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Treatment efficacy for adult persistent immune thrombocytopenia: a systematic review and network meta-analysis

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Summary

Persistent immune thrombocytopenia (ITP) patients require second-line treatments, for which information on clinical outcomes are lacking. A systematic review and network meta-analysis (NMA) were conducted. Only randomised controlled trials (RCT) of second-line drugs in adult persistent ITP patients with platelet response, platelet count, any bleeding or serious adverse events (SAE) outcome were eligible. Twelve RCTs (n = 1313) were included in NMA. For platelet response outcome, eltrombopag and romiplostin were the best relative to placebo; the former had a non-significant advantage [risk ratio (RR) = 1·10 (95% confidence interval: 0·46, 2·67)]. Both treatments were superior to rituximab and recombinant human thrombopoietin (rhTPO)+rituximab, with corresponding RRs of 4·56 (1·89, 10·96) and 4·18 (1·21, 14·49) for eltrombopag; 4·13 (1·56, 10·94) and 3·79 (1·02, 14·09) for romiplostim. For platelet count, romiplostim ranked highest, followed by eltrombopag, rhTPO+rituximab, and rituximab. For bleeding, rituximab had lowest risk, followed by eltrombopag and romiplostim. For SAEs, rhTPO+rituximab had highest risk, followed by rituximab, eltrombopag and romiplostim. From clustered ranking, romiplostim had the best balance between short-term efficacy and SAEs, followed by eltrombopag. In conclusion, romiplostim and eltrombopag may yield high efficacy and safety. Rituximab may not be beneficial due to lower efficacy and higher complications compared with the thrombopoietin receptor agonists. RCTs with long-term clinical outcomes are required.

Keywords: monoclonal antibodies, immunosuppressive agents, persistent immune thrombocytopenia, thrombopoietin receptor agonists, network meta-analysis.

Immune thrombocytopenia (ITP) is a heterogeneous disease caused by autoantibody-mediated reaction of B cells and T cells to megakaryocytes leading to thrombocytopenia and life-threatening bleeding (Cooper & Bussel, 2006; Rodeghiero *et al*, 2009). Patients who fail to respond to initial treatment within 3–12 months are diagnosed with persistent ITP (Rodeghiero *et al*, 2009). These patients require second-line medical treatment with or without splenectomy if they are at risk of bleeding due to comorbidities (e.g., hypertension, renal insufficiency), use of antiplatelet or anticoagulant, risk for trauma or corticosteroid intolerance (Provan *et al*, 2010; Neunert *et al*, 2011; Lu *et al*, 2014). Several second-line treatments were used, including immunosuppressive agents (i.e., azathioprine, danazol, ciclosporin, cyclophosphamide, vincristine, vinblastine, mycophenolate mofetil and dapsone), monoclonal antibodies (i.e., rituximab), thrombopoietin receptor agonists (TPO-RAs, i.e., eltrombopag and romiplostim), or combinations thereof, which aim to improve the platelet count to $\geq$20–30 $\times$ 10^9/l without bleeding symptoms (Provan *et al*, 2010; Neunert *et al*, 2011; Toltl & Arnold, 2011; Moulis *et al*, 2014). These treatments are appropriate for patients with significant bleeding, platelet count <10–20 $\times$ 10^9/l, or platelet count 20–30 $\times$ 10^9/l after first-line treatment (Provan *et al*, 2010; Lu *et al*, 2014). Physicians tend to select a second-line therapy based on their experience (Stasi &

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Provan, 2004), whereas splenectomy is reducing worldwide due to the effectiveness of medical treatment (Palandri *et al*, 2016). Therefore, this review focuses on the efficacy of second-line medical treatments for ITP.

Eight meta-analyses assessed second-line medical therapy in paediatric and adult patients with newly diagnosed, relapsed and persistent ITP (Cooper *et al*, 2012; Chugh *et al*, 2015; Feng *et al*, 2016; Wang *et al*, 2016; Elgebaly *et al*, 2017; Arai *et al*, 2018; Zhang *et al*, 2018; Bylsma *et al*, 2019). Among them, 4 (Cooper *et al*, 2012; Wang *et al*, 2016; Elgebaly *et al*, 2017; Zhang *et al*, 2018), 2 (Chugh *et al*, 2015; Feng *et al*, 2016) and 2 (Arai *et al*, 2018; Bylsma *et al*, 2019) meta-analyses assessed efficacy of TPO-RAs, monoclonal antibody and both, respectively. For the TPO-RAs, 2 meta-analyses (Wang *et al*, 2016; Elgebaly *et al*, 2017) combined paediatric and adult ITP patients, 1 (Wang *et al*, 2016) combined randomised controlled trials (RCTs) with observational studies, and the rest (Cooper *et al*, 2012; Elgebaly *et al*, 2017; Arai *et al*, 2018; Zhang *et al*, 2018; Bylsma *et al*, 2019) considered only RCTs. Three of them directly pooled the effects of eltrombopag and romiplostim individually or combined them as TPO-RAs (Wang *et al*, 2016; Elgebaly *et al*, 2017; Bylsma *et al*, 2019), while 3 (Cooper *et al*, 2012; Arai *et al*, 2018; Zhang *et al*, 2018) indirectly pooled the effects of romiplostim relative to eltrombopag. For the 2 direct meta-analyses on monoclonal antibody, 5 (Chugh *et al*, 2015) and 7 (Feng *et al*, 2016) RCTs comparing rituximab with placebo or standard treatments were pooled. The most recent network meta-analysis (NMA) compared the efficacy across different types of second-line drugs (Arai *et al*, 2018). However, platelet count as a quantitative outcome was not considered, and risk-benefit analysis was not carried out. Therefore, this systematic review and NMA was conducted to estimate the relative treatment efficacy (i.e., on platelet response, platelet count and bleeding) and safety (i.e., on adverse events) of the second-line treatments (i.e., immunosuppressive agents, monoclonal antibodies and TPO-RAs) for adult persistent ITP patients. The probability of being the best treatment with highest efficacy and lowest serious adverse events (SAE) was also estimated. Risk and benefit were then considered simultaneously.

