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Review Article

Evaluation of safety, efficacy and pharmacokinetics of Eltrombopag in patients with chronic immune thrombocytopenia: Meta-analysis of randomized controlled trials

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Abstract

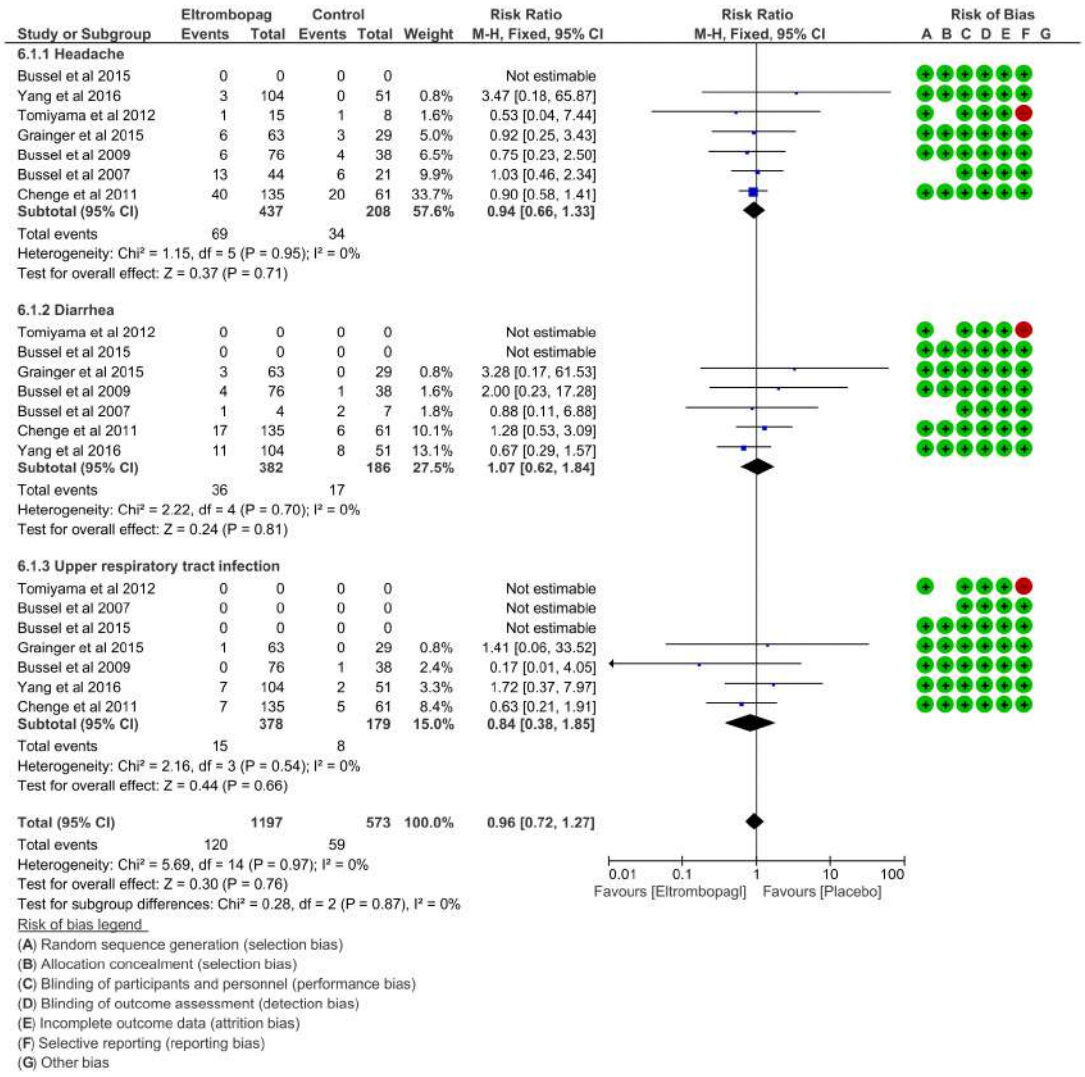
Introduction: Immune thrombocytopenia (ITP) is a complex autoimmune syndrome associated with low platelet count. Eltrombopag is an oral thrombopoietin receptor agonist that used in the treatment of chronic ITP. **The aim of the study**: The present meta-analysis is to evaluate the safety and efficiency of Eltrombopag in the prevention and therapy of ITP.

