Cost-effectiveness of eltrombopag vs intravenous immunoglobulin for the perioperative management of immune thrombocytopenia

Manraj N. Kaur,¹ Donald M. Arnold,^{2,3,4,5} Nancy M. Heddle,^{2,3,6} Richard J. Cook,⁷ Cyrus Hsia,⁸ Mark Blostein,⁹ Erin Jamula,³ Michelle Sholzberg,¹⁰⁻¹³ Yulia Lin,¹¹ Jeannine Kassis,¹⁴ Loree Larratt,¹⁵ Alan Tinmouth,^{16,17} Julie Carruthers,³ Na Li,^{3,18} Yang Liu,³ and Feng Xie^{19,20}

¹Department of Surgery, Brigham and Women's Hospital, Harvard Medical School, Boston, MA; ²Department of Medicine, Michael G. DeGroote School of Medicine, McMaster University, Hamilton, ON, Canada; ³Department of Medicine, McMaster Centre for Transfusion Research, McMaster University, Hamilton, ON, Canada; ⁴Canadian Blood Services, Hamilton, ON, Canada; ⁵Department of Pathology and Molecular Medicine, McMaster University, Hamilton, ON, Canada; ⁶Centre for Innovation, Canada Blood Services, Ottawa, ON, Canada; ⁷Department of Statistics and Actuarial Science, University of Waterloo, Waterloo, ON, Canada; ⁸Division of Hematology, Department of Medicine, University of Western Ontario, London, ON, Canada; ⁹Department of Medicine, McGill University, Montreal, QC, Canada; ¹⁰Department of Medicine, St. Michael's Hospital, University of Toronto, Toronto, ON, Canada; ¹¹Department of Laboratory Medicine and Molecular Diagnostics, Sunnybrook Health Sciences Centre, Toronto, ON, Canada; ¹²Department of Laboratory Medicine, University of Toronto, Quality in Utilization, Education and Safety in Transfusion Research Program, Toronto, ON, Canada; ¹⁴Faculty of Medicine, Université de Montréal, Montreal, QC, Canada; ¹⁵Division of Hematology, University of Alberta, Edmonton, AB, Canada; ¹⁶Department of Medicine, University of Ottawa, ON, Canada; ¹⁷Centre for Innovation and Ottawa Hospital Centre for Transfusion Research, Ottawa Hospital Research Institute, Ottawa, ON, Canada; ¹⁸Community Health Sciences, Cumming School of Medicine, University of Calgary, AB, Canada; ¹⁹Health Research Methods, Evidence, and Impact, Faculty of Health Sciences, McMaster University, Hamilton, ON, Canada; and ²⁰Centre for Health Economics and Policy Analysis, Faculty of Health Sciences, McMaster University, Hamilton, ON, Canada; and ²⁰Centre for Health Economics and Policy Analysis, Faculty of Health Sciences, McMaster University, Hamilton, ON, Canada; and ²⁰Centre for Health Economics and Policy Analysis, Facu

Key Points

- Compared with IVIG, eltrombopag was noninferior and less costly for the perioperative management of adult patients with ITP.
- Direct cost of the eltrombopag or IVIG was the main driver of overall cost for the perioperative management of ITP.

Eltrombopag has been shown to be noninferior to intravenous immunoglobulin (IVIG) for improving perioperative platelet counts in patients with immune thrombocytopenia (ITP) in a randomized trial; thus, cost is an important factor for treatment and policy decisions. We used patient-level data from the trial to conduct a cost-effectiveness analysis comparing perioperative eltrombopag 50 mg daily starting dose, with IVIG 1 or 2 g/kg (according to local practice) from a Canadian public health care payer's perspective over the observation period, from preoperative day 21 to postoperative day 28. Resource utilization data were obtained from the trial data (eltrombopag, n = 38; IVIG, n = 36), and unit costs were collected from the Ontario Schedule of Benefits, Ontario Drug Formulary, and secondary sources. All costs were adjusted to 2020 Canadian dollars. We calculated the incremental cost per patient for all patients randomized. Uncertainty was addressed using nonparametric bootstrapping. The use of perioperative eltrombopag for patients with ITP resulted in a cost-saving of \$413 Canadian per patient. Compared with IVIG, the probability of eltrombopag being cost effective was 70% even with no willingness to pay. In a sensitivity analysis based on IVIG dose, we found that with the higher dose of IVIG (2 g/kg), eltrombopag saved \$2,714 per patient, whereas with the lower dose of IVIG (1 g/kg), eltrombopag had a higher mean cost of \$562 per patient. In summary, based on data from the randomized trial that demonstrated noninferiority, the use of eltrombopag for the management of ITP in the perioperative setting was less costly than IVIG.

