Eltrombopag versus romiplostim in treatment of children with persistent or chronic immune thrombocytopenia: a systematic review incorporating an indirect-comparison meta-analysis

Jiaxing Zhang1,2, Yi Liang3, Yuan Ai4, Xiaosi Li5, Juan Xie2, Youping Li1, Wenyi Zheng6 & Rui He6

In absence of direct comparison, we conducted an indirect-comparison meta-analysis to evaluate the efficacy and safety of thrombopoietin-receptor agonists (TPO-RAs) in treatment of pediatric persistent or chronic immune thrombocytopenia (ITP). PubMed, Embase, Cochrane Library, Clinical Trials.gov, China National Knowledge Infrastructure, and Chinese Biomedical Literature Database were searched from their earliest records to May 2017. Randomized controlled trials comparing the TPO-RAs with placebo in pediatric ITP were included. Outcomes included overall response rate (primary), durable response, overall or clinically significant bleeding, the proportion of patients receiving rescue medication, and safety. Five randomized placebo-controlled studies (N = 261) were analyzed. The overall response (Risk Ratio RR 0.57, 95% confidence interval CI 0.21–1.56), the incidence of adverse events (RR 0.96, 95% CI 0.66–1.39), durable response (RR 2.48, 95% CI 0.31–19.97), and the proportion of patients receiving rescue treatment (RR 0.73, 95% CI 0.20–2.73) were similar between eltrombopag and romiplostim group. Nevertheless, eltrombopag might have lower risk of overall bleeding (RR 0.43, 95% CI 0.23–0.80) and clinically significant bleeding (RR 0.33, 95% CI 0.12–0.89) than romiplostim. This meta-analysis suggests that eltrombopag might be similar to romiplostim in efficacy and safety, but seems to reduce the risk of bleeding compared to romiplostim. Furthermore, cost of the treatment, comorbidity of patients and drug compliance should also be considered in clinical decision making.

Immune thrombocytopenia (ITP) is an immune-mediated disease characterized by transient or persistent decrease in the platelet count and increased risk of bleeding. The pediatric ITP incidence reported in recent population-based studies varied greatly in different countries: 1.91 per 10^5 in Japan, 2.83 per 10^5 in France, 4.2 per 10^5 in the United Kingdom and 14.5 per 10^5 in Korea, respectively. Most children with ITP achieve remission spontaneously over time, however, 23.1%–47.3% of them develop a disease course of more than 6 months.

For management of pediatric ITP, the first-line treatments include observation, corticosteroids, intravenous immunoglobulin (IVIg) and anti-D immunoglobulin. If previous treatments fail, subsequent treatments may include splenectomy, rituximab, thrombopoietin receptor agonists (TPO-RAs), or more potent immunosuppression. Eltrombopag (ELT), an oral non-peptide TPO-RA which could facilitate the proliferation and differentiation of megakaryocytes and increase platelet production, has been approved by the United States Food

1Chinese Evidence-based Medicine Center, Sichuan University, Chengdu, China. 2Department of Pharmacy, Guizhou Provincial People’s Hospital, Guiyang, China. 3Health Outcomes and Pharmacy Practice, College of Pharmacy, the University of Texas at Austin, Texas, United States. 4Department of Pediatric Hematology and Oncology, West China Second University Hospital, Sichuan University, Chengdu, China. 5Department of Pharmacy, Hospital of Chengdu Office of People’s Government of Tibetan Autonomous Region, Chengdu, China. 6Experimental Cancer Medicine, Clinical Research Center, Department of Laboratory Medicine, Karolinska Institute, Huddinge, 14186, Stockholm, Sweden.

Correspondence and requests for materials should be addressed to Y.L. (email: yzymylab@hotmail.com)
and Drug Administration (FDA) for pediatric patients (≥1 year old) who have “not achieved an appropriate response using other ITP medicines or splenectomy” 11. Romiplostim (ROM), a subcutaneously administered peptide mimetic TOP-RA, was found effective in children with chronic ITP by randomized clinical trials and observational studies 12–19. A systematic review including both adult and pediatric patients concluded that TPO-RAs substantially increased the rates of platelet response or durable response in children subgroup 20. Nevertheless, ROM binding to the extracellular TPO-receptor and ELT binding to a transmembrane site of the TPO-receptor have different mechanisms of action 21,22. They also have different ways of administration, as ROM is given by subcutaneous injection, while ELT is given orally. Therefore, their efficacy and safety might be different. Unfortunately, there are no head-to-head randomized controlled trials (RCTs) comparing ROM with ELT in treatment of pediatric ITP. Hence indirect comparisons of the therapeutic outcomes across separate RCTs are recommended in the UK National Institute for Health and Clinical Excellence (NICE) methods guide 23. The indirect comparison method proposed by Bucher preserves within-trial randomization by comparing treatment effects (RR) relative to a common comparator (placebo) from each trial, rather than comparing individual treatment arms from different trials 24, and thus becomes a standard source of comparative evidence. An indirect comparison between ROM and ELT in treatment of adult patients with ITP was previously conducted 25, but these conclusions may not be applicable for children due to different disease characteristics. This study aims to evaluate the efficacy and safety of ELT versus ROM for children with ITP using an indirect-comparison meta-analysis.

