Immune thrombocytopenia: exploring antibodies, scintigraphy and immune modulation. Moving towards a new era for patients with ITP

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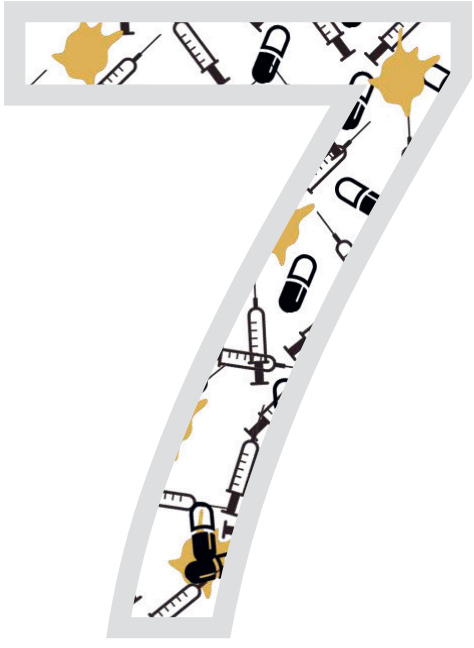

Chapter 7

Risk of thrombosis with thrombopoietin receptor agonists for ITP patients: A systematic review and meta-analysis

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Abstract

Background One possible side effect of thrombopoietin receptor agonists in immune thrombocytopenia is thrombosis. Our aim is to systematically review whether patients with ITP that were treated with a TPO-RA have an increased risk for thrombosis as compared to ITP patients without TPO-RA.

Methods Patients in the intervention group were required to receive TPO-RA therapy. The primary outcome was the incidence of thromboembolic events.

Results Eleven studies were included in the pooled analysis. More thromboembolic events were noted in the TPO-RA group than in the control group: 25 compared to 4. Ten out of 11 studies showed a relative risk greater than 1. However, none of these individual risk ratios was statistically significant. The meta-analysis showed a RR of 1.82 [95 % CI 0.78-4.24].

Conclusion Our findings indicate there is a non-significant higher chance of thrombosis in ITP patients with TPO-RA treatments versus ITP patients without TPO-RA treatment.

1. Introduction

Immune thrombocytopenia (ITP) is an acquired isolated thrombocytopenia (platelets below 100×10^9/L), without an obvious underlying condition or other cause for the thrombocytopenia (Cooper and Ghanima, 2019). ITP is an autoimmune disorder that is primarily associated with antibody-mediated platelet destruction, but decreased platelet production may play a role as well. Treatment is usually started when the platelet count is low ($< 30\times10^9$/L) or when the patient experiences symptoms of bleeding (Neunert et al., 2011). The initial treatment for newly diagnosed ITP usually comprises corticosteroids as a single therapy or in combination with intravenous immune globulin (Cooper and Ghanima, 2019). If these agents fail, second-line treatment should be started. The main options for second-line treatment are rituximab or thrombopoietin receptor agonists (TPO-RAs).

For the past ten years, TPO-RAs have increasingly been used as a second line treatment for ITP. TPO-RA agents have demonstrated to induce megakaryocytic maturation and platelet production and thereby increase platelet levels and reduce bleeding episodes (Bussel et al., 2019). There are currently three TPO-RAs approved for the treatment of immune thrombocytopenia in the United States and the European Union: romiplostim, eltrombopag, and avatrombopag.

TPO-RAs are able to increase the platelet count well with relatively few side effects (Ghanima et al., 2019; Catalá-Lopez et al., 2015; Gernsheimer et al., 2010). However, one possible side effect of concern is thrombosis. TPO-RA's could potentially increase the risk for thrombosis by their ability to increase the platelet count and stimulate the production of young and hemostatically more active platelets and microparticles (Rodeghiero, 2016). Both single-arm and controlled trials report cases of thrombosis with TPO-RA treatment. The RAISE study, a large randomized controlled trial on the safety and efficacy of eltrombopag, reported an incidence of 2% for thrombosis with TPO-RA usage as compared to 0% in the control group (Cheng et al., 2011). The EXTEND study, which was an open-label extension study of the RAISE study, reports a total rate of 6% for thromboembolic events (Wong et al., 2017). Similar rates for thrombosis have been reported for romiplostim (Kuter et al., 2013) and avatrombopag (Bussel et al., 2014).

