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Use of eltrombopag in immune thrombocytopenia and acquired idiopathic aplastic anemia

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Abstract
Eltrombopag has been used in Immune Thrombocytopenic Purpura (ITP) and also found effective in Aplastic Anemia (AA) recently. We prospectively analyzed 50 patients at Dhaka Shishu Hospital in Dhaka from January 2019 to December 2023. We included patients with severe AA who were refractory to at least one course of immunosuppressive therapy and persistent/chronic ITP who have received at least one previous treatment for ITP. Responses to Eltrombopag in our population were comparable to real-world experiences while tolerable hepatotoxicity and GI issues were notable. We found Eltrombopag to be a safe and efficacious agent for treating patients with ITP and AA.

Keywords: Eltrombopag, immune thrombocytopenia, severe aplastic anemia, platelet response, complete response

Introduction

Aplastic anemia (AA) is a form of bone marrow failure caused by T-cell mediated destruction of hematopoietic stem cells (HSCs) and is life-threatening if untreated [1]. Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is potentially curative, however, for those not eligible, the standard therapy consists of immunosuppression with horse anti-thymocyte globulin (ATG) and cyclosporine A (CYA) [2]. About 70% of patients do respond, but survival with good marrow function without relapse is in the order of only 30-40% [3]. Treatment options are unsatisfactory for patient's refractory to or relapsing after first-line treatment especially when they are transplant ineligible. Furthermore, the intensive immunosuppressive ATG-CYA combination cannot be applied in a proportion of AA patients due to severe infections [4]. Immune thrombocytopenia (ITP) is an autoimmune disorder characterized by an abnormally low number of circulating platelets, $<100 \times 10^3/\mu l$ which promotes bleeding tendency. Intracranial hemorrhage is a life-threatening complication and occurs especially when the platelet count drops below $10 \times 10^3/\mu l$ [5]. Childhood ITP has an estimated incidence of 4.0- 5.3 per 100,000, while adult ITP has lower incidence of 1.6 - 2.6 per 100,000. ITP incidence is multimodal and exhibits three peaks in children, young adults, women aged 30-40 years, and the elderly. The mechanism that leads to ITP is seems to antiplatelet autoantibodies. These appear because of an altered T-cell response, in which the splenic T follicular helper cells are involved as inducers of the proliferation and differentiation of autoreactive B-cells [6]. These produce antiplatelet autoantibodies, predominantly of the immunoglobulin (Ig) G isotype, which can react with a series of platelet receptors, mainly glycoprotein (GP) IIb/IIIa and GPIb/IX, but also GPV, GPIa/IIa, or GPIV. These auto epitopes [7] induce cell destruction. These platelets experience splenic sequestration and subsequent phagocytosis by mononuclear macrophages, which react with the cell-complexed autoantibodies. Macrophages still play an additional harmful role in ITP since they behave as the main antigen-presenting cell [8]. $CD8^+$T-cells also contribute to thrombocytopenia by increasing platelet apoptosis [[9]. Recently, the Ashwell-Morell receptor (AMR), which is an asialoglycoprotein counter receptor predominantly expressed in hepatocytes, has also been shown to play an important role in anti-GPIbα antibody-mediated platelet clearance. Consequently, the circulating half-life of platelets is markedly reduced. In addition, bone marrow megakaryocytes are unable to produce platelets normally, which further increases thrombocytopenia. The likely reason is that on one hand, there are autoimmune responses against megakaryocytes while on the other hand, the

