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

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Chapter 9

Perioperative oral eltrombopag versus intravenous immunoglobulin in patients with immune thrombocytopenia: a non-inferiority, multicentre, randomised trial

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Abstract

Background Patients with immune thrombocytopenia are at risk of bleeding during surgery, and intravenous immunoglobulin is commonly used to increase the platelet count. We aimed to establish whether perioperative eltrombopag was non-inferior to intravenous immunoglobulin.

Methods We did a randomised, open-label trial in eight academic hospitals in Canada. Patients were aged at least 18 years, with primary or secondary immune thrombocytopenia and platelet counts less than 100 × 109 cells per L before major surgery or less than 50 × 109 cells per L before minor surgery. Previous intravenous immunoglobulin within 2 weeks or thrombopoietin receptor agonists within 4 weeks before randomisation were not permitted. Patients were randomly assigned to receive oral daily eltrombopag 50 mg from 21 days preoperatively to postoperative day 7 or intravenous immunoglobulin 1 g/kg or 2 g/kg 7 days before surgery. Eltrombopag dose adjustments were allowed weekly based on platelet counts. The randomisation sequence was generated by a computerised random number generator, concealed and stratified by centre and surgery type (major or minor). The central study statistician was masked to treatment allocation. The primary outcome was achievement of perioperative platelet count targets (90 × 109 cells per L before major surgery or 45 × 109 cells per L before minor surgery) without rescue treatment. We did intention-to-treat and per-protocol analyses using an absolute non-inferiority margin of –10%. This trial is registered with ClinicalTrials.gov, NCT01621204.

Findings Between June 5, 2013, and March 7, 2019, 92 patients with immune thrombocytopenia were screened, of whom 74 (80%) were randomly assigned: 38 to eltrombopag and 36 to intravenous immunoglobulin. Median follow-up was 50 days (IQR 49–55). By intention-to-treat analysis, perioperative platelet targets were achieved for 30 (79%) of 38 patients assigned to eltrombopag and 22 (61%) of 36 patients assigned to intravenous immunoglobulin (absolute risk difference 17·8%, one-sided lower limit of the 95% CI 0·4%; pnon-inferiority=0·005). In the per-protocol analysis, perioperative platelet targets were achieved for 29 (78%) of 37 patients in the eltrombopag group and 20 (63%) of 32 in the intravenous immunoglobulin group (absolute risk difference 15·9%, one-sided lower limit of the 95% CI –2·1%; pnon-inferiority=0·009). Two serious adverse events occurred in the eltrombopag group: one treatment-related pulmonary embolism and one vertigo. Five serious adverse events occurred in the intravenous immunoglobulin group (atrial fibrillation, pancreatitis, vulvar pain, chest tube malfunction and conversion to open splenectomy); all were related to complications of surgery. No treatment-related deaths occurred.

Interpretation Eltrombopag is an effective alternative to intravenous immunoglobulin for perioperative treatment of immune thrombocytopenia. However, treatment with eltrombopag might increase risk of thrombosis. The decision to choose one treatment over the other will depend on patient preference, resource limitations, cost, and individual risk profiles.

1. Introduction

Immune thrombocytopenia is an autoimmune disease characterised by a low platelet count (<100 × 109 cells per L) and an increased risk of bleeding. Patients with stable immune thrombocytopenia are typically asymptomatic despite ongoing thrombocytopenia. When such patients require surgery or other invasive procedures, they often need treatment to increase the platelet count preoperatively and lower the risk of bleeding associated with the surgery.

Intravenous immunoglobulin is commonly used to increase the platelet count before surgery for patients with immune thrombocytopenia because it can produce a rapid, transient rise in the platelet count. In the surgical setting, intravenous immunoglobulin might be preferable over corticosteroids, which can cause impaired wound healing and other toxic effects.1 Intravenous immunoglobulin is a blood product that is in short supply, with side-effects that include headache, allergic reactions, and aseptic meningitis.2 Eltrombopag is a small, non-peptide oral thrombopoietin receptor agonist indicated for the treatment of patients with chronic immune thrombocytopenia.3, 4 Platelet count responses typically occur within 1–2 weeks and responses are generally sustained as long as the medication is continued. Eltrombopag can cause liver toxicity in approximately 10% of patients, and has been associated with thrombosis.5 We designed the Bridging ITP Trial to assess whether eltrombopag was not inferior to intravenous immunoglobulin for achieving platelet count targets in the perioperative setting.

Research in context

Evidence before this study

We searched electronic databases (MEDLINE, PubMed) from June 1, 2009, to March 2, 2020, to identify primary studies written in English describing the efficacy and safety of eltrombopag and other thrombopoietin receptor agonists for patients with immune thrombocytopenia undergoing surgery. We identified six observational studies that enrolled 206 patients treated with either romiplostim or eltrombopag. None of these studies included a control group and none was a randomised trial. One additional cohort study described 42 patients receiving recombinant human thrombopoietin perioperatively. The data showed that thrombopoietin receptor agonists raised platelet counts in advance of surgical procedures for patients with immune thrombocytopenia. Thrombosis and rebound thrombocytopenia were reported infrequently. The risk of bias from these studies was high and preoperative care was not standardised.

Added value of this study

This is, to our knowledge, the first randomised trial of perioperative management for patients with immune thrombocytopenia. The findings show that eltrombopag was non-inferior to intravenous immunoglobulin for achieving surgical platelet count targets preoperatively and maintaining those targets in the postoperative period. In the eltrombopag group, one treatment-related pulmonary embolism occurred and two patients developed thrombocytosis after splenectomy. Our data show that eltrombopag is an alternative to intravenous immunoglobulin for perioperative management of immune thrombocytopenia.

