/ uL and were evaluated after at least 6 months of therapy. The study was approved by the academic and medical ethics committee of Zagazig University and a written informed consent was obtained from all patients.

Results: Thirty patients (75%) responded to eltrombopag with a mean platelet count of 100.9 X103/ uL while 10 patients (25%) did not respond to the drug. Mean platelet count was significantly higher after eltrombopag therapy (100.9 ± 65.97 versus 14.4 ± 8.87, $P < 0.001$). The longer the duration of treatment, the higher the mean platelet count after treatment ($r = 0.4$, $P < 0.001$). Only 43.3% of responders received combined treatment with IVIG and steroids versus 20% of non-responders ($p = 0.006$).

Conclusion: Eltrombopag is an effective, well tolerated and safe drug to restore platelet counts at levels high enough to prevent bleeding events in children with chronic ITP.

Keywords: Eltrombobag, Chronic ITP, Treatment, Children, Efficacy, Safety.

INTRODUCTION

Immune thrombocytopenic purpura (ITP) is an autoimmune disease in which antiplatelet antibodies accelerate the destruction of platelets. In addition, platelet production can be impaired because the antiplatelet antibodies can also damage megakaryocytes [(1)]. Its prevalence being approximately 8 per 100,000 children [(2)].

It is characterized by transient or persistent decrease of the platelet count to less than 100×10^9/liter. The term 'newly diagnosed ITP' is used to describe all cases at diagnosis. Persistent ITP is defined as ITP lasting between 3 and 12 months from diagnosis while chronic ITP is defined as the presence of ITP for more than 12 months [(3)].

Patients with ITP have an increased risk of bleeding ranging from minor to life-threatening events and a diminished health related quality of life HRQoL [(4)].

The treatment goal in chronic ITP is to increase and then maintain platelets in a safe range to prevent bleeding; in addition, improving HRQoL is an important goal for the majority of patients. Since most fatal bleeding occurs with platelet counts lower than 30×10^9/liter [(5)]. Current guidelines suggest that treatment should only be considered in symptomatic patients with counts less than 30×10^9/liter [(3, 6)].

Guidelines issued by different groups recommend corticosteroids as first-line therapy and splenectomy as one of several second-line therapies. Different options exist for patients who do not undergo or do not respond to splenectomy including IVIg, IV anti-D, Rituximab, danazol, azathioprine, Vinca alkaloids and cyclophosphamide [(6)].

Recent consensus statements and guidelines recommend thrombopoietin-receptor (TPO-R) agonists as second and third line of treatment [(7)].

Eltrombopag is the first oral, nonpeptide TPO-R agonist approved for the treatment of chronic ITP in patients with insufficient response to at least one other therapy [(8)].

It increases platelet production by binding to the transmembrane domain of the TPO-R. It does not compete with endogenous TPO in vitro and it induces proliferation and differentiation of BM progenitor cells in the megakaryocytic lineage [(9)].

Several studies have shown that as a result of eltrombopag treatment for up to 6 months, platelets increase to 50×10^9/liter in up to 80% of patients [(10)].

The aim of the study is to evaluate the efficacy and safety of eltrombopag for the treatment of children and adolescents with chronic ITP.

SUBJECT AND METHODS

The prospective cohort study was conducted at hematology outpatient clinic of Zagazig University Hospitals during a period from January 2018 to August 2019.

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Ethical approval and written informed consent:
The study was approved by the academic and medical ethics committee of Zagazig University and a written informed consent was obtained from all patients.

All patients were subjected to full history taking including age, age at diagnosis, initial clinical presentations with special emphasis on bleeding history, type and response outcome of first line therapy, complete physical examination with special emphasis on site and type of bleeding "petechiae, bruises, Epistaxis, etc." and routine laboratory investigations according to our local standards including complete blood count with manual platelet count and platelet trend.