The full-text version of this article contains a data supplement.

Submitted 25 June 2021; accepted 19 October 2021; prepublished online on *Blood Advances* First Edition 15 November 2021; final version published online 31 January 2022. DOI 10.1182/bloodadvances.2021005627.

Deidentified individual patient-level clinical data that underlie the reported results are available from arnold@mcmaster.ca, and economic data are available from fengxie@mcmaster.ca.

^{© 2022} by The American Society of Hematology. Licensed under Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0), permitting only noncommercial, nonderivative use with attribution. All other rights reserved.

Introduction

Immune thrombocytopenia (ITP) is an autoimmune hematological disorder characterized by increased platelet destruction and impaired platelet production. Due to the resulting thrombocytopenia, individuals with ITP are at an increased risk of spontaneous bleeding events that range from minor bruising and petechiae to intracranial hemorrhage.¹⁻⁴ In addition, the thrombocytopenia poses particular concerns for ITP patients who require surgery due to the risk of bleeding with invasive procedures. Previous research has found that adults with ITP who undergo surgery have a 75% higher risk of receiving a blood transfusion and a 90% higher risk of death at 30 days postoperatively after adjusting for preoperative risk factors compared with adults without ITP who undergo similar surgical procedures.⁵⁻⁷

Optimal treatment of patients with ITP around the time of surgery is controversial and may vary based on the patient's age, comorbidities, medications, type and urgency of the surgical procedure, and patient and provider preferences.⁸ In this setting, patients are commonly prescribed intravenous immunoglobulin (IVIG) infusion(s) in preparation for surgery; however, IVIG is resource-intensive, costly, and has been associated with side-effects including headache and allergic reactions. Furthermore, efforts to conserve IVIG use are needed, particularly during imminent shortages. Thrombopoietin receptor agonists (TPO-RAs) represent a class of engineered platelet growth factors that simulate the action of endogenous TPO on megakaryocytes and megakaryocytes precursors, boosting their growth and differentiation and increasing platelet production. Eltrombopag is an orally active, small-molecule nonpeptide TPO-RA that increases platelet production within 7 days of repeated dosing. It is approved for the treatment of thrombocytopenia in adults and children with chronic ITP.9

In a multicenter, parallel-arm, open-label, noninferiority trial (Bridging ITP trial; clinicaltrials.gov #NCT01621204), adult patients with primary or secondary ITP were randomized to receive oral daily eltrombopag from 21 days preoperatively to 7 days postoperatively or IVIG administered 7 days preoperatively and repeated within 7 days postoperatively if needed. In the trial, eltrombopag was noninferior to IVIG for improving perioperative platelet count levels.¹⁰ The aim of the current study was to assess the cost-effectiveness of eltrombopag compared with IVIG for achieving platelet count targets in adults with ITP undergoing elective surgical procedures.

Methods

Bridging ITP trial

The Bridging ITP trial was a multicenter, randomized, parallel-arm, open-label, noninferiority trial (clinicaltrials.gov #NCT01621204) that compared eltrombopag and IVIG for the primary outcome of treatment success, defined as the achievement of platelet count targets of 45×10^9 /L or higher for minor surgery or 90×10^9 /L or higher for major surgery from 1 day preoperatively until 7 days post-operatively without the use of rescue treatment. Rescue treatment was defined as any additional treatment administered during the perioperative period to increase the platelet count or prevent bleeding, such as prednisone, dexamethasone, methylprednisolone, IVIG, or platelet transfusions.¹¹

Adult patients with primary or secondary ITP with platelet count $<100 \times 10^{9}$ /L before major surgery or $<50 \times 10^{9}$ /L before minor surgery were recruited across 8 academic hospitals in Canada. Patients were excluded if they had abnormal liver enzymes, thrombosis within the previous 12 months, known bone marrow reticulin or fibrosis, or active malignancy. Using a centralized, secure webbased system, patients were randomly assigned in a 1:1 ratio to receive oral eltrombopag 50 mg daily from 21 days preoperatively to 7 days postoperatively or IVIG 1 to 2 g/kg administered 7 days preoperatively (and repeated within 7 days postoperatively in case a significant drop in platelet count or excess bleeding risk was anticipated during the treatment period). Eltrombopag dose adjustments were done weekly based on platelet count levels. Patients were followed at weekly intervals from preoperative day 21 to postoperative day 28. Ethics approval for the trial was obtained from research ethics boards at each participating center. Written informed consent was obtained from all participants.