Results

Search result and characteristics of included studies. A total of 3,499 citations were obtained from the literature search and Fig. 1 showed the selection process. Five randomized, placebo-controlled studies (261 participants) 18,19,26–28 were included in this systematic review. Agreement between two reviewers for study selection was excellent (K = 0.89). As shown in Table 1, four multicenter studies were conducted in 16 countries or regions (USA, UK, Canada, Spain, France, the Netherlands, Argentina, Czech Republic, Germany, Hong Kong, Israel, Italy, Russia, Taiwan, Thailand and Australia) 18,19,27,28, except one single-center study conducted in Egypt 26. All participants were aged 1–17 years old, with disease duration more than 6 months and baseline platelet count less than 30 × 10^9/L. Two studies (159 participants) evaluated the efficacy and safety of ELT in comparison to placebo 27,28 (Table 2). The initial dose of ELT was based on age and weight, and the following dose was adjusted according to individual platelet counts, with a target of 50–200 × 10^9/L 27. The initial dosage and adjustment were shown in Table 3. Three studies evaluated the efficacy and safety of ROM 18,19,26. It was administrated at the initial...
The overall incidence of any AEs in ELT group was similar to that in ROM (RR: 0.97, 95% CI: 0.72–1.29, P = 0.31). The pooled results with a fixed-effect model (Table 4) showed that proportion of participants achieving overall response was significantly higher in the TPO-RAs group than in the placebo group (RR = 2.64, 95% CI: 1.58–4.44, P < 0.05 for ELT and RR = 5.05, 95% CI: 2.21–11.53, P < 0.05 for ROM). The result of indirect comparison (Fig. 3) indicated that the overall response between ELT and ROM was not significantly different (RR = 0.57, 95% CI: 0.21–1.56, P > 0.05).

Adverse events (AEs). Four studies (197 participants) reported the overall incidence of any adverse events reported in participants receiving TPO-RAs or placebo. The pooled analysis (Table 4) showed that the incidence was not significantly different between two groups (RR = 0.97, 95% CI: 0.72–1.29, P > 0.05 for ELT and RR = 1.00, 95% CI: 0.69–1.45, P > 0.05 for ROM). And the result of indirect comparison (Fig. 4) also showed that the overall incidence of any AEs in ELT group was similar to that in ROM (RR = 0.96, 95% CI: 0.66–1.39, P > 0.05).

SAEs were reported in all studies and the results of both direct and indirect comparison (Table 4 and Fig. 3) indicated that the incidences of SAEs of ELT, ROM and placebo were not significantly different (ELT vs Placebo: RR = 0.70, 95% CI: 0.26–1.86, P > 0.05; ROM vs Placebo: RR = 3.28, 95% CI: 0.65–16.60, P > 0.05; ELT vs ROM: RR = 0.24, 95% CI: 0.03–1.65, P > 0.05; respectively). The most common AEs in TPO-RAs and placebo were headache, vomiting, upper respiratory tract infection, pyrexia, cough, epistaxis, oropharyngeal pain, abdominal pain, and upper abdominal pain. However, the results of head-to-head comparison (Table 4) of the incidences demonstrated no significant difference between TPO-RAs and placebo, except that vomiting was less likely to occur in ELT than in placebo (RR = 0.31, 95% CI: 0.12–0.82, P < 0.05). According to the result of indirect comparison (Fig. 4), the incidences of these AEs in ELT were similar to that in ROM, except that cough was more frequent in ELT than in ROM (RR = 14.40, 95% CI: 1.21–171.13, P < 0.05).
Table 2. Characteristics of included patients. ELT: Eltrombopag; ROM: Romiplostim; PLA: Placebo; PC: Platelet counts. NA: not applicable.