However, ITP itself is also associated with an increased risk of thrombosis (Nørgaard et al., 2016; Sarpatwari et al., 2010). A systematic review by Doobaree et al. compared patients with ITP to age and gender matched non-ITP individuals (Doobaree et al., 2016). They found a relative risk (RR) of 1.60 (1.34–1.86) for any thrombotic event and respectively a RR of 1.52 (1.25–1.80) for arterial thrombotic events (ATE's) and a non-significant RR of 1.70

(0.96–2.43) for venous thrombotic events (VTE's). Additionally, another systematic review (Langeberg et al.) found an increased risk for both ATE (aRR 1.5 (1.3–1.8)) and VTE (aRR 1.9 (1.4–2.7)) (Langeberg et al., 2016). Finally, a review by Rodeghiero found an approximately two times higher risk for VTE in ITP but no significant increased risk for ATE (Rodeghiero, 2016).

This review aims to provide an overview and update of the current findings in literature on the risk of thrombosis with TPO-RAs as compared to placebo or standard of care.

Methods

Search strategy and inclusion criteria

The literature search was conducted in the databases MEDLINE, EMBASE, and the Cochrane library. Additionally, the reference lists of included articles were screened for relevant articles. Articles that are not published commercially are not included in this review. The search strategies are based on the inclusion criteria and were composed with help from an experienced librarian of the Central Medical Library of the University in Groningen, the Netherlands. The search was focused on articles that included terms relating to both ITP (immune thrombocytopenia) and terms related to thrombopoietin receptor agonists (romiplostim, eltrombopag and/or avatrombopag). No filters were used to reduce the possibility of accidental exclusion of relevant articles. The search is included in the supplemental materials. The three databases were searched over the period from 01-05-2020 until 01-06-2020.

To meet inclusion criteria, studies were required to have an intervention and control group. The study population needed to comprise patients with persistent or chronic ITP (> 3 months after diagnosis) and all included patients needed to be adults (18 years and older). Patients in the intervention group were required to receive TPO-RA therapy; patients in the control group needed to receive either placebo or standard of care. Only articles with publication dates between the year 2000 and the present were included.

Data collection and quality analysis

Selection process

Articles were screened and included or excluded based on title and abstract. This was done by two independent reviewers. When the independent reviewers' opinions differed on the

inclusion or exclusion, a third reviewer was involved to come to an agreement. Afterwards, the articles were fully read and were included in the review and meta-analysis.

Data collection process

Data was extracted from the studies using a format. This format included the following data: reference (author, title, journal, year), study design, study population (sample size and patient demographics), intervention group, control group, outcome (prevalence or relative risk on thrombosis for both intervention and control group), and study quality (risk of bias).

Outcomes and prioritization

The primary outcomes are:

1. The incidence of thrombosis in the intervention group (with TPO-RA), compared to the incidence of thrombosis in the control group.
2. The relative risk (RR) of thrombosis in the intervention group (TPO-RA), compared to the relative risk of thrombosis in the control group.

Quality analysis

The risk of bias was assessed with the Revised Cochrane risk-of-bias tool for randomized trials (RoB 2) (Higgins et al., 2019). For studies that are not randomized, the Risk of Bias in Non-Randomized Studies- of Interventions assessment tool (ROBINS-I) was used (Sterne et al., 2016). Studies could be rated as low risk, some concerns/moderate risk, or high risk for bias.