Implications of all the available evidence

Treatment choices for perioperative management of immune thrombocytopenia can be expanded beyond intravenous immunoglobulin, a blood product that is in relatively short supply, or corticosteroids, which might be less desirable in the surgical setting owing to their potential toxic effects. These data raise awareness about potential thrombotic risks and consideration for perioperative thromboprophylaxis with thrombopoietin receptor agonists.

Methods

Study design and patients

We did a randomised, parallel arm, open-label, non-inferiority trial at eight academic hospitals in Canada (appendix p 106). Adult patients (≥18 years) with primary or secondary immune thrombocytopenia as per American Society of Hematology Guidelines6 who had a platelet count lower than 100 × 109 cells per L before major surgery or lower than 50 × 109 cells per L before minor surgery were eligible. Surgery was designated as major or minor by the treating surgeon and haematologist on the basis of the duration and complexity of the surgery and the bleeding risk of the patient. Exclusion criteria were abnormal liver enzymes (aspartate or alanine aminotransferase >2 × upper limit of normal [ULN] or bilirubin 1·5 × ULN in the absence of clinically benign liver disease), thrombosis or myocardial infarction within 12 months, known bone marrow reticulin or fibrosis, or active malignancy. New immune thrombocytopenia treatments or increases in the dose of a regular immune thrombocytopenia treatment within 2 weeks, intravenous immunoglobulin within 2 weeks, or use of a thrombopoietin receptor agonist within 4 weeks before randomisation were not permitted. Perioperative thromboprophylaxis was prescribed as per institutional protocols, which were similar across centres.

The trial was approved by the research ethics boards at each participating centre. The study was done in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. All protocol amendments implemented over the course of the study received approval from the local research ethics boards (appendix pp 57–105). Written informed consent was obtained from all patients.

Randomisation and masking

Patients were randomly assigned (1:1) using a centralised, secure, web-based, electronic system accessed by authorised study personnel at each site. Randomisation was stratified by centre and surgery type (major or minor) with undisclosed variable block sizes between two and six.7 The allocation sequence was generated by an independent statistician using a computerised random number generator and concealed. Patients, investigators, and

outcome assessors were not masked, but the central study statistician was masked to treatment allocation.

Procedures

Oral eltrombopag 50 mg daily was administered from day –21 before surgery until day 7 after surgical haemostasis. Dose adjustments were done weekly according to platelet counts, with instructions for early discontinuation for patients with platelet counts greater than 400 × 109 cells per L.8 Intravenous immunoglobulin was administered on day –7 (give or take 2 days) at a dose of 1 g/kg or 2 g/kg, according to local centre protocols.6 The timing of intravenous immunoglobulin allowed for the administration of up to 2 g/kg before day –1 (which was reserved for rescue treatment), and for the maximum anticipated response at 1 week.9 A repeat dose of intravenous immunoglobulin (1 g/kg or 2 g/kg) was permitted up to day 7 after surgical haemostasis if needed. Patients were followed up at weekly intervals from day –21 before surgery to day 28 after surgical haemostasis. At each follow-up, patients were assessed for adverse events measured using the Common Terminology Criteria for Adverse Events, with causality determined by local site investigators.8 Laboratory tests (complete blood count and selected serum chemistry tests [creatinine, sodium, potassium, aspartate aminotransferase, alanine aminotransferase, total bilirubin, albumin, lactate dehydrogenase]) were done at each visit. Serious adverse events were defined as any untoward occurrence that resulted in death, was life threatening, required (or prolonged) hospitalisation, caused persistent or substantial disability or incapacity, or resulted in congenital anomalies or birth defects. Criteria for removal from the study were a change in diagnosis or eligibility, occurrence of an adverse event that would endanger the patient's safety according to the treating physician, or request to withdraw. An independent committee consisting of three haematologists (WL, PV, and MW) adjudicated all rescue treatments.

Bleeding was measured with the immune thrombocytopenic purpura bleeding score.10 Patient-reported treatment satisfaction was measured by the Treatment Satisfaction Questionnaire for Medication (TSQM), a validated tool that includes 11 items pertaining to medication effectiveness, side-effects, convenience, and overall satisfaction, with each item scored from 0 to 100.11

Outcomes

The primary outcome was the achievement of platelet count targets of 45 × 109 cells per L or higher for minor surgery or 90 × 109 cells per L or higher for major surgery from day –1 before surgery to day 7 after surgical haemostasis without rescue treatment. These conservative platelet count targets were selected to avoid unnecessary criteria for surgery

cancellations or overuse of rescue treatment. Rescue treatment was defined as any additional treatment administered during the perioperative period to increase the platelet count or prevent bleeding.8 Stress doses of corticosteroids and intraoperative platelet transfusions without thrombocytopenia were not considered rescue treatment. Secondary outcomes were thrombosis; bleeding; platelet count measurements over time; surgical delays or cancellations; rescue treatment; patient-reported treatment satisfaction; time to treatment failure; adverse events; thrombocytosis; and use of blood transfusions.

