Safety of non-peptide thrombopoietin receptor agonists in patients with immune thrombocytopenia: A systematic review and meta-analysis of short-term double-blind randomized clinical trials

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Abstract. The aim of the present study was to analyze the safety of non-peptide thrombopoietin receptor agonists (TPO-RAs) for immune thrombocytopenia (ITP) treatment. All studies reporting adverse events (AEs) in relation to ITP treatment with eltrombopag, avatrombopag, and hetrombopag were retrieved from PubMed, Web of Science, and Embase databases. RevMan 5.4.1 was used for meta-analysis, heterogeneity and bias analyses. A total of 1,078 patients from seven eligible studies were enrolled. In the enrolled clinical trials, the double-blind period was between 6 weeks and 6 months. The results revealed that the chances of any AEs [relative risk (RR)=1.16; 95% confidence interval (CI), 0.90-1.51; I^2=78%; P=0.26], grade 3/4 AEs (RR=1.07; 95% CI, 0.63-1.80; I^2=0%; P=0.81), elevated transaminase levels (RR=1.09; 95% CI, 0.68-1.74; I^2=0%; P=0.72), thrombosis (RR=1.92; 95% CI, 0.55-6.66; I^2=0%; P=0.31) and cataracts (RR=0.83; 95% CI, 0.38-1.83; I^2=0%; P=0.65) were not significantly higher in patients with ITP that received non-peptide TPO-RAs compared with patients with ITP treated with a placebo. The present study indicated that non-peptide TPO-RAs were relatively safe for patients with ITP, at least within 6 months of administration.

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Abbreviations: TPO-RAs, thrombopoietin receptor agonists; ITP, immune thrombocytopenia; AEs, adverse events; RR, relative risk; CI, confidence interval

Key words: eltrombopag, avatrombopag, hetrombopag, thrombopoietin receptor agonists, immune thrombocytopenia

Introduction

Immune thrombocytopenia (ITP) is a common hemorrhagic disease (1-3). The main pathogenesis of this disease stems from autoantibodies mediated by T cells and B cells that specifically adhere to the platelet and megakaryocyte membranes in the bone marrow, leading to increased platelet destruction and megakaryocyte maturation disorder (4). A platelet count <$100x10^9$/l in peripheral blood and skin purpura are the most characteristic manifestations of the disease and are the basis for an ITP diagnosis (1,3). The bleeding symptoms of ITP are typically mild and not fatal. However, potential bleeding events seriously affect the quality of life and psychological status of patients (5-9).

Generally, the purpose of ITP treatment is to maintain a relatively safe platelet count (>$50x10^9$/l), which can reduce the risk of severe bleeding (10,11). Glucocorticoids and intravenous immunoglobulins are the first-line drugs for ITP treatment since their initial treatment effectiveness is 60-80% (12). However, only ~30% of patients experience a sustained response (13). Due to the side effects of the long-term use of glucocorticoids, such as osteoporosis, infections and emotional disorders, second-line drugs have become a necessary choice for certain patients (13-17). In recent years, second-line drugs, thrombopoietin receptor agonists (TPO-RAs), have been used in ITP treatment (1,10,11).

TPO-RAs can simulate the binding of natural thrombopoietin to receptors on the surface of megakaryocytes and bone marrow hematopoietic stem cells, specifically promoting the differentiation and proliferation of megakaryocytes, thereby increasing platelet production (18-20). TPO-RAs can be mainly divided into two categories: Peptide TPO-RAs (subcutaneous injection) and non-peptide TPO-RAs (oral administration), typically administered as romiplostim and eltrombopag, respectively (1,21,22). Compared with subcutaneous injection, the oral dosage form significantly improves the continuity of treatment for patients with ITP (23).

Avatrombopag and hetrombopag are other non-peptide TPO-RAs used to treat ITP, which were approved by the USA in 2020 and China in 2021, respectively (24,25). With the gradual increased use of non-peptide TPO-RAs in clinical treatment, controversial adverse events (AEs) such as thrombosis, cataracts and aminotransferase abnormalities have become the focus for clinicians (26-30). Therefore, the present study aimed to update and summarize the AEs of non-peptide TPO-RAs (including eltrombopag, avatrombopag and hetrombopag), compared with placebo, from previous studies to provide a theoretical basis for monitoring clinical AEs.