circulating thrombopoietin (TPO), which is the main growth factor of megakaryocytes, does not increase to a level high enough to cause sufficient stimulation [10]. Currently, ITP is categorized according to duration, acute (<3 months), persistent (3-12 months), or chronic (> 12 months) [11]. ELT is a synthetic, low molecular weight thrombopoietin receptor agonist (TPO-RA). It has been used in ITP and recently found its use in the AA therapy armamentarium. Unlike native TPO, which binds to the extracellular domain of thrombopoietin receptor (TPO-R), ELT interacts with the transmembrane domain of the latter. Therefore, the Janus kinases (JAKs), signal transducer, and activator of transcription proteins (STAT) i.e., JAK/STAT signaling pathway stimulate megakaryocytopoiesis, while not detecting autoantibody generation [12]. ELT does not influence agonist-induced platelet aggregation or activation. With good oral bioavailability, circulating peaks are found 2-6 h after oral administration. Metabolism takes place in the liver via cytochrome P450 isoenzymes with a half-life of 21-32 h [13]. In contrast to previous failed attempts to stimulate the HSC compartment by diverse growth factors such as G-CSF, GM-CSF, or EPO, ELT induced trilinear hematopoietic responses in refractory AA patients [14]. Mechanistically, ELT binds to the TPO receptor c-MPL expressed on HSCs and leads to their proliferation and expansion [15, 16]. Additional immunomodulatory effects may be involved. Results of a phase II trial examining ELT monotherapy in refractory AA patients showing a 40% response rate led to the approval of ELT as monotherapy in relapsed-refractory AA in the USA and Europe. Recently, the increased response rate to ELT in combination with standard ATG-CYA immunosuppression as compared to historical controls has been reported by the NIH group [17] and the use of ELT in the first-line setting is currently underway. We hypothesize that ELT will be effective in both ITP and severe AA [18, 19].

Methods

This prospective study was conducted on 50 male and female patients who were treated with ELT for Severe Aplastic anemia and Immune thrombocytopenia from January 2019 to December 2023 at Dhaka Shishu Hospital, Bangladesh. Severe Aplastic anemia was defined as having a hypocellular bone marrow when two of three blood counts were met (Absolute neutrophil count <500/μL, total reticulocyte count <20, 000/μL, platelet count <20,000/μL). Included patients were refractory to at least one course of immunosuppressive therapy, initiated at least in the last 6 months, and were not candidates for stem cell transplant. Patients were excluded if they had a diagnosis of Fanconi anemia on peripheral chromosomal breakage analysis; MDS (Ruled out on morphology and cytogenetics); and/or diagnosed with paroxysmal nocturnal hemoglobinuria based on the absence of CD 55 and CD 59 by gel card method.

Immune thrombocytopenia was defined as having platelets, <100 × 103/μl in the absence of any underlying disorder. Included patients had more than 3-month history of ITP (Persistent/Chronic); included both primary and secondary (Associated with autoimmune diseases, malignancy, infections, and others cause) ITP; received at least one previous treatment for ITP and had a platelet count of less than 20, 000 per cubic millimeter at enrollment. Patients who were receiving maintenance immunosuppressive regimens, primarily glucocorticoids, were eligible if the dose had been stable for at least 1 month. The dose had to remain unchanged throughout the study. Patients were excluded if they had hemoglobin levels of less than 10 gm per deciliter; had congestive heart failure; had a history of arrhythmias; had a history of thrombosis or myocardial infarction within 3 months.

After admission detailed history, physical examination and investigations were recorded in questionnaire and ethical approval: patient age, sex, severe aplastic anemia (SAA), ITP, presenting complete blood counts, history of bleeding, and splenectomy status in ITP patients. Following post-intervention variables were extracted in AA: 1) platelet response; 2) erythroid lineage response; 3) leucocyte response; and 4) treatment failure. While post-intervention variables extracted in ITP were as follows: 1) good response; 2) partial response and 3) no response. Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 was used to assess the toxicity profile. It included hepatotoxicity, thromboembolic event, portal vein thrombosis, nasopharyngitis, upper respiratory tract infection, nausea, vomiting, diarrhea, and skin rash. ELT treatment was initiated at a minimum daily dose of 25 mg and a maximum of 75 mg. This was adjusted as per response during a total duration of at least 6 weeks. Lower doses compared to the western population were used based on the population pharmacokinetics of ELT in East Asia [20, 21]. Response to the treatment in each group was assessed according to National Institutes of Health (NIH) criteria, which is as follows.

Response for aplastic anemia

A platelet response was defined by a platelet count increase of 20×10^9/L above baseline or stable platelet counts with no transfusions for at least 8 weeks. An erythroid lineage response was defined as a hemoglobin increase of >1.5 g/dL or a reduction of >4 units of transfused erythrocytes for 8 consecutive weeks. A leukocyte response was defined as an absolute neutrophil increase of 100% or an absolute neutrophil count increase of $>0.5 \times 10^9$/L. Not achieving at least one of these criteria during ELT treatment was considered a treatment failure.

