Am J Blood Res 2020;10(5):240-251
www.AJBlood.us /ISSN:2160-1992/AJBR0117288

Original Article

Real-world experience of eltrombopag in immune thrombocytopenia

Kundan Mishra[1], Suman Pramanik[1], Aditya Jandial[1], Kamal Kant Sahu[2], Rajeev Sandal[3], Ankur Ahuja[4], Uday Yanamandra[1], Rajiv Kumar[1,5], Rajan Kapoor[1,6], Tarun Verma[1], Sanjeevan Sharma[1,7], Jasjit Singh[1,8], Satyaranjan Das[1,9], Tathagata Chatterjee[4], Ajay Sharma[1,10], Velu Nair[1,11]

[1]Dept of Clinical Hematology and Stem Cell Transplant, Army Hospital (Research & Referral) Delhi, India; [2]Department of Internal Medicine, Saint Vincent Hospital, Worcester, Massachusetts, USA; [3]Department of Health and Family Welfare, Himachal Pradesh, India; [4]Dept of Lab Sciences and Molecular Medicine, Army Hospital (Research & Referral) Delhi, India; [5]Department of Internal Medicine, INHS Asvini, Mumbai, India; [6]Department of Internal Medicine, Command Hospital (Eastern Command), Kolkata, India; [7]Department of Internal Medicine, Command Hospital (Central Command), Lucknow, India; [8]Department of Internal Medicine, Command Hospital (Western Command), Chandimandir, India; [9]Department of Internal Medicine, Command Hospital (Southern Command), Pune, India; [10]Dept of Clinical Hematology and Stem Cell Transplant, Sir Ganga Ram Hospital, Delhi, India; [11]Chief Consultant-Haemato-Oncology & Bone Marrow Transplant, Medical Services & Comprehensive Blood & Cancer Center (CBCC), Ahmedabad, India

Received June 30, 2020; Accepted August 22, 2020; Epub October 15, 2020; Published October 30, 2020

Abstract: Immune thrombocytopenia (ITP) is characterized by decreased platelet count in the peripheral circulation. The first-line therapy is corticosteroids with 53-80% overall response rate. Eltrombopag has been used as second-line therapy in ITP for over a decade now. The long-term efficacy and safety profile have been widely reported in the western world. However, the data from the resource-constraint settings of the developing world is scarce. We aim to present the real-life experience of efficacy and safety of eltrombopag from the resource-constraint settings. This was a retrospective, single-center study conducted at a tertiary care hospital in Northern India from 2012-2019. On audit of medical records, patients of ITP receiving eltrombopag were screened for inclusion. Patients whose treatment outcomes were not available were excluded. Finally, 53 patients were analyzed using statistical packages of Python v3.7. The patients' median age was 35 years (range 17-78), with 23 (43.4%) being female. The median time to response was 35 days (range 28-50 days) and the cumulative overall response rates (ORR) at day 30, day 60 and day 90 were 41.5%, 69.8%, and 81.1% respectively. A total of 10 patients on eltrombopag relapsed during follow up. The cumulative rate of relapse at one year, three years, and five years were 6.6%, 25.3%, and 47.7%, respectively. There was no significant difference in outcome (response rate or relapse) in any subgroups depending on age, sex, duration of disease, number of prior lines of treatment, splenectomy, or baseline platelet count. Six patients stopped eltrombopag after having a median sustained response for 796 days (range 658-1185), and after a median follow up of 624 days (range 92-1339), they continued to be in remission. Seventeen patients (17/53, 32%) reported one or more adverse events while on eltrombopag therapy. A total of 49 adverse events (n=4, grade ≥3 CTCAEv4) were noted. Anemia was the most frequent adverse event followed by hepatobiliary dysfunction as reflected by deranged AST/ALT or raised bilirubin. The use of eltrombopag among adult ITP patients in resource-constraint settings was well-tolerated and yielded excellent overall response. The benefit was found to be sustained on long-term follow up. However, events like anemia, hepatobiliary, and thrombotic complications merit closer follow up.