Data analysis

With the prevalence data, the relative risk on thrombosis for each study was calculated. Risk ratios were shown in a Forest plot. Based on the results from the tests for assessing heterogeneity (chi-square test, I2 test), the data was pooled and a meta-analysis was conducted. For the meta-analyses the Mantel-Haenszel's test was used with a random effect model. A p-value of <0.05 was considered statistically significant. All of the data analyses were conducted with Review Manager (RevMan) Version 5.4.

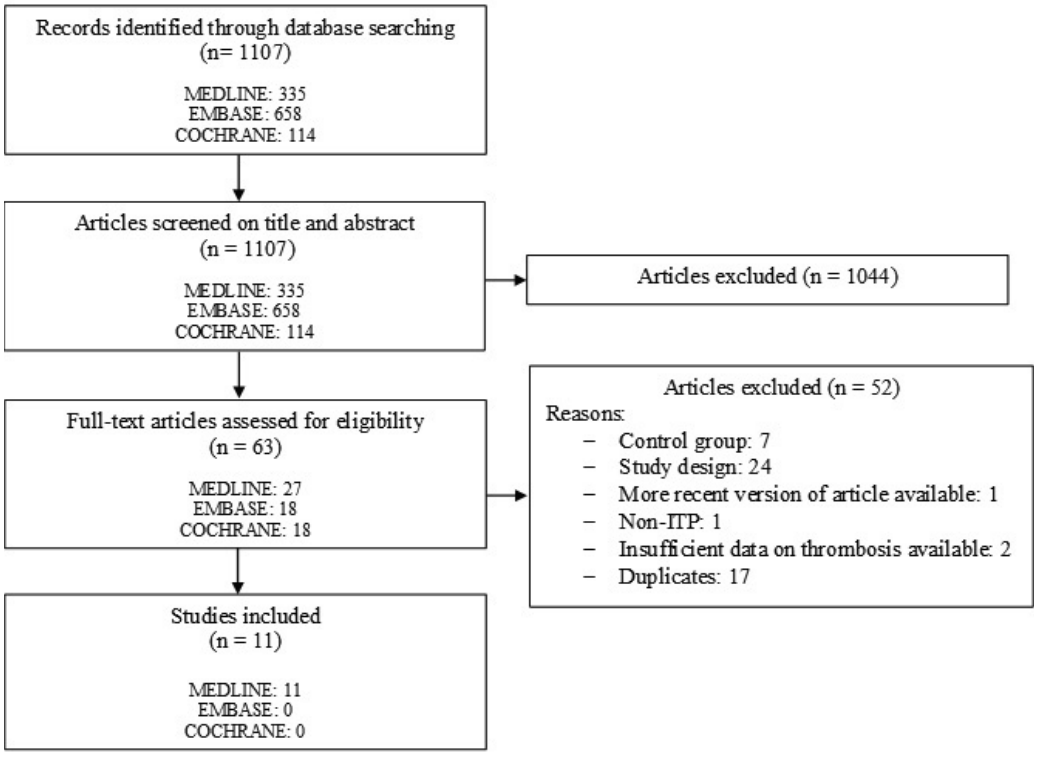
Results

Study identification and selection

The initial search found a total of 1107 records. Of these, 1044 articles were excluded based on title and abstract. Reasons for exclusion were amongst others: subject not related to ITP or TPO-RA, different study design and lack of control group. Afterwards, 63 articles

were assessed for eligibility. Of these, 52 articles were excluded (**Fig. 1**). A total of 11 studies were finally included in this review (Fig. 1)