Materials and methods

Literature search. This analysis was completed according to the PRISMA guidelines (31) and the Cochrane Handbook (32). Information from PubMed (www.pubmed.gov), Web of Science (www.webofscience.com) and Embase (www.embase.com) was retrieved using a computer by combining mesh terms and near-synonyms. For example, the key word searches for the PubMed database were: (Idiopathic thrombocytopenic purpura*) OR (purpura*, idiopathic thrombocytopenic) OR (thrombocytopenic purpura*, idiopathic) OR (immune thrombocytopenic purpura*) OR (purpuras, immune thrombocytopenic) OR (thrombocytopenic purpura*, immune) OR (immune thrombocytopenia*) OR (thrombocytopenia*, immune) OR (thrombocytopenic purpura, autoimmune) OR (autoimmune thrombocytopenia*) OR (thrombocytopenia*, autoimmune) OR (autoimmune thrombocytopenic purpura*) OR (purpura*, autoimmune thrombocytopenic) OR (purpura, thrombocytopenic, autoimmune) AND (thrombopoietin receptor agonist*) OR (eltrombopag) OR (avatrombopag) OR (hetrombopag) OR (TPO-RA*). The key words used to search Web of Science and Embase were similar. The references of all the articles included in each study were also searched. If the original data in trials were incomplete or missing, the author was contacted via email to supplement the missing data. Filters were not used for any database retrieval. The last day of literature search was November 5th, 2022.

Eligibility criteria. The inclusion criteria to exclude confounders were: i) The study was a randomized double-blind clinical trial with a placebo as the control; ii) all patients who received non-peptide TPO-RAs were adults (aged >18 years old) with ITP; iii) the duration of the double-blind study was at least 6 weeks, and the AEs data during this period could be extracted; and iv) the study was a multicenter trial, regardless of ethnicity or region. Exclusion criteria: i) Literature with duplicate publications of the same data; ii) articles were not published or it was not possible to obtain the full text.

Data extraction. Two researchers (YJ and ML) assessed all titles and/or abstracts of the retrieved literature to exclude articles that did not meet the inclusion criteria. The selected literature was then imported into EndNote software to delete duplicates. The full text of the selected literature was then reviewed.

Data were extracted using standardized data collection tables. The information extracted from each study included the first author, publication year, clinical trial design, duration of the double-blind study, study population, clinical classification of ITP, name and dosage of the drug and number and type of AEs. AEs were graded according to the National Cancer Institute Common Terminology Criteria for AEs (version 3.0) (33). If the clinical trials included a double-blind and open-label extension phase, only data from the double-blind period were collected. All research data included in the present study were obtained from the previous literature. Therefore, approval from an ethics committee and informed consent of the participants were not required.

Quality assessment. Bias risk assessment was conducted according to Risk of Bias (RoB) 2.0, a revised tool for assessing risk of bias in randomised trials developed by the Cochrane Collaboration (34). The evaluation content includes random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other bias. All seven items evaluated as low RoB led to an overall rating of 'low risk', >1 item evaluated as high RoB led to an overall rating of 'high risk' and the remaining studies were rated as having 'unclear risk'. In case of any discrepancy in the quality evaluation, the team discussed it collectively or negotiated with a third investigator (HY).

Statistical analysis. RevMan 5.4.1 software (The Cochrane Collaboration) was selected to analyze the data of all included studies. The heterogeneity of the collected studies was tested using the chi-square test and I^2 test. Regardless of the P-value and I^2-value, the random-effects model was chosen. The relative risk (RR) index was used to evaluate the strength of the association between non-peptide TPO-RAs and AEs. $P<0.05$ was considered to indicate a statistically significant difference.

Results

Study selection. From the screening process, 5,702 records were initially obtained from the databases. A total of 5,427 records were removed after assessing the titles and/or abstracts. After reading the entire text, 268 articles that were repetitive or did not conform to the inclusion criteria were removed. Finally, seven articles (35-41) were used for the present meta-analysis, with a publication period of 2007 to 2021. The screening process is illustrated in Fig. 1.