| Study ID         | Participants(n): TPO-RA vs Control | Gender: Female/Male(n): TPO-RA vs Control | Age(years): TPO-RA vs Control | Duration of ITP(years): TPO-RA vs Control | Splenectomy status(yes/no)(n): TPO-RA vs Control | Baseline platelet count(10^9/L): TPO-RA vs Control | Previous ITP medication(n): TPO-RA vs Control |
|------------------|------------------------------------|------------------------------------------|------------------------------|------------------------------------------|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|
| Bussel 2015      | 45(ELT) vs 22(PLA)                 | 27/18 vs 13/9                             | 9(8–10) vs 10(8–12)         | 6–12 months: 8/45 vs 2/22 ≥ 12 months: 37/45 vs 20/22 | 5/40 vs 0/22                                  | 15.5 ± 8.0 vs 12.4 ± 8.8 PC < 15 × 10^9/L; 23/45 vs 11/22 | ≥ 2 agents: 38/45 vs 19/22                    |
| Grainger 2015    | 63(ELT) vs 29(PLA)                 | 30/33 vs 14/15                             | 9.4(8.2–10.5) vs 9.8(8.3–11.3) | 3.4 ± 2.8 vs 4.4 ± 3.4 | 4/59 vs 0/29                                  | 15 × 10^9/L; 38/63 vs 19/29                      | ≥ 1 agents: 60/63 vs 28/29 ≥ 2 agents: 46/63 vs 26/29 |
| Bussel 2011      | 17(ROM) vs 5(PLA)                  | 4/13 vs 2/3                               | 9(1–17) vs 11(2–14)         | 2.4/0.8–14.0 vs 4.1/0.6–8.6    | 6/11 vs 2/3                                   | ≤ 8/45 × 10^9/L                                   | ≥ 1 agents: 16/17 vs 5/5                       |
| Tarantino 2016   | 42(ROM) vs 20(PLA)                 | 24/18 vs 11/9                             | 10(6–14) vs 7.5(6.5–13.5)   | 1.9/1.0–4.2 vs 2.2/1.5–3.7    | 1/41 vs 1/19                                  | 17.8(7.5–24.5) vs 17.9(9.8–24.1)                | ≥ 1 agents: 42/42 vs 20/20 ≥ 2 agents: 34/42 vs 14/20 |
| Elalfy 2011      | 12(ROM) vs 6(PLA)                  | 2/10 vs 3/3                               | 9.5(2.5–16) vs 7(4–15)      | 2.3/1.2–7.0 vs 3.0(1.5–6.5)   | 0/12 vs 0/6                                   | 10.5(2–20) vs 10.5(6–20)                         | NA                                            |

Table 3. The initial dose and dose adjustment of thrombopoietin-receptor agonists. PC: Platelet counts.

| Study ID | Medication | TPO-RA Initial dose                                                                 | Dose adjustment                                                                 | Follow-up during double-blind phase |
|----------|------------|-------------------------------------------------------------------------------------|---------------------------------------------------------------------------------|-----------------------------------|
| Bussel 2015 | Eltrombopag | 1–5 years: 1.5 mg/kg/day for 8–10 mg/kg once for day (0.8–10 for east Asian patient); 6–11 years: ≥ 27 kg: 50 mg/day or (25 mg/day for east Asian patient); < 27 kg: 25 mg/day (12.5 mg/day for east Asian patient). | Decreased dose by 12.5 mg/day if PC > 200 × 10^9/L; increased dose by 12.5 mg/day if PC < 50 × 10^9/L, max 75 mg/d or 2 mg/kg/d. Interrupted treatment if PC < 400 × 10^9/L. | 7 weeks |
| Grainger 2015 | Eltrombopag | 1–5 years: 1.2 mg/kg/day for 8.8 mg/kg once for day (6.5–10 for east Asian patient), doses were adjusted based on pre-treatment counts: 6–11 years: ≥ 27 kg: 50 mg/day (25 mg/day for east Asian patient); < 27 kg: 37.5 mg/day (25 mg/day for east Asian patient). | Doses were adjusted on PC: Decreased dose if PC > 200 × 10^9/L. Interrupted treatment if PC > 400 × 10^9/L. | 13 weeks |
| Bussel 2011    | Romiplostim | 1 μg/kg, once weekly.                                                                | Dose was adjusted to achieve target PC of 50 to 250 × 10^9/L.                     | 12 weeks |
| Tarantino 2016 | Romiplostim | 1 μg/kg, once weekly.                                                                | Dose was adjusted to achieve target platelet counts of 50 to 200 × 10^9/L.        | 24 weeks |
| Elalfy 2011    | Romiplostim | 1 μg/kg, once weekly.                                                                | Doses were escalated to 5 μg/kg and then tapered.                                   | 18 weeks |

**Durable Platelet Response.** Three studies (221 participants)\(^{18,27,28}\) reported durable platelet response. The direct and indirect comparison analyses (Table 4 and Fig. 3) showed that the proportion of participants achieving durable platelet response in TPO-RAs was significantly higher than placebo (RR = 13.14, 95% CI: 2.76–64.64, \(P < 0.05\) for ELT and RR = 5.24, 95% CI: 1.36–20.13, \(P < 0.05\) for ROM), while there was no significant difference between ELT and ROM (RR = 2.48, 95% CI: 0.31–19.97, \(P > 0.05\)).