Methods

This study was performed following the Preferred Reports of Systematic Review and Meta-Analysis (PRISMA) guideline (Hutton, 2015), and was registered in PROSPERO (CRD42016044038).

Study identification

Studies were identified from MEDLINE (via PubMed) and Scopus databases. The search was performed up to 21 September 2018. Search strategies are described in Tables SI and SII.

Eligibility criteria

Only RCTs that included the following criteria were analysed: adult persistent ITP patients (failing initial treatment within 3–12 months or longer), compared a second-line drug with placebo or another second-line drug, reported any of following outcomes: platelet response, platelet count, bleeding and SAEs. Studies were excluded if they had insufficient data and no response after 3 attempts of contacting authors.

Treatments

The second-line treatments for persistent ITP included TPO-RA monotherapy (i.e., recombinant human thrombopoietin (rhTPO), eltrombopag and romiplostim), monoclonal antibody (rituximab), immunosuppressive agents (i.e., azathioprine, ciclosporin, cyclophosphamide, danazol, dapsone, mycophenolate mofetil, vincristine and vinblastine), or combination(s) of the aforementioned monotherapies.

Outcomes of interest

The primary outcome of interest was platelet response, i.e., achievement of platelet count $\geq 30 \times 10^9$/l or $\geq 50 \times 10^9$/l, as originally defined by each study, at 4–6 weeks after receiving second-line treatment. The 3 secondary outcomes were quantitative platelet count at 6 weeks after treatment, any bleeding and composite SAEs, including death, thrombosis (i.e., occurrence of arterial/venous occlusion), and serious infection (i.e., grade 3–4) (https://www.eortc.be/services/doc/ctc/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf). Frequency of the most common event among them was used as the composite SAE data for studies reporting individual SAE but not the composite.

Study selection and data extraction

Two reviewers independently selected studies by screening titles and abstracts, and retrieved the full articles if a decision could not be made. Selection results were then validated; any disagreements were resolved by senior authors.

Data extraction was performed independently by 2 reviewers. Study characteristics were extracted, including country, study design, period of study, treatment regimens, baseline platelet count, cut-off for platelet response, treatment duration, mean age, sex and percent splenectomy. In addition, data for pooling were extracted, including total number of subjects, any bleeding events, composite SAE, risk ratio (RR) with 95% confidence interval (CI) and mean with standard deviation of continuous outcomes.

Risk of bias assessment

The quality of studies was independently assessed by 2 reviewers. Disagreement was resolved by a senior author. The

risk of bias was assessed using the Cochrane Collaboration's tool for RCTs (Higgins *et al*, 2011). Each item was graded as "low risk" or "high risk"; if there was insufficient information to judge, it was classified as "unclear".

Statistical analysis

Direct meta-analysis (DMA) was performed on 3 dichotomous outcomes (i.e., platelet response, any bleeding, and composite SAEs) and 1 quantitative platelet count outcome. Relative treatment effects were estimated for these corresponding outcomes using RRs and un-standardised mean difference (USMD). Heterogeneity was assessed using Q test and I^2 statistic (Thompson & Sharp, 1999; Petitti, 2001). The sources of heterogeneity were explored by fitting each study characteristic in a meta-regression model. A characteristic was considered a source of heterogeneity if the I^2 decreased following its inclusion in the model. A subgroup analysis was then performed accordingly.

NMA with consistency model was applied to assess relative treatment effects between different second-line drugs, which were coded as 1–9 for placebo, eltrombopag, romiplostim, rituximab, danazol, rhTPO, rhTPO+danazol, rhTPO+ciclosporin and rhTPO+rituximab, respectively. Indirect comparisons between active treatments were performed by borrowing information from a common comparator (i.e., placebo).

Treatments were ranked using rankogram and surface under the cumulative ranking curve (SUCRA). The consistency assumption was assessed using a design-by-treatment interaction model (Higgins *et al*, 2012; Jackson *et al*, 2016). Publication bias was assessed by comparison-adjusted funnel plot (Chaimani *et al*, 2013). Finally, clustered ranking plot for 2 outcomes was constructed according to the treatments' SUCRA values to demonstrate their ranks simultaneously in terms of both benefit and risk. All analyses were performed using Stata version 15.1 (StataCorp LLC, College Station, TX, USA).

Role of the funding source

This study has no funding source. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

A total of 116 and 1670 studies were identified from MEDLINE and Scopus, respectively. Eighty-nine duplicates were removed, leaving 1697 studies to be screened on titles and abstracts. Fourteen studies (Bussel *et al*, 2006; Bussel *et al*, 2007; Kuter *et al*, 2008; Bussel *et al*, 2009; Kuter *et al*, 2010; Cheng *et al*, 2011; Shirasugi *et al*, 2011; Arnold *et al*, 2012; Tomiyama *et al*, 2012; Wang *et al*, 2012; Cui *et al*, 2013; Ghanima *et al*, 2015; Zhou *et al*, 2015; Yang *et al*, 2017) were finally eligible (Fig 1).