Statistical analysis

A statistical analysis plan was developed a priori. We chose a non-inferiority design because the objective was to establish an alternative treatment option to intravenous immunoglobulin with comparable effectiveness. The non-inferiority margin was set at a 10% absolute risk reduction, such that eltrombopag could be considered not inferior to intravenous immunoglobulin as long as the lower bound of the one-sided 95% CI for the difference in effect did not exceed –10%. The non-inferiority margin was informed by the evidence, a formal investigator meeting, expert consultation, and implications for sample size given the infrequent nature of immune thrombocytopenia and surgery. A post-hoc superiority analysis was done once non-inferiority was first shown. We estimated that 74 patients would provide 80% power at a one-sided significance level of 0·05 for the primary intention-to-treat analysis, assuming an expected response of 70% with intravenous immunoglobulin and 84% with eltrombopag inferred from indirect evidence.5, 12, 13 For the primary outcome, two-sided 95% CIs were computed for the probability of response in each group using one-proportion Z test, while a one-sided 95% CI was computed for the difference in the probabilities using Farrington-Manning test. The populations analysed were all randomised patients (intention to treat) and all patients who received the intervention as planned and completed surgery (per protocol).

For secondary outcomes, a Wilcoxon rank sum test was used to compare platelet counts and overall treatment satisfaction scores between groups, where the estimated difference (95% CI) in location parameters of distributions between the two groups and the test p value are reported. Fisher's exact tests were used to assess the difference between the groups for rescue treatment, postoperative transfusion, thrombocytosis, rebound thrombocytopenia, surgical delays or cancellation, venous thromboembolism, and serious adverse events. Odds ratios and associated 95% CIs are reported, and p values were calculated to test the null hypothesis of no difference. A p value less than 0·05 (two-sided) was considered statistically significant for the secondary outcomes. The analysis of TSQM scores was done for patients who completed study visits on day –1 and day 7. A planned subgroup analysis was done for surgery type (major vs minor) and an exploratory analysis

was planned for patients who underwent splenectomy. All analyses were done using R (version 3.5.2).

Independent site monitoring was done to verify data accuracy and protocol compliance. The steering committee oversaw the conduct of the trial. The data monitoring committee reviewed all safety data after a third of patients, two-thirds of patients, and when all patients completed the trial and if an unexpected treatment-related serious adverse event occurred, as judged by the treating physician.
The study is registered with ClinicalTrials.gov, NCT01621204.

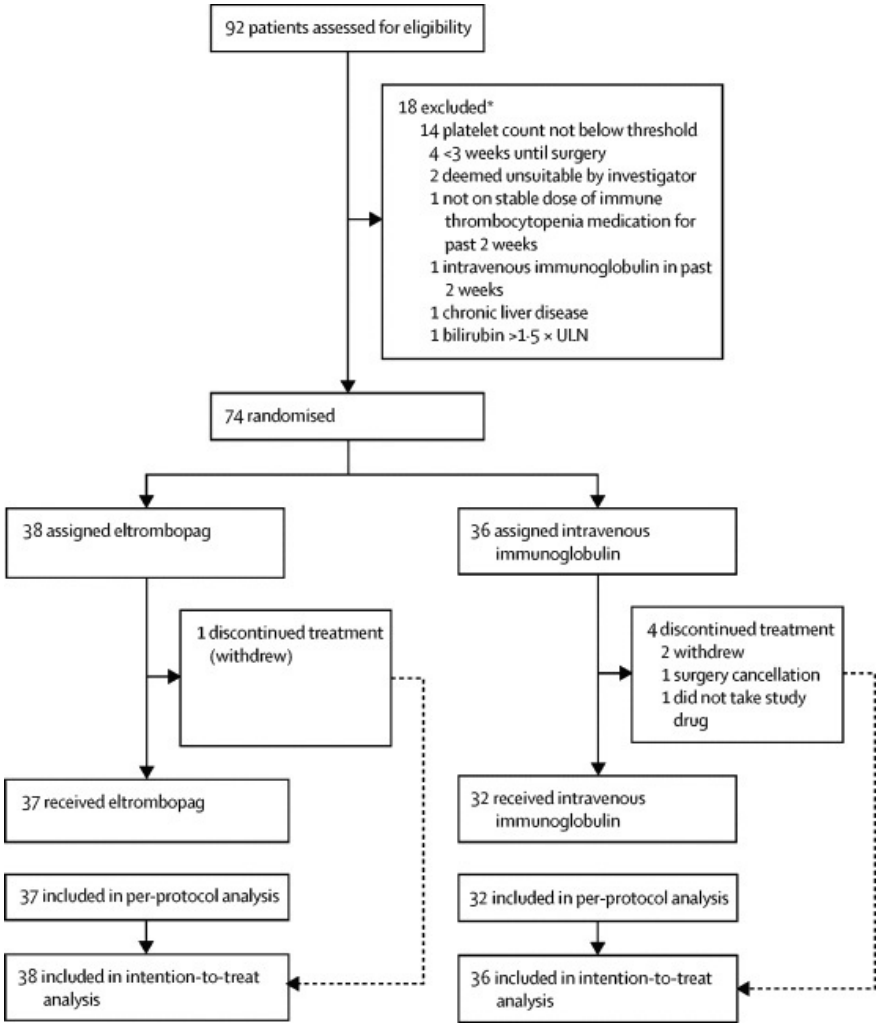
Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All investigators had full access to all the data in the study and the corresponding author had final responsibility for the decision to submit for publication.

Results

From June 5, 2013, to March 7, 2019, 74 patients with immune thrombocytopenia were randomly assigned to receive eltrombopag (n=38) or intravenous immunoglobulin (n=36) perioperatively (**figure 1**). The final patient completed follow-up on April 25, 2019. Median follow-up was 50 days (IQR 49–55). Recruitment ended because the target sample size was reached. One patient in the eltrombopag group and four patients in the intravenous immunoglobulin group did not complete study treatment. No patients in the intravenous immunoglobulin group needed a second dose. More patients in the eltrombopag group than the intravenous immunoglobulin group underwent major surgery (**table 1**). 19 patients underwent splenectomy (ten in the eltrombopag group and nine in the intravenous immunoglobulin group). Surgical haemostasis was achieved on the same day as the surgery for 28 (74%) of 38 patients in the eltrombopag group and 24 (73%) of 33 patients in the intravenous immunoglobulin group. There were no missing data for the primary and secondary outcomes.