**Clinically significant bleeding.** Four studies (242 participants)\(^{18,19,27,28}\) reported the incidence of clinically significant bleeding (grade 2–4). According to the direct comparison (Table 4), the incidence was significantly lower in participants receiving ELT than those receiving placebo (RR = 0.37, 95% CI: 0.15–0.93, \(P < 0.05\)), while the incidence was not significantly different between ROM and placebo (RR = 1.11, 95% CI: 0.78–1.58, \(P > 0.05\)). As to indirect comparison (Fig. 3), the incidence was significantly lower in ELT group than in ROM group (RR = 0.33, 95% CI: 0.12–0.89, \(P < 0.05\)).

**All bleeding events.** Four studies (242 participants)\(^{18,19,27,28}\) reported the incidence of all bleeding events (grade 1–4). The pooled results (Table 4) demonstrated that the incidence was significantly lower in ELT group compared with placebo group (RR = 0.50, 95% CI: 0.29–0.87, \(P < 0.05\)), while the incidence was not statistically different between ROM and placebo (RR = 1.22, 95% CI: 0.89–1.66, \(P > 0.05\)). According to the indirect comparison (Fig. 3), the incidence was significantly lower in ELT group than in ROM group (RR = 0.43, 95% CI: 0.23–0.80, \(P < 0.05\)).

**Rescue treatment.** All studies (261 participants)\(^{18,19,26–28}\) reported the proportion of participants receiving rescue treatment in TPO-RAs or placebo group. The results of both direct and indirect comparison (Table 4 and Fig. 3) indicated that the proportion was not significantly different between ELT, ROM and placebo. (ELT vs Placebo: RR = 0.46, 95% CI: 0.16–1.34, \(P > 0.05\); ROM vs Placebo: RR = 0.70, 95% CI: 0.41–1.20, \(P > 0.05\); ELT vs ROM: RR = 0.73, 95% CI: 0.20–2.73, \(P > 0.05\); respectively).
Discussion

This is the first systematic review incorporating an indirect-comparison meta-analysis summarizing the evidence of efficacy and safety of TPO-RAs in children with persistent or chronic ITP. Our study suggests that the use of TPO-RAs may improve the durable and overall platelet response compared with placebo, while ELT resembles ROM in efficacy. It's shown that ELT might be superior to ROM or placebo in reducing bleeding risk (including clinically significant bleeding). The incidences of AEs (including SAEs) of ELT, ROM and placebo were similar. Neither ELT nor ROM could reduce the need for rescue treatment.

A systematic review on the efficacy and safety of TPO-RAs in adults and children concluded that TPO-RAs were effective and safe second-line options for primary ITP patients. According to its subgroup analysis for children, TPO-RAs could significantly improve platelet response ($RR = 2.49, 95\% CI: 1.46\textendash 4.23, P < 0.05$) and durable response ($RR = 7.64, 95\% CI: 2.73\textendash 21.36, P < 0.05$), without increasing the incidence of AEs (including SAEs) compared with placebo or standard care. Those findings are mostly consistent with the results of this review on children. However, our research indicated that ELT might reduce the risk of bleeding compared to ROM or placebo, and the TPO-RAs did not reduce the need for rescue treatment, which are inconsistent with previous study results. These differences might be caused by the different ways in pooling data: the previous study pooled the results from studies on ELT and ROM together, while our study conducted analysis on the two drugs separately.

An indirect comparison conducted in adult ITP patients demonstrated that ROM significantly improved overall platelet response compared to ELT, while the durable platelet response of the two TPO-RAs was similar. Our research drew a different conclusion that ELT and ROM were similar in overall or durable platelet response for children with persistent or chronic ITP, probably due to population difference.