Figure 1 – Flowchart of study inclusion



Study characteristics

Of the 11 included studies, 9 were double blind placebo controlled randomized trials. The remaining two studies were open-label non randomized trials. In total, 1093 patients were enrolled in the studies, of which 740 patients were enrolled in the intervention group and 352 in the control group. Three different TPO-RAs were used as intervention: in four studies romiplostim was used, in six studies eltrombopag, and in one study avatrombopag. Most studies used a placebo as control, however for the two open-label studies respectively standard of care (Kuter et al., 2010) and steroid/no treatment (Haselboeck et al., 2012) were applied. The study duration ranged from 4 weeks to 52 weeks. Thrombotic events occurred in both the intervention and control group. However, more thrombotic events were noted in the intervention (TPO-RA) group: 25 events compared to 4 events in the control group. In the intervention group 5 of these events were arterial thrombotic events (ATE's), and 8 of these events were venous thrombotic events (VTE's). For 12 events it was not specified if the thrombosis was venous or arterial. In the control group there

were no ATE, 2 VTE, and no information for 2 events. All events were included in the analysis. The median platelet counts during treatment in the intervention group ranged from 26×109/L to 183×109/L. The median platelet counts during treatment in the control group ranged from 8×109/L to 71,5×109/L (**Table 1**). All of the studies except one (Haselboeck et al., 2012) found higher platelet counts in the intervention than control group. Haselboeck et al. attribute this discrepancy to confounding: patients in the intervention group had lower baseline platelet counts and more previous therapies and therefore presumably represented more severe ITP cases. More detailed study characteristics are presented in Table 1.

Table 1 – Study characteristics

Study	Study design	Study duration	Population	Intervention		Control		Thrombotic events		Risk of bias
				Drug	N	Method	N	Intervention group	Control group	
(Bussel et al., 2006)	Double-blind, placebo controlled, phase II	6 weeks	Chronic ITP n=21	Romiplostim (1, 3 or 6µg/kg)	17	Placebo	4	0	1: popliteal deep-vein thrombosis	Low
(Bussel et al., 2007)	Double blind, placebo controlled	6 weeks	Chronic ITP n=118 (117 treated)	Eltrombopag (30, 50 or 75mg)	88	Placebo	29	1: thromboembolism in the small vessels of the liver and kidneys	0	Low
(Kuter et al., 2008)	Double blind, placebo controlled, phase III	24 weeks	ITP n=125	Romiplostim (1 or 2µg/kg)	83	Placebo	42	2: popliteal artery thrombosis CVA	1: pulmonary embolism	Low
(Bussel et al., 2009)	Double blind, placebo controlled	6 weeks	Chronic ITP n=114	Eltrombopag (50 or 75mg)	76	Placebo	38	0	0	Low
(Kuter et al., 2010)	Open-label, controlled	52 weeks	ITP n=234	Romiplostim (3–10µg/kg)	157	Standard of care	77	11 (in 6 patients)	2 (in 2 patients)	Low
(Cheng et al., 2011)	Double blind, placebo controlled, phase III	24 weeks	Chronic ITP n=197	Eltrombopag (50mg, could be increased to 75mg or decreased to 25mg)	135	Placebo	62	3 pulmonary embolism (gr4) deep vein thrombosis (gr 3) pulmonary embolism (gr 4)	0	Low
(Shirasugi et al., 2011)	Double-blind, placebo controlled, phase III	12 weeks	Chronic ITP n=34	Romiplostim (3–10µg/kg)	22	Placebo	12	0	0	Low
(Haselboeck et al., 2013)	Open label, non-randomized controlled	4 weeks	ITP n=23	Eltrombopag(25–75mg)	11	Steroid treatment or no treatment	12	2: deep vein thrombosis cerebral	0	Moderate

Study	Study design	Study duration	Population	Intervention		Control		Thrombotic events		Risk of bias
				Drug	N	Method	N	Intervention group	Control group	
								venous thrombosis		
(Tomiyama et al., 2012)	Double-blind, placebo controlled	6 weeks	Chronic ITP n=23	Eltrombopag (12.5–25mg)	15	Placebo	8	1: TIA	0	Low
(Yang et al., 2017)	Double-blind, placebo controlled, phase III	8 weeks	Chronic ITP n=155	Eltrombopag (25–75mg)	104	Placebo	51	2: cerebral infarction deep vein thrombosis	0	Low
(Jurczak et al., 2018)	Double-blind, placebo controlled, phase III	26 weeks	Chronic ITP n=49	Avatrombopag(20mg, could be increased to 40mg or decreased to 5mg)	32	Placebo	17	3: deep vein thrombosis asymptomatic pulmonary embolism cerebrovascular event	0	High