Cost-effectiveness analysis

We did a cost-effectiveness analysis using data from the Bridging ITP trial. We conducted the intention-to-treat analysis comparing direct cost and effect of eltrombopag vs IVIG from the Canadian public health care payer's perspective over a time horizon of the 49-day observation period of the study (ie, preoperative day 21 to postoperative day 28). Direct cost is defined as the expense directly related to the delivery of health care services and excludes operational costs (eg, capital cost, maintenance, administrative salaries) and costs incurred by the patients and caregivers (eg, productivity loss, parking fees).¹²

The treatment success rate was used as the effect measure in the cost-effectiveness analysis. Health care resource utilization was collected prospectively using the study case report forms, which were completed weekly throughout the study period. All relevant resources used were considered including laboratory and diagnostic investigations, surgical procedure, procedure-related health care professionals, hospital stays, treatments of adverse events, medications (eltrombopag and others), blood product transfusion, and IVIG. The unit costs of surgery were obtained from the 2020 Schedule of Benefits for Physician Services from the Ontario (the province with the highest population in Canada) Ministry of Health and Long-Term Care,¹³ and the cost of medications was obtained from the Ontario Drug Benefit Formulary.¹⁴ The cost of medications that were not included in the Ontario Drug Benefit Formulary was obtained from the hospital or community pharmacy. The costs associated with blood-product transfusions and IVIG (including preparation and dispensing fees) were obtained from Canadian Blood Services.¹⁵ Where applicable, unit costs were adjusted to 2020 Canadian dollars using the inflation rate between the price base year and 2020¹⁶ (supplemental Appendix 1). Costs were calculated by multiplying the natural unit by the corresponding unit cost for each health care use item. Ontario-based unit costs for all resource categories were applied across all patients and centers.

Base case and sensitivity analyses

The incremental cost-effectiveness ratio was computed by dividing the difference in the mean cost per patient between groups by the difference in the success rates, or incremental effect between groups. In the base case analyses, costs of medications that were not related to ITP were not included. In a sensitivity analysis, all

medication costs were included. Further sensitivity analyses were conducted by excluding cost associated with surgery and adverse events and using a range of eltrombopag costs that have been reported in the literature.¹⁷⁻²² In the IVIG group, sensitivity analyses were done for patients who received 1 g/kg IVIG vs 2 g/kg IVIG. We also varied the cost per gram of IVIG by adding and subtracting \$10 and \$20 from the cost used in the base case analysis (\$50.84 per gram of IVIG) because published costs for IVIG vary from \$45 to \$72 per gram.²³⁻²⁶ Lastly, we used a more conservative cost estimate of \$51.95 per physician visit (ie, cost for repeat medical consult) instead of \$85.80 (full medical consult) per visit used in base case analysis. The nonparametric bootstrapping method was used to analyze the uncertainty of the estimated incremental cost-effectiveness ratio based on 1000 bootstrap samples. A cost-effectiveness acceptability curve was used to show the probability of eltrombopag being cost-effective across a range of willingness-to-pay values per additional successfully treated patient compared with IVIG.

Role of the funding source

The main Bridging ITP trial was funded by Novartis and GlaxoSmithKline, and this economic analysis was funded by Novartis. Program funding for the McMaster Center for Transfusion Research was provided by Canadian Blood Services, the Federal Government of Canada (Health Canada), and provincial and territorial ministries of health. The funders had no role in the design of the study, the collection of data, or the interpretation of the results.

Results

In the clinical trial, 74 patients were randomized to receive either eltrombopag (n = 38, 51.4%; median age = 64 years, interquartile range [IQR] = 23) or IVIG (n = 36, 48.6%; median age = 63.5 years, IQR = 19) preoperatively (Table 1). Patients receiving concomitant ITP therapies were eligible for inclusion provided they had not started a new therapy or had any changes to an existing therapy for 2 weeks prior to randomization. Patients were excluded if they had