In addition, a multicenter retrospective study including 87 pediatric ITP patients (36 in ELT and 51 in ROM, respectively) found that the durable platelet response ($RR = 1.00, 95\% CI: 0.76\textendash 1.30, P > 0.05$), overall platelet response ($RR = 0.93, 95\% CI: 0.77\textendash 1.13, P > 0.05$), the incidence of AEs ($RR = 2.83, 95\% CI: 0.27\textendash 30.07, P > 0.05$), and the proportion of patients receiving rescue treatment ($RR = 0.89, 95\% CI: 0.46\textendash 1.72, P > 0.05$) were not significantly different between ELT and ROM, which are also consistent with the results of our study. Similar findings were also reported in other small sample observational studies.

Nonetheless, an updated systematic review and meta-analysis of RCTs suggested that TPO-RAs were associated with higher risk of thromboembolic events compared with placebo or standard care. And another meta-analysis of three large, population-based observational studies concluded that the risk of arterial and venous thromboembolism should be considered when evaluating the risk of thromboembolism attributed to ITP treatments (e.g. TPO-RAs). A disproportionality analysis in the World Health Organization global individual case safety report (ICSR) database (VigiBase) suggested the presence of a signal for an increased risk of thrombosis.
with ELT compared to ROM (adjusted reporting odds ratio = 1.72, 95% CI 1.47–2.02, P < 0.05)\(^{34}\). Although these AEs were not reported in the RCTs due to small sample size, physicians should be cautious when administering TPO-RAs to patients with higher risk of thromboembolism, especially for ELT.

In spite of increasing pharmacoeconomic studies revealing the advantage of ELT in cost-effectiveness for adult patients with ITP\(^{35–37}\), further studies are still needed to compare the benefits and cost of different TPO-RAs for pediatric persistent or chronic ITP to facilitate better clinical decision making.

There are several limitations in this study. As we only included RCTs in this review, the results may not have good generalizability for strict inclusion criteria and small sample size in those studies. These studies were also not sensitive enough to find rare AEs related to the drugs, as the sample size was relatively small. On the other hand, the results of indirect comparisons between ELT and ROM should be interpreted with caution because of low power of test and heterogeneity caused by different study designs, patient populations, and outcome definitions.

In summary, ELT and ROM might lead to similar overall and durable platelet response and incidence of adverse events in children with persistent or chronic ITP, but patients receiving ROM might have lower risk of bleeding compared to those receiving ROM. Cost of treatments, comorbidity and drug compliance should also be considered when making decisions in the management of pediatric persistent or chronic ITP with thrombopoietin-receptor agonists.

### Table 4. The direct comparison meta-analysis results of outcomes

| Outcomes                                | TPO-RA vs PLA | n   | N (TPO-RA vs PLA) | Heterogeneity | Model | RR  | 95% CI      | P      |
|-----------------------------------------|---------------|-----|------------------|---------------|-------|-----|------------|--------|
| Overall platelet response               | ELT vs PLA    | 108 | 29               | NA            | NA    | 0.61| [0.23, 1.61]| 0.0002|
| Durable platelet response               | ELT vs PLA    | 108 | 29               | NA            | NA    | 0.32| [1.36, 20.13]| 0.02   |
| Clinically significant bleeding         | ELT vs PLA    | 108 | 29               | NA            | NA    | 0.37| [0.15, 0.93]| 0.04   |
| All bleeding events                     | ELT vs PLA    | 108 | 29               | NA            | NA    | 0.31| [0.07, 1.58]| 0.57   |
| Rescue treatment                        | ELT vs PLA    | 108 | 29               | NA            | NA    | 0.32| [1.36, 20.13]| 0.02   |
| All adverse events                      | ELT vs PLA    | 108 | 29               | NA            | NA    | 0.37| [0.15, 0.93]| 0.04   |
| Serious adverse events                  | ELT vs PLA    | 108 | 29               | NA            | NA    | 0.32| [0.15, 0.93]| 0.04   |
| Headache                                | ELT vs PLA    | 108 | 29               | NA            | NA    | 0.32| [0.15, 0.93]| 0.04   |
| Vomiting                                | ELT vs PLA    | 108 | 29               | NA            | NA    | 0.32| [0.15, 0.93]| 0.04   |
| Upper respiratory tract infection       | ELT vs PLA    | 108 | 29               | NA            | NA    | 0.32| [0.15, 0.93]| 0.04   |
| Pyrexia                                 | ELT vs PLA    | 108 | 29               | NA            | NA    | 0.32| [0.15, 0.93]| 0.04   |
| Cough                                   | ELT vs PLA    | 108 | 29               | NA            | NA    | 0.32| [0.15, 0.93]| 0.04   |
| Epistaxis                               | ELT vs PLA    | 108 | 29               | NA            | NA    | 0.32| [0.15, 0.93]| 0.04   |
| Oropharyngeal pain                      | ELT vs PLA    | 108 | 29               | NA            | NA    | 0.32| [0.15, 0.93]| 0.04   |
| Abdominal pain                          | ELT vs PLA    | 108 | 29               | NA            | NA    | 0.32| [0.15, 0.93]| 0.04   |
| Upper abdominal pain                    | ELT vs PLA    | 108 | 29               | NA            | NA    | 0.32| [0.15, 0.93]| 0.04   |
| Diarrhoea                               | ELT vs PLA    | 108 | 29               | NA            | NA    | 0.32| [0.15, 0.93]| 0.04   |
| Nausea                                  | ELT vs PLA    | 108 | 29               | NA            | NA    | 0.32| [0.15, 0.93]| 0.04   |
| Nasopharyngitis                         | ELT vs PLA    | 108 | 29               | NA            | NA    | 0.32| [0.15, 0.93]| 0.04   |
Methods