Study quality

Nine out of the eleven included studies have a low risk of bias (**Table 1**). The study conducted by Jurczak et al. 2018 scored high risk of bias based on the Revised Cochrane risk-of-bias tool for randomized trials (RoB 2). The domain in which the bias was found was the risk of bias due to deviations from the intended interventions (effect of adhering to intervention). In this study a proportionally large part of the control group did not complete the study. The study conducted by Haselboeck et al. 2012 scored moderate risk of bias on the ROBINS-I assessment tool. The risk of bias for confounding was rated high due to heterogeneity in number of previous treatment lines between the intervention and control group. A higher number of previous treatments is likely to represent a group with more severe ITP. Other domains for risk of bias in this study were rated as low.

Patient characteristics

On average 66.5 % of the patients in the TPO-RA groups were female, compared to 69.5 % in the controlled groups. The overall median age of patients in the intervention group is 50 years, compared to 52 years in the control group. The age of patients in the included studies ranged from 18 to 90. The duration of ITP (years since diagnosis) was not stated for the majority of studies. The majority of the included patients have had multiple previous treatment lines for ITP. Eight out of the eleven included studies used a history of thromboembolism as an exclusion criterium for patients entering the study. Additional demographic characteristics of enrolled patients are presented in **Table 2**.

Study	Female sex No. (%)		Age (years) median [range] or mean (sd)		Duration of ITP (years since diagnosis) median [range] or mean (sd)		Number of previous treatments No. of patients (%)**		History of thromboembolism as exclusion criterium (yes/no)
	Interv.	Control	Interv.	Control	Interv.	Control	Interv.	Control	
(Bussel et al., 2006)	12 (71)	3 (75)	45 [19–63]	55 [39–64]	6.4 [0.4–37.0]	3.4 [0.8–3.7]	1–3: 5 (29 %)4–6: 9 (53 %)>6: 3 (18 %)	1–3: 1 (25 %)4–6: 3 (75 %) >6: 0	Yes: any known risk factor for thromboembolic events or a history of cardiovascular disease.
(Bussel et al., 2007)	73 (62)	16 (55)	50 [18–85]	42 [18–85]	NA	NA	≥3: 60 (51)	≥3: 14 (48)	Yes: excluded patients with thrombosis within 1year before enrolment or MI within 3 months before enrolment.
(Kuter et al., 2008)	54 (65)	27 (64)	52 [31–88]	52 [23–88]	NA	NA	≥3: 54 (65 %)	≥3: 26 (60 %)	No
(Bussel et al., 2009)	43 (57)	27 (71)	47 [19–84]	51 [21–79]	NA	NA	≥3: 42 (55 %)	≥3: 16 (42 %)	No
(Kuter et al., 2010)	85 (54)	46 (60)	58 [18–90]	57 [18–86]	2.1 [0.0–44.2]	2.3 [0.0–33.2]	≥ 2: 110 (70)	≥ 2: 60 (78)	No
(Cheng et al., 2011)	98 (69)	43 (69)	47.0 [34–56]	52.5 [43–63]	NA	NA	≥3: 75 (56 %)	≥3: 32 (52 %)	Yes: excluded patients with arterial or venous thrombosis plus two or more thrombosis risk factors.
(Shirasugi et al., 2011)	14 (64)	10 (83)	58.5 (± 12.6)	27.6 (± 13.4)	9.7 (± 10.4)	7.6 (± 5.9)	Median number of treatments: 4 [1–19]	Median number of treatments: 4 [1–7]	Yes: excluded patients with arterial thrombosis or a history of venous thrombosis necessitating anticoagulation therapy.
(Haselboeck et al., 2013)	9 (90)	9 (75)	30 [20–58]	32 [24–53]	0.79 [0.42–2.92]	1.08 [0.38–2.58]	Median number of treatments: 2 [1–3]	Median number of treatments: 1 [1–2]	Yes: excluded patients with a history of thromboembolic disease.
(Tomiyama et al., 2012)	8 (53)	7 (88)	58.0 (26–72)	60.5 (38–72)	NA	NA	NA	NA	Yes: excluded patients with a history of arterial or venous thrombosis within 1year before enrolment.
(Yang et al., 2017)	77 (74)	40 (78)	48 [18–84]	42 [22–66]	NA	NA	≥1: 19 (18 %)	≥1: 10 (20 %)	Yes: excluded patients with any prior history of cardiovascular disease.
(Jurczak et al., 2018)	23 (72)	8 (47)	46.4 (±14.2)	41.2 (±14.7)	NA	NA	NA	NA	Yes: excluded patients with clinically significant arterial or venous thrombosis and cardiovascular disease.