Keywords: Eltrombopag, ITP, second line therapy, resource constraint settings

Introduction

Immune thrombocytopenia (ITP) is characterized by decreased platelet count in peripheral circulation with or without decreased platelet production in the bone marrow [1]. Clinically, it may manifest as mucocutaneous bleeding or rarely as life-threatening bleeding, making it one of the most commonly encountered hematological emergency [2-4].

The first-line therapy is a corticosteroid (prednisolone, methylprednisolone or dexamethasone); while the Intravenous Immunoglobulin

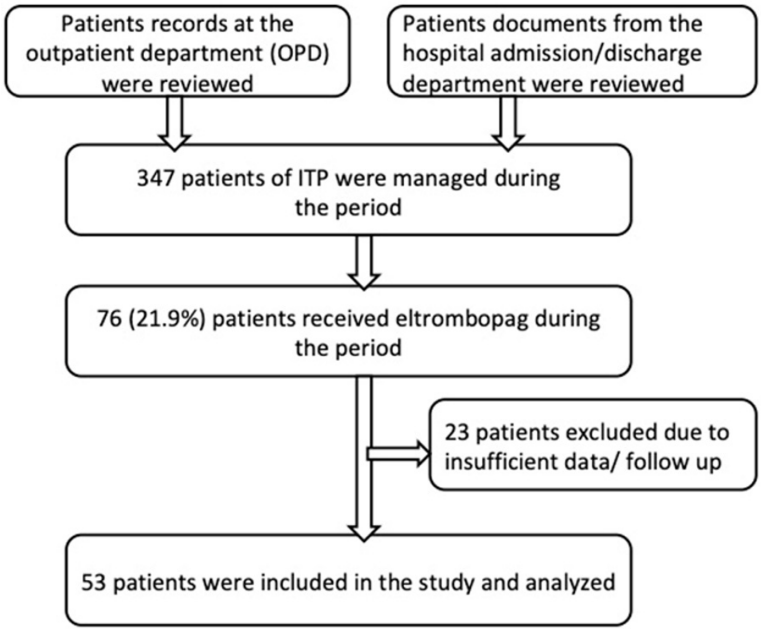

Figure 1. Patient screening flow diagram.

(IVIG) can be used in individual cases with or without steroids in cases where immediate platelet count elevation is desired [5]. While the overall response to corticosteroids in ITP varies from 53-80%, half of the responders finally relapse on follow-up, which leads to a waxing-waning course of the disease [6]. The reason for steroid resistance is attributable to the diverse underlying pathogenesis of ITP. The steroids act through suppression of immune-mediated destruction of platelets but have limited scope when megakaryocytic suppression plays dominant role [7-9].

In steroid-resistant ITP patients, thrombopoietin receptor agonists (TPO-RAs), rituximab and splenectomy are the standard second-line therapy options [5, 10]. TPO-RAs have been used successfully in the management of ITP for over a decade now and have been found to stimulate production of platelets in both the normal as well as dysfunctional bone marrow [6, 11]. Eltrombopag is one of the TPO-RA which acts through stimulation of thrombopoeitin receptors on megakaryocytes and increases the platelet production thereby overcoming the deficit due to the peripheral platelet destruction by the immune system [11].

The efficacy and safety of eltrombopag has been widely reported in the literature but predominantly from developed world [12]. In the developing countries, due to the resource constraints, the drug has poor availability restricting its use. This also results in a very limited data on efficacy and safety of eltrombopag from the developing countries. We aim to present, the real-world data on efficacy and safety of eltrombopag in ITP from resource constraint settings.

Methods

This retrospective study was conducted at a tertiary care institute in Northern India. The institutional ethics committee approved the study (AHRR IEC44/2020). The patients' records were accessed from the outpatient department and hospital discharge and death summaries. After careful screening of the documents, data were recorded and later entered in the excel sheet. The missing data were minimized by making phone calls to the patient or the family.