Figure 1 – Trial-profile



ULN=upper limit of normal. *Some patients had more than one reason for exclusion.

Table 1 – Demopgrahics and baseline characteristics

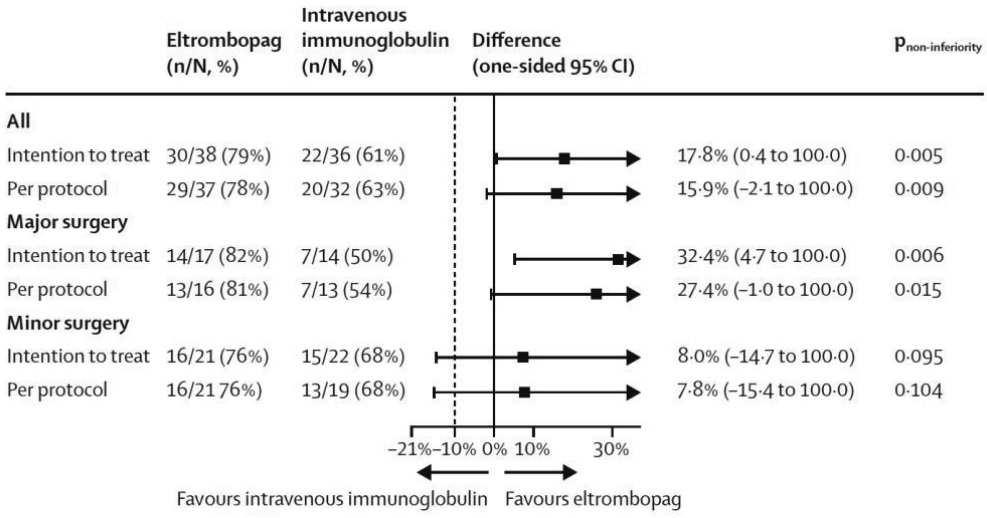
	Eltrombopag (n=38)	Intravenous immunoglobulin (n=36)
Sex		
Female	20 (53%)	18 (50%)
Male	18 (47%)	18 (50%)
Age, years	59·8 (17·9)	62·1 (14·8)
Weight, kg	84·0 (70·1–101·7)	82·0 (71·2–94·2)
Secondary immune thrombocytopenia	4 (11%)	5 (14%)
Chronic immune thrombocytopenia	29 (76%)	29 (81%)
Duration of immune thrombocytopenia, years	8·0 (1·2–13·7)	5·6 (1·8–15·1)
Concomitant prednisone use at baseline	8 (21%)	3 (8%)
Number of prior immune thrombocytopenia treatments	1·0 (1·0–3·0)	2·0 (1·0–3·0)
Splenectomy	5 (13%)	4 (11%)
Prednisone	20 (53%)	23 (64%)
High-dose dexamethasone	5 (13%)	6 (17%)
Prednisolone	1 (3%)	1 (3%)
Intravenous immunoglobulin	22 (58%)	24 (67%)
Anti-D	1 (3%)	1 (3%)
Rituximab	2 (5%)	3 (8%)
Romiplostim	2 (5%)	0
Eltrombopag	1 (3%)	1 (3%)
Danazol	2 (5%)	5 (14%)
Azathioprine	5 (13%)	3 (8%)
Mycophenolate mofetil	1 (3%)	1 (3%)
Vincristine	1 (3%)	0
Major surgery	17 (45%)	14 (39%)
Minor surgery	21 (55%)	22 (61%)
Splenectomy*	10 (26%)	9 (25%)
Baseline platelet count, × 10^9/L	42 (31–56)	37 (21–53)

*Considered major surgery for two patients in the eltrombopag group because of spleen enlargement and unknown reason.

By intention-to-treat analysis, 30 (79%) of 38 patients in the eltrombopag group achieved perioperative platelet count targets compared with 22 (61%) of 36 in the intravenous immunoglobulin group, meeting the criteria for non-inferiority (absolute risk difference [ARD] 17·8%, one-sided lower limit of the 95% CI 0·4%; pnon-inferiority=0·005; figure 2). Similarly, in the per-protocol analysis, 29 (78%) of 37 patients in the eltrombopag group and 20 (63%) of 32 in the intravenous immunoglobulin group achieved perioperative platelet count targets (ARD 15·9%, one-sided lower limit of the 95% CI −2·1%; pnon-inferiority=0·009). In a post-hoc analysis, eltrombopag was superior to intravenous immunoglobulin by intention to treat (ARD 17·8%, one-sided lower limit of the 95% CI 0·4%; p=0·047), but not in the per-protocol analysis (ARD 15·9%, one-sided lower limit of the 95% CI −2·1%; p=0·074).