Materials and Methods: The analysis was performed according to the PRISMA guideline with use of Excerpta Medica Database (EMBASE) as well as Web of Science and the Cochrane (CENTAL) databases.

Results: Seven randomized controlled trials (N=766 patients) were included in the final analysis. Overall platelet response was significantly higher in the Eltrombopag group than in placebo (RR=3.90; 95%CI [2.89-5.25]; P<0.00001) showing mild heterogeneity (I^2=45%). Incidences of significant bleeding events in Eltrombopag group (World Health Organization [WHO] grades II-IV) (RR=0.63; 95% CI: [0.47-0.85]; P=0.003) showed lower heterogeneity (I^2=18%) in comparison to placebo group. Cases of use of rescue medications in Eltrombopag group compared to placebo group (RR=0.40; 95% CI: [0.29- 0.55]; P<0.00001) in all considered studies showed low heterogeneity (I^2=41 %; P=0.16). Incidences of any bleeding in Eltrombopag group compared to placebo group (RR=0.77; 95% CI: [0.70-0.86]; P<0.00001; I^2=65%) showed substantial heterogeneity. Finally, subgroup analysis of Eltrombopag efficiency revealed significant difference in frequency of bleeding cases between adults (RR=0.84) and children (RR=0.51); (P=0.005).

Conclusion: This systematic review presents class one evidence suggesting Eltrombopag as safe and effective drug for therapy of both children and adult patients with ITP.

Graphical abstract:



Keywords

Eltrombopag, immune thrombocytopenia, safety and efficacy, thrombopoietin agonists, meta-analysis

Introduction

Immune thrombocytopenia (ITP) is a complex autoimmune disorder characterized by a dramatic decrease in platelet count. While antibody and/or T cell-mediated platelet destruction are essential processes, ITP's pathogenesis remains uncertain. First-line therapies are mostly oriented to prevent autoantibodies production and subsequent platelet loss, whereas second-line therapies include immunosuppressive medicines. Finally, third-line therapies seek to promote the production of platelets (Blickstein 2019). Prevalence of ITP in all population is estimated to be 2 to 5 per 100,000 people. According to recent guidelines, newly diagnosed ITP patients with a platelet count of less than 30×10^9/L are recommended for treatment with use of thrombopoietin-receptor agonist (TPO-RAs) as second-line therapy. Rituximab is reserved as a third-line agent for patients who have failed a TPO-RA (Neunert et al. 2019). ITP therapy aims to avoid bleeding and maintain a platelet count consistent with optimal hemostasis, rather than a regular platelet count (Ahmed et al. 2020). Eltrombopag is oral TPO-RAs that is approved for the treatment of ITP (Agarwal and Mangla 2021). It induces platelet production by binding to the transmembrane domain of the thrombopoietin receptor and causing megakaryocyte proliferation and differentiation (Bhat et al. 2018; Levchenkova et al. 2023). It has recently been used without serious side effects for thrombocytopenia. This offers an interesting opportunity for more studies to evaluate both effectiveness and safety of Eltrombopag (Nampoothiri and Kumar 2020).

Material and Methods

The current meta-analysis was designed to comply with the PRISMA guideline (Page et al. 2021).

Databases

To identify specific randomized controlled trials (RCT) studies of safety and efficacy of Eltrombopag in both adults and children with chronic ITP, we used the following databases: PubMed/Medline, the Web of Science, the Excerpta Medica Database (EMBASE) and the Cochrane Central Registry of Controlled Trials (CENTAL) from September 2019 to March 2021. The following search queries or Medical Topic Headings (Mesh) were used in the PubMed search strategy: ((“Eltrombopag” [Mesh]) AND ”Thrombocytopenia” [Supplementary Concept]) OR (”Idiopathic, Purpura, Thrombocytopenic,”[Mesh]) AND ”Eltrombopag” Some filters were used to restrict PubMed. Finally, a search in Google Scholar was used in manual mode to identify additional trials and relevant studies.

Study selection

Three authors thoroughly checked the title and abstract of the retrieved studies, screening for eligible studies to conduct a meta-analysis based on screening of full text and extraction of data according to the inclusion criteria, prepared review and editing of methodology. Any queries were arbitrated by fully discussing with the third and second senior’s reviewers to get final arbitration. The included RCTs were to meet the following inclusion criteria:

1. Studies which examined the efficacy of Eltrombopag in chronic ITP;
2. Studies with adequate data reliable to be pooled in a meta-analysis;
3. The study design was RCT;
4. The studies included adults or children patients suffering from chronic ITP and have platelet count $<30\times10^9$/L.