The characteristics of these 14 studies are described in Table I. All studies were RCTs and mainly multi-centre, except for one (Shirasugi *et al*, 2011), with sample sizes ranging from 21 to 234. All studies were two-arm comparisons, including 5 studies (Bussel *et al*, 2007; Bussel *et al*, 2009; Cheng *et al*, 2011; Tomiyama *et al*, 2012; Yang *et al*, 2017) for eltrombopag *versus* placebo, 4 (Bussel *et al*, 2006; Kuter *et al*, 2008; Kuter *et al*, 2010; Shirasugi *et al*, 2011) for romiplostim *versus* placebo, 2 (Arnold *et al*, 2012; Ghanima *et al*, 2015) for rituximab *versus* placebo, 1 (Cui *et al*, 2013) for rhTPO+ciclosporin *versus* rhTPO, 1 (Zhou *et al*, 2015) for rhTPO+rituximab *versus* rituximab and 1 (Wang *et al*, 2012) for rhTPO+danazol *versus* danazol. Nine RCTs (Bussel *et al*, 2006; Bussel *et al*, 2007; Bussel *et al*, 2009; Cheng *et al*, 2011; Shirasugi *et al*, 2011; Tomiyama *et al*, 2012; Cui *et al*, 2013; Zhou *et al*, 2015; Yang *et al*, 2017) included exclusively patients with persistent ITP, while 4 (Kuter *et al*, 2008; Kuter *et al*, 2010; Arnold *et al*, 2012; Ghanima *et al*, 2015) included mixed newly diagnosed and persistent ITP patients and 1 (Wang *et al*, 2012) did not mention ITP phase. Median age ranged from 34 to 59 years and the percentage of females ranged from 56% to 75%. Median platelet count at baseline ranged from 10×10^9/l to 29×10^9/l. Platelet response was defined as platelet $\geq 50 \times 10^9$/l in 11 studies (Bussel *et al*, 2006; Bussel *et al*, 2007; Kuter *et al*, 2008; Bussel *et al*, 2009; Kuter *et al*, 2010; Cheng *et al*, 2011; Shirasugi *et al*, 2011; Arnold *et al*, 2012; Tomiyama *et al*, 2012; Wang *et al*, 2012; Yang *et al*, 2017), and $\geq 30 \times 10^9$/l in 3 studies (Cui *et al*, 2013; Ghanima *et al*, 2015; Zhou *et al*, 2015). The treatment duration ranged from 2 to 52 weeks (median = 6 weeks), while the follow-up period ranged from 4 to 78 weeks (median = 24 weeks). One (Wang *et al*, 2012) and 11 studies (Bussel *et al*, 2006; Bussel *et al*, 2007; Kuter *et al*, 2008; Bussel *et al*, 2009; Kuter *et al*, 2010; Cheng *et al*, 2011; Shirasugi *et al*, 2011; Arnold *et al*, 2012; Tomiyama *et al*, 2012; Ghanima *et al*, 2015; Yang *et al*, 2017) reported platelet response at 4 and 6 weeks, respectively. Only 2 studies (Bussel *et al*, 2006; Kuter *et al*, 2008) of romiplostim *versus* placebo reported baseline thrombopoietin level. History of having received 3 or more treatment regimens was reported in 5 studies (Bussel *et al*, 2006; Bussel *et al*, 2007; Kuter *et al*, 2008; Bussel *et al*, 2009; Cheng *et al*, 2011). Corticosteroids were the most common previous treatment followed by intravenous immunoglobulin. Percentage of splenectomy was reported in 10 studies (Bussel *et al*, 2006; Bussel *et al*, 2007; Kuter *et al*, 2008; Bussel *et al*, 2009; Cheng *et al*, 2011; Shirasugi *et al*, 2011; Tomiyama *et al*, 2012; Wang *et al*, 2012; Zhou *et al*, 2015; Yang *et al*, 2017) ranging from 10·4% to 69·6%, with a median time after splenectomy of 6·6–8·1 years.

Ten studies (Bussel *et al*, 2006; Bussel *et al*, 2007; Kuter *et al*, 2008; Bussel *et al*, 2009; Cheng *et al*, 2011; Shirasugi *et al*, 2011; Tomiyama *et al*, 2012; Wang *et al*, 2012; Zhou