Major surgeries (as classified by local investigator) were aortic valve replacement, arthrodesis, back surgery (placement of titanium wedge L4-5-6), breast reduction, colonoscopy, coronary artery bypass graft, epidural injection, gum graft, hip arthroplasty, invasive spinal denervation, knee arthroplasty, laparoscopic splenectomy, pelvic organ prolapse repair, peritoneal dialysis catheter insertion, platelet-rich plasma injection, thyroidectomy, or thyroid goiter resection. Minor surgeries (as classified by local investigator) were breast augmentation, cardiac defibrillator implant, carpal tunnel repair, cataract surgery, cholecystectomy, colonoscopy (with or without polypectomy), dental extraction, inguinal hernia repair, laparoscopic splenectomy, lung biopsy, myomectomy, nipple reconstruction, or skin biopsy. In the subgroup of patients with major surgery, perioperative treatment success was achieved in 14 (82%) of 17 patients with eltrombopag and seven (50%) of 14 with intravenous immunoglobulin (ARD 32·4%, one-sided lower limit of the 95% CI 4·7%; pnon-inferiority=0·006), whereas success rates for minor surgery were 16 (76%) of 21 versus 15 (68%) of 22, respectively (ARD 8·0%, one-sided lower limit of the 95% CI −14·7%; pnon-inferiority=0·095).

Figure 2 – Achievement of perioperative platelet count targets analysed by intention to treat and per protocol



Dashed line represents the non-inferiority margin.

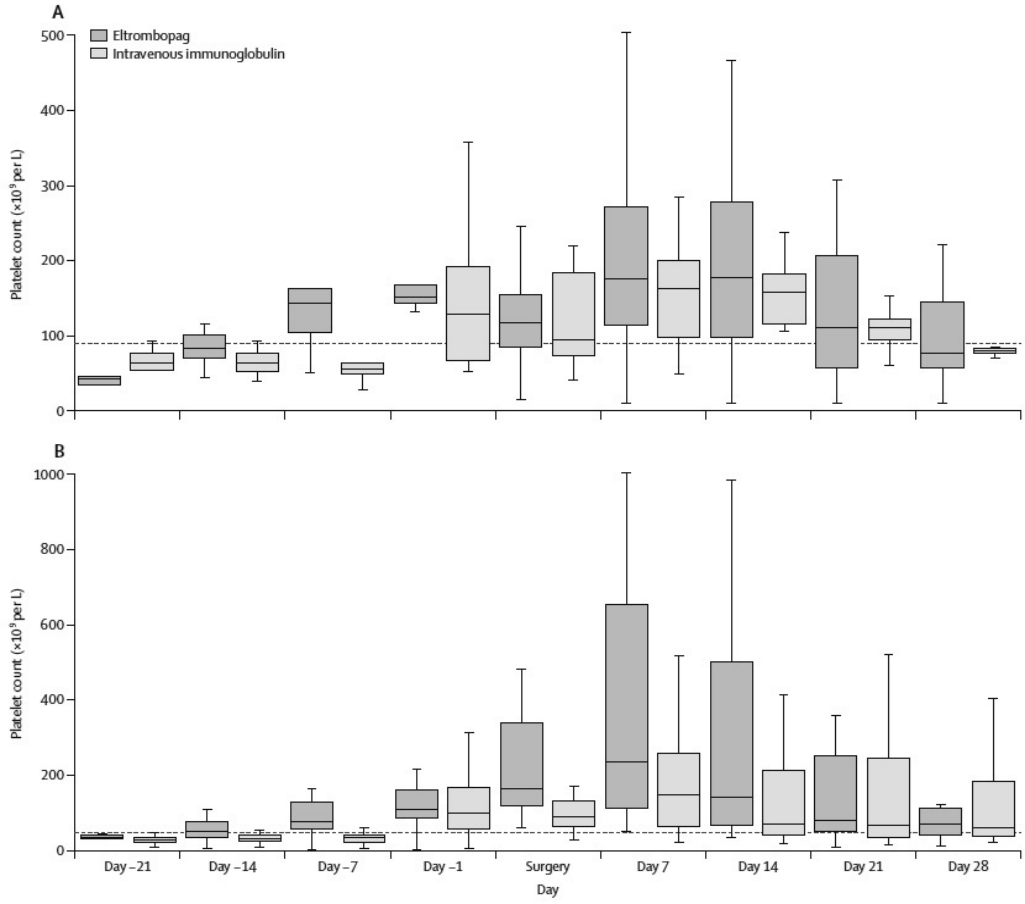
The median time to reach the platelet count targets was 6 days for intravenous immunoglobulin and 12 days for eltrombopag (**figure 3**). The daily dose of eltrombopag was 50 mg for 19 (50%) of 38 patients, 18 (95%) of whom achieved the platelet count target. 15 patients required a dose escalation to 75 mg preoperatively, nine (60%) of whom achieved the platelet count target. Four patients required a dose reduction of eltrombopag to 25 mg daily preoperatively, three (75%) of whom achieved the platelet count target. In the eltrombopag group, 14 (37%) of 38 patients reached the platelet target within 7 days, and six additional patients (20 [53%] of 38) reached the target after 2 weeks. In the intravenous immunoglobulin group, 23 (66%) of 35 patients received 1 g/kg on day –7, 13 (57%) of whom achieved the platelet count target. 12 patients [53%] received intravenous immunoglobulin 2 g/kg on day –7, eight (67%) of whom achieved the platelet count target.

14 treatment failures occurred in the intravenous immunoglobulin group: ten (71%) by day 0 and four (29%) between day 0 and day 7. Eight treatment failures occurred in the eltrombopag group: five (63%) by day 0 and three (38%) between day 0 and day 7. Severe (grade ≥2) bleeding events occurred in nine (24%) of 38 patients in the eltrombopag group and eight (22%) of 36 in the intravenous immunoglobulin group. The proportion of patients with grade 1 bleeds were similar (27 of 38 [71%] and 25 of 36 [69%], respectively).