Patients

Written consents were obtained from the patients. Patients with ITP who were diagnosed as per the American Society of hematology guidelines [13], and treated with eltrombopag between 2012 and 2019 were included in this study. All these patients had received at least one prior line of therapy before recieving eltrombopag. Patients who had received the additional drug with eltrombopag, and/or missing follow-up information were excluded from the study (**Figure 1**).

Adverse events were noted and graded as per the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v4.0 [14]. The bleeding scores were recorded as per the World Health Organisation (WHO) bleeding scale [15].

Drug

Eltrombopag was started at 25 mg once daily dose, to be taken empty stomach in the morn-

ing. The patients were advised to avoid dairy products for four hours after intake of the drug. The patients were followed every two weeks in the clinic with complete hemogram and liver function tests. In the absence of any response, the drug dose was increased by 25 mg per week, up to maximum of 75 mg daily, if tolerated by the patients. If platelet count was increased over 2.5 lacs/μL, the dose was decreased to the previous one, or half-dose was given. For platelet count over 4.5 lacs/μL, eltrombopag was temporarily withheld till the platelet came below 2.5 lacs/μL, and the dose was decreased to the previous one or the dose was reduced by 50%.

Definitions for the study [1, 13]

Partial response (PR): A platelet count of >30,000/μL or double from the baseline, with no active bleeding manifestations.

Complete response (CR): A platelet count of >100,000/μL with no active bleeding manifestations.

Relapse: Any new-onset bleeding manifestation necessitating therapy or platelet counts <30,000/μL or patients who were started on another line of therapy or underwent splenectomy for low platelet.

Response duration: The time duration from the day of receiving eltrombopag to the day of documented relapse.

Statistical analysis

The data was stored in Microsoft Excel (R) and was analysed using statsmodels package (ver 0.11) [16] in Python 3.7 (httlps://www.python.org) and survival package [17] in R 3.5.1 [18].

Baseline variables were summarised using standard summarisation measures.

A timeline was made for each patient with entry time being the time when eltrombopag was started. Baseline clinical and laboratory characteristics were noted for each patient. Dose of eltrombopag was entered as time varying covariate.

Each patient would start in a state with disease (state 0), and then would transit into one of the following states: no disease (CR/PR) (state 1) and death (state 2). From this dataset, Kaplan Meier analysis and Cox proportional hazards regression analysis was done to assess overall response (state 0→1), relapse (state 1→0) and overall survival (0, 1→2). For the analysis of complete remission, timeline was subdivided into following states: disease present (state 0), PR (state 1), CR (state 2) and death (state 3) and same above techniques were used to analyse it. 95% confidence interval and P value <0.05 were used to assess significance of variables.

Results

Demographics and baseline laboratory parameters

A total of 347 patients of ITP were managed at our institute from 2012 to 2019. Seventy-six patients received eltrombopag during this period. After screening for inclusion and exclusion criteria, the treatment outcomes of 53 patients were analyzed. The baseline demographic characteristics and pre-eltrombopag parameters are summarised in **Table 1**. The median age of the study population was 35 years (range 17-78); 23/53 patients (43.4%) were females. Patients with acute, persistent, and chronic ITP who had received at least one prior line of treatment were included in the study. The median duration from diagnosis to eltrombopag was 2.06 years (32 days-14.227 year). These patients had received a median of 3 (range 1-8) prior lines of therapies; 38/53 patients (71.7%) had received ≥3 prior therapies. Eight patients (15.09%) had relapsed after splenectomy, and 16 patients (30.19%) relapsed after rituximab. The patients included in the study had a platelets counts 30000/μL or less at the time of initiation of eltrombopag. The baseline median hemoglobin, WBC, and platelets were 12.9 g/dL, 8000/μL, and 10000/μL, respectively.

Response rate

The median time to response was 35 days (range 28-50 days) and the cumulative overall response rate (complete and partial response) at day 30, day 60 and day 90 were 41.5%, 69.8%, and 81.1%, respectively (**Figure 2** and **Table 2**). Nine, 14, and 18 patients achieved complete response with eltrombopag on day 30, day 60, and day 90, respectively.