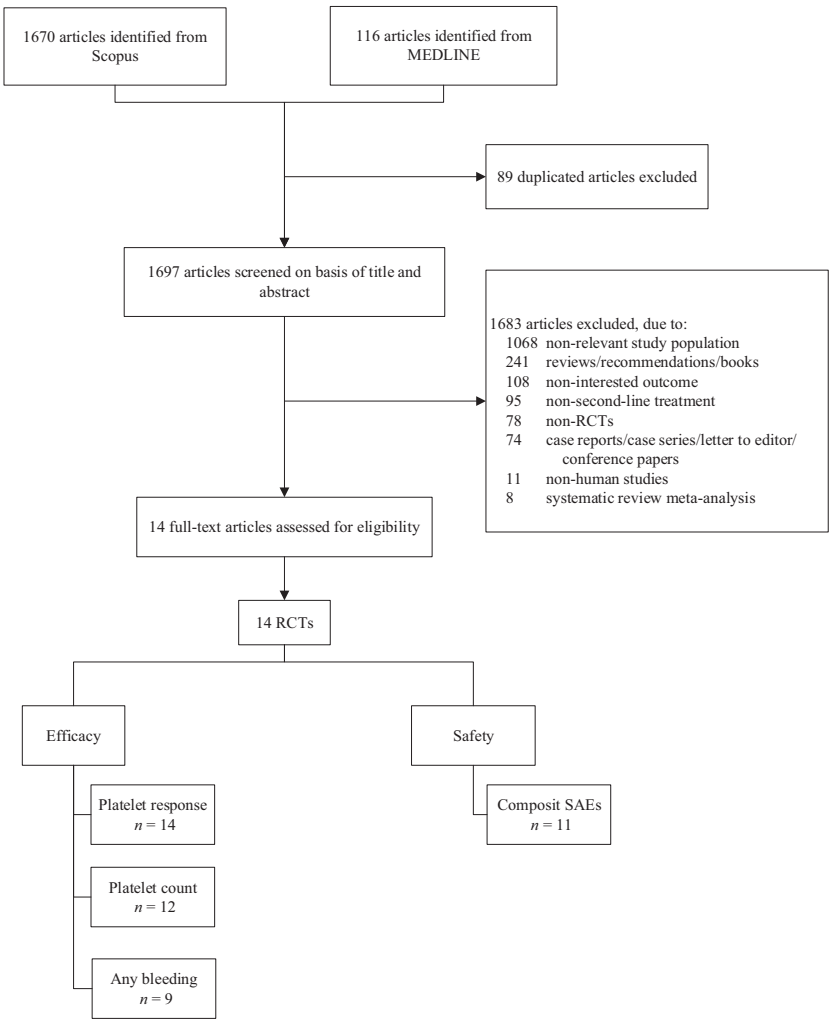

Fig 1. Flow chart of study selection. RCT, randomised controlled trial; SAE, serious adverse event.

et al, 2015; Yang *et al*, 2017) reported the percentage of concurrent treatments, which ranged from 11% to 83%. For eltrombopag *versus* placebo, dosage of eltrombopag was 12·5–50 mg/day for 24 weeks (Tomiyama *et al*, 2012), 25–75 mg/day for 8 weeks (Yang *et al*, 2017), 30–75 mg/day for 6 weeks (Bussel *et al*, 2007), 50–75 mg/day for 6 weeks (Bussel *et al*, 2009) and 24 weeks (Cheng *et al*, 2011). For romiplostim *versus* placebo, dosage of romiplostim was 1–2 μg/kg subcutaneously (SC) once a week for 24 weeks (Kuter *et al*, 2008), 1–6 μg/kg SC once a week for 6 weeks (Bussel *et al*, 2006) and 3–10 μg/kg SC once a week for 52 weeks (Kuter *et al*, 2010) and 12 weeks (Shirasugi *et al*, 2011). For rituximab *versus* placebo, dosage of rituximab for patients in both studies (Arnold *et al*, 2012; Ghanima *et al*, 2012) was 375 mg/m^2 intravenously once a week for 4 weeks. For rhTPO studies, dosage of rhTPO was 1 μg/kg SC once daily for 2 weeks (Wang *et al*, 2012; Cui *et al*, 2013; Zhou *et al*, 2015).

The results of risk of bias assessment are described in Table SIII. Most items were assessed as unclear because of insufficient information including random sequence generation (57·1%), allocation concealment (57·1%), blinding (85·7%) and other sources of bias (57·1%). However, all studies were judged low risk for selective outcome reporting.

The results of DMA are reported in Tables SIV–SVII and Figures S1–S4. For platelet response, eltrombopag and romiplostim resulted in a 3·99 (2·54, 6·26) and 4·82 (1·77, 13·12) times higher response than placebo, respectively. In addition, these corresponding treatments and rituximab also resulted in significantly higher platelet counts than placebo with USMDs of 51·06 (32·85, 69·26) and 82·68 (45·21, 123·81) and 22·05 (4·42, 39·67) $\times 10^9$/l, respectively. Risk of bleeding was lower for all treatments but only eltrombopag was significant [RR = 0·82 (0·74, 0·91)]. Meanwhile, romiplostim had significantly lower risk for SAEs than placebo [RR = 0·39 (0·17, 0·93)] but eltrombopag did not [RR = 1·17 (0·35, 3·92)].

Heterogeneity was moderate to high except for rituximab *versus* placebo on platelet response, rituximab *versus* placebo on platelet counts, eltrombopag and rituximab *versus* placebo on any bleeding and eltrombopag and romiplostim *versus* placebo on SAEs. Sources of heterogeneity (study and patient characteristics) were explored, but none were found.

Table I. Characteristics of included studies.

