ORIGINAL ARTICLE

Effectiveness and Optimal Dose of Eltrombopag in ITP: Real-World Single Site Study

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Background: Immune thrombocytopenia (ITP) is an autoimmune condition characterized by low platelet counts caused by mechanisms such as antibody-mediated platelet destruction, impaired megakaryocyte production, and inadequate thrombopoietin levels. First-line corticosteroid treatment fails in a significant proportion of patients. Eltrombopag, a thrombopoietin receptor agonist (TPO-RA), is widely used in Thailand and supported by the Civil Servant Medical Benefits Scheme as a second-line treatment. While 50 mg/day is the standard dose in Western populations, studies in East Asia suggest that lower doses may be effective. This study aims to evaluate the effectiveness and safety of eltrombopag in Thai ITP patients, with a focus on dose optimization in real-world settings where clinical data are limited.

Objective: To evaluate the real-world effectiveness of eltrombopag and demonstrate the median time to response for each initial dose (25 mg/day and 50 mg/day) in the treatment of ITP.

Materials and Methods: This 5-year retrospective study analyzed adult ITP patients treated with eltrombopag. Data included patient characteristics, treatment responses, and adverse events. Descriptive statistics and Kaplan–Meier analysis with a log-rank test were used to compare the time to overall response between dose groups.

Results: A total of 25 patients (mean age 57.5 years, 68% female) were included. Eltrombopag was used as a second-line treatment in 72% of patients. The median time from diagnosis to treatment initiation was 280 days, and the mean baseline platelet count was $27.7\times10^3/mm^3$. Initial doses were 25 mg/day (52%) and 50 mg/day (48%). The best overall response rate was 92% (80% complete, 12% partial). Both groups had a favorable median time to response (21 vs. 26 days, p=0.92). Adverse events, including hepatitis and deep vein thrombosis, did not significantly differ between dose groups.

Conclusion: The present study confirms the effectiveness of eltrombopag in real-world treatment of ITP, with a high overall response rate. Both 25 mg/day and 50 mg/day initial doses were effective, suggesting that lower initial doses may be sufficient for Thai patients.

Keywords: Immune thrombocytopenia; Eltrombopag; Effectiveness; Initial dose

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Immune thrombocytopenia (ITP) is a condition characterized by low platelet counts due to several mechanisms: 1) the immune system destroys its own platelets, often via antibodies targeting the platelet GPIIb/IIIa complex; 2) a reduction in regulatory T-cell lymphocytes leading to cytotoxic T cells destroying both platelets and megakaryocytes; and 3) thrombopoietin levels are lower than expected for the given platelet count[1]. This disease can occur spontaneously or be triggered by other factors such as medications, viral or bacterial infections, autoimmune diseases, and cancers.

The incidence of ITP is approximately 1.6 to 3.9 per 100,000 person-years[2]. It is more prevalent in females and in two major age groups: children under 17 years and adults aged 60 to 75 years. Patients typically present with abnormal bleeding manifestations that may appear mild relative to their platelet count, such as gum bleeding, heavy menstrual bleeding, or petechiae. However, life-threatening bleeding (e.g., intracranial hemorrhage) can occur, especially in older adults or those with additional bleeding risk factors[2].

Diagnosis of ITP is made by excluding other potential causes of thrombocytopenia and evaluating for possible triggering factors. The current standard first-line treatment remains corticosteroids[3], such as dexamethasone or prednisolone. Dexamethasone increases platelet counts more rapidly but carries a higher risk of steroid-induced psychosis, whereas long-term response rates are similar

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between the two[4].

Despite treatment, approximately 70% to 80% of ITP patients in the United States fail corticosteroid therapy, either due to non-response, inability to taper steroids, or steroid-related adverse effects[5]. Currently accepted second-line therapies for ITP include thrombopoietin receptor agonists, anti-CD20 antibodies, and splenectomy for chronic cases lasting more than one year[3]. In Thailand, thrombopoietin receptor agonists, particularly eltrombopag, have become more widely used and are covered by the Civil Servant Medical Benefits Scheme (CSMBS). There are real-world effectiveness data from the US and European countries[6].

Objective

The present study aims to evaluate the effectiveness and side effects such as hepatotoxicity of eltrombopag in Thai ITP patients under real-world conditions. In larger trials, the initial dose of eltrombopag is typically 50 mg/day, mostly in Western populations[7]. However, Japanese studies have shown that lower initial doses can be effective[8], and the FDA label recommends 25 mg/day for East Asian populations. Moreover, in treating aplastic anemia in Asian patients, eltrombopag doses are commonly halved to reduce adverse events[9]. These findings raise the possibility that lower doses may also be effective in Thai ITP patients. However, no such data are currently available, underscoring the importance of the present study.