Table 1. Demographic profile and baseline clinical characteristics of the ITP patients who received eltrombopag

Variable	Median (range) or *n* (%)
Evaluable pateints	53
Females	23 (43.4%)
Age (years)	35 (17-78)
Interval from ITP diagnosis to Eltrombopag	2.06 year (32 days-14.227 year)
Number of prior therapies	3 (1-8)
One line	1 (1.89%)
Two lines	12 (22.64%)
Three lines	14 (26.41%)
Four lines	12 (22.64%)
Five lines	5 (9.43%)
Six lines	2 (3.77%)
Seven lines	3 (5.66%)
Eight lines	2 (3.77%)
Different therpaies received prior to Eltrombopag	
Corticosteroids	51 (96.23%)
Intravenous Immunoglobulin (IVIg)	24 (45.28%)
Anti-RhD Immunoglobulin	9 (16.98%)
Splenectomy	8 (15.09%)
Rituximab	16 (30.19%)
Dapsone	44 (83.02%)
Danazol	23 (43.39%)
Azathioprine	18 (33.96%)
Vincristine	5 (9.43%)
Hemoglobin (g/dL)	12.9 (6.9-17.1)
WBC (/μL)	8000 (4200-19900)
Platelet count (/μL)	10000 (1000-30000)

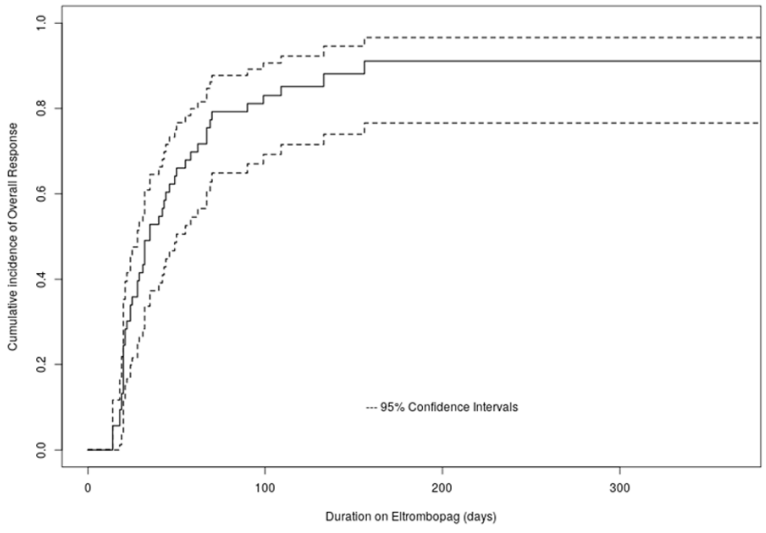

Figure 2. Kaplan-Meier curve showing the cumulative incidence of overall response.

Factors affecting the response to eltrombopag

On univariate analysis, there was no effect of age, sex, duration of disease, prior lines of therapy received, splenectomy, and platelet count on the overall response to eltrombopag in the study population (**Table 3**).

Response evaluation at follow up

The was no significant (WHO bleeding scale ≥3) bleeding episode in the study population necessitating platelet transfusion or rescue therapy.

Table 2. Response to eltrombopag in ITP patients

Variable	n (%) or median (range)	95% CIs
Time to response	35 days (28-50 days)	
Cumulative incidence of overall response	48	
At day-30 of Eltrombopag	22 (41.5%)	26.6-53.4%
At day-60 of Eltrombopag	37 (69.8%)	54.5-80%
At day-90 of Eltrombopag	43 (81.1%)	67-89.2%
Patients achieving complete response		
At day-30 of Eltrombopag	9 (17%)	6.2-26.5%
At day-60 of Eltrombopag	14 (26.4%)	13.5-37.4%
At day-90 of Eltrombopag	18 (34%)	19.9-45.6
Time to relapse in days	not reached	
Cumulative incidence of relapse	10	
At 1-year	3 (6.6%)	0-13.6%
At 2-year	6 (15.3%)	3.1-26%
At 3-year	8 (25.3%)	6.7-41.1%
At 5-year	10 (47.7%)	8.5-70.1%