Author, year	Country	Treatments	Median platelet count ($\times 10^9$/l)	Platelet response ($\times 10^9$/l)	Duration of treatment (weeks)	Duration of follow-up (weeks)	Median age (years)	% Female	% Splenectomy
Bussel *et al* (2006)	USA	Romiplostim *versus* placebo	16	Platelet count ≥50	6	12	49	71·4	67
Bussel *et al* (2007)	USA	Eltrombopag *versus* placebo	16	Platelet count ≥50	6	12	50	62	47
Kuter *et al* (2008)	Europe, USA	Romiplostim *versus* placebo	16	Platelet count ≥50	24	36	52	65	50·4
Bussel *et al* (2009)	23 countries	Eltrombopag *versus* placebo	19·7	Platelet count ≥50	6	12	48	61	39
Kuter *et al* (2010)	Australia, Europe, USA	Romiplostim *versus* placebo	29	Platelet count >50	52	78	57	56	–
Cheng *et al* (2011)	23 countries	Eltrombopag *versus* placebo	16	Platelet count ≥50	24	24	48·7	69	36
Shirasugi *et al* (2011)	Japan	Romiplostim *versus* placebo	17·5	Platelet count ≥50	12	24	58·3	70·6	44
Arnold *et al* (2012)	Canada	Rituximab *versus* placebo	14·6	Platelet count ≥50	4	26	40	58·3	–
Tomiyama *et al* (2012)	Japan	Eltrombopag *versus* placebo	17	Platelet count ≥50	6	26	58·9	65·2	69·6
Wang *et al* (2012)	China	rhTPO+danazol *versus* danazol	10·4	Platelet count ≥50	2	4	40·8	63·2	12·5
Cui *et al* (2013)	China	rhTPO+ciclosporin *versus* rhTPO	11·9	Platelet count ≥30	2	12	33·9	55·6	–
Ghanima *et al* (2015)	France, Norway, Tunisia	Rituximab *versus* placebo	18·5	Platelet count ≥30	4	78	46	72·5	–
Zhou *et al* (2015)	China	Rituximab+rhTPO *versus* rituximab	10·2	Platelet count ≥30	4	26	42·2	65·2	10·4
Yang *et al* (2017)	China	Eltrombopag *versus* placebo	13·75	Platelet count ≥50	8	6	45	75·4	16·1

rhTPO, recombinant human thrombopoietin.

The results of NMA are detailed as follows. Fourteen studies (Bussel *et al*, 2006; Bussel *et al*, 2007; Kuter *et al*, 2008; Bussel *et al*, 2009; Kuter *et al*, 2010; Cheng *et al*, 2011; Shirasugi *et al*, 2011; Arnold *et al*, 2012; Tomiyama *et al*, 2012; Wang *et al*, 2012; Cui *et al*, 2013; Ghanima *et al*, 2015; Zhou *et al*, 2015; Yang *et al*, 2017) reported platelet response as an outcome. Two studies (Wang *et al*, 2012; Cui *et al*, 2013) comparing rhTPO+danazol *versus* danazol and rhTPO+ciclosporin *versus* rhTPO were disconnected from other comparisons, and were therefore excluded from the network. A network map was constructed for 12 studies (Bussel *et al*, 2006; Bussel *et al*, 2007; Kuter *et al*, 2008; Bussel *et al*, 2009; Kuter *et al*, 2010; Cheng *et al*, 2011; Shirasugi *et al*, 2011; Arnold *et al*, 2012; Tomiyama *et al*, 2012; Ghanima *et al*, 2015; Zhou *et al*, 2015; Yang *et al*, 2017) (1313 subjects) consisting of 4 direct comparisons among 5 treatments (Fig 2A). Among them, 11 studies (Bussel *et al*, 2006; Bussel *et al*, 2007; Kuter *et al*, 2008; Bussel *et al*, 2009; Kuter *et al*, 2010; Cheng *et al*, 2011; Shirasugi *et al*, 2011; Arnold *et al*, 2012; Tomiyama *et al*, 2012; Wang *et al*, 2012; Yang *et al*, 2017) used a platelet cut-off of 50×10^9/l, but 1 study (Arnold *et al*, 2012) used a platelet cut-off of 30×10^9/l. For all relative treatment comparisons (Table II, above diagonal line), eltrombopag and romiplostin provided the most effective outcomes compared with placebo, with the former having a slight (non-significant) advantage in terms of platelet response [RR = 1·10 (0·46, 2·67)]. Both eltrombopag and romiplostim were significantly more effective than rituximab and rhTPO+rituximab with corresponding pooled RRs of 4·56 (1·89, 10·96) and 4·18 (1·21, 14·49) for eltrombopag; 4·13 (1·56, 10·94) and 3·79 (1·02, 14·09) for romiplostim. Eltrombopag was ranked as the best treatment for platelet response according to its SUCRA of 89·6, followed by romiplostim, rhTPO+rituximab, placebo and rituximab, respectively (Table III). There was no evidence of inconsistency effects (global $\chi^2 = 0{\cdot}04$, $P = 0{\cdot}850$) or publication bias for platelet response (Figure S5A).

Twelve studies (Bussel *et al*, 2007; Kuter *et al*, 2008; Bussel *et al*, 2009; Kuter *et al*, 2010; Cheng *et al*, 2011; Shirasugi *et al*, 2011; Arnold *et al*, 2012; Tomiyama *et al*, 2012; Wang *et al*, 2012; Cui *et al*, 2013; Ghanima *et al*, 2015; Zhou *et al*, 2015) reported platelet count as an outcome with 1301 subjects, which included 4 direct comparisons among 5 treatments (Fig 2B). All possible pairwise comparisons were made (Table II, below diagonal line), indicating that romiplostim produced the most effective platelet count compared to placebo, followed by eltrombopag, rhTPO+rituximab and rituximab with pooled USMD of $81{\cdot}66 \times 10^9$/l (49·63, 113·69), $53{\cdot}79 \times 10^9$/l (28·27, 79·32), $49{\cdot}11 \times 10^9$/l (−19·80, 118·01) and $26{\cdot}87 \times 10^9$/l (−17·67, 71·40), respectively. In 6 comparisons, none of the active drugs were statistically significantly associated with platelet count outcome. Romiplostim ranked as the best treatment for platelet count (SUCRA = 92·8), followed by eltrombopag, rhTPO+rituximab, and rituximab, respectively (Table III). There was no