Studies were excluded for the following reasons: studies lacking enough detailed information, studies written in a language other than English. Thesis or conference papers were also excluded.

Data extraction

Three authors extracted the data using a standard data extraction form. The extracted study elements from each study included: first author’s name, study design, total number of participants, their mean age, exposure’s doses, baseline platelet count, duration of follow-up, study outcomes: overall platelet response, incidence of significant bleeding (World Health Organization [WHO] grades II-IV), and incidence of any bleeding, number of cases needed for rescue treatment.

Quality assessment

To protect the study results from bias, we used Cochrane risk of bias assessment scale to assess the quality of methodology of each RCT (Farrah et al. 2019). The quality assessment included the following elements: method for 1) random sequence generation (selection bias), 2) allocation sequence concealment (selection bias), 3) number of patients and personnel (performance bias), 4) blinding of outcome assessment (detection bias), 5) incomplete outcome data (attrition bias), 6) selective outcome reporting (reporting bias) and 7) other bias.

Statistical analysis

Herein, we calculated the hazard ratio (HR) and 95% confidence intervals (CI) as described in the Cochrane Handbook. Dichotomous results were pooled in a fixed-effect model as relative risk (RR) by using Mantel-Haenszel (M-H) method; the fixed-effect model was used on the basis that the RCTs included are similar in terms of study design, quality evaluation and treatment effect calculation (Etminan et al. 2020). Data processing was performed using Check Manager 5.3 for Windows.

Statistical heterogeneity of treatment effect among trials was assessed using the I^2 and X^2 statistic. The X^2 was used to test the existence of significant heterogeneity, I^2 represents the variability in effect estimates that is not attributed to chance or random error. I^2 test was interpreted according to the recommendations of Cochrane Handbook of Systematic Reviews and meta-analysis, results ranging from 0 to 100% and values of 0–40%, 30–60%, 50–90%, 75–100% reflecting low, moderate, substantial and considerable levels of heterogeneity, respectively (Koletsi et al. 2018). In case of significant heterogeneity (X^2; $P<0.1$), a random effect model was used to evaluate the reasons. Otherwise, a fixed-effect model was applied and P-value <0.05 was considered statistically significant.

Sensitivity analyses were carried out to assess the effects of selected measures of study designs, to make sure that no single study is affecting the results, and to test whether the total effect size is statistically robust. We performed sensitivity analysis excluding one study in each scenario. All p-values were considered statistically significant when <0.05.

Publication Bias

Herein, we included fewer than 10-pooled RCTs studies in this meta-analysis; therefore, we could not assess the potential publication bias by Egger test for funnel plot asymmetry (Furuya-Kanamori et al. 2018).

Results

Literature search and study selection

The process of study selection is summarized in the PRISMA flow diagram as shown in Figure 1. After a comprehensive web search, we initially retrieved 937 relevant records, 563 of which were duplicates. After screening the title and abstract on the basis of inclusion/exclusion criteria, 534 records were excluded. Further screening of 29 full-text articles was assessed for eligibility, 22 articles were excluded: irrelevant (n=10), no outcome of interest (n=1), other language (n=2), not RCT (n=5) or review articles (n=4), and the remaining 7 RCTs with (766 patients in sum) were included in this meta-analysis (Fig. 1).

Study characteristics and quality assessment

According to the Cochrane risk of bias assessment tool, one of include RCTs were judged to have from a moderate to high risk of bias. Sequence generation and allocation concealment were reported adequately in most studies.

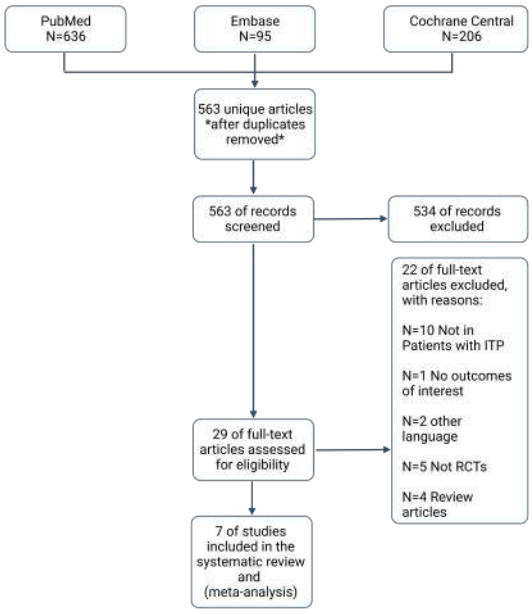


Figure 1. The PRISMA flow diagram of studies' screening and selection.