Fourty patients (22 males and 18 females) with chronic ITP were treated with eltrombopag for a period ranged from 6 months to 2 years (mean = 1.125 years), the mean age was 9.9 ± 4.0 years (range 3 – 18 years), the mean age at diagnosis was 6.97 years (range 2 – 16 years). According to initial WHO grading of bleeding, 26 patients (65%) were grade 1, 10 patients (25%) were grade 2 and 15 patients (37.5%) were grade 3. **(Table 1).** Patients were resistant to 1st line treatment (22 patients were treated with steroids, 3 patients with IVIG and 15 patients with combined steroids and IVIG) **(Table 2).** Patients started eltrombopag with mean initial platelet count 14.4 x 10^3/ uL (range 0 – 44 x 10^3/ uL) and were evaluated after at least 6 months of therapy.

Table 1: Demographic data and clinical characteristics of patients.

Demographic Data	N = 40
Age (y)	
mean ± SD	9.9 ± 4
Gender	
Male	22 (55%)
Female	18 (45%)
Age at Diagnosis (y)	
mean ± SD	6.97 ± 3.5
Initial platelet count ($x10^3/uL$)	
mean ± SD	14.4 ± 8.87
Initial WHO Grading of bleeding	
1	26 (65%)
2	10 (25%)
3	15 (37.5%)

Table 2: Efficacy, safety and duration of eltrombopag in our patients.

Data	N = 40
Response to treatment	
responders	30 (75%)
non-responders	10 (25%)
Mean platelet count ($x10^3/\mu L$) after Eltrombopag	
mean ± SD	100.9 ± 65.97
WHO Grading of bleeding after treatment zero	31 (77.5%)
1	6 (15%)
2	3 (7.5%)
Side effects	
No	21 (52.5%)
Yes	19 (47.5%)
Grade of side effects	
Grade 1	3 / 19 (15.8%)
Grade 2	16 / 19 (84.2%)
Duration of Eltrombopag treatment (years)	
mean ± SD	1.125 ± 0.5

Table 3: First line treatment in our patients

1st line treatment	N = 40
Steroids	22 (55%)
IVIG	3 (7.5%)
Combined	15 (37.5%)

Statistical analysis

All data were collected, tabulated and statistically analyzed using SPSS version 19 (Armonk, NY: IBM Corp).Continuous quantitative variables were expressed as the mean ± SD & median (range) and categorical qualitative variables were expressed as an absolute frequencies (number) & relative frequencies (percentage).Independent student's T test was used to compare between two groups of normally distributed data. Paired t test was used to compare between two groups before and after therapy. Correlation coefficient (r) was used when appropriate. Categorical data were compared using Chi square t tests.

The tests were two sided with p-value <0.05 was considered statistically significant (S), p-value < 0.001 was considered highly statistically significant (HS) and p-value ≥ 0.05 was considered statistically insignificant (NS).

RESULTS

Table 4 shows that there was highly significant difference in mean platelet count before and after eltrombopag therapy, where mean platelet count was significantly higher after eltrombopag therapy.

Table 4: Changes in mean platelet count before and after treatment with eltrombpag .

	X ±SD	Paired T	P
Mean platelet count (x10³/µL) before treatment with Eltrombopag	14.14± 8.87	9.07	< 0.001**
Mean platelet count (x10³/µL) after treatment with Eltrombopag	100.9 ± 65.97		

Table 5 shows that there was highly significant difference in WHO grading of bleeding before and after treatment. Seventy-seven and half % of patients didn't show any bleeding after the therapy. Also, none of the patients after treatment with had grade 3 bleeding compared to 10% before treatment with.

Table 5: WHO Grade of bleeding before and after treatment with eltrombopag.

WHO Grade	Before treatment		After treatment		P
	N.	%	N.	%	
0	0	0.0	31	77.5	< 0.001**
1	26	65	6	15	
2	10	25	3	7.5	
3	4	10	0	0	

Table 6 shows that duration of treatment was significantly high in responders to treatment.

Table 6: Relationship between response to eltrombopag and duration of treatment.

	Non responders N=10	Responders N=30	Test of significance	p
Duration of treatment Mean ± SD	0.5 ± 0	1.4 ± 0.4	T= 6.5	<0.001 **

Table 7 shows that the mean platelet count after therapy was significantly higher in responders to treatment when compared to non-responders.

Table 7: Relationship between response to eltrombopag and mean platelet count after treatment with eltrombopag.