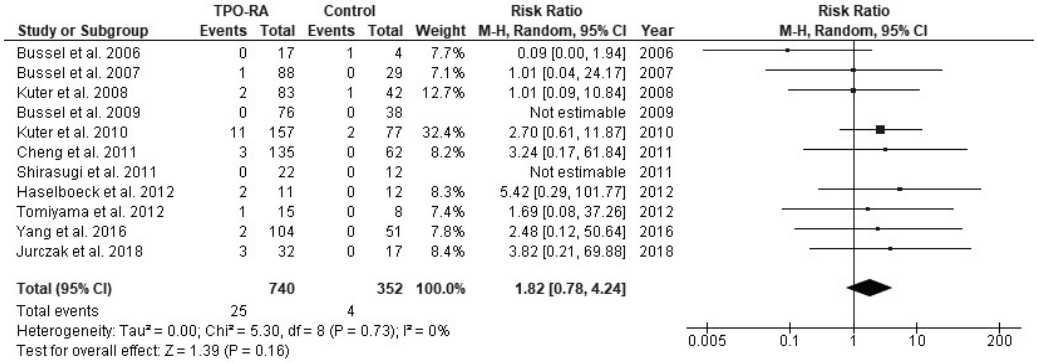
*NA = Not available.

** Except if stated otherwise.

Main results

The Risk Ratios (RR) for each study are presented in **Fig. 2**. The study of Bussel et al. in 2006 is the only study with a RR of less than 1, namely 0.09. Other studies show a RR that is either close to 1 or bigger than 1. For two studies it was impossible to estimate the RR, because thrombotic events did not occur neither in the intervention nor in the control group. The majority of included studies show that there is a positive relation between TPO-RA usage and thrombosis, however none of the individual risk ratios is statistically significant.

Figure 2 – Forrest plot including all studies



The chi-square test and the I2 test were used to assess heterogeneity. Because the chi-square test has a p>0.10 and the I2 test has a value of 0, we assume there is low heterogeneity. The meta-analysis also showed a positive relation between TPO-RA use and thrombosis (RR 1.82 [0.78–4.24]), however also in this case the result is not significant (p=0.16). We decided to conduct a sensitivity analysis, that only included studies with a low risk of bias. We wanted to see whether this changed the outcome of the results. This sensitivity analysis generated a RR of 1.52 [0.60–3.83] with a p-value of 0.38 (**Fig. 3**). A final sensitivity analysis was conducted in order to see whether the risk of thrombosis in studies with a longer follow up (>12 weeks), differed from studies with a shorter follow up. This sensitivity analyses generated a RR of 2.20 [0.69–6.98] and a p-value of 0.18 (**Fig. 4**).