Seven RCTs were reported as double-blinded. Summary of quality assessment domains of the included studies is shown in Figure 2 and in Table 1.

Assessment of the efficacy of Eltrombopag

Seven RCTs were included in the meta-analysis for assessment of the pooled effect estimate in terms of platelet response after administration of Eltrombopag, the results showing a statistical significant increase in platelet counts among total (n=766 patients) with chronic ITP compared with placebo (RR=3.90; 95%CI [2.89-5.25]; P<0.00001), moderate heterogeneity (I^2=45%) (Fig. 3).

Figure 2. Risk of bias overview and risk of bias graph based on the Cochrane Risk of Bias evaluation tool.

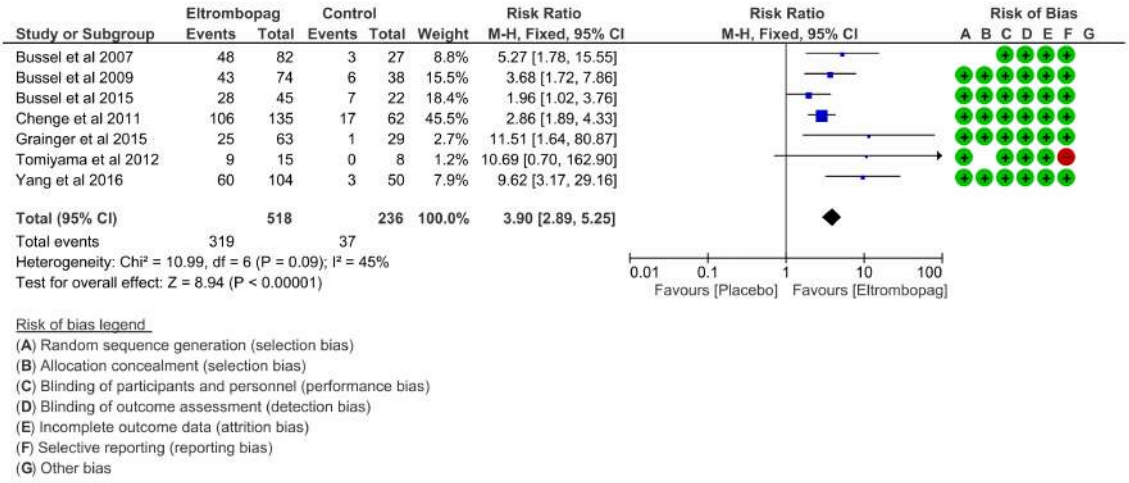


Figure 3. Forest plots (A) of relative risk for effectiveness tests. The overall response of the platelet. CI indicates confidence intervals; M-H, Mantel-Haenszel; RR, relative risk.

Eltrombopag use and the incidence of significant bleeding

For assessment of the association of Eltrombopag administration and improvement of the incidence of bleeding events compared with controls, four RCTs were included in this meta-analysis, the pooled results show no significant reduction in the incidence of bleeding events among the Eltrombopag users compared with controls (WHO grades II-IV; (RR=0.63; 95% CI: [0.47-0.85]; P=0.003), reported low heterogeneity I^2=18%) (Fig. 4).