	Non responders N=10	Responders N=30	Test of significance	P
Mean platelet count (x10³/*µL*) after Eltrombopag Mean ± SD	37.9 ± 5.8	132.5 ± 59.4	T= 4.9	<0.001 **

Table 8 shows that there was significant association between response to treatment and 1st line therapy where 43.3% of responders received combined treatment with IVIG and steroids versus 20% of non-responders.

Table 8: Relationship between response to eltrombopag and 1st line treatment .

	Non responders N=10	Responders N=30	Test of significanc	P
1st line of treatment	(N) (%)	(N) (%)	X^2= 10.15	0.006 *
Steroids	5 (50%)	7 (56.7%)		
IVIG	3 (30%)	0 (0%)		
Steroids+IVIG	2 (20%)	3 (43.3%)		

Table 9 shows that there was significant association between response to treatment with eltrombopag and WHO grading of bleeding before treatment. where WHO grade 1 of bleeding was prevalent in responders to treatment (76.7%), while grade 2 and grade 3 were prevalent in non-responders (70%).

Table 9: Relationship between response to eltrombopag and initial WHO grading of bleeding.

	Non responders N=10	Responders N=30	Test of significance	P
Initial WHO Grading of bleeding	(N) (%)	(N) (%)	X^2= 9.05	0.01*
1	3 (30.3%)	23 (76.7%)		
2	4 (40.0%)	6 (20%)		
3	3 (30.0%)	1 (3.3%)		

Table 10 shows that there was highly significant association between response to treatment and WHO grading of bleeding where grade zero was prevalent (100 %) , while grade 1 and grade 2 were prevalent (90%) in non-responders

Table 10: Relationship between response to eltrombopag and WHO grading of bleeding after treatment with eltrombopag .

	Non responders N=10	Responders N=30	Test of significance	P
WHO grading of bleeding After treatment	(N) (%)	(N) (%)		
Zero	1 (10%)	30 (100%)	X^2= 34.84	<0.001**
1	6 (60%)	0 (0%)		
2	3 (30%)	0 (0%)		

Table 11 shows that there was highly significant positive correlation between mean platelet count after treatment and duration of treatment with eltrombopag.

Table 11: Correlation between mean platelet count after treatment and duration of eltrombopag treatment.

	r	P
Mean platelet count & duration of treatment	0.4	< 0.001

DISCUSSION

The present results were matched with many other previous studies. **Bussel *et al.*** [11] in PETIT study which was a randomized, multicenter, placebo controlled study that evaluated eltrombopag for the treatment of children with persistent and chronic immune thrombocytopenia, found that 62% of patients who received eltrombopag, compared with 32% who received placebo, achieved the primary endpoint of platelet count 50×10^3 per µl or more at least once without rescue (odds ratio 4·31, 95% CI 1·39–13·34, p=0·011).

Also **Grainger *et al.*** [12] in PETIT2 study which was a randomized, multicenter, placebo-controlled trial that investigated eltrombopag for children with chronic immune thrombocytopenia, reported that 40% of patients who received eltrombopag compared with 3% of patients who received placebo achieved the primary outcome of platelet counts of at least 50×10^3 per µl for 6 of the last 8 weeks of the double-blind period (odds ratio 18·0, 95% CI, 2·3–140·9; p=0·0004). Responses were similar in all cohorts (eltrombopag vs placebo: 39%vs 10% for patients aged 12–17 years, 42% vs 0% for patients aged 6–11 years, and 36% vs 0% for patients aged 1–5 years).

Following PETIT and PETIT2 studies, **Guo *et al.*** [13] conducted their large meta-analysis to evaluate efficacy and safety of thrombopoietin receptor agonists in 238 children with chronic immune thrombocytopenia**.** An overall platelet response (OR) was conducted in five studies. Subgroup meta-analysis based on TPO-RA regimens demonstrated that both romiplostim and eltrombopag were associated with higher rates of OR (RR = 5.05, 95% CI (2.21, 11.53); RR = 2.73, 95% CI (1.67, 4.44), respectively). In short, the TPO-RA group had a higher rate of OR. Durable response (DR) was conducted in four studies. Subgroup meta-analysis based on TPO-RA regimens demonstrated that both romiplostim and eltrombopag were associated with higher rates of DR (RR = 4.62, 95% CI (1.58, 13.51); RR = 13.14, 95% CI (2.67, 64.64), respectively). In brief, the TPO-RA group had a higher rate of DR.