Figure 3 – Forrest plot of studies with low risk of bias

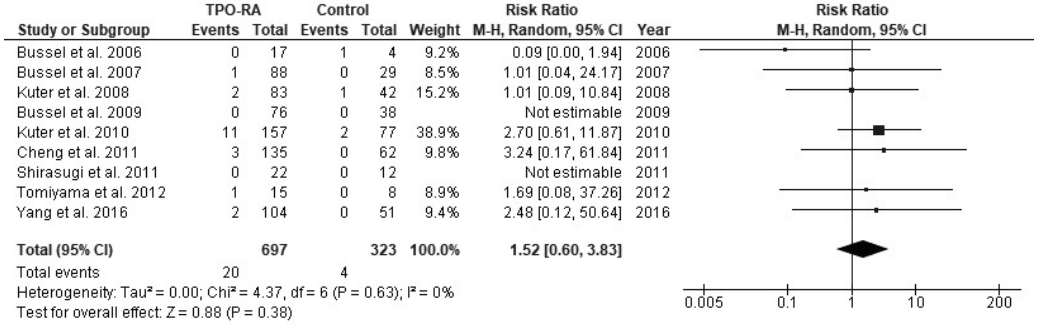
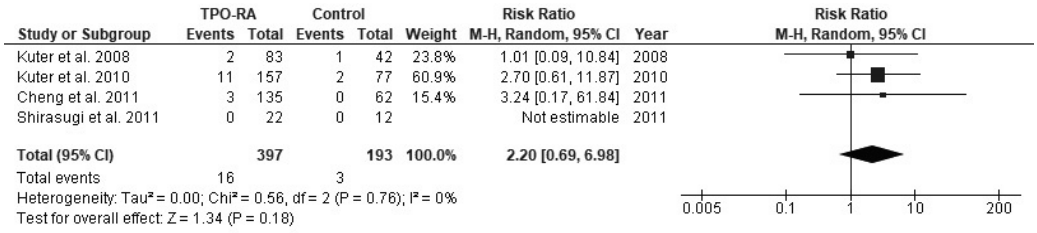


Figure 4 – Forrest plot of studies with a follow up > 12 weeks



Discussion

More thromboembolic events were noted in the TPO-RA group than in the control group: 25 events compared to 4 events respectively. Furthermore, most of the relative risk ratios (RR) also showed a positive relation between TPO-RA treatment and thrombosis. The only study that showed a RR smaller than 1 for thrombosis is the study conducted by Bussel et al. in 2006 (Bussel et al., 2006). However, none of these risk ratios appeared to be statistically significant. This is in line with the result from our meta-analysis: RR: 1.82 [0.78–4.24], p=0.16. Therefore, it appears that the number of thrombotic events does not translate into a statistically significant higher risk of thrombosis due to the treatment with a TPO-RA.

Sensitivity analyses

Remarkably, the study by Bussel et al. 2006 is the only study with a RR of less than 1 for thrombosis. There was only one single thromboembolic event and this event occurred in the control (placebo) group. Probably, due to the small number of participants (n=21), the study population was too small for more thrombotic events to occur. Another possible explanation could be that the median age in the control group was higher than in the intervention group (respectively 55 [39–64] and (49 [19–63]). A higher age is associated with a higher risk for atherosclerotic plaques, which could influence the risk of thrombosis. We conducted sensitivity analyses for better understanding of the data using studies with low risk of bias (Fig. 3) and studies using longer follow up (Fig. 4). Additionally, we used the person-time at risk due to the difference of inclusion length in the studies (data not shown). All sensitivity analyses showed a non-significant (positive) relation between TPO-RA use and thrombosis. Therefore, the results of the sensitivity analyses are in line with the results from our initial analysis. However, the non-significant effect could be caused by the low incidence of thrombosis. It is possible that bigger groups would generate a positive relation between TPO-RA use and thrombosis.