Table 3. Univariate analysis for response assessment at day+30 and day+90 after eltrombopag

	Hazard ratio	p	30-day expected events (SE)	90-day expected events (SE)
Age (per decade)	0.875	0.136		
26-year			0.62 (0.063)	1.94 (0.15)
50-year			0.45 (0.15)	1.41 (0.2)
Sex	0.937	0.826		
Male			0.51 (0.06)	1.58 (0.19)
Female			0.54 (0.09)	1.68 (0.26)
Duration of ITP (years)	1 (per 1 log year)	0.999		
1-year			0.52 (0.05)	1.62 (0.17)
6-year			0.52 (0.06)	1.62 (0.21)
Prior therapy	1.164	0.612		
≤3 prior lines of therapy			0.51 (0.8)	1.57 (0.22)
>3 prior lines of therapy			0.6 (0.08)	1.82 (0.28)
Splenectomy	0.846	0.688		
Yes			0.54 (0.03)	1.67 (0.18)
No			0.45 (0.18)	1.42 (0.58)
Hemoglobin (g/dL)	0.955	0.458		
11.7			0.55 (0.04)	1.72 (0.11)
14.9			0.48 (0.06)	1.48 (0.18)
WBC (/μL)	0.892 (per 1000 WBC/μL)	0.066		
6700			0.64 (0.09)	2.06 (0.23)
10000			0.44 (0.05)	1.41 (0.16)
Paltelets	1.03 (per 1000 platelets/μL)	0.077		
≤5000			0.42 (0.09)	1.36 (0.21)
17000			0.59 (0.04)	1.94 (0.14)
Eltrombopag dose	1	0.566		
25 mg			0.52 (0.05)	1.49 (0.15)
50 mg			0.61 (0.09)	1.75 (0.27)

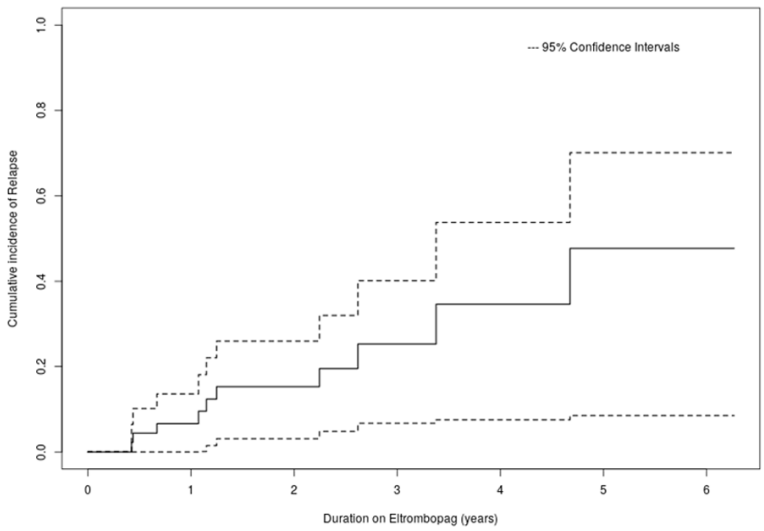

Figure 3. Kaplan-Meier curve showing the cumulative incidence of relapse following Eltrombopag.

There were only seven bleeding episodes during the follow-up, and all were WHO grade 1. A total of 10 patients on eltrombopag relapsed during follow up. The cumulative rate of relapse at one year, three years, and five years were 6.6%, 25.3%, and 47.7%, respectively. There was no significant difference in outcome (response rate or relapse) in any subgroups depending on age, sex, duration of disease, lines of prior therapies, splenectomy, or baseline platelet count (**Figure 3**; **Table 4**).

Six patients stopped eltrombopag after having a sustained response for a median duration of 796 days (range 658-1185), and after a follow up of 624 days (92-1339), they continued to be in remission.