A large meta-analysis, which was conducted by **Wang *et al.*** [14] included 1126 patients from 13 RCT performed in eight adult and five pediatric ITP populations, showed that TPO-RA significantly increased platelet response by 3-fold and durable response rates by almost 8-fold as compared to placebo or standard of care.

Similarly, **Massaro *et al.*** [15] performed a systematic review and meta-analysis in children with chronic ITP. Five randomized controlled trials with total of 261 pediatric patients from 1–17 years of age were included. The efficacy and safety analysis showed TPO-RA groups were superior over placebo, and there was no difference in adverse event occurrence between TPO-RA (Romiplostim and Eltrombopag) and placebo groups.

In our study, There was highly significant positive correlation between mean platelet count after treatment and duration of treatment with eltrombopag (r = 0.4, P < 0.001) as the longer the duration of treatment, the higher the mean platelet count after treatment.

In PETIT study, patients who had completed the randomized phase were allowed to enter an extension phase to continue treatment for up to 24 weeks, during which platelet counts were kept >50 × 103/µl in the majority of cases. Furthermore, in this period concomitant medication was discontinued or reduced in roughly half the patients **[11].**

In PETIT 2 study, similar to what happened in PETIT, the need for a rescue therapy was reduced, and platelet counts were mostly maintained >50 × 103/µl during the subsequent extension phase which was prolonged for up to 24 weeks **[12].**

The duration of these studies was short (24 weeks) and not enough to address this correlation between the duration of treatment and mean platelet count after treatment.

However, extended studies were conducted in adults. The EXTEND trial explored the efficiency of prolonged treatment of ITP with eltrombopag, and,

furthermore, made it possible to control patients for a follow-up period of up to 5 years. The EXTEND trial recruited patients who had completed the four adult large trials , irrespective of their platelet counts at entry, and provided that they had not previously experienced any eltrombopag-related serious AEs (SAEs). A total of 302 patients were involved. The mean average daily dose was 50.2 mg, and the overall median duration of exposure was 2.4 years. The overall response was 85%. The median platelet counts had increased to >50 × 103/μl by 2 weeks, and remained increased throughout the study. At 1 year after the start, bleeding symptoms decreased from 57% to 16%. Serious bleeding was uncommon. Furthermore, 33.7% of patients who were taking some other form of ITP medication at baseline stopped at least one of these medications **(16).**

In our study, symptomatic bleeding has stopped in 77.5 % of patients and WHO grading of bleeding after treatment shows better results compared to grading before treatment. Incidence of bleeding in patients after treatment was 22.5 %; 15% with grade 1 and 7.5% with grade 2. None of patients after treatment with eltrombopag had grade 3 bleeding compared to 10% before treatment with eltrombopag.

Bussel *et al.* **(11)** in PETIT study found that clinically significant grade 2-4 bleeding was reduced with eltrombopag (32% vs. 9% in eltrombopag and placebo respectively)**.**

Also, **Grainger *et al.*** **(12)** in the PETIT2 study that 37% of patients treated with eltrombopag in the double-blind period (12 week) had bleeding (grades 1- 4) compared to 55 % of placebo patients.

Wang *et al.* **(14)** in their large meta-analysis showed that TPO-RA significantly reduced incidences of any or severe bleeding events (RR: 0.8, 95%CI: 0.7-0.9; RR: 0.5, 95%CI: 0.3-0.99, respectively). Especially with eltrombopag, there were substantial reductions in any or severe bleeding events in treated patients compared with controls (RR: 0.7, 95%CI: 0.5-0.9; and RR: 0.3, 95%CI: 0.1-1.0, respectively). In parallel with reduced bleeding episodes, pooled results indicated a significant reduction in the need for rescue medications in the TPO-RA groups compared with control groups (RR: 0.5, 95%CI: 0.4-0.6). Treatment studies with both agents have also demonstrated an ability to reduce or stop concomitant medications (RR: 1.8, 95%CI: 1.1-3.0).

On the contrary, **Guo *et al.*** **(13)** in their large meta-analysis found that both romiplostim and eltrombopag did not differ with the control group in any bleeding events (RR = 1.17, 95% CI (0.87, 1.56); RR = 0.64, 95% CI (0.24, 1.73), respectively.