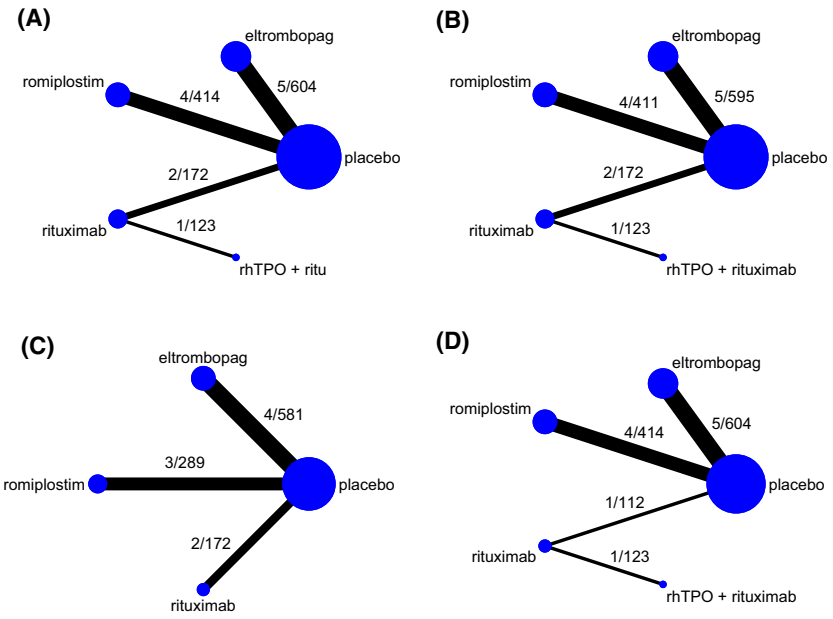

Fig 2. Network map for all outcomes. (A) Platelet response. (B) Platelet count. (C) Any bleeding. (D) Composite serious adverse events. The number of studies and patients, indicated above each line, are depicted by the size of nodes and line thickness, respectively. Ritu, rituximab; rhTPO, recombinant human thrombopoietin. [Colour figure can be viewed at wileyonlinelibrary.com]

evidence of inconsistency effects (global $\chi^2 = 0{\cdot}69$, $P = 0{\cdot}407$). There was evidence of publication bias for platelet count (Figure S5B).

Nine studies (Bussel *et al*, 2007; Bussel *et al*, 2009; Kuter *et al*, 2010; Cheng *et al*, 2011; Shirasugi *et al*, 2011; Arnold *et al*, 2012; Ghanima *et al*, 2015) reported any bleeding outcome. Data from these 9 studies (1042 subjects) included 3 direct comparisons among 4 treatments (Fig 2C). All possible pairwise comparisons were made, which indicated that rituximab had the lowest risk for any bleeding when compared to placebo, followed by eltrombopag and romiplostim, with pooled RR of 0·76 (0·49, 1·18), 0·79 (0·65, 0·96) and 0·82 (0·59, 1·13), respectively. However, all placebo and active controlled comparisons were not statistically significant, except eltrombopag *versus* placebo (Table IV, above diagonal line). The highest probability of bleeding was found in placebo, followed by romiplostim, eltrombopag, and rituximab, respectively (Table III). There was no evidence of inconsistency effects (global $\chi^2 = 0{\cdot}99$, $P = 0{\cdot}319$) or publication bias (Figure S5C).

Eleven studies (Bussel *et al*, 2007; Kuter *et al*, 2008; Bussel *et al*, 2009; Kuter *et al*, 2010; Cheng *et al*, 2011; Shirasugi *et al*, 2011; Tomiyama *et al*, 2012; Ghanima *et al*, 2015; Zhou *et al*, 2015) reporting composite SAE outcome were included in the network with 1253 total subjects. These consisted of 4 direct comparisons among 5 treatments (Fig 2D). All possible pairwise comparisons were made (Table IV, below diagonal line), and rhTPO+rituximab had the highest risk of composite SAEs when compared to placebo followed by rituximab and eltrombopag with pooled RR of 4·54 (0·10, 210·26), 1·86 (0·17, 19·95) and 1·09 (0·34, 3·45), respectively. Romiplostim had the lowest composite SAEs when compared to placebo with a statistically significant pooled RR of 0·39 (0·17, 0·93). In addition, the latter 3 active treatments had non-significantly lower risk for composite SAEs than rhTPO+rituximab, with pooled RRs of 0·41 (0·02, 8·34), 0·24 (0·00, 13·11) and 0·09 (0·00, 4·40), respectively. The treatment with greatest probability for highest SAEs was rhTPO+rituximab, followed by rituximab, eltrombopag, placebo and romiplostim, respectively (Table III). There was no evidence of inconsistency effects (global $\chi^2 = 0{\cdot}34$, $P = 0{\cdot}562$) or publication bias (Figure S5D).

A clustered ranking plot was constructed between SAEs on *x*-axis and the other 3 outcomes (i.e., platelet response, platelet count, and any bleeding) on *y*-axis (Fig 3). Romiplostim ranked highest for platelet count (with highest SUCRA) and SAEs (with lowest SUCRA). It ranked second for platelet response with a SUCRA slightly lower than eltrombopag, which seemed most efficacious in this outcome but had higher risk for SAEs than romiplostim and placebo. The rhTPO+rituximab combination and rituximab carried the greatest risk of SAEs, although the latter had the smallest risk of bleeding.

