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ORIGINAL ARTICLE

Eltrombopag For Immune Thrombocytopenic Children in a Single Region

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Abstract *Objective* Child patients of chronic thrombocytopenic purpura with severe and resistant thrombocytopenia were evaluated to observe whether their clinical or laboratory states improve by one of the thrombomimetic therapeutic agent called Eltrombopag as in adults in a single center of different country from previous studies. *Materials and Methods* Nineteen patients with chronic immune thrombocytopenia were treated with Eltrombopag to dose in international guidelines. *Results* Approximately half (11/19:58%) of the patients benefitted from the treatment with Eltrombopag either by an increase of platelet levels at safe levels with a decrease in the frequency of bleedings which needed rescue treatment. *Conclusion* Thrombomimetic treatment options have strengthened the clinician's hand where the regular treatment options became insufficient.

Keywords Immune thrombocytopenia · Children · Eltrombopag

Introduction

Eltrombopag is a drug generated for thrombocytopenic disorders especially in production defects which affects an agonistic mechanism to thrombopoietin receptors, and it is associated with an increase in number and maturation of megakaryocytes [1, 2]. It was approved by FDA in November 2008 for the treatment of chronic immune thrombocytopenic purpura unresponsive to steroids, immunoglobulin and/or splenectomy in adults, and at August 2015 for the same disorder in children above 1 year.

While the bleeding complication in pediatric patients is rare, 3% of these complications required hospitalization [3]. Most of the time at bleeding events rescue treatment is administered because most of these children are followed without any chronic treatment. So children with frequent bleeding and very low platelet counts are always at risk of further bleeding complications. Also, the stress of possible bleeding affects both patients and families [4]. Splenectomy is avoided especially in pediatric patients and not an easy way as in adults because of infectious risks and surgical intervention is always the later choice for most of the clinics and families. The recent guideline revealed that in immune thrombocytopenia the mechanism of thrombocytopenia also includes relative low thrombopoietin levels so that agonistic mechanisms are in the treatment option while supplying stable desired levels even after treatment cessation [5].

Because the pediatric physicians in some countries are not included in petit studies, they may have less experience with the use of this drug and its effects. Hence, we want to present our single-center eltrombopag use and its results in a short but sufficient period to decide drug response.

Method

Although some hematologists argue for later cutoff point (like 12 months), the term "Chronic ITP" is defined as the persistence of thrombocytopenia (platelet count $< 150{,}000/\mu L$) for longer than 6 months after the initial clinical presentation to whom we consider Eltrombopag treatment. Also, two cases having the persistant disease (unresponsive

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to first medical treatment options like steroid or IVIG) were included to study with 3 months of disease history while they are on cyclosporin treatment. The patients were 19 children diagnosed with persistant and chronic ITP, and within the last 6 months who required 1–2 rescue treatments due to symptomatic bleeding or severe thrombocytopenia (Plt $< 10{,}000/mm^3$). All the patients received an eltrombopag treatment and were followed up clinically for 3–18 months (mean: 6 months) at the Pediatric Hematology Departments of Hospitals (State University Hospital and Other State Hospital) in Adana, a south city of Turkey. Before the onset of Eltrombopag, the patients were on an alternative treatment of Intravenous immunoglobulin (0, 4–1 g/kg/day for 1–3 day) or steroid regimens (Methyl prednisolone 2–30 mg/kg/day for 1–3 week or dexamethasone 20 mg/m2/day for 4 days [6]) when the rescue treatment was needed. All of the patients were evaluated for hepatosplenomegaly, autoimmunity (ANA, Anti-DNA, etc.) bone marrow aspiration, megakaryocyte morphology and sufficiency at diagnosis. None of them had hepatosplenomegaly and their bone marrow examinations revealed normal or increased megakaryocytes with immaturity findings as decreased nucleus lobulation. The bone marrow investigations and clinical evaluations confirmed to diagnosis of immune thrombocyte destruction. A work up including viral markers, immunoglobulin profile and platelet volume assessment were done for all of the patients. Two of the patients were on chronic cyclosporin treatment as immune suppressive medications before and after the use of eltrombopag. Only one patient was splenectomized before the onset of treatment with Eltrombopag. This was continued for 3 months then her platelet level dropped to $3000/mm^3$ and she has been treated almost monthly with IVIG or high dose steroid since then. Before the treatment, informed consent of families and permission of national health authority were obtained. Some of the demographic data of the patients were given in Table 1.