Response for immune thrombocytopenia

Platelet count of more than 50×10^9/L was considered a good response; partial response when the platelet count ranged between 30 and 50×10^9/L with at least a 2-fold increase in the initial platelet count; and no response when the platelet count was 20×10^9/L and less.

No missing data on scale variables were observed. Median and Interquartile range (IQR) was computed for continuous variables like age, length of hospital stays, and blood parameters. Frequencies and percentages were calculated for categorical variables like gender, bleeding, and toxicity. The data was stratified accordingly i.e., SAA and ITP, baseline, clinical characteristics, and treatment response was compared using the Chi-Square test. In addition, a comparative analysis of response between ELT versus non-ELT (Standard treatment) group was also performed**.** One-way ANOVA test was used to compare the pre- and post-treatment quantitative data. A p-value less than or equal to 0.05 was considered significant. The data were analyzed using SPSS version-24.

Results

From January 2019 to December 2023, 50 patients including 25 Severe Aplastic Anemia (SAA) and 25 Immune

Thrombocytopenia (ITP) received ELT. The baseline characteristics of patients are presented in Table 1.

Table 1: Patients' baseline characteristics received ELT in immune thrombocytopenia and acquired idiopathic aplastic anemia (*n* = 50).

Characteristics	Disease n (%)		p-value
	IAA (n = 25)	ITP (n = 25)	
Median Age (Years)	7 (1-18)	4 (1-18)	<0.001
Gender			
Male	11 (44%)	15 (60%)	0.029
Female	14 (56%)	10 (40%)	
WHO bleeding scale			
None	09 (36%)	10 (40%)	0.033
Grade I	03 (12%)	02 (08%)	
Grade II	02 (8%)	09 (36%)	
Grade III	10 (40%)	03 (12%)	
Grade IV	01 (04%)	01 (04%)	

Table 2: Patient's toxicity profile received ELT in immune thrombocytopenia and acquired idiopathic aplastic anemia (*n* = 50).

Characteristics	Disease n (%)		p-value
	IAA (n = 25)	ITP (n = 25)	
Hepatotoxicity			
Grade 1/2	3 (12%)	4 (16%)	0.046
Grade 3/4	2 (08%)	1 (04%)	
Thromboembolic event			
Grade 1/2	0 (0.0%)	1 (04%)	0.568
Grade 3/4	1 (04%)	1 (04%)	
UTI			
Grade 1/2	01 (04%)	01 (04%)	0.033
Grade 3/4	04 (16%)	01 (04%)	
Gastrointestinal			
Grade 1/2	04 (16%)	01 (04%)	0.008
Grade 3/4	05 (20%)	01 (04%)	
Rash			
Grade 1/2	01 (04%)	01 (04%)	0.260
Grade 3/4	03 (12%)	01 (04%)	

Table 3: Response and Outcomes of ELT vs. standard (non-ELT) treatment in immune thrombocytopenia and acquired idiopathic aplastic anemia

Characteristic	ELT (n = 50)		Non-ELT (n = 50)		p-value
	IAA	ITP	IAA	ITP	
Median Hb pre-treatment (g/dl)	7.6	11.3	7.5	11.1	0.045
Median Hb post-treatment (g/dl)	11.1	12.5	9.2	12.1	0.033
Median WBC pre-treatment (10E9/L)	1.4	3.0	3.0	7.9	0.042
Median WBC post-treatment (10E9/L)	6.9	14.0	3.5	10.9	0.038
Median Platelets pre-treatment (10E9/L)	9	6	12	12	0.028
Median Platelets post-treatment (10E9/L)	70	166	19	128	0.021
Response					
No	11 (44%)	04 (16%)	20 (80%)	04 (16%)	0.0006
Yes	14 (56%)	21 (84%)	05(20%)	21 (84%)	

The median (IQR) age of AA patients was 7 (1-18) years and 4 (1-18) years of ITP patients. Most of the AA patients were female 14 (56%), unlike the ITP patients who were mostly males, 15 (60%). World Health Organization (W.H.O.) bleeding scale was used to grade bleeding. At presentation 10 (40%) AA patients had grade III bleeding and 09 (36%) ITP patients had grade II bleeding. The toxicity profile of Immune Thrombocytopenia and Aplastic Anemia patients are presented in Table 2. Hepatotoxicity and GI issues were notable in both groups. Response to ELT was classified into two groups for both AA and ITP. The response of AA patients was categorized as platelet, erythroid lineage, and leucocyte response respectively, which when all present considered a complete response. In this population, platelet response was seen in 22 (88%), erythroid lineage in 21 (84%), and leucocyte response in 20 (80%) patients respectively **(**Fig. 1**)**. A complete response to ELT was seen in 13 (52%) AA patients (p = 0.001). There was only 1 (4%) patient who failed treatment in the AA group (p = 0.692).