Comparison to literature

Two previous systematic reviews studied the risk of thrombosis with TPO-RA treatment as compared to the risk of thrombosis without TPO-RA use. The first study (Catalá-Lopez et al. 2015), found that the relative risk of thrombosis for ITP patients with TPO-RA was 1.09 [0.40–2.96] and non-significant (p=0.66). This study included six studies in its meta-analysis, with the most recent study conducted in 2012 (Catalá-Lopez et al., 2015). The second study (Birocchi et al. 2020), concluded a pooled RR of 1.25 [0.52–2.99], p=0.62 for thrombosis with TPO-RA use. This study included 15 randomized controlled trials/cohort studies in its meta-analysis. Five of these papers studied specifically the risk of thrombosis with TPO-RA treatment in children (Birocchi et al., 2020).
The pooled RR of our systematic review is higher than the risk ratio noted in previous studies. An explanation for the difference in RR between our study and the study by Catalá-Lopez et al., is that their study included six studies, compared to the eleven studies in our review. There are three studies included in our review and missing in their review, that have relatively high relative risks: 5.42 (Haselboeck et al. 2012), 2.48 (Yang et al. 2016) and 3.82 (Jurczak et al. 2018). Because these risk ratios are higher, the pooled RR is higher as well. The difference found between our review and the review by Birocchi et al. is likely due to the fact that they included studies with children. Overall, it was found that thrombosis occurred less often in the studies that included children and therefore reduced the pooled RR.

Strengths and limitations

Only one other systematic review has looked primarily into the relation between thrombosis and the treatment with TPO-RA, which dated from 20155. However, this review did not solely focus on ITP patients, but included patients with myelodysplastic syndrome, chronic liver disease and advanced solid tumors as well. Since then, more studies on the safety of TPO-RA use in ITP patients have been conducted. Therefore, a need existed for an updated systematic review and meta-analysis, which our review fulfils. Furthermore, our review is systematically conducted. The screening of articles by title and abstract was peer reviewed, which reduced the chance of missing an article.

This review also has several limitations. Firstly, the median study duration of included studies is 8 weeks. Because patients in the included studies were not followed for a long period of time, the long-term risk for thrombosis is still unclear. Secondly, most of the studies did not include thrombosis in their primary outcomes. Hence, not many studies provide information on the patients in which the thrombosis has occurred. It is therefore difficult to identify risk groups. Furthermore, the population that was included in the studies may not be entirely representative for patients admitted to the hospital. Eight out

of the eleven included studies used a history of thromboembolism as an exclusion criterium for patients entering the study, which causes a selection bias. In a "real life" setting TPO-RAs are prescribed to patients with a history of thromboembolisms as well. The rate of thrombosis in a real life setting may therefore be higher than what was noted in the studies. Finally, the initial and sensitivity analyses show a corresponding result and are in line with each other, which adds to the power of our review.

Further research recommendations

There is a need for more trials with ITP patients that include thrombosis in their primary outcome measures. By doing so, more data about the occurrence of thrombosis in certain risk groups (for example older age, hypertension, diabetes mellitus, hypercholesterolemia, or patients after splenectomy) could be identified.

Implication

From this study it can be concluded that there is no statistically significant relation between thrombosis and TPO-RA usage. This implies that no higher risk of incident thromboembolic event can be demonstrated in patients on TPO-RA therapy as compared to ITP patients without TPO-RA therapy. Obviously the current treatment guidelines for ITP should be followed. One should be cautious, however, in prescribing TPO-RAs to patients with a history of thromboembolic events, due to the lack of studies that have included this population in their analyses. Furthermore, it is unknown what the risk of thrombosis is for ITP-patients with higher platelet counts. Most of the studies stopped or reduced the TPO-RA dose when the platelet counts increased to a level of 200×109/L. It is therefore unknown what the risk for thrombosis is when the platelet levels rise above 200×109/L. Therefore, it is also advisable to be careful in prescribing TPO-RAs to these patients and monitor them conscientiously for the risk of thrombosis. Studies with larger groups could generate a significant result and show that there is a higher risk of thrombosis with ITP use. However, considering the very low incidence of thrombosis in patients without known risk factors for thrombosis, it is debatable to what matter this would influence the clinical practice.

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