Treatment doses were arranged according to ages as follows; the initial dose was 25 mg for children aged between 1 and 5 years, 50 mg for children above 6 years. The complete response regarded as the platelet count was $100 \times 109/L$ and above, while partial response when the platelet count was between 30 and $100 \times 109/L$ [8]. Because target thrombocyte level was not achieved in one patient, dose increment were intended as stated in literature [7]. The patients were followed up weekly for the first month and monthly for the following 6 months. When the cost of eltrombopag is considered in a month, 25 mg tablet/day use costs aproximately 400$ and 50 mg tablet form use costs 800$ with the price determined in our country. The platelet levels before and after the treatment were compared. Parameters like significant platelet increase to target level ($> 30{,}000/mm^3$) or decrease in rescue treatment need (less then 1 treatment/month) were evaluated as the treatment success.

During the initial weekly follow up, physical examination performed beside the hemogram, liver and renal function tests evaluation and also the patients were questioned for any side effects (like abdominal-stomach pain, headache). They are also referred to ophthalmologic examination after 3 months treatment period.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent: Informed consent was obtained from all all the families of patients included in the study.

Results

The successful response to eltrombopag use was found to decrease clinical bleedings or increase the platelet levels above $30{,}000/mm^3$ without any rescue treatments in 11 of 19 patients as seen in Table 1. Overall follow up with patients lasted 18 months duration. Generally, the drug is well tolerated with per oral use and no adverse events took place while its use by the patients. Because none of the patients had the side effects mentioned before it was not needed to stop the drug.

Eleven of the 19 (58%) patients thrombocyte levels were found to significantly increase ($> 30{,}000$) and the bleeding symptoms were found to decrease, hence they were regarded as to be successfully treated with Eltrombopag. When the target level of thrombocyte elevated to $50{,}000/mm^3$, the ratio of patients responded to this level was found to be 31%. Platelet levels of patient #6 showed no significant respond to first 25 mg dose and aggravated above $500{,}000/mm^3$ with 50 mg dose. Therefore, an interval without drug use was planned to lower levels of platelets.

Discussion

Although it seems as an unusual treatment method by augmenting thrombocyte production in immune thrombocytopenia or increased thrombocyte destruction, this method is recently widely used effectively in adult hematology clinics as in the reported studies [9, 10]. The proposed beneficial mechanisms treating thrombocytopenia by this method are inappropriately low thrombopoietin levels in immune thrombocytopenia and platelet function abnormalities in ITP that improves by thrombomimetic use, and also others related to long term steroid use result in decreased production capacity. Hence, it can be asserted

Table 1 Demographic and clinical data's of the patients

No	Duration of disease	Use of drug	Age	Platelets (onset)	Min.–Max platelets	Frequency of bleeds/ hospitalization	Response status
1	20 month	3 months (splenectomy)	18	6000	3000–9000	1–2/month	F
2	66 month	12 months	8	9000	32,000–279,000	0–1/month	PR
3	71 month	3 months (splenectomy)	8	11,000	5000–22,000	1–2/month	F
4	3 month	12 months	3	15,000	9000–23,000	1–2/month	F
5	42 month	6 months (splenectomy)	16	6000	2000–15,000	2–3/month	F
6	35 month	12 months	11	2000	50,000–98,000	0/month	PR
7	12 month	18 months	4	11,000	93,000–195,000	0/month	CR
8	6 month	6 months	3	7000	48,000–116,000	0/month	PR
9	15 month	12 months	4	12,000	13,000–397,000	0–1/month	F
10	52 month	11 months	18	2000	45,000–456,000	0/month (Splenectomized)	PR
11	3 month	12 months	5	17,000	239,000	0/month	CR
12	6 month	6 months	7	12,000	12,000–	1–2	F
13	17 month	7 months	5	16,000	32,000–215,000	0/month	PR
14	12 month	9 months	3	12,000	4000–15,000	2–3/month	F
15	27 month	4 months	9	3000	29,400–136,000	0/month	PR
16	31 month	3 months	12	4000	28,000–	0–1/month	PR
17	21 month	11 months	5	17,000	58,000–144,000	0/month	PR
18	11 month	6 months	7	3000	3000–4000	1–2/month	F
19	9 month	6 months	4	21,000	32,000–44,000	0/month	PR