Materials and Methods

Primary objective

To evaluate the response rate to eltrombopag in the treatment of immune thrombocytopenia in Thailand. A complete response is defined as platelet count of 100x103 /mm3 or greater and partial response is defined as platelet count between 30 and 100×103 /mm^3, which is at least double the baseline count, without any clinically significant bleeding.

Secondary objective

To determine the effectiveness of each initial dose of eltrombopag for patients with immune thrombocytopenia in Thailand.

To investigate the prevalence of complications arising from the use of eltrombopag in Thailand.

The present study was approved by the Human Research Ethics Committee, project ID: HE671107.

Sample size calculation

The sample size was calculated using the formula: $n=Z^2\times p(1-p)/d^2$

Where:

Z = standard normal deviation at a 95% confidence level = 1.96

P = proportion of response rate = 0.79

D = acceptable margin of error = 0.2

n = 1.96×1.96×0.79(0.21)/0.04

n = 16

Inclusion criteria

The inclusion criteria were patients aged 18 years or older who had been diagnosed with immune thrombocytopenia and had received treatment at a single tertiary care hospital in Thailand between January 1, 2019, and December 31, 2023.

Data collection

This retrospective study collected data from the medical records of patients diagnosed with immune thrombocytopenia and treated with eltrombopag at a single tertiary care hospital in Thailand between January 1, 2019, and December 31, 2023.

Collected data included patient demographics, relevant medical history, laboratory results, eltrombopag dosage, treatment response, and treatment-related adverse events.

Statistical analysis

Descriptive statistics such as percentage, mean, standard deviations (SD), and medians were used to describe the baseline characteristic of the patients, response rate, and side effects. Kaplan-Meier analysis and the log-rank test were used to compare the time to response between initial 25 and 50 mg/day doses.

Results

A total of 25 eltrombopag-treated ITP patients met the inclusion criteria and were included in the analysis.

Baseline characteristics revealed a predominance of females (68%) with a mean age of 57.5±17.4 years. Primary ITP was the most common etiology, followed by ITP associated with hepatitis C infection. Antiphospholipid antibodies (APS) and antinuclear antibodies (ANA) were each positive in 16% of patients. These tests were ordered at the discretion of the primary care physicians; however, all patients in this study were tested for both ANA and APS antibodies.

Eltrombopag was primarily used as second-line therapy (72%), with a median time from diagnosis to treatment initiation of 280 days. The mean baseline platelet count was 27.7×10^3/mm^3. Initial doses of eltrombopag were nearly equally distributed between 25 mg/day and 50 mg/day (52% and 48%, respectively), depending on the primary care physician's decision (Table 1).

The best overall response at any time was 92%, consisting of 80% complete responses and 12% partial

Table 1. Patient characteristics

Variable	Overall (n=25)	Initial dose 25 mg/day (n=13)	Initial dose 50 mg/day (n=12)
Mean age at diagnosis (year)	57.5±17.4	62.2±17.9	59.9±9.4
Sex			
Male	8 (32%)	3 (23.1%)	5 (41.7%)
Female	17 (68%)	10 (76.9%)	7 (58.3%)
Cause of ITP			
Primary	8 (32%)	7 (53.9%)	1 (8.3%)
ANA and/or aPL	8 (32%)	3 (23%)	5 (41.7%)
HCV infection	4 (16%)	1 (7.7%)	3 (25%)
IBD	2 (8%)	1 (7.7%)	1 (8.3%)
SLE	1 (4%)	1 (7.7%)	0
Solid organ cancer	2 (8%)	0	2 (16.7%)
Line of Eltrombopag			
First-line (off-labeled)	2 (8%)	0	2 (16.7%)
Second-line	18 (72%)	9 (69.2%)	9 (75%)
Third-line	5 (20%)	4 (30.8%)	1 (8.3%)
Prior splenectomy (%)	2 (8%)	1 (7.7%)	1 (8.3%)
Median day from diagnosis to start Eltrombopag (IQR)	280 (1,977 to 31.25)	995 (182 to 2,311)	144 (29 to 447)
Mean baseline plt x103 (SD)	27.7 (22.2)	21.7 (12.3)	34.2 (28.7)
Side effect			
Hepatitis	3 (12%)	2 (15.4%)	1 (8.3%)
Thrombosis	2 (8%)	1 (7.7%)	1 (8.3%)

responses (Figure 1), with favorable response rates observed for both initial doses. Both the 25 mg/day and 50 mg/day initial doses were effective, with median times to response of 21 days and 26 days, respectively (p=0.92) (Figure 2). The median lowest dose required to maintain a platelet count above $50\times10^3/mm^3$ was one tablet every two days.