Side effects to eltrombopag therapy

Seventeen patients (17/53, 32%) reported one or more adverse events while on eltrombopag therapy. A total of 49 adverse events (n=4 with grade ≥3 CTCAEv4) were noted. Anemia was the most frequent adverse event followed by hepatobiliary laboratory dysfunction as measured by deranged aspartate aminotransferase (AST)/alanine aminotransferase (ALT) or raised bilirubin (**Table 5**).

Discussion

Eltrombopag is recommended as second-line therapy for ITP [5]. Clinical trials and real-world experiences have described its efficacy and long-term safety in the setting of ITP. However, there is a paucity of data from resource-constraint settings of the developing world. As estimated in the western world, the higher cost is a significant hurdle for its wider use in developing countries [19]. There have also been safety concerns for this drug in the Asian population due to a difference in pharmacokinetics from the western population [20]. Moreover, as we anticipate more frequent use of eltrombopag in future, there is a need to explore the data from the developing world.

The median time to response in our study was 35 days (range 28-50 days). Our study's cumulative ORRs at day 30, day 60, and day 90 were 41.5%, 69.8%, and 81.1%, respectively. In the landmark phase 3, double-blind, placebo-controlled study (RAISE trial), the overall response rate observed was 79% [21]. Subsequently, in a retrospective study from Turkey, Ali Eser *et al*. reported the median time to response as 16 days (range 8-28 days) and an overall response rate of 83.9% in patients treated with eltrombopag [22]. In another study, retrospective studies from Spain, Tomas *et al.* reported the median time to response as 12 days (9-13 days) and an overall response rate of 88.8% in chronic ITP patients treated with eltrombopag (**Table 6**) [23].

A longer median time to respond and an inferior response rate at 30 days was observed in our study compared to the clinical trials and post-marketing retrospective studies. However, the response rate slowly improved in our study and reached 69.8% & 81.1% at day 60 and day 90 of the therapy, respectively, which is comparable to the clinical trials and post-marketing real-life experiences.

In both the RAISE trial and the study by Ali Eser *et al.*, 47% and 35.5% of patients were on concomitant anti-ITP medication in the form of corticosteroids. Both these studies also used 50 mg eltrombopag as the initial dose, and the dose was subsequently changed (increased or

Table 4. Univariate analysis for relapse assessment at 1 year and 3 years after eltrombopag.

	Hazard ratio	p	1-year expected events (SE)	3-year expected events (SE)
Age (per decade)	0.8	0.293		
22-year			0.08 (0.02)	0.39 (0.04)
46-year			0.05 (0.01)	0.23 (0.06)
Sex	0.897	0.866		
Male			0.06 (0.01)	0.26 (0.08)
Female			0.07 (0.02)	0.29 (0.11)
Duration of ITP (years)	0.726 (per 1 log year)	0.198		
1-year			0.07 (0.007)	0.33 (0.04)
6-year			0.04 (0.01)	0.19 (0.06)
Prior therapy	0.879	0.845		
≤3 prior lines of therapy			0.07 (0.02)	0.3 (0.09)
>3 prior lines of therapy			0.06 (0.02)	0.26 (0.1)
Splenectomy	1.375	0.689		
Yes			0.06 (0.006)	0.27 (0.02)
No			0.08 (0.04)	0.37 (0.18)
Hemoglobin (g/dL)	1.243	0.144		
11.7			0.03 (0.009)	1.77 (0.06)
14.9			0.09 (0.02)	1.42 (0.12)
WBC (/μL)	1.125 (per 1000 WBC/μL)	0.3		
6700			0.05 (0.009)	0.23 (0.04)
10000			0.07 (0.009)	0.34 (0.05)
Paltelets	1.016 (per 1000 platelets/μL)	0.627		
≤5000			0.05 (0.02)	0.25 (0.07)
17000			0.07 (0.01)	0.32 (0.06)