We followed the standard set by Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) in this systematic review (Table 1). The study was registered in PROSPERO International Prospective Register of Systematic Review (PROSPERO 2017: CRD42017068657).

Searching. Pubmed, Embase, and Cochrane Central Register of Controlled Trials (CENTRAL) published in Cochran Library were searched using the search strategies detailed in Table S2, from their earliest records to May 2017. Clinical Trials.gov was searched using the terms “immune thrombocytopenia”, “children”, “eltrombopag”, and “romiplostim”. The China National Knowledge Infrastructure(CNKI) and Chinese Biomedical Literature Database(CBM) were also searched in Chinese.

Eligibility Criteria. All included studies met the following criteria: (1) randomized controlled studies; (2) participants were children <18 years with ITP lasting for 6 months or longer; (3) the intervention was ELT or ROM irrespective of dosage and schedule; (4) the comparison was placebo; (5) studies included at least one of the following outcomes: overall platelet response (primary outcome), defined as achieving at least once platelet response (50 × 10^9/L or more) during treatment; incidence of overall and serious adverse events (SAEs); durable platelet response, defined as achieving platelet counts of 50 × 10^9/L or more for 4 or more weeks; incidence of clinically significant bleeding (WHO Grade 2~4); all bleeding events; and the proportion of patients who received rescue treatment[e.g. receiving any unscheduled or new treatment (including new drugs, increase the dose of a concomitant drug from baseline, platelet transfusion or splenectomy) for immediate risk or treatment failure]; (6) publication written in English or Chinese. We excluded the patients with Evans syndrome or secondary ITP and the studies including both children and adults when children data could not be extracted separately.

Study Selection and Data Extraction. Two authors independently screened the titles and abstracts of all studies identified by the search strategies, and assessed the studies using predetermined inclusion criteria. The full texts of all potentially relevant articles were retrieved for detailed review. We resolved any disagreements by discussion until consensus was achieved. We used a pre-designed data collection form to extract data from each eligible study. The following data were extracted: (1) authors; (2) year of publication; (3) country or region where the study conducted; (4) study design and use of control; (5) number of participants randomized into each group; (6) gender, age, and disease duration of participants; (7) baseline platelet count, previous ITP medication, and splenectomy status; (8) dose and schedule of TPO-receptor agonists; (9) outcomes of each study and their definitions; (10) numerical data for assessment of included outcomes; (11) sources of funding.

Risk of Bias Assessment. Two authors independently assessed the risk of bias of each included study using the checklist developed by Cochrane Collaboration. The items included random sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and other bias. We categorized the judgments as low, high or unclear risk of bias and created plots of risk of bias assessment in Review Manager Software (RevMan 5.3).

Figure 3. The efficacy results of indirect-comparison meta-analysis.
Figure 4. The safety results of indirect-comparison meta-analysis. URT: upper respiratory tract.

Statistical Synthesis. We calculated a kappa statistic for measuring the agreement level between two authors making decisions on study selection. The value of kappa (K) between 0.40 and 0.59 was considered as fair agreement, between 0.60 and 0.74 as good and 0.75 or more as excellent.