Study characteristics. Of the seven included studies, five were Phase III clinical trials that were all multicenter studies (36,37,39-41). However, two of these trials were conducted in a single country (39,41). A total of four studies added an open-label stage after the double-blind period (38-41). However, data from the added period were not collected. In total, three non-peptide TPO-RAs were selected as interventions: Eltrombopag was used in five studies, avatrombopag in one study and hetrombopag in one study. A total of 1,078 adult patients with ITP were enrolled, including 789 and 289 patients in the intervention and placebo groups, respectively. All enrolled patients had persistent or chronic ITP. The number of participants in the selected studies ranged from 23 to 424. All studies used a placebo as a control. The duration of double-blinding was between 6 weeks and 6 months.

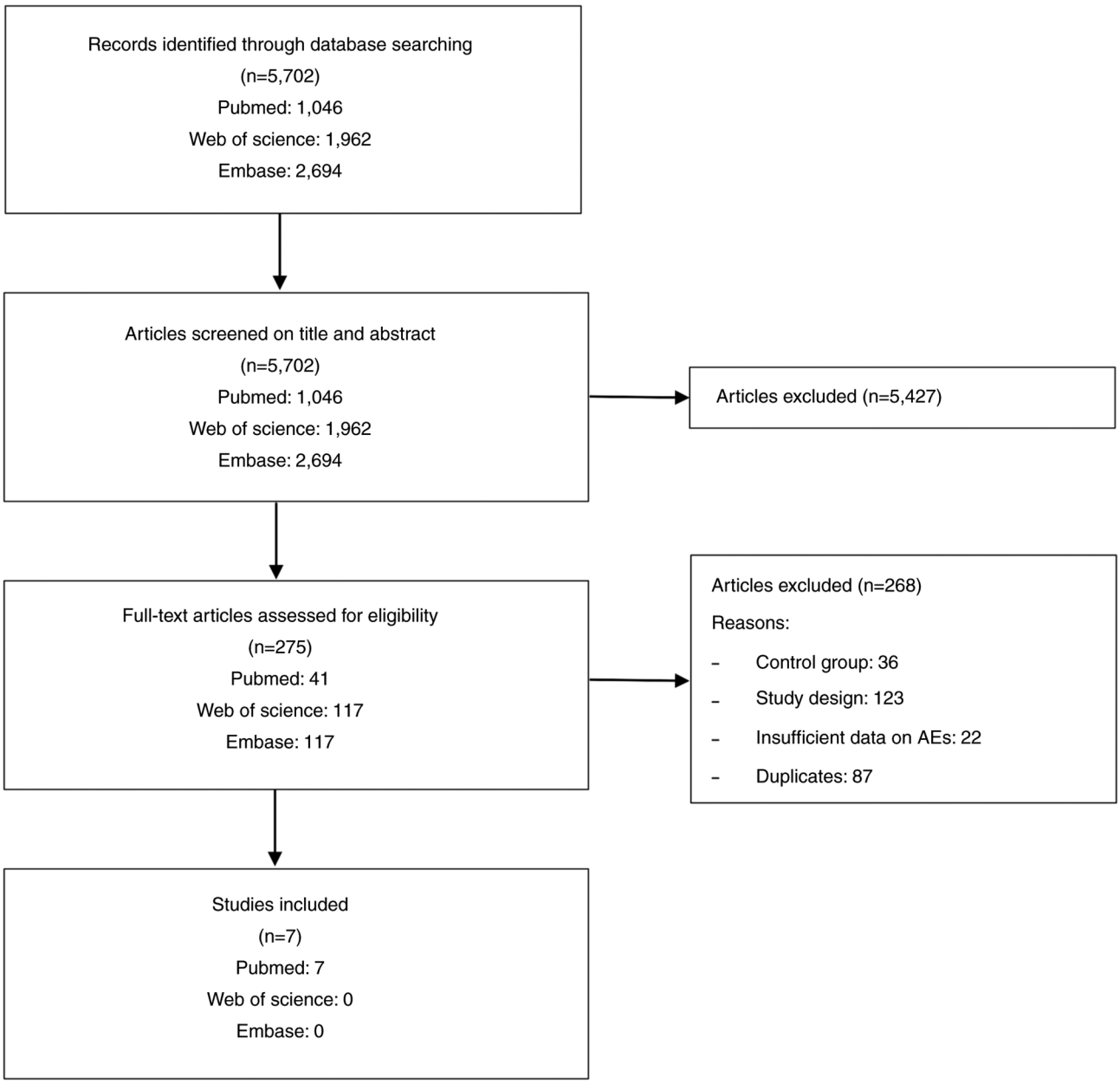

Figure 1. Flowchart of study inclusion. AEs, adeverse events.

Thrombosis was the only AE not observed in the placebo group. Table I provides further details on study characteristics.

Quality assessment. Cochrane Collaboration RoB 2.0 was used to assess the RoB in all selected studies. The evaluation revealed that none of the seven randomized controlled trials had a high RoB. 'Unclear' RoB occurred only in selection and detection biases. The RoB graph and summary are illustrated in Fig. 2A and B, respectively.

Incidence of any AEs and grade 3/4 AEs. A total of six studies involving 882 patients with ITP were included to compare the incidence of any AE between both the non-peptide TPO-RA treated and placebo groups. The results revealed no significant difference in the incidence of any AEs between the two groups (RR=1.16; 95% CI, 0.90-1.51; I^2=78%; P=0.26; Fig. 3). Due to high heterogeneity, this result must be interpreted carefully. There was also no significant difference in the incidence of grade 3/4 AEs between both groups (RR=1.07; 95% CI, 0.63-1.80; I^2=0%; P=0.81; Fig. 4).