Table 5. Adverse events noted with eltrombopag therapy

	Total Adverse Events, n(%)	Grade ≥3 AEs*	Comments
Anemia	25 (47.1%)	0	
Thrombocytosis	2 (3.7%)	0	
Thrombosis	2 (3.7%)	1 (1.9%)	Died due to CVT**
TMA	1 (1.9%)	1 (1.9%)	Died due to AKI#+MODS##
Increased AST/ALT@	7 (13.2%)	1 (1.9%)	
Increased Bilirubin	2 (3.7%)	0	
Sepsis	2 (3.7%)	1 (1.9%)	Died due to MODs
Erythromelalgia	1 (1.9%)	0	
Headache	2 (3.7%)	0	
Arthralgia	1 (1.9%)	0	
Nausea/vomiting	2 (3.7%)	0	
Diarrhoea	1 (1.9%)	0	
Skin rash	1 (1.9%)	0	
Total	49	4	

*AEs: adverse events; **CVT: cerebral venous thrombosis; #AKI: acute kidney injury; ##MODS: multi-organ dysfunction syndrome; @AST/ALT: aspartate aminotransferase/alanine aminotransferase.

decreased) depending upon the response. The concomitant corticosteroid treatment may have a synergistic effect on the availability of eltrombopag [24]. Therefore, patients receiving concomitant steroids are likely to have a better response rate, as is the case in the above studies.

Eltrombopag is used in the dose of 50-75 mg once daily on empty stomach. However, a lower dose has been advocated in people of Asian origin due to the higher (almost double) area under the curve in the Asian population compared to the widely reported western population [25]. With

Table 6. Comparison of results from index study with the published studies on utility of eltrombopag as second-line therapy in ITP

Study	Tomas et al. 2015 (21)	Eser et al. 2016 (20)	Tomas et al. 2017 (32)	Çekdemir et al. 2019 (31)	Present study
Study design	Retrospective	Retrospective	Retrospective	Retrospective	Retrospective
Number of patients (n)	152	31	220	285	53
Median age, years(range)	63 (45-75)	51 (33-59)	62 (47-75)	43.9 ± 20.6	35 (17-78)
Females, n (%)	109 (72%)	16 (51.6%)	47 (41.6%)	187 (65.6%)	23 (43.4%)
Duration of ITP, months (range)	81 (30-192)	-	79 (31-193)	-	2.06 year (32 days-14.23 year)
Median number of prior lines of therapy, n (range)	3 (2-4)	4 (3-5)	3 (2-4)	-	3 (1-8)
Prior splenectomy, n (%)	104 (68%)	24 (77.4)	11 (11%)	-	8 (15.09%)
Prior Rituximab, n (%)	17 (23%)	19 (61.3)	47 (30.7%)	-	16 (30.19%)
Overall response, n (%)	135 (88.8%)	26 (83.9%)	127 (90%)	247 (86.7%)	81.1% (on day+90)
Median time to response	12 days (9-13)	16 days (8-28)	13 days (7-18)	14 days (3-210)	35 days (28-50)
Follow up Median	15 months	29 weeks (11-74)	15 months	18 ± 6.4 months	Not reached
Sustained response	75.2% at 15 months	-	71%	-	
1-year					93.4%
3-year					74.7%
5-year					52.3%
All ADRs*	28 (18.4%)	-	70 (31.8%)	62 (21.8%)	17 (32%)
ADRs ≥ gd3	2 (1.32%)	One SCD**	15 (6.82%)	18 (6.3%) One SCD*	4 (7.55%)

*ADRs: adverse drug reactions; **SCD, sudden cardiac death.

reduced initial eltrombopag doses, a lower early response rate has been reported by some studies. In a study from Japan, Tomiyama et al., reported a response rate of 22% at three weeks when 12.5 mg of eltrombopag was used. The response rate increased to 60% at six weeks, with an increase in the dose to 25 mg once daily [26]. In another study from Korea, Kim *et al*. reported a response rate of 72.2% when 25 mg to 50 mg of eltrombopag was used [20]. In another landmark randomized controlled trial published earlier, the use of low-dose eltrombopag (30 mg OD) was associated with an overall response rate of 28% at day 43 of therapy [27]. Therefore, the lower initial dose (25 mg) and lack of concomitant anti-ITP drugs (corticosteroids) may explain a longer time to respond as well as a lower initial cumulative response rate in our study.