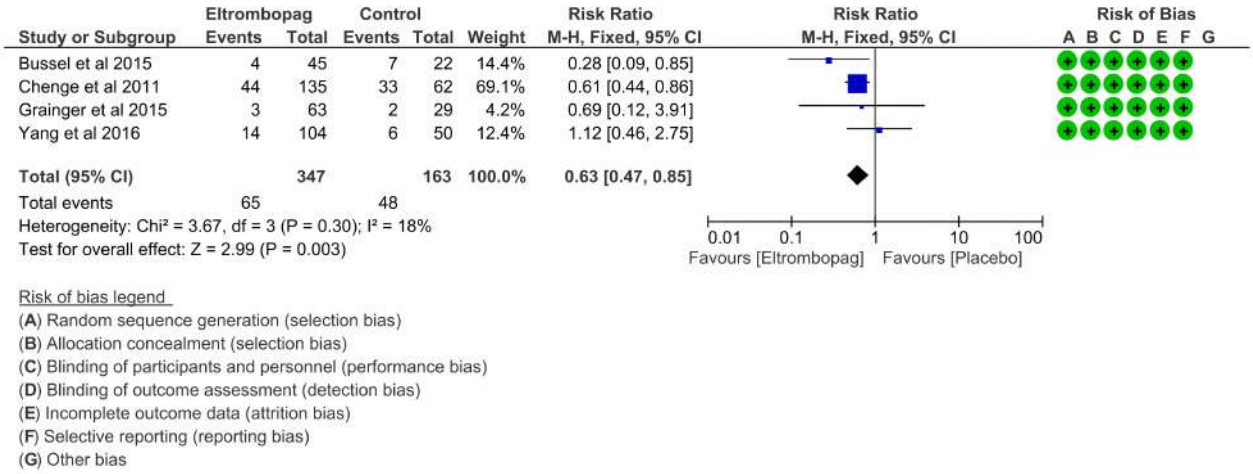


Figure 4. Forest plots (B), Incidence of significant bleeding. CI indicates confidence interval; M-H, Mantel-Haenszel; RR, relative risk.

Number of Eltrombopag users required rescue medications

Herein, we analyzed four studies; the pooled results of which indicated that there was a significant association between Eltrombopag administration and a decreased number of patients requiring rescue medications compared to placebo group (RR=0.40; 95% CI: [0.29-0.55]; P<0.00001). Pooled studies showed low heterogeneity (I^2=41 %; P=0.16) (Fig. 5).

This meta-analysis reports a significant reduction in the incidence of any bleeding among Eltrombopag treated patients in comparison with placebo group (RR=0.77; 95% CI: [0.70-0.86]; P<0.00001; I^2=65%) (Fig. 6).

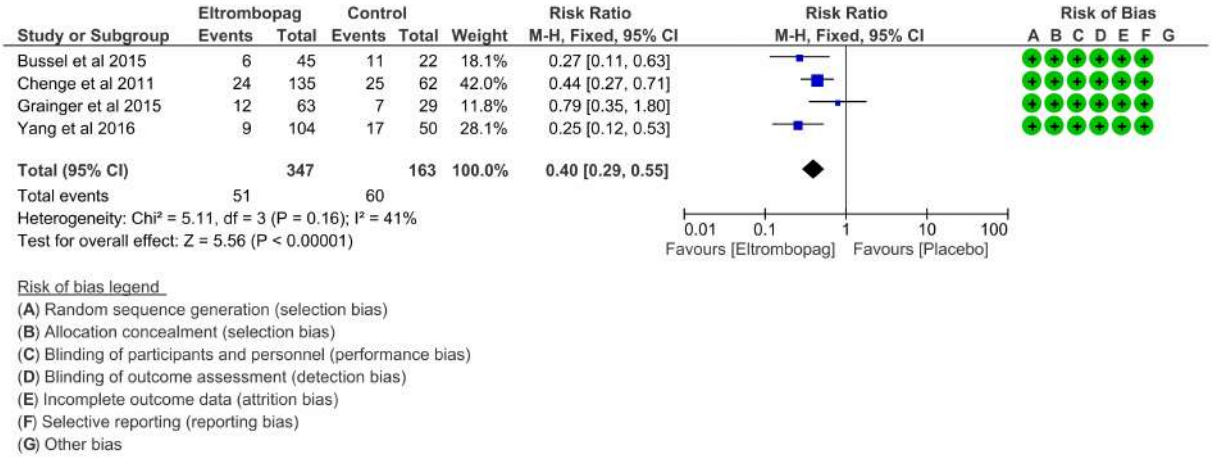


Figure 5. Forest plots (C), Number of cases needed rescue treatment. CI indicates confidence interval; M-H, Mantel-Haenszel; RR, relative risk.