Incidence of elevated transaminase levels/hepatotoxicity. Transaminases include alanine aminotransferase and aspartate aminotransferase. The summary results based on six studies revealed no significant difference in the incidence of elevated transaminase levels between the non-peptide TPO-RA treated and placebo groups (RR=1.09; 95% CI, 0.68-1.74; I^2=0%; P=0.72; Fig. 5).

Incidence of thrombosis and cataracts. Thrombotic events were fully described in all the included studies. The incidence of thrombotic events was 1.39 and 0% in the non-peptide TPO-RA treated and placebo groups, respectively. From the RR value, the incidence of thrombosis in the non-peptide

Table I. Study characteristics.

First author, year	Type of ITP (n)	Country	Study duration	Intervention			Control	Intervention (n) / control (n)					
				Drug	Dose per day, mg	Number of patients	Number of patients	Any AEs	Grade 3/4 AEs	Elevated transaminase levels	Thrombosis	Cataracts	(Refs.)
Bussel *et al*, 2007	Persistent (117)	Multiple	6 weeks	Eltrombopag	30, 50 or 75	29	88	45/17	9/4	3/0	1/0	0/0	(35)
Bussel *et al*, 2009	Persistent (114)	Multiple	6 weeks	Eltrombopag	50	38	76	45/14	2/1	4/0	0/0	5/2	(36)
Cheng *et al*, 2011	Persistent (196)	Multiple	6 months	Eltrombopag	50	61	135	N	20/7	17/6	3/0	11/6	(37)
Tomiyama *et al*, 2012	Persistent (23)	Japan	6 weeks	Eltrombopag	12.5-50	8	15	11/2	1/0	4/0	1/0	0/1	(38)
Yang *et al*, 2017	Chronic (155)	China	8 weeks	Eltrombopag	25-75	51	104	66/34	8/5	13/6	2/0	0/0	(39)
Jurczak *et al*, 2018	Chronic (49)	Multiple	6 months	Avatrombopag	20	17	32	31/10	6/0	N	3/0	N	(40)
Mei *et al*, 2021	Persistent (424)	China	10 weeks	Hetrombopag	2.5 or 5	85	339	316/81	N	24/8	1/0	0/0	(41)

ITP, immune thrombocytopenia; AE, adverse event; N, not mentioned.