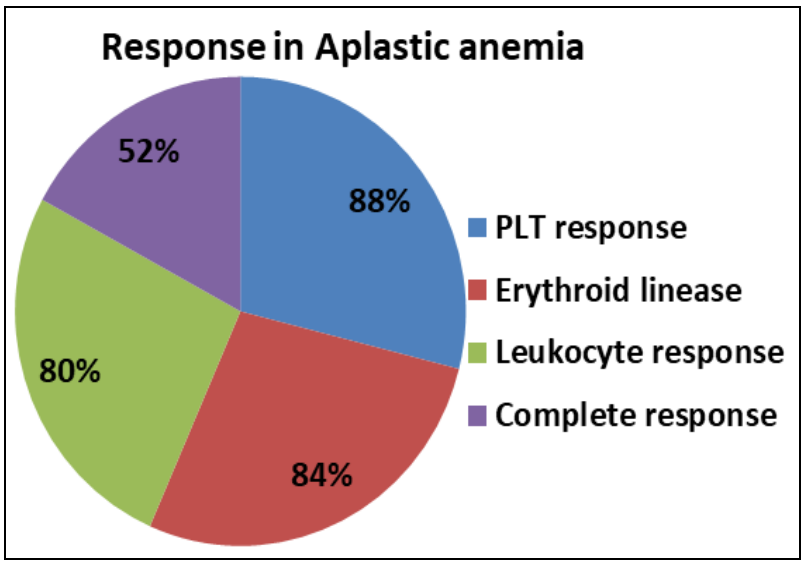

Fig 1: Treatment response to ELT in acquired idiopathic aplastic anemia

The response of ITP patients to ELT was classified as a 'no', 'partial', and 'good response' respectively. In this group 25 (86.2%, $p = 0.033$) ITP patients showed good response to the ELT **(**Fig. 2).

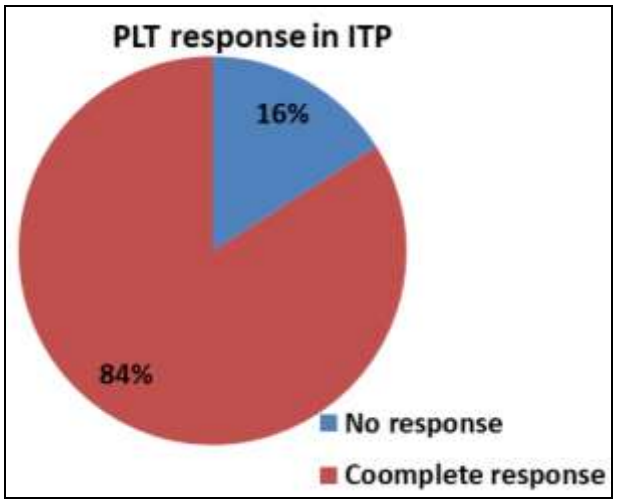

Fig 2: Treatment response to ELT in immune thrombocytopenia.

Analysis on the outcomes of AA and ITP patients who received ELT compared with those who received standard (non-ELT) treatment was also performed. Both treatment groups had an equivalent number of patients (25 vs. 25). ELT group showed significant improvement in clinical characteristics compared with the non-ELT group. Median hemoglobin (g/dl) pre- vs. post-treatment in AA patients who received ELT was 7.6 vs. 11.1 g/dl while in the non-ELT group was 7.5 vs. 9.2 g/dl. Likewise, the median white blood cell count in AA who received ELT pre- vs. post-treatment was (1.4 vs. 6.9) x 10^9/L, while in the non-ELT group was (3.0 vs. 3.5) x 10^9/L. Similarly, platelets count also showed an increase in both groups but significantly in the ELT group. The median platelet counts in AA and ITP patients who received ELT pre- vs. post-treatment were (9 vs. 70) x 10^9/L and (6 vs. 166) x 10^9/L respectively while (12 vs. 19) x 10^9/L and (12 vs. 128) x 10^9/L in the non-ELT group. Similarly 17 (53.1%) AA and 25 (86.2%) ITP patients in ELT group gave complete/good response to treatment, while four (13.3%) AA and 23 (76.7%) ITP patients in non-ELT group gave complete/good response to treatment, which was significant (Table 3).