Two patients developed thrombosis. One patient in the eltrombopag group developed a treatment-related pulmonary embolism 14 days after minor surgery (skin biopsy). The platelet count at diagnosis of pulmonary embolism was 71 × 109 cells per L. One patient in the intravenous immunoglobulin group developed a distal deep vein thrombosis (DVT) 30

days after major surgery (hip arthroplasty) with mechanical thromboprophylaxis. The DVT was judged to be unrelated to the intravenous immunoglobulin. The platelet count at DVT diagnosis was 81 × 109 cells per L.

Figure 3 – Platelet count changes over time after major surgery (A) or minor surgery (B)



Dashed line represents preoperative platelet count target.

Rescue treatment, consisting of prednisone, methylprednisolone, intravenous immunoglobulin, platelet transfusions, or dexamethasone, was required for seven (18%) of 38 patients in the eltrombopag group and seven (19%) of 36 patients in the intravenous immunoglobulin group (p=1·00). Postoperative blood transfusion (red blood cell, platelet, plasma, or cryoprecipitate) was administered to two (5%) of 38 patients in the eltrombopag group and four (11%) of 36 patients in the intravenous immunoglobulin group (p=0·42). Two surgical delays or cancellations occurred in the eltrombopag group, both caused by changes to the surgery schedule for administrative reasons. Three surgical delays or

cancellations occurred in the intravenous immunoglobulin group, one due to thrombocytopenia and two due to surgical scheduling changes for administrative reasons. TSQM scores were higher for patients who received eltrombopag than for those who received intravenous immunoglobulin on day –1 (median 91·7 [IQR 75·0–100·0] vs 83·3 [66·7–83·3]; p=0·012) and on day 7 (91·7 [83·3–100·0] vs 75 [66·7–83·3]; p=0·0002). Most of these differences were attributable to ease of administration, planning, and dosing (data not shown).

Two serious adverse events occurred in the eltrombopag group: pulmonary embolism and vertigo (**table 2**). Only the pulmonary embolism was possibly related to study treatment. Five serious adverse events occurred in the intravenous immunoglobulin group after major surgery (atrial fibrillation, pancreatitis, and vulvar pain) or minor surgery (chest tube malfunction and conversion to open splenectomy); none was related to the intravenous immunoglobulin. No patients died during the study. In the eltrombopag group, two (5%) of 38 patients developed increased liver enzymes and two (5%) developed rebound thrombocytopenia after stopping eltrombopag. One patient with rebound thrombocytopenia had a drop in platelet count from 289 × 109 cells per L to 21 × 109 cells per L with resultant bruising, gum bleeding, and oral purpura. The other patient had a drop in platelet count from 78 × 109 cells per L to 34 × 109 cells per L, with no clinical sequelae. In the exploratory subgroup of 19 patients (ten in the eltrombopag group and nine in the intravenous immunoglobulin group) undergoing splenectomy, 14 (74%) achieved perioperative platelet count targets (six in the eltrombopag group and eight in intravenous immunoglobulin group), and two (20%) of ten patients receiving eltrombopag developed postoperative thrombocytosis (platelets >1000 × 109 cells per L) without clinical sequelae.

Table 2 – Adverse events

	Eltrombopag (n=38)		Intravenous immunoglobulin (n=36)	
	Grade 1–2	Grade 3	Grade 1–2	Grade 3
Pain	24	0	15	1
Abnormal laboratory value	16	0	12	0
Headache	12	0	16	1
Fatigue	4	0	6	0
Nausea	5	0	5	0
Constipation	5	0	4	0
Intravenous immunoglobulin reaction	0	0	9	0
Diarrhoea	7	0	1	0

	Eltrombopag (n=38)		Intravenous immunoglobulin (n=36)	
	Grade 1–2	Grade 3	Grade 1–2	Grade 3
Cough	4	0	3	0
Infection	5	0	2	0
Dizziness	0	1	1	0
Atrial fibrillation	0	0	0	1
Nystagmus	0	0	0	1
Pancreatitis	0	0	0	1
Pulmonary embolism	0	1	0	0
Vertigo	0	1	0	0

Data are number of patients. Grade 1 or 2 adverse events reported in ≥10% of patients and all grade 3 adverse events are listed by severity in patients allocated to eltrombopag or intravenous immunoglobulin. No grade 4 or 5 adverse events were reported.

Discussion

In this randomised trial, eltrombopag was non-inferior to intravenous immunoglobulin for achieving and maintaining platelet count targets during the 7-day perioperative period for patients with immune thrombocytopenia. The observed effect was influenced largely by patients undergoing major surgery. In the eltrombopag group, one patient had a treatment-related pulmonary embolism, two patients had rebound thrombocytopenia after stopping eltrombopag, and two patients had thrombocytosis after splenectomy. No such events occurred in the intravenous immunoglobulin group. These results suggest that eltrombopag could be used as an alternative to intravenous immunoglobulin for perioperative management of immune thrombocytopenia, with attention to the risk of thrombosis and platelet count fluctuations.

Patients with immune thrombocytopenia are at increased risk of bleeding during surgery. We used a platelet count level less than 100 × 109 cells per L before major surgery or less than 50 × 109 cells per L before minor surgery as inclusion criteria, informed by prior recommendations and consensus, despite the paucity of evidence to support these thresholds.6, 12, 14 Although lower targets might be safe for some procedures, our protocol reflected current practice and allowed for the inclusion of all procedures for which the treating physician judged that an increase in platelet count was required. Before enrolment, the platelet target was established by the clinical team by designating the surgery as major or minor. Depending on the patient's risk factors or bleeding occurrences with previous surgeries, some procedures that might typically be considered minor were

classified as major when a higher platelet count threshold was desired. We used conservative platelet targets of 90 × 109 cells per L for major surgery and 45 × 109 cells per L for minor surgery to avoid unnecessary surgery cancellations or excess use of rescue treatment. Optimum surgical platelet count targets in immune thrombocytopenia require further evaluation.