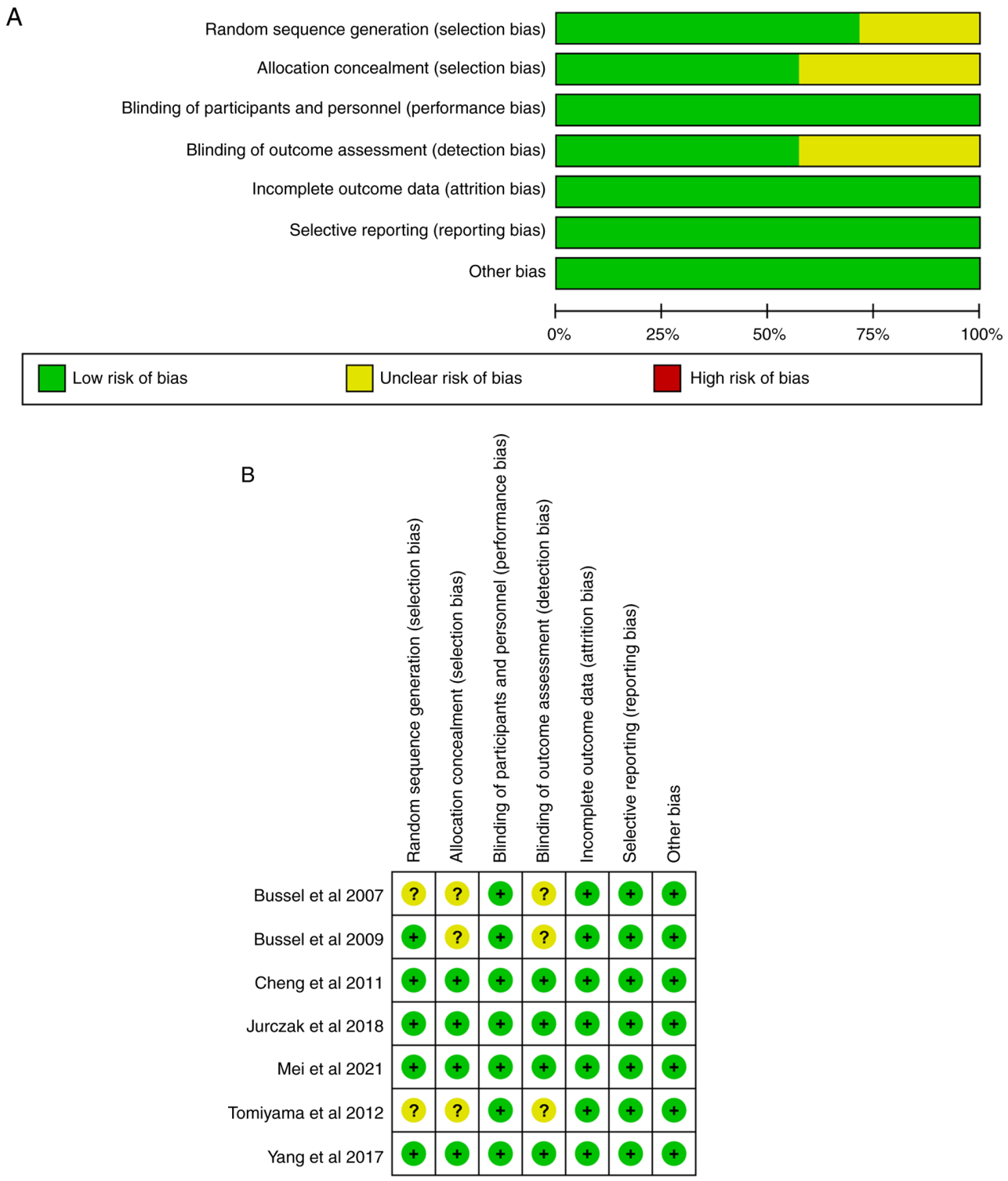

Figure 2. Risk of bias assessment using the ROB 2.0 tool. (A) Risk-of-bias graph. (B) Risk of bias summary. +, low risk of bias; ?, unclear risk of bias.

TPO-RA treated group was 1.92 times higher than that in the placebo group (RR=1.92; 95% CI, 0.55-6.66; I^2=0%; P=0.31; Fig. 6). However, the P-value revealed no statistically significant difference.