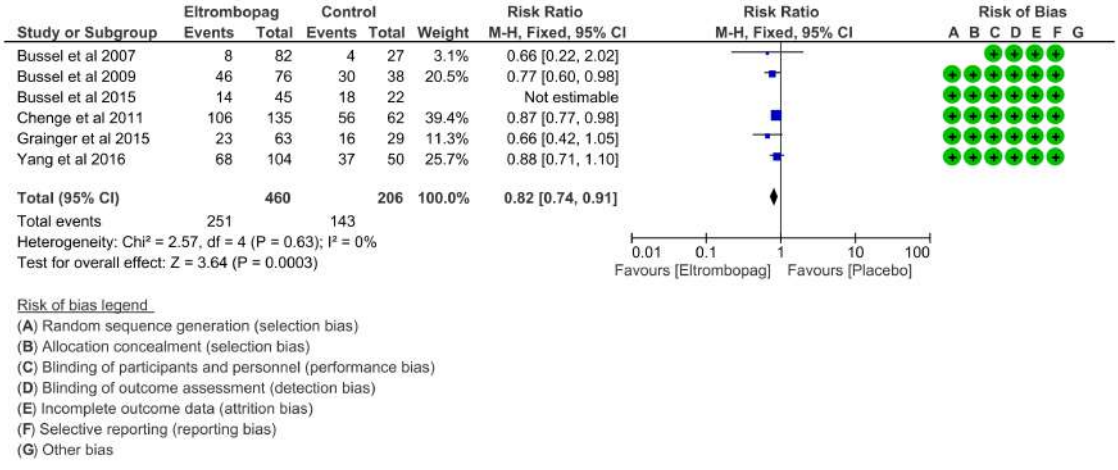


Figure 6. Forest plots (D), incidence of any bleeding. CI indicates confidence interval; M-H, Mantel-Haenszel; RR, relative risk.

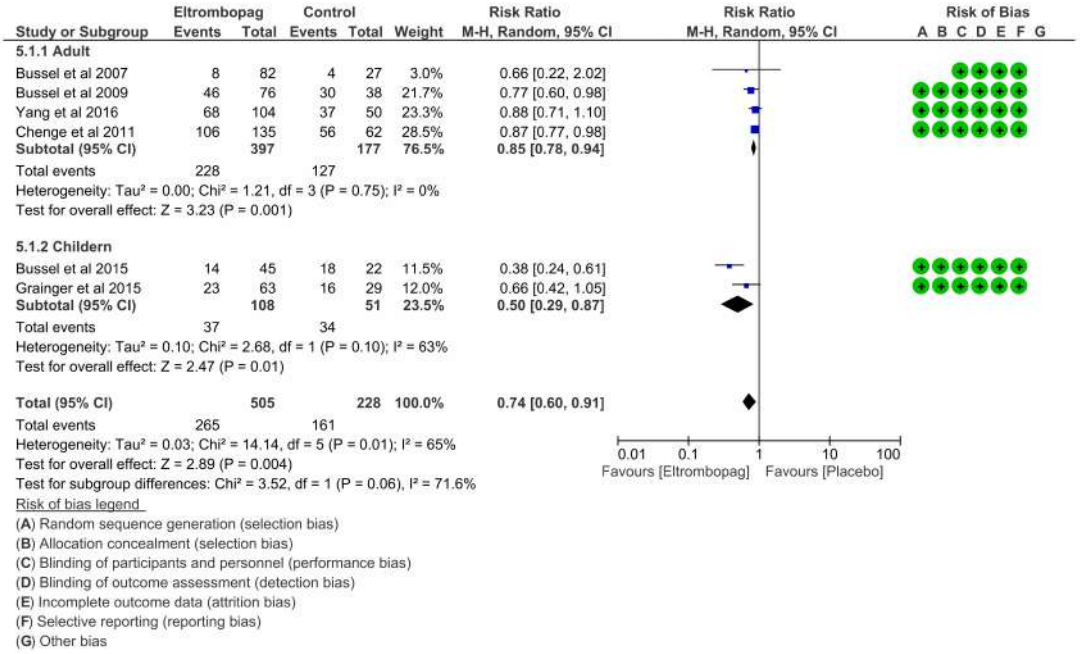


Figure 7. Forest plots (F) of subgroup analysis with 95 % confidence intervals for the incidence of any bleeding. Confidence interval is indicated in CI; M-H, Mantel-Haenszel; RR, relative risk.