that agonistic mechanism may improve production in these circumstances [4].

While the literature review gives raise to approximately five hundred papers about the drug eltrombopag, when children are concerned it decreases to below 50 with mostly case reports. So the results of new case series of children may courage the use and help understand some other aspects. In the Petit 2 study, 38 centers of 12 countries were included with a total of 64 patients followed as a result of chronic immune thrombocytopenia between 1 and 17 years. Their results revealed that at least in 40% of the patients there was a significant rise of platelet levels with the use of eltrombopag. The result of our group was similar to this study although the patients are from a different country and an ethnicity. Another crowded study called ICON2 revealed that 81% of 28 patients who used Eltrombopag responded positevely at the beginning but only 40% kept stable levels of platelets after [11]. Other papers are mostly case reports of children of which some include other thrombomimetic agent use.

When the values defined as adequate platelet response in patients treated with eltrombopag therapy were compared; PETIT-PETIT2, the most important studies in this regard, has accepted 50×10^3/dL values as a response [1, 2]. In another important study (The Pediatric ITP Consortium of North America Study (ICON2)), two different responses were accepted. A consecutive response was a platelet count 20×10^3/dL above baseline for two consecutive weeks without any new or increased concomitant ITP treatment. A single response was any platelet count 50×10^3/dL without rescue therapy in the previous 7 days [11]. In another study by Ramaswamy et al.the primary response measures were 50×10^3 or 20×10^3/dL above baseline for 2 consecutive weeks and 50% platelet counts 50×10^3/dL [12]. In a single-center study, unlike the others, response (R) was defined as a platelet count $\geq 30 \times 10^3$/dL and at least a two fold increase in the baseline count and complete response (CR) as a platelet count $\geq 100 \times 10^3$/dL, in the absence of bleeding. In other studies performed, the most accepted response was a platelet count $\geq 50 \times 10^3$/dL [4, 10, 13–18]. The results of our patients revealed that 11/19 (58%) of them reached the platelet count above 30,000/mm^3 while 6/19 (31%) patients were above 50,000/mm^3.

In clinical trials with eltrombopag, rescue treatments were allowed regardless of eltrombopag use, but patients needed these treatments significantly less frequently with eltrombopag [2]. As in most of our patients, the rescue

treatment need decreased while their platelet count increased. Because most of the clinicians treat chronic ITP patients in a wait and treat-on-demand way and the severe bleeding is considered in 3% of chronic ITP patients, the clinician must also consider the quality of life in the family (as physical activity restrictions both for patient and family, frequent hospital visits and its negative effects) besides mathematical calculations.

ITP itself is a heterogeneous disorder in which there are some chronic ITP patients resistant to steroids or other treatments as in this study group and spontaneous recovery is not expected generally. Spontaneous remission rates are not expected to improve by 50%, and spontaneous remission is expected to result in completely normal platelet counts, while platelet counts still not completely normal in the majority of eltrombopag responders.

In conclusion, although this study is limited with a small patient group, because of its single-center nature and being one of the first national studies in the region of children, its positive results in approximately half of the patients encourage the clinicians to at least to try the drug to relieve both themselves and the families.

Compliance with Ethical Standards

Conflict of interest All authors declare that they have no conflict of interest.

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