The data on cataracts (new or aggravated) were available in six articles. Its incidence rate was 2.11% in the non-peptide TPO-RAs group and 3.30% in the placebo group. However, there was no significant difference between the two groups (RR=0.83; 95% CI, 0.38-1.83; I^2=0%; P=0.65; Fig. 7).

Discussion

In the present study, the safety of non-peptide TPO-RAs and placebo in patients with ITP was compared. The results revealed no significant differences in the incidence of any AEs, grade 3/4 AEs, elevated transaminase levels, thrombosis or cataracts between the two study groups. Thus, it is concluded that it is relatively safe to use non-peptide TPO-RAs to treat ITP within at least 6 months of treatment.

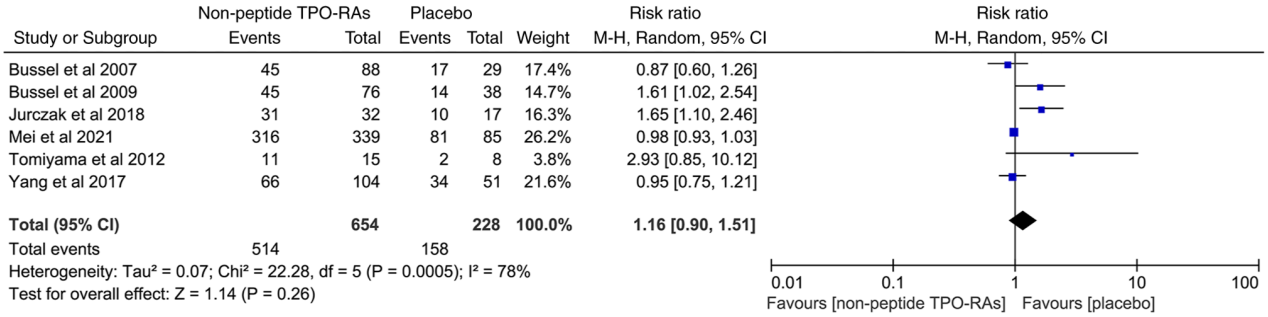

Figure 3. Forest plot of the incidence of any adverse events. CI, confidence interval; df, degrees of freedom; M-H, Mantel-Haenszel; TPO-RAs, thrombopoietin receptor agonists.

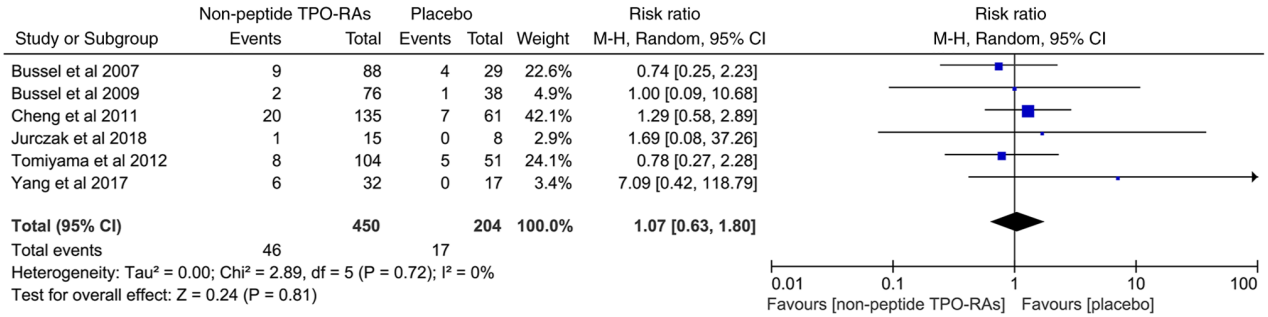

Figure 4. Forest plot of the incidence of grade 3/4 adverse events. CI, confidence interval; df, degrees of freedom; M-H, Mantel-Haenszel; TPO-RAs, thrombopoietin receptor agonists.