The time to achievement of platelet count targets was shorter for intravenous immunoglobulin than for eltromobopag, which might be relevant for different planned surgeries. In a previous study,15 intravenous immunoglobulin has been associated with a platelet count rise (>50 × 109 cells /L) in approximately 85% of patients within 7 days, and in 70% of patients beyond day 7. Responses to intravenous immunoglobulin occur rapidly, usually within 48 h.13 The use of intravenous immunoglobulin as the control group was justified by its reliable response rate and common use before surgery. Since intravenous immunoglobulin was given as a single dose and eltrombopag was given daily for 3 weeks, we equalised exposure to either intervention by allowing a second dose of intravenous immunoglobulin between day 0 and day 7 if needed for dropping platelet counts, but no patients needed this. Furthermore, treatment failures were equally distributed over the 7-day assessment period. We felt that intravenous immunoglobulin was a more suitable control than corticosteroids, which are associated with less reliable response rates, variable dosing schedules, and toxic effects such as delayed wound healing and poor glycaemic control.16, 17

The rationale for the non-inferiority design was to have an alternative treatment option to intravenous immunoglobulin with proven comparable effectiveness. High-dose intravenous immunoglobulin is an expensive blood product in short supply that requires administration in a hospital or clinic setting. We did not feel that it was necessary to show superiority to add eltrombopag to the list of viable options for treatment of patients with immune thrombocytopenia around the time of surgery, and a superiority study would have imposed feasibility issues with respect to sample size.

In observational studies, preoperative platelet count improvements have been shown with thrombopoietin receptor agonists. For romiplostim, a small study (n=18)18 showed that platelet counts increased sufficiently to allow surgery to proceed, with four postoperative bleeds and one urinary catheter thrombosis reported. Another study of perioperative romiplostim (n=22)19 reported good platelet count responses, and described two patients with rebound thrombocytopenia. In a study of eltrombopag or romiplostim before splenectomy,20 24 (71%) of 34 patients achieved a sufficient platelet count response, with two bleeds and two thromboses reported. In a study of romiplostim,21 45 (96%) of 47

patients proceeded with surgery as planned, with bleeding reported in four patients and thrombosis reported in two. In another study with eltrombopag,22, 23 66 (75%) of 88 patients achieved platelet targets although 16 patients required rescue intravenous immunoglobulin, corticosteroids, or platelet transfusion before surgery; two patients had major bleeding; and one patient developed pulmonary embolism after colectomy. One study describing the perioperative use of recombinant human thrombopoietin24 reported the achievement of platelet targets in 27 (64%) of 42 patients, with no adverse events reported. Published experience with avatrombopag25 suggests that this newer thrombopoietin receptor agonist is likely to also be effective perioperatively. None of these studies were randomised and none included a comparator group.

In this trial, one patient in the eltrombopag group developed treatment-related pulmonary embolism. Immune thrombocytopenia, thrombopoietin receptor agonists, and surgery have all been associated with an increased thrombotic risk.26, 27 Use of thrombopoietin receptor agonists around the time of splenectomy represented a unique clinical challenge owing to the risk of post-splenectomy thrombocytosis, which has been reported previously.28 We observed two patients on eltrombopag who developed platelet counts above 1000 × 109 cells per L after splenectomy. Similarly, rebound thrombocytopenia was observed in two patients after eltrombopag was stopped. Rebound thrombocytopenia might be avoidable if eltrombopag is tapered rather than abruptly discontinued postoperatively.

Strengths of this trial were randomisation of a rare disease population, inclusion of a broad range of surgery types, use of conservative platelet count targets, use of a dose-adjusted protocol for perioperative eltrombopag, and incorporation of patient-important outcomes. Limitations were the absence of confirmatory test for the immune thrombocytopenia diagnosis, which might have favoured eltrombopag,29 slow recruitment due to the rarity of immune thrombocytopenia, and schedule constraints with surgery. The timing of intravenous immunoglobulin administration on day –7 (give or take 2 days) was based on the anticipated time to response and the need to distinguish treatment from so-called rescue.

To our knowledge, this is the first randomised trial of perioperative management for patients with immune thrombocytopenia. The non-inferior result suggests that either eltrombopag or intravenous immunoglobulin are reasonable treatment options. The decision to choose one over the other will depend on other factors including patient preference, resource limitations, cost, and individual risk profiles.