If more than one study reported the same outcome, the pairwise meta-analysis was conducted to calculate the pooled estimate of the risk ratio (RR) of different TPO-RAs versus placebo by RevMan 5.3. Statistical heterogeneity among studies was examined by the Chi-square test and quantified by the I² statistic. We used a fixed-effect model to synthesize data when heterogeneity was not significant (P > 0.1 and I² ≤ 50%). When heterogeneity was significant (P ≤ 0.1 and I² ≥ 50%) and could not be explained by subgroup analyses or in terms of clinical or methodological features of the trials, the random-effect model was used. If both the ELT-placebo and ROM-placebo trials reported the same outcome, the relative treatment effect (RR) for ELT versus ROM was estimated using indirect procedure of Stata12.0 software, with the formula as follow:

\[
RR_{\text{ELT/ROM}} = RR_{\text{ELT/Placebo}} / RR_{\text{ROM/Placebo}}
\]

\[
\text{Variance}(\log RR_{\text{ELT/ROM}}) = \text{Variance}(\log RR_{\text{ELT/Placebo}}) + \text{Variance}(\log RR_{\text{ROM/Placebo}})
\]

The subgroup analysis was also conducted according to the different types of adverse events.

References
1. Rodeghiero, F. et al. Standardization of terminology, definitions and outcome criteria in an international working group immune thrombocytopenic purpura of adults and children: report from an international working group. Blood 113, 2386–2393 (2009).
2. Kurata, Y., Fujimura, K., Kuwana, M., Tomiyama, Y. & Murata, M. Epidemiology of primary immune thrombocytopenia in children and adults in Japan: a population-based study and literature review. Int J Hematol 93, 329–335 (2011).
3. Moulis, G. et al. Epidemiology of incident immune thrombocytopenia: a nationwide population-based study in France. Blood 124, 3308–3315 (2014).
4. Yong, M. et al. Epidemiology of paediatric immune thrombocytopenia in the General Practice Research Database. Br J Haematol 149, 855–864 (2010).
5. Lee, J. Y. et al. Epidemiology and management of primary immune thrombocytopenia: A nationwide population-based study in Korea. Thromb Res 155, 86–91 (2017).
6. Kühne, T. et al. A prospective comparative study of 2540 infants and children with newly diagnosed idiopathic thrombocytopenic purpura (ITP) from the Intercontinental Childhood ITP Study Group. J Pediatr 163, 208–213 (2015).
7. American Society of Hematology. Clinical practice guideline on the evaluation and management of immune thrombocytopenia (ITP). https://www.hematology.org/Clinicians/Guidelines-Quality/Quick-Ref/526.aspx (2011).
8. Bussel, J. B., Hsieh, L. & Buchanan, G. R. Long-Term Use of the thrombopoietin-mimetic romiplostim in children with severe chronic immune thrombocytopenia. Blood 117, 4190–4207 (2011).
9. Garzon, A. M. & Mitchell, W. B. Use of Thrombopoietin receptor agonists in childhood immune thrombocytopenia. Front Pediatr 3, 70 (2015).
10. U.S. Food & Drug Administration(FDA). FDA extends use of promacta in young children with rare blood disorder. http://www.fda.gov/NewsEvents/PressAnnouncements/ucm459430.htm (Accessed on September 09, 2015).
11. Bussel, J. B., Hsieh, L. & Buchanan, G. R. Long-Term Use of the thrombopoietin-mimetic romiplostim in children with severe chronic immune thrombocytopenia (ITP). Pediatr Blood Cancer 62, 208–213 (2015).
12. Mokhtar, G. M., Tantawy, A. A. & El Sherif, N. H. Romiplostim therapy in children with unresponsive chronic immune thrombocytopenia. Platelets 23, 264 (2012).
13. Vilaplana, V. E. et al. Use of romiplostim for primary immune thrombocytopenia in children. Pediatr Hematol Oncol 29, 197–205 (2012).
14. Pasquet, M. et al. Romiplostim in children with chronic immune thrombocytopenia (ITP): the French experience. Br J Haematol 164, 266–271 (2014).
15. Ramaswamy, K. et al. Thrombopoietic agents for the treatment of persistent and chronic immune thrombocytopenia in children. J Pediatr 165, 600–605 (2014).
16. Neunert, C., Despotovic, J., Haley, K. & Lambert, M. P. et al. Thrombopoietin Receptor Agonist Use in Children: Data From the Pediatric ITP Consortium of North America ICON2 Study. Pediatr Blood Cancer 63, 1407–1413 (2016).
17. Tarantini, M. D. et al. Romiplostim in children with immune thrombocytopenia: a phase 3, randomised, double-blind, placebo-controlled study. Lancet 388, 45–54 (2016).