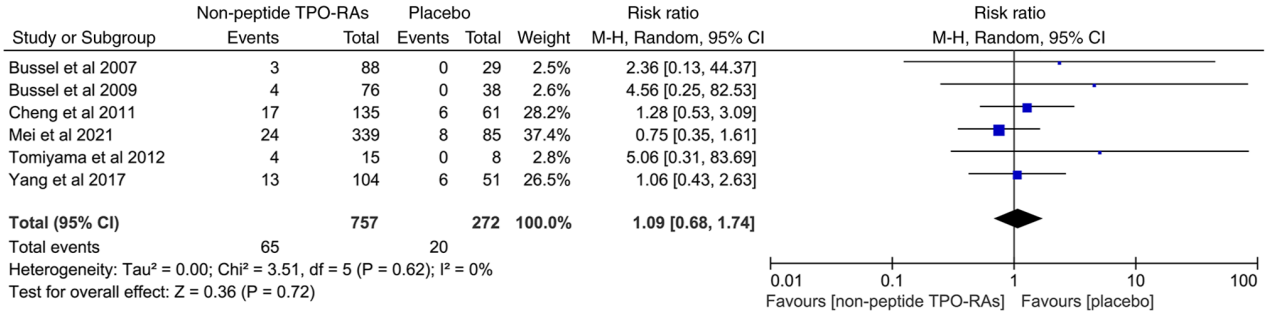

Figure 5. Forest plot of the incidence of elevated transaminase levels. CI, confidence interval; df, degrees of freedom; M-H, Mantel-Haenszel; TPO-RAs, thrombopoietin receptor agonists.

Thrombosis is one of the most damaging effects of ITP treatment with TPO-RAs (27). TPO-RAs increase the risk of thrombosis by increasing platelet count and stimulating the production of young and more hemostatic platelets (42). Thrombosis was the only event in the present meta-analysis that occurred in the intervention group but not in the placebo group, with an incidence of 1.39%. As this study only collected thrombosis events during the double-blind clinical trial period, the incidence rate may have been underestimated. A large phase III RCT on the safety of eltrombopag reported a thrombosis incidence of 2% (37). However, in an expanded study, the median treatment time for eltrombopag was 2.37 years and the incidence of thrombosis reached 6% (43). This indicates that treatment duration may be one of the main factors affecting the incidence of thrombosis.

It was discovered in preclinical animal model experiments that TPO-RAs may cause cataracts in rodents (44-46). Thus, eye examinations have become screening criteria for patients using TRO-RAs (35). In the present study, the incidence rates of cataracts in the non-peptide TPO-RA and placebo groups were 2.11 and 3.30%, respectively. TPO-RAs are second-line drugs for ITP (1). They are recommended only when glucocorticoid drugs are ineffective, as observed in all the included studies. Therefore, all patients with cataracts had used glucocorticoids in the past, which is an important risk factor for cataract formation (47). Thus, whether non-peptide TPO-RAs can cause cataracts in ITP patients requires further clarification.

Any AEs, grade 3/4 AEs and elevated transaminase levels are side effects of most drugs (48). The results revealed that, compared with placebo, non-peptide TPO-RAs did not increase