Heterogeneity was ideally treated by removing Bussel et al. 2015 study that recruited children with chronic ITP (I^2=0; P=0.63). Subgroup analysis of Eltrombopag efficacy and incidence of any bleeding were analyzed among children in 2 studies and adult – in 4 studies. Population with chronic ITP as shown in Figure 7, the results showed a non-significant difference in Eltrombopag efficacy between the two groups. However, there was a significant difference in the incidence of any bleeding between Eltrombopag adult users (RR=0.84) and children (RR=0.51) users; (I^2=87.2% P=0.005).

Table 1. Summary of included studies

Study ID/ Ref	Design	Population	Dose	Sample Size	Follow Up	Results
(Bussel et al. 2007)	Multicenter, Double- blind, RCT	Adults with relapsed or refractory chronic ITP	30,50 and 75 mg/ day	118	6 weeks	In patients with relapsed or refractory ITPP, Eltrombopag showed improved platelet counts in a dose-dependent manner
(Bussel et al. 2009)	Multicenter, Double- blind, RCT	Adults with previously treated chronic ITP who were naive to thrombopoietic agents	50 mg/day	114	6 weeks	Eltrombopag tends to be efficient in chronic ITP control, with good tolerability
(Bussel et al. 2015)	Multicenter, Double- blind, RCT	Children (1-17 years) old with persistent or chronic ITP	25 to 50 mg/day	67	7 weeks	Eltrombopag can be used in children with recurrent or chronic ITP as an effective therapy. The prevalence of increased laboratory liver values was equivalent to that seen in adults.
(Cheng et al. 2011	Multicenter, Double- blind, RCT	Adults with chronic ITP	50 mg/day	197	24 weeks	In particular, Eltrombopag proved to be effective in treating chronic ITP in patients who do not respond to splenectomy or prior care. Drug toxicity, however, can restrict its use.
(Grainger et al. 2015)	Multicenter, Double- blind, RCT	Children (1-17 years) old with chronic ITP	25 to 50 mg/day	92	13 weeks	Eltrombopag is an effective medication choice with no new safety issues for children with chronic symptomatic ITP.
(Tomiyama et al. 2012)	Multicenter, Double- blind, RCT	Adults with previously treated chronic ITP	12.5 to 50 mg/day	23	6 weeks	Eltrombopag (12.5-50 mg) is effective in the therapy of chronic ITP patients in Japan
(Yang et al. 2017)	Multicenter, Double- blind, RCT	Chinese adults aged ≥18 years previously treated for chronic ITP	25–75 mg/ day	155	8 weeks	In summary, Eltrombopag 25 mg once daily in Chinese patients with chronic ITP has increased platelet counts to a safe range and decreased bleeding.

Note: ITP – immune thrombocytopenia; RCT – randomized controlled trial.

Another adverse effects

There was no any major difference in the overall number of adverse effects reported in both groups; the incidence of adverse effects was not higher in the Eltrombopag group compared with placebo group. The pooled RR for adverse events was as follows: severe adverse events (RR=0.96; 95% CI [0.72-1.27]; P=0.76); headache (RR=0.94; 95% CI [0.66, 1.33]; P=0.71), diarrhea (RR=1.07; 95% CI [0.62-1.48]; P=0.81); and abdominal pain (RR=0.84; 95% CI [0.38-1.85]; P=0.66) for all effect estimate of adverse events were not heterogeneous (X^2; P>0.1).

Sensitivity analysis

For all efficacy outcomes, the superiority of Eltrombopag remains significant after excluding one study at the time (data not shown).

Discussion

This systematic study, including a direct-comparison meta-analysis, summarizes the effectiveness and safety of Eltrombopag in adults and children with ITP. Our study indicates that Eltrombopag drug can increase the long-lasting and overall response of platelets and decrease the use of rescue drugs without increasing the frequency of adverse effects compared to placebo.

Furthermore, an observational retrospective study involving (n=766 patients) with ITP concluded that the clinical outcomes reported that increase platelet count with patients used Eltrombopag in comparable with Placebo (RR=3.90; 95%CI [2.89-5.25]; P<0.00001 (Fig. 3).

The pooled results show no significant reduction in the incidence of bleeding events among the Eltrombopag users compared with controls (WHO grades II-IV; (RR=0.63; 95% CI: [0.47- 0.85]; P=0.003), reporting low heterogeneity I^2 = 18%) (Fig. 4).