19. Bussel, J. B. et al. A randomized, double-blind study of Romiplostim to determine its safety and efficacy in children with immune thrombocytopenia. Blood 118, 28–36 (2011).
20. Wang, L. et al. Efficacy and safety of thrombopoietin receptor agonists in patients with primary immune thrombocytopenia: a systematic review and meta-analysis. Sci Rep-UK 6, 39003 (2016).
21. Inbach, P. & Crowther, M. Thrombopoietin-receptor agonists for primary immune thrombocytopenia. N Engl J Med 365, 734–741 (2011).
22. Erhardt, J. A. et al. Comparative analyses of the small molecule thrombopoietin receptor agonist eltrombopag and thrombopoietin on in vitro platelet function. Exp Hematol 37, 1030–1037 (2009).
23. National Institute for Health and Clinical Excellence (NICE). Guide to the methods of technology appraisal. www.nice.org.uk/aboutnice/bowenec/developtech/guidetothemethodsoftechnologyappraisal.jsp (2008).
24. Jansen, J. P. et al. Interpreting indirect treatment comparisons and network meta-analysis for health-care decision making: Report of the ISPOR Task Force on Indirect Treatment Comparisons Good Research Practices: Part 1. Value in Health 14, 417–428 (2011).
25. Cooper, K. L., Dillingham, K., Helme, K., Fitzgerald, P. & Akehurst, R. Romiplostim and eltrombopag for immune thrombocytopenia: methods for indirect comparison. Int J Technol Assess 28, 249–258 (2012).
26. Elalfy, M. S., Abdelmaksoud, A. A. & Eltonbary, K. Y. Romiplostim in children with chronic refractory ITP: randomized placebo controlled study. Ann Hematol 90, 1341–1344 (2011).
27. Grainger, J. D. et al. Eltrombopag for children with chronic immune thrombocytopenia (PETIT2): a randomised, multicentre, placebo-controlled trial. Lancet 386, 1649–1658 (2015).
28. Bussel, J. B. et al. Eltrombopag for the treatment of children with persistent and chronic immune thrombocytopenia (PETIT): a randomised, multicentre, placebo-controlled study. Lancet Haematol 2, e315–e325 (2015).
29. Cooper, K., Matcham, J., Helme, K. & Akehurst, R. Update on romiplostim and eltrombopag indirect comparison. Int J Technol Assess 30, 129–130 (2014).
30. Elena, V. S. et al. Bleeding tendency and platelet function during treatment with romiplostim in children with severe immune thrombocytopenic purpura. Int J Hematol 105, 841–848 (2017).
31. Leven, E. et al. Safe and effective use of romiplostim and eltrombopag in children with ITP. Blood 122, 3541–3541 (2013).
32. Catala-Lopez, F. et al. Risk of thromboembolism with thrombopoietin receptor agonists in adult patients with thrombocytopenia: An updated systematic review and meta-analysis of randomized controlled trials. Medical Clinica 145, 511 (2015).
33. Langeberg, W. J., Schoonen, W. M., Eisen, M., Gamelin, L. & Stryker, S. Thromboembolism in patients with immune thrombocytopenia (ITP): a meta-analysis of observational studies. J Int Hematol 103, 655–664 (2016).
34. Thi-Thanh, L. N., Aurore, P., Francois, M., Maryse, L. M. & Guillaume, M. Signal for thrombosis with eltrombopag and romiplostim: a disproportionality analysis of spontaneous reports within Vigi Base. Drug Saf 38, 1179–1186 (2015).
35. Marzal, A., M. B.; Margueix, A. I., Escudero, V. V., Pernia, L. S. & Sanjurjo, S. M. Cost-minimization analysis of immune thrombocytopenia treatment with romiplostim and eltrombopag. Int J Clin Pharm-Net 35, 975–976 (2013).
36. Frolow, M., Pyadushkina, E. & Axentjevya, M. Eltrombopag vs romiplostim in adult patients with chronic immune thrombocytopenia: Economic evaluation. Value in Health 19, A583–A583 (2016).
37. Allen, R., Bryden, P., Grotzinger, K. M., Stapelkamp, C. & Woods, B. Cost-effectiveness of eltrombopag versus romiplostim for the treatment of chronic immune thrombocytopenia in England and Wales. Value in Health 19, 614–622 (2016).
38. Higgins, J. & Green, S. The Cochrane Collaboration.Cochrane handbook for systematic reviews of interventions version 5.1.0. http://handbook.cochrane.org/ (2011).
39. Higgins, J. P. & Thompson, S. G. Quantifying heterogeneity in a meta-analysis. Stat Med 21, 1539–1558 (2002).
40. Li, S., Zhang, C., Yuan, R. X., Xu, C. & Zeng, X. T. Brief introduction of indirect comparison software. Clin J Evid-based Med 15, 362–366 (2015).