References

1. Godeau B, Caulier MT, Decuypere L, Rose C, Schaeffer A, Bierling P. Intravenous immunoglobulin for adults with autoimmune thrombocytopenic purpura: results of a randomized trial comparing 0·5 and 1 g/kg b.w. Br J Haematol 1999;107: 716–19.
2. Caress J, Kennedy B, Eikman K. Safety of intravenous immunoglobulin treatment. Expert Opin Drug Saf 2010; 9: 971–79.
3. Bussel JB, Provan D, Shamsi T, et al. Effect of eltrombopag on platelet counts and bleeding during treatment of chronic idiopathic thrombocytopenic purpura: a randomised, double-blind, placebocontrolled trial. Lancet 2009; 373: 641–48.
4. Cheng G, Saleh MN, Marcher C, et al. Eltrombopag for management of chronic immune thrombocytopenia (RAISE): a 6-month, randomised, phase 3 study. Lancet 2011; 377: 393–402.
5. Wong RSM, Saleh MN, Khelif A, et al. Safety and efficacy of longterm treatment of chronic/persistent ITP with eltrombopag: final results of the EXTEND study. Blood 2017; 130: 2527–36.
6. Neunert C, Lim W, Crowther M, Cohen A, Solberg Jr L, Crowther MA. The American Society of Hematology 2011 evidencebased practice guideline for immune thrombocytopenia. Blood 2011; 117: 4190–207.
7. Knuth D. The art of computer programming, volume 2: seminumerical algorithms, 3rd edn. Reading, MA: Addison-Wesley, 1997.
8. Arnold DM, Jamula E, Heddle NM, et al. Peri-operative eltrombopag or immune globulin for patients with immune thrombocytopaenia (The Bridging ITP Trial): methods and rationale. Thromb Haemost 2019; 119: 500–07.
9. Qin YH, Zhou TB, Su LN, Lei FY, Zhao YJ, Huang WF. The efficacy of different dose intravenous immunoglobulin in treating acute idiopathic thrombocytopenic purpura: a meta-analysis of 13 randomized controlled trials. Blood Coagul Fibrinolysis 2010;21: 713–21.
10. Page LK, Psaila B, Provan D, et al. The immune thrombocytopenic purpura (ITP) bleeding score: assessment of bleeding in patients with ITP. Br J Haematol 2007; 138: 245–48.
11. Atkinson MJ, Kumar R, Cappelleri JC, Mass SL. Hierarchical construct validity of the Treatment Satisfaction Questionnaire for Medication (TSQM version II) among outpatient pharmacy consumers. Value Heal 2005; 8: S9–24.
12. British Committee for Standards in Haematology General Haematology Task Force. Guidelines for the investigation and management of idiopathic thrombocytopenic purpura in adults, children, and in pregnancy. Br J Haematol 2003; 120: 574–96.
13. Godeau B, Chevret S, Varet B, et al. Intravenous immunoglobulin or high-dose methylprednisolone, with or without oral prednisone, for adults with untreated severe autoimmune thrombocytopenic purpura: a randomised, multicentre trial. Lancet 2002; 359: 23–29.
14. Estcourt LJ, Birchall J, Allard S, et al. Guidelines for the use of platelet transfusions. Br J Haematol 2017; 176: 365–94.
15. Bussel JB, Eldor A, Kelton JG, et al. IGIV-C, a novel intravenous immunoglobulin: evaluation of safety, efficacy, mechanisms of action, and impact on quality of life. Thromb Haemost 2004; 91: 771–78.
16. Guo S, DiPietro LA. Critical review in oral biology & medicine: factors affecting wound healing. J Dent Res 2010; 89: 219–29.
17. Neunert CE. Management of newly diagnosed immune thrombocytopenia: can we change outcomes? Blood Adv 2017; 1: 2295–301.
18. Marshall AL, Goodarzi K, Kuter DJ. Romiplostim in the management of the thrombocytopenic surgical patient. Transfusion 2015; 55: 2505–10.
19. Ramakrishna R, Rehman A, Ramakrishna S, Alexander W, Yeo WW. Use of romiplostim in patients with chronic idiopathic thrombocytopenic purpura during perioperative period. Intern Med J 2015; 45: 718–24.
20. Zaja F, Barcellini W, Cantoni S, et al. Thrombopoietin receptor agonists for preparing adult patients with immune thrombocytopenia to splenectomy: results of a retrospective, observational GIMEMA study. Am J Hematol 2016; 91: E293–95.
21. Al-Samkari H, Marshall AL, Goodarzi K, Kuter DJ. Romiplostim for the management of perioperative thrombocytopenia. Br J Haematol 2018; 182: 106–13.
22. Tarantino MD, Fogarty PF, Shah P, Brainsky A. Dental procedures in 24 patients with chronic immune thrombocytopenia in prospective clinical studies of eltrombopag. Platelets 2015; 26: 93–96.
23. Tarantino MD, Bakshi KK, Brainsky A. Hemostatic challenges in patients with chronic immune thrombocytopenia treated with eltrombopag. Platelets 2014; 25: 55–61.

24. Sun H, Hu Q, You J, et al. Efficacy and safety of recombinant human thrombopoietin in adult patients with primary immune thrombocytopenia during the perioperative period. Zhonghua Xue Ye Xue Za Zhi 2019; 40: 191–94.
25. Długosz-Danecka M, Zdziarska J, Jurczak W. Avatrombopag for the treatment of immune thrombocytopenia. Expert Rev Clin Immunol 2019; 15: 327–39.
26. Anderson FA, Spender F. Risk factors for venous thromboembolism. Circulation 2003; 107: 9–16.
27. Balitsky AK, Kelton JG, Arnold DM. Managing antithrombotic therapy in immune thrombocytopenia: development of the TH2 risk assessment score. Blood 2018; 132: 2684–86.
28. Zimmerman J, Norsworthy KJ, Brodsky R. Balancing therapy with thrombopoietin receptor agonists and splenectomy in refractory immune thrombocytopenic purpura: a case of postsplenectomy thrombocytosis requiring plateletpheresis. Case Rep Hematol 2016;2016: 1–4.
29. Arnold DM, Nazy I, Clare R, et al. Misdiagnosis of primary immune thrombocytopenia and frequency of bleeding: lessons from the McMaster ITP Registry. Blood Adv 2017; 1: 2414–20.