Among the responders, four patients were able to discontinue eltrombopag treatment and maintain stable platelet counts. The first patient, diagnosed with secondary ITP due to ulcerative colitis, used eltrombopag as a third-line treatment following steroids and cyclophosphamide. At the time of discontinuation, the ulcerative colitis was in remission. The initial eltrombopag dose was 50 mg/day, with a treatment duration of 10 months. The platelet count at discontinuation was $135\times10^3/mm^3$. The second patient, diagnosed with primary ITP, received eltrombopag as a second-line treatment for 22 months. The initial dose was 25 mg/day, and the platelet count at the time of discontinuation was $346\times10^3/mm^3$. The third patient, also diagnosed with primary ITP, received eltrombopag as a second-line treatment for 51 months. The initial dose was 25 mg/day, with a platelet count of $244\times10^3/mm^3$ at the time of discontinuation. The third patient, also with primary ITP, used eltrombopag as a second-line treatment for 51 months. The fourth patient, diagnosed with primary ITP with ANA positivity, received eltrombopag as a third-line treatment following steroids and cyclophosphamide. The initial dose was 50 mg/day, with a treatment duration of 36 months. The platelet count at discontinuation was $175\times10^3/mm^3$.

Adverse events included three cases of hepatitis and two cases of venous thromboembolism (VTE), which were more frequent at higher eltrombopag doses (Table 1). The first case of VTE occurred in a 59-year-old female with secondary ITP due to systemic lupus erythematosus (SLE) and a history of minor thrombotic stroke without antiphospholipid antibodies. She received eltrombopag as second-line therapy due to steroid dependence. The initial dose was 50 mg/day, which was subsequently increased by the primary care physician to 75 mg/day approximately three weeks after initiation to maintain platelet counts above $50\times10^3/mm^3$. She developed cerebral venous sinus thrombosis while on the 75 mg/day dose, with a platelet count of $74\times10^3/mm^3$ at the time of the event. The second case of VTE occurred in an 84-year-old male with secondary ITP due to Crohn's disease. He was started on eltrombopag at 25 mg/day and later developed deep vein thrombosis in the right leg while on a 50 mg/day dose, with a platelet count of $68\times10^3/mm^3$ at the time of the event. No cases of bone marrow fibrosis were observed during eltrombopag therapy.

Discussion

Most of our patients were diagnosed with primary ITP, characterized by seronegative status, ANA positivity without clinical manifestations of SLE, and antiphospholipid

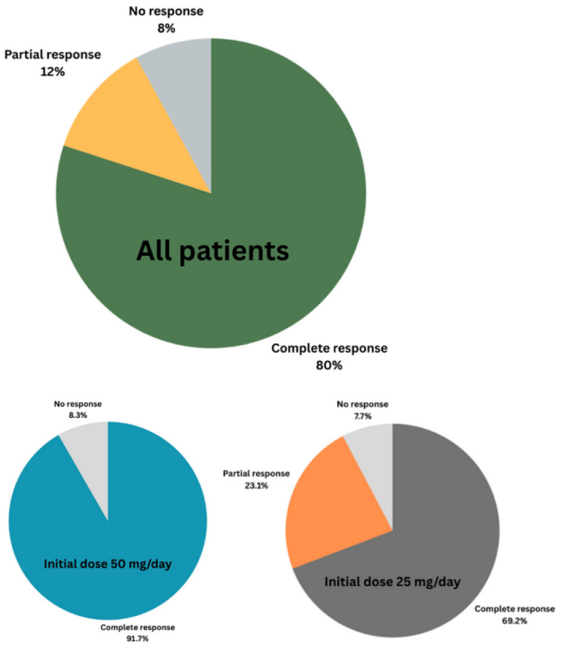

Figure 1. The best overall response rate at any time of patients receiving eltrombopag. These results include patients who received both 25 mg/day and 50 mg/day as the initial eltrombopag dose.