Discussion

Our NMA included 12 RCTs evaluating both short-term efficacy and adverse events of second-line medical treatment for persistent ITP in adults. The overall results from NMA were consistent and indicated that romiplostim and eltrombopag

Table II. All possible pairwise comparisons of treatments for persistent ITP on platelet response and platelet count: a network meta-analysis.

	Platelet response				
Platelet count	Eltrombopag	1·10 (0·46, 2·67)	4·56 (1·89, 10·96)	4·18 (1·21, 14·49)	4·32 (2·36, 7·88)
	−27·86 (−68·48, 12·75)	Romiplostim	4·13 (1·56, 10·94)	3·79 (1·02, 14·09)	3·91 (1·88, 8·16)
	26·93 (−24·21, 78·06)	54·79 (0·12, 109·46)	Rituximab	0·92 (0·38, 2·21)	0·95 (0·50, 1·79)
	4·69 (−68·65, 78·03)	32·55 (−43·30, 108·40)	−22·24 (−74·82, 30·35)	rhTPO+rituximab	1·03 (0·35, 3·05)
	53·79 (28·27, 79·32)	81·66 (49·63, 113·69)	26·87 (−17·67, 71·40)	49·11 (−19·80, 118·01)	Placebo

Results are risk ratios (95% confidence intervals [CIs]) for platelet response and un-standardised mean difference (95% CIs) for platelet count between each pair of treatments from network meta-analysis. Comparisons are read from left to right. rhTPO, recombinant human thrombopoietin.

Table III. The surface under the cumulative ranking curve and rank of each treatment for platelet response, platelet count, any bleeding and composite serious adverse events outcomes.

	Platelet response		Platelet count		Any bleeding		Composite serious adverse events	
Treatment	SUCRA	Rank	SUCRA	Rank	SUCRA	Rank	SUCRA	Rank
Placebo	26·2	4	5·1	5	92·7	1	48·3	4
Eltrombopag	89·6	1	62·8	2	32·8	3	51·4	3
Romiplostim	84·5	2	92·8	1	42·2	2	8·1	5
Rituximab	20·8	5	32·8	4	32·3	4	62·6	2
rhTPO+rituximab	28·8	3	56·5	3	–	–	79·6	1

rhTPO, recombinant human thrombopoietin; SUCRA, surface under the cumulative ranking curve.

had significantly higher efficacy in terms of platelet response and platelet count when compared with placebo. In addition, both treatments were also more efficacious than rituximab monotherapy or rhTPO+rituximab combination. Considering clinical efficacy and adverse events simultaneously using clustered ranking indicated that the treatment with the best balance between high short-term efficacy with regard to platelet response, platelet count low risk of bleeding and adverse events was romiplostim, followed by eltrombopag. Rituximab had the lowest clinical efficacy and highest risk for SAEs.

The results of this study are compatible with the mechanism of action of TPO-RAs and rituximab in ITP. Romiplostim is a peptide TPO-RA which binds to the extracellular domain of thrombopoietin receptor, activates JAK-STAT, MAPK and PI3K-AKT pathways, stimulates proliferation and maturation of megakaryocytes, and inhibits apoptosis of megakaryocytes; resulting in increased platelet production (Vishnu & Aboulafia, 2016; Cooper, 2017). Eltrombopag is a non-peptide TPO-RA that binds to the transmembrane domain of thrombopoietin receptor and activates the same pathways as romiplostim (Cooper, 2017; Gonzalez-Porras & Bastida, 2018). Being less specific to ITP than the TPO-RAs, rituximab is a monoclonal antibody which binds to the surface of CD20-positive B lymphocytes and induces B-cell depletion (Braendstrup *et al*, 2005).

Our study was considerably similar to the recent NMA by Arai *et al* (2018), which was published whilst our manuscript was in submission. Although the total number of RCTs meeting their inclusion criteria were different from ours (i.e., 24 *Versus* 14 RCTs), the number of RCTs included in the

Table IV. All possible pairwise comparisons of treatments for persistent ITP on any bleeding and composite serious adverse events: network meta-analysis.

	Any bleeding				
Composite serious adverse events	Eltrombopag	0·97 (0·69, 1·35)	1·04 (0·64, 1·68)	–	0·79 (0·65, 0·96)
	2·77 (0·65, 11·71)	Romiplostim	1·07 (0·61, 1·86)	–	0·82 (0·59, 1·13)
	0·58 (0·04, 8·15)	0·21 (0·02, 2·63)	Rituximab	–	0·76 (0·49, 1·18)
	0·24 (0·00, 13·11)	0·09 (0·00, 4·40)	0·41 (0·02, 8·34)	rhTPO+rituximab	–
	1·09 (0·34, 3·45)	0·39 (0·17, 0·93)	1·86 (0·17, 19·95)	4·54 (0·10, 210·26)	Placebo

Results are risk ratios (95% confidence intervals) between each pair of treatments from network meta-analysis. Comparisons are read from left to right. rhTPO, recombinant human thrombopoietin.