The loss of follow-up had a median of 724 days (108-2288 days). After a median follow-up of 633 days (65 days-2347 days), a total of 10 patients on eltrombopag relapsed. The cumulative rate of relapse at one year, three years, and five years were 6.6%, 25.3, and 47.7%, respectively. The relapse rate in our study was comparable to a 24.8% relapse rate at a median follow up of 15 months reported by Tomas *et al*. in chronic ITP patients receiving eltrombopag [23].

Eltrombopag was discontinued in six patients (11.3%), after having a median duration of sustained response for 796 days (range 658-1185); after a median follow up of 624 days (range 92-1339), they continued to be in remission. Tomas et al. reported that 21% patients discontinued eltrombopag after persistent response, and 51% of evaluable patients continued to have sustained response after six months of drug discontinuation [23]. Although any direct comparison is difficult due to smaller size of our study, but our findings do suggest that eltrombopag discontinuation can be safely considered in a subgroup of patients who demonstrate sustained response despite lowering the dose.

On univariate analysis, there was no significant difference in the treatment outcome (response rate or relapse) in any subgroups depending on age, sex, duration of disease, lines of prior therapies, splenectomy, or baseline platelet count. These observations are in congruence with the findings reported earlier by Tomas et al. Similar findings, including no effect of splenectomy on the overall response rate, were also reported in the landmark RAISE trial [21, 23]. However, contrary to our study, the study published by Mazza et al. suggested that splenectomy significantly reduced the response to eltrombopag therapy ($P \leq 0.05$) [28]. A smaller size may have affected the outcome of our study.

Seventeen patients (17/53, 32%) reported one or more adverse events while on eltrombopag therapy. A total of 49 adverse events were noted, including four grade 3 or more. Anemia was the commonest adverse event followed by hepatobiliary dysfunction as measured by deranged AST/ALT or raised bilirubin.

Ever since eltrombopag came into the clinical practice, hepatobiliary laboratory abnormalities (HBLAs), thrombosis, and myelofibrosis have been three significant areas of concern for long term use as also reported in the EXTEND trial [12, 29].

As far as the real-life experience from the Asian continent is concerned, thrombosis and myelofibrosis have been infrequently reported. In a study from India, Tripathi et al. reported no thrombosis in a cohort of 27 patients, while 12% had asymptomatic HBLAs [30, 31]. In another study from Korea, Kim et al. reported no thrombosis in a cohort of 18 patients, while 38.9% of patients had asymptomatic HBLAs, and one patient had myelofibrosis (reversed after stopping eltrombopag) [20].

Our study reported a higher incidence of anemia (47.2%) in patients treated with eltrombopag. Iron deficiency anemia in developing countries has a prevalence of up to 43%, which is much higher than in developed countries (9%) [32]. Moreover, eltrombopag has been shown to have iron chelation properties [33]. Eltrombopag has also been implicated in the development of iron deficiency in children treated for ITP [34]. The EXTEND study also reported anemia as an adverse effect of eltrombopag in up to 10% of ITP patients [12]. Iron chelating property of eltrombopag and the higher prevalence of iron deficiency anemia in developing countries can explain a higher number of anemic patients.

The subjective findings of headache, arthralgia, and nausea in our study were comparable to the reported studies so far [35, 36].

Our study had the shortcoming of being a retrospective study and a small sample size. However, to the best of our knowledge, this is the largest series on eltrombopag use in ITP from India.

Conclusion

The impressive overall response and long-term sustained response with eltrombopag in ITP patients living in resource-constraint settings were comparable to the published data from clinical trials and real-world experiences from developed nations. It also has a favourable long term safety profile. However, events like anemia, hepatobiliary, and thrombotic complications need to be carefully looked for during follow up.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Suman Pramanik, Dept of Clinical Hematology & Stem Cell Transplant, Army Hospital (Research & Referral), Delhi 110010, India. Tel: +91-8697973509; E-mail: hematology-hod@gmail.com

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