This discrepancy can be attributed to the different inclusion criteria where we included patients on eltrombopag only while **Guo *et al.*** **(13)** included patients on eltrombopag or romiplostim. It is also supported by the data reported by **Wang et al**. **(14)** where substantial reductions in any or severe bleeding events were notable with eltrombopag treated patients.

As regards safety of eltrombopag in the present study, 21 patients (52.5%) had no side effects to the drug compared to 19 patients (47.5%) who had side effects, 16 patients (84.2 %) were grade 2 and 3 patients were grade 1 (15.8 %).

No serious side effects were reported in our study. Headache was reported in 6 patients, GIT upset (3 patients), cold symptoms (3 patients), arthralgia (3 patients) , anorexia (2 patients) , diarrhea (2 patients) , insomnia (2 patients) , blurred vision (2 patients) , fatigue (2 patients) , myalgia (2 patients) , skin rash (1 patient) , pruritus (1 patient).

In PETIT study, the most common adverse events with eltrombopag were headache (13 [30%] patients receiving eltrombopag vs nine [43%] patients receiving placebo), upper respiratory tract infection (11 [25%] patients vs two [10%] patients), and diarrhea (seven [16%] patients vs one [5%] patient). Grade 3 or 4 adverse events occurred in five (11%) patients receiving eltrombopag and four (19%) patients receiving placebo, and serious adverse events (four [9%] patients receiving eltrombopag and two (10%) patients receiving placebo) were similarly infrequent in both groups. No thrombotic events or malignancies occurred. Increased alanine aminotransferase concentrations caused two (3%) of 65 patients to discontinue eltrombopag in the open-label phase **(11).**

In PETIT 2 study, adverse events that occurred more frequently with eltrombopag than with placebo included nasopharyngitis (11 [17%] patients), rhinitis (10 [16%] patients), upper respiratory tract infection (7 [11%] patients), and cough (7 [11%] patients). Serious adverse events occurred in five (8%) patients who received eltrombopag and four (14%) who received placebo. Safety was consistent between the open-label and double-blind periods. No deaths, malignancies, or thromboses occurred during the trial **(12).**

Wang et al. (14) in their large meta-analysis included 13 studies which reported the incidence of any or severe AEs. Based on data from 10 studies, the rates of any AEs were similar between the TPO-RA and control regimens (RR: 1.01, 95% CI: 0.92–1.10, P = 0.913). Additionally, based on data from 11 studies, the rates of severe AEs tended to be lower in the TPO-RA groups than in the control groups (RR: 0.74, 95% CI: 0.54–1.01, P = 0.054). Also, there was no substantial difference in thrombotic events between the TPO-RA and control regimens (RR: 1.08; 95% CI: 0.40–2.93). There was a trend toward an increased incidence of liver function abnormalities with eltrombopag vs. placebo (RR: 2.13, 95% CI: 0.74–6.17). There was no considerable difference between the eltrombopag and control regimens with respect to the incidence of cataracts (RR: 0.89, 95% CI: 0.42–1.91) **(14).**

Guo *et al.* **(13)** in their large meta-analysis included 4 studies which reported any adverse events. The results showed no great difference in any adverse events between the TPO-RA and control groups (RR = 1.00, 95% CI (0.86, 1.17), P = 0.974). Subgroup meta-analysis based on TPO-RA regimens demonstrated that both romiplostim and eltrombopag had no significant

difference with the control group in any adverse events (RR = 1.00, 95% CI (0.69, 1.45); RR = 1.00, 95% CI (0.85, 1.18), respectively). At the same time, Guo et al included five studies which reported severe adverse events. The results showed no great difference in severe adverse events between the TPO-RA and control groups (RR = 1.12, 95% CI (0.52, 2.44), P = 0.974). Subgroup meta-analysis based on TPO-RA regimens demonstrated that both romiplostim and eltrombopag had no significant difference with the control group in any adverse events (RR = 2.29, 95% CI (0.56, 9.30); RR = 0.71, 95% CI (0.27, 1.88), respectively).

CONCLUSION

Eltrombopag is an effective, well tolerated and safe drug to restore platelet counts at levels high enough to prevent bleeding events in children with chronic ITP.

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