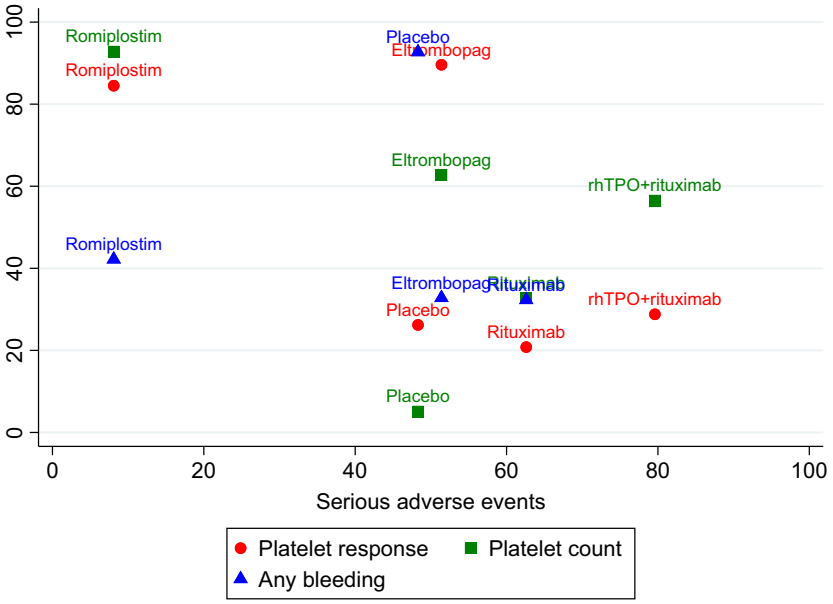

Fig 3. Clustered ranking plot of surface under the cumulative ranking curve (SUCRA) for composite serious adverse events *versus* platelet response, platelet count and any bleeding. [Colour figure can be viewed at wileyonlinelibrary.com]

pooling of primary outcome of platelet response was the same (i.e., 12 RCTs). Among them, 1 study of a new TPO-RA (i.e., avatrombopag) *versus* placebo (Bussel *et al*, 2014) was included in their NMA but not in ours because it was a phase II RCT; whereas another study of rituximab *versus* placebo (Arnold *et al*, 2012) was included in our NMA but not in theirs. Their outcomes of interest were mostly similar to ours except they considered early response within 1–2 weeks, rescue treatments, and quality of life, with small number of RCTs for each, and could not perform NMA. For platelet response, their NMA indicated that eltrombopag had the first rank, similar to ours. For the bleeding outcome, the ranking was considerably different: TPO-RAs (i.e., eltrombopag and romiplostim) ranked first and second in lowering bleeding while rituximab was the first in our study. This was probably because a different endpoint for bleeding was used (i.e., clinically significant bleeding *versus* any bleeding in our study). However, the quantitative platelet count was not considered in their review, nor were the efficacy and safety evaluated simultaneously.

Our study has a number of strengths. The results of NMA can demonstrate relative treatment effects between any pair of active treatments and their ranking as best/worst treatments. Risk (i.e., SAEs) and benefit (i.e., efficacy) are also considered simultaneously using clustered ranking plot. Romiplostim and eltrombopag have significantly higher efficacy and lower adverse events than rituximab, with romiplostin having a safer adverse event profile than eltrombopag; this provides a comprehensive summary of these treatment options. Our study has some limitations that should be considered. First, the number of relevant studies and most of their sample sizes were small. Second, variations in drug dosage and protocol may cause heterogeneity and affect the clinical outcomes. Working on summary data does not allow us to re-categorise treatment regimens or adjust for differences like individual patient data meta-analysis does, but the latter is time-consuming and requires willingness to share data. Third, the clinical outcomes evaluated in the included studies were only short-term; these treatments might possibly give different results in the long term. Lastly, we focused on treatments for persistent ITP, but 4 RCTs (Kuter *et al*, 2008; Kuter *et al*, 2010; Arnold *et al*, 2012; Ghanima *et al*, 2015) had mixed acute and persistent ITP patients with median disease duration of 0·5–7·4 years.

In conclusion, this systematic review and NMA indicates that romiplostim and eltrombopag have high efficacy and safety as second-line treatments in the short term for adult patients with persistent ITP. Rituximab may not be beneficial due to lower efficacy and higher complications compared with TPO-RAs. Further evaluation of long-term outcomes, as well as cost-effectiveness and impact analyses for both TPO-RAs should be performed to guide healthcare policy makers.

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Conflict of interests

The authors have no competing interests.

Author contributions

TP, SR, and AT designed and organised research for this study. SR, AI, and AT supervised the study. TP and SR acquired the data. KT, SR, and AT did the statistical analysis. TP, KT, and AT wrote the report. MM and JA revised the report for important intellectual content.

Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table SI. Search strategy for MEDLINE.

Table SII. Search strategy for Scopus.

Table SIII. Risk of bias assessment of included studies.

Table SIV. Efficacy of second-line drugs on platelet response in adult persistent ITP patients: direct meta-analysis.

Table SV. Efficacy of second-line drugs on platelet count in adult persistent ITP patients: direct meta-analysis.

Table SVI. Efficacy of second-line drug on bleeding in adult persistent ITP patients: direct meta-analysis.

Table SVII. Safety of second-line drugs on composite serious adverse events in adult persistent ITP: direct meta-analysis.

Fig S1. Direct meta-analysis of platelet response of second-line drugs in adult persistent ITP patients.

Fig S2. Direct meta-analysis of platelet count of second-line drugs in adult persistent ITP patients.

Fig S3. Direct meta-analysis of any bleeding of second-line drugs in adult persistent ITP patients.

Fig S4. Direct meta-analysis of composite serious adverse events of second-line drugs in adult persistent ITP patients.

Fig S5. Comparison-adjusted funnel plot for all outcomes in adult persistent ITP patients.

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