Discussion

ELT is approved by both, the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) as a single agent in severe AA patients who show an inadequate response to initial immunosuppression. FDA has also approved ELT as a component of triple IST in treatment-naïve AA patients. There has been no consensus yet about the most effective dose of ELT in either AA or ITP. Individuals of East or Southeast Asian ancestry have known population pharmacokinetic dynamics [22] and so are recommended to use lower doses (75 mg) of ELT compared to its normal dose of 150 mg. The usual starting dosage at our center is 25 mg, increased to 50 mg at maximum. Two important considerations with ELT are the cost and long-term compliance to medications. The financial issues in third-world countries like Bangladesh remain a significant hindrance to its use. Previous medical literature has shown promising results with ELT in different populations spanning different parts of the globe. A prospective phase 1, 2 study on 92 patients by Danielle *et al*. found that the addition of ELT to immunosuppressive therapy was associated with markedly higher rates of hematologic response among patients with severe aplastic anemia than in a historical cohort [23]. A phase 2 study by Matthew J *et al*. involving patients with aplastic anemia that were refractory to immunosuppression was performed to determine the response of ELT on blood counts. Eleven of 25 patients (44%) had a hematologic response in at least one lineage at 12 weeks, with minimal toxic effects [24]. In previous studies, ELT has been considered generally safe, although skin reactions or elevation of hepatic transaminases have been noted [23]. Common adverse events (≥20%) include nausea, fatigue, cough, diarrhea, and headache while mild to moderate increase in indirect bilirubin is a common finding, however without any clinically significant consequence to the patient [25]. It is notable, however, that the effects of long-term use of ELT in AA have not been thoroughly evaluated. This includes the risk of clonal evolution. In relevance to ITP, the ELT extended Dose study (EXTEND), in which patients were followed for 3 years, the median daily dose was approximately 50 mg in ITP patients [26]. Polyvalent cations such as iron, calcium, aluminum, magnesium, selenium, and zinc are known to reduce the absorption of ELT. Xiaofan *et al*. in phase III, randomized, placebo-controlled study assessed the long-term efficacy and safety of ELT use in chronic immune thrombocytopenia (ITP) among the Chinese population. 32% of patients achieved platelet counts ≥50 × 10^9/L in more than 75% of platelet count assessments overall. The results further established a sustainable long-term efficacy and tolerability of ELT in these patients [27]. Overall EXTEND trial demonstrated that long-term use of ELT was effective in maintaining a reliable platelet count of 50 × 10^9/L or more while reducing bleeding in most patients with ITP of more than 6 months. Adverse events were also very infrequent [18]. In a randomized phase 3 trial (RAISE) by Gregory *et al*. that included 197 patients, 13 percent had adverse events of which the most common were liver enzyme abnormalities and thromboembolic events [28]. They found no significant differences in the development of malignancies or cataracts in the ELT and placebo groups. In a study by Brynes *et al*. 2 of 117 patients (1.7%) showed moderate reticulin fibrosis of the bone marrow in patients receiving ELT who were followed for up to 5.5 years [29]. However monitoring of bone marrow is not generally recommended nor part of guidelines by the American Society of Hematology [30]. The reason is, the absence of any evidence of progression to myelofibrosis or serial bone marrow testing leading to better outcomes. In addition, bone marrow biopsy is an uncomfortable procedure for patients. Hence, patients in our center did not undergo bone marrow biopsy post-treatment. Our study has several limitations. We also have a relatively smaller sample size with a shorter follow-up. Further studies that monitor patients for a longer duration would help us ascertain the durability of response and toxicity profile.

Conclusion

This study found very good results for ELT in both ITP and AA. This makes it a reasonable choice for patients who can afford the treatment and are compliant with long-term medications. ELT showed complete response in 53.1% AA

patients while approximately 90% platelet response in both AA and ITP patients. We also found a significantly better response in AA and ITP patients when comparing ELT with other standard treatment options. ELT is a reasonably efficacious and safe drug.

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