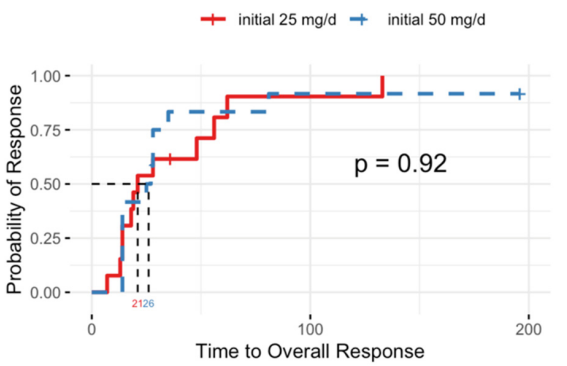

Figure 2. Kaplan–Meier curve showing time to overall response in patients receiving eltrombopag at initial doses of 25 mg/day and 50 mg/day.

antibody positivity, which is consistent with other studies[2]. The frequent use of eltrombopag as a second-line therapy in Thailand is primarily due to the reimbursement policy under the Civil Servant Medical Benefits Scheme (CSMBS), whereas rituximab is not reimbursed. The treatment goal is to maintain a platelet count of at least 30 to $50\times10^3/mm^3$, with a mean baseline platelet count of $27.7\times10^3/mm^3$ before starting eltrombopag.

The initial dose of eltrombopag was determined individually by the physician, with equal distribution between 25 mg/day and 50 mg/day. The overall response rate was very high, similar to that reported in landmark studies[7], and the median time to response did not differ between the two initial doses, although our study was not designed to demonstrate non-inferiority between them. These findings support a Japanese randomized controlled trial that demonstrated the efficacy of an initial dose of 25 mg/day compared to placebo[8]. Starting with a 25 mg/day dose may reduce treatment costs and lower the risk of potential adverse events such as hepatitis, thrombosis, and myelofibrosis, the latter confirmed by bone marrow biopsy and reticulin staining. However, due to limited statistical power, our study was not able to demonstrate a significant difference in adverse events between the two initial dose groups.

The median lowest dose required to maintain platelet counts above $50\times10^3/mm^3$ was one tablet every two days, which is consistent with findings from a Korean study[10]. Some patients were able to discontinue eltrombopag while maintaining stable platelet counts. This could be attributed to either spontaneous regression of the autoimmune condition[11] or the immunomodulatory effects of eltrombopag[12]. Evidence suggests that approximately 56% of patients with a complete response may sustain platelet levels after discontinuation[13]. Further studies are needed to confirm the immunomodulatory effects of eltrombopag. Unfortunately, our data could not identify predictive factors for successful discontinuation due to the limited sample size.

Our patients experienced adverse events similar to those reported in clinical trials, and these were manageable[7]. Patients who developed thrombosis had underlying conditions associated with a thrombophilic state, such as systemic lupus erythematosus (SLE) and ulcerative colitis. These thrombotic events occurred in the absence of thrombocytosis. Our findings suggest that eltrombopag should be used cautiously in patients with thrombophilic conditions, and the dose should be reduced to the lowest effective level to maintain platelet counts around $50\times10^3/mm^3$.

The present study has several limitations. First, the small sample size, while sufficient to demonstrate the effectiveness of eltrombopag due to the high response rate, was inadequate to assess associations between treatment outcomes and clinical variables or to identify predictors of successful discontinuation. Second, as a retrospective study conducted in real-world clinical practice, it was susceptible to potential confounding factors. To compare the efficacy and safety of initial 25 mg/day versus 50 mg/day dose regimens, larger randomized controlled trials are warranted to optimize cost-effectiveness and minimize side effects.

Conclusion

In real-world practice, eltrombopag demonstrated a high response rate and favorable time to initial response with

both 25 mg/day and 50 mg/day starting doses. Hepatitis was the most common but manageable adverse event. Several patients were able to taper and discontinue treatment while maintaining stable platelet counts.

What is already known on this topic?

Eltrombopag is a thrombopoietin receptor agonist (TPO-RA) commonly used as a second-line treatment for immune thrombocytopenia (ITP) when corticosteroids fail. Clinical trials and real-world studies from Western populations suggest an initial dose of 50 mg/day, but studies in East Asia indicate that 25 mg/day may be effective. Limited data exist regarding the effectiveness and safety of eltrombopag in Thai ITP patients, particularly in real-world settings.

What this study adds?

The present study demonstrates the effectiveness of eltrombopag in Thai ITP patients, with a high response rate comparable to previous international studies. Both initial doses resulted in good response rates and time to response, suggesting that lower doses may be sufficient for Thai patients. Adverse events such as hepatitis and thrombosis were observed but were comparable between dose groups, reinforcing the safety of eltrombopag in the Thai population.

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Conflicts of interest

The authors declare no conflict of interest.

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