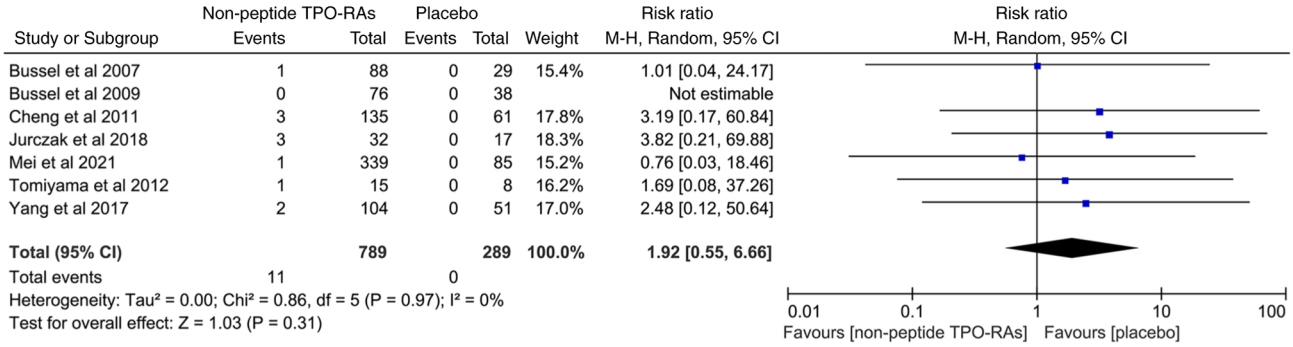

Figure 6. Forest plot of the incidence of thrombosis. CI, confidence interval; df, degrees of freedom; M-H, Mantel-Haenszel; TPO-RAs, thrombopoietin receptor agonists.

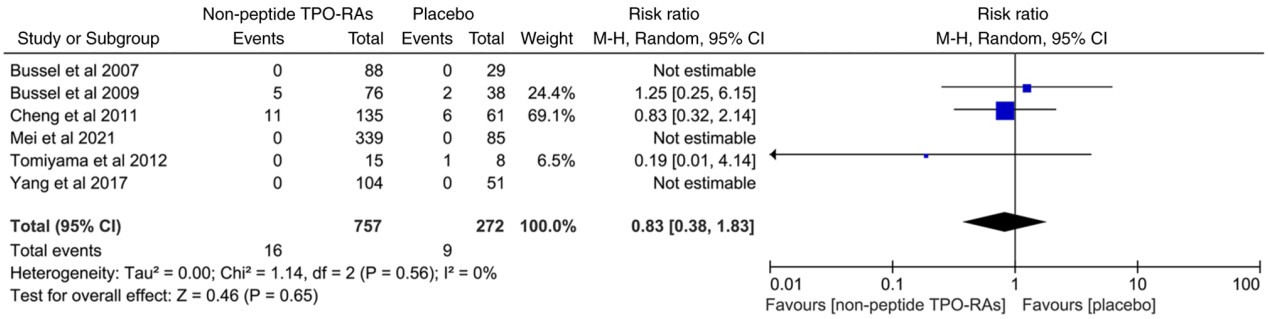

Figure 7. Forest plot of the incidence of cataracts. CI, confidence interval; df, degrees of freedom; M-H, Mantel-Haenszel; TPO-RAs, thrombopoietin receptor agonists.

the total number of AEs, serious AEs or elevated transaminase levels, which is consistent with previous meta-analyses on TPO-RAs (49-51). However, unlike in the past, this study is the meta-analysis on the safety of non-peptide TPO-RAs, and we have demonstrated that it is relatively safe as a second-line drug for the treatment of ITP.

The mechanism of ITP varies between children and adults, and the self-reported symptoms of adverse reactions in children may be inacurrate (52). Therefore, age is an important factor affecting drug-related AEs. In addition, the route of administration generally affects the absorption rate and metabolism of drugs, so it may be also related to AEs (53). The present study only included adult patients treated with oral TPO-RAs for ITP, effectively avoiding the impact of age and medication route in the results. Moreover, clinical data were from randomized double-blind placebo-controlled clinical trials, which further enhanced the reliability of the results.

The present study does however have some limitations. Firstly, the treatment period of ITP with non-peptide TPO-RAs in all clinical trials included was ≤6 months. Thus, it was impossible to analyze the occurrence of long-term AEs. Moreover, time has a significant effect on the incidence of AEs. Secondly, the present analysis only included adults as study participants thus, the results may not be applicable to children. Finally, a strict inclusion standard was set to improve the accuracy of the results, which reduced the study sample size.

In conclusion, the safety of non-peptide TPO-RAs for ITP treatment was evaluated and it was discovered that the incidence of any AEs, grade 3/4 AEs, elevated transaminase levels, thrombosis and cataracts were not statistically different from those in the placebo group. These results indicate that non-peptide TPO-RAs are relatively safe for patients with ITP, within at least 6 months of treatment.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Authors' contributions

SZ and JL designed the study. YJ, ML, HY and JQ collected the data. NS, JQ and SZ performed the data analysis and wrote the manuscript. All authors have read and approved the final manuscript. NS and SZ confirm the authenticity of all the raw data.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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