Herein, we analyzed four studies; the pooled results of which indicated that there was a significant association between Eltrombopag administration and a decreased number of patients requiring rescue medications compared to placebo group (RR=0.40; 95% CI: [0.29-0.55]; P<0.00001). Pooled studies showed low heterogeneity (I2=41 %; P=0.16) (Fig. 5).

This meta-analysis reported a significant reduction in the incidence of any bleeding among Eltrombopag treated patients over placebo group (RR=0.77; 95% CI: [0.70-0.86]; P<0.00001; I^2=65%), and showed substantial heterogeneity (Fig. 6).

The Eltrombopag efficacy and incidence of any bleeding in subgroup study was evaluated between children (2 studies) and adults (4 studies) with chronic ITP, as shown in Figure 6. The results showed a non-significant difference in the efficacy of Eltrombopag between the two groups, but there was a significant difference in the incidence of any bleeding events between adult (RR=0.84) and children (RR=0.51) users, thus pooled studies were homogeneous (I^2=87.2 % P=0.005). Subgroup study of the meta-analyzed data referred to in Table 2.

Table 2. Basic characters of the studies included

Study ID/Ref	Group	Male, N (%)	Age, Median (Range)	Weight, Median (Range)	Prior Therapy 2, N (%)	Splenec-tomy, N (%)	Baseline Platelet Count (10^9 per L), Median (IQR)	Platelets 15000/mm^3; N (%)
(Bussel et al. 2007)	Placebo	13 (45)	42 (18-85)	NA	21 (72)	14 (48)	NA	14 (48)
	Eltrombopag 30 mg	14 (47)	51 (23-79)	NA	26 (87)	15 (50)	NA	15 (50)
	Eltrombopag 50 mg	9 (30)	45 (23-81)	NA	24 (80)	15 (50	NA	12 (40)
	Eltrombopag 75 mg	8 (29)	55 (18-85)	NA	16 (57)	11 (39)	NA	15 (54)
(Cheng et al. 2011)	Placebo	19 (30.6)	52.5 (43-63)	NA	50 (81)	21 (34)	16000 (9000-24000)	30 (49)
	Eltrombopag	42 (31)	47 (34-56)	NA	105 (78)	50 (37)	16000 (8000-22000)	67 (50)
(Bussel et al. 2009)	Placebo	11 (29)	48 (16)[a]	NA	26 (68)	14 (37)	NA	17 (45)
	Eltrombopag	33 (43)	51 (17)[a]	NA	56 (74)	31 (41)	NA	38 (50)
(Bussel et al. 2015)	Placebo	9 (41)	10 (8-12)	43 (33-53)	19 (86)	0	12.4 (8.8)[a]	11 (50)
	Eltrombopag	18 (40)	9 (8-10)	39 (34-45)	38 (84)	5 (11)	15.5 (8.0)[a]	23 (51)
(Tomiyama et al. 2012)	Placebo	1 (13)	60.5 (38-72)	57.48+6.613[a]		5 (63)	9500 (7500-19000)	6 (75)
	Eltrombopag	7 (47)	58.0 (26-72)	61.68+ 10.390[a]		11 (73)	21000 (16000-25000)	3 (20)
(Grainger et al. 2015)	Placebo	15 (52)	9.8 (8.3-11.3)[a]	42.7 (33.2-52.3)[a]	26 (90)	0	NA	19 (66)
	Eltrombopag	33 (52)	9.4 (8.2-10.5)[a]	41 (35.5-46.4)[a]	46 (73)	4(6)	NA	38 (60)
(Yang et al. 2017)	Placebo	11 (21.6)	42 (22–66)	62 (42–92)	10 (19.6)	7 (13.7)	28 (54.9)	13 (5)
	Eltrombopag	27 (26.0)	48 (18–84)	62 (44–96)	19 (18.3)	18 (17.3)	54 (51.9)	14 (0)

The meta-analysis of the RCTs and systematic review concluded that these TPO-RAs had an increased risk of thrombotic events comparable with standard medication or placebo. This review has some limitations. We only included RCTs in this analysis; the findings may not have a strong generalization for strict systematic review and a limited sample size in those trials.

Conclusion

This systematic review suggests that Eltrombopag is a safe and efficient drug for the treatment of both children and young adult patients with ITP.

Conflict of Interests

No conflict of interests are reported by the authors.

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