	Eltrombopag (n = 38)	Intravenous immunoglobulin (n = 36)
Recruitment site		
Ontario	32 (84.2%)	31 (86.1%)
Alberta	2 (5.3%)	0
Quebec	4 (10.5%)	5 (13.9%)
Females	20 (53%)	18 (50%)
Age, median (IQR)	64 (50-73.3)	63.5 (56-74.5)
Weight in kgs, median (IQR)	84 (69.8-102.6)	81.7 (68-93.6)
Immune thrombocytopenia		
Secondary	4 (11%)	5 (14%)
Chronic	29 (76%)	29 (81%)
Duration in years	8 (1.2-13.7)	5.6 (1.8-15.1)
Surgery classification		
Major	17 (45%)	14 (39%)
Minor	21 (55%)	22 (61%)

received IVIG within 2 weeks or eltrombopag (or another medication in that drug class) within 4 weeks of randomization. One patient in each group had received eltrombopag prior to study participation, whereas 22 (58%) and 24 (67%) patients had previously received IVIG in the eltrombopag and IVIG groups, respectively. Of the 36 patients in the IVIG group, none received a second treatment of IVIG within 7 days postoperatively. By intention to treat, 30 (79%) patients in the eltrombopag group and 22 (61%) patients in the IVIG group achieved treatment success because they reached the perioperative platelet count targets. The clinical trial concluded that eltrombopag was noninferior to IVIG for perioperative treatment of ITP. The clinical findings of the Bridging ITP trial have been published elsewhere.¹⁰

When all medication costs, including non-ITP medications, were included, eltrombopag was \$1,101 Canadian less expensive per patient than IVIG (Table 2). The direct cost of eltrombopag (ie, cost of eltrombopag and dispensing fee) was \$166199, and the direct cost associated with IVIG (ie, cost of nursing time, infusion material, physician visit, immunoglobulin, preparation and dispensing fee, and pre-IVIG infusion medications) was \$188,660 (supplemental Appendix 2). These were the largest cost drivers, accounting for 56% and 64% of the total costs in the 2 treatment groups, respectively. The eltrombopag group also incurred \$30 474 for rescue IVIG infusions. The costs of blood product transfusions (non-IVIG) were \$1,031 in the eltrombopag group and \$6259 for the IVIG group; the higher costs in the IVIG group were associated with more red blood cell units (n = 4) and platelet transfusions (n = 7) administered to patients in the IVIG group compared with the eltrombopag group (red blood cell units. n = 1: platelet transfusions. n = 1). Surgery-related costs (ie, costs associated with the surgeon, anesthetist, surgical assistant, operating room nurse, and surgery-related hospitalization) were the second largest driver of overall costs, amounting to \$86147 (29.3% of total cost) in the eltrombopag group and \$77 613 (26,1% of total cost) in the IVIG group. In the eltrombopag group, 1 patient had 1 emergency department visit and a 4-day hospitalization for suspected pulmonary embolism that was possibly related to the eltrombopag, and another patient had 1 emergency department visit and a 2-day hospitalization for vertigo that was unrelated to eltrombopag, amounting to a total of \$5531 in adverse event-related costs. In the IVIG group, 3 patients had adverse events requiring a total of 1 emergency department visit and 17 hospitalization days due to surgery-related vulvar pain, air leak from chest tube, and pancreatitis, with a total cost of \$14553. All unplanned emergency department visits and hospital admissions in the IVIG group were unrelated to the IVIG. Overall, the mean plus or minus standard deviation total cost for treating 38 patients in the eltrombopag group was \$294242, or \$7743 plus or minus \$4897 per patient, and the total cost for treating 36 patients in the IVIG group was \$293628, or \$8156 plus or minus \$4255 per patient (Figure 1). In the base case, eltrombopag was less expensive than IVIG, saving \$413 per patient.

In the eltrombopag group, the success rate was 78.9% (30/38), and in the IVIG group, the success rate was 61.1% (22/36). The cost-effectiveness plane showing the results of 1000 bootstrap cost-effect pairs demonstrates that the majority of the cost-effect pairs appeared in the "southeast quadrant" of the plane, indicating that eltrombopag was both more effective and less costly (Figure 2). Eltrombopag had a 70% probability of being cost-effective if the willingness-to-pay was \$0 per additional successfully treated patient and an 88.9% probability if the willingness-to-pay increased to \$10,000 compared with IVIG (Figure 3).

	Total cost Mean \pm SD	Treatment success	Incremental cost (CAD)	Incremental effect*
Base case				
Eltrombopag	7743 ± 4897	30 (78.9%)		
IVIG	8156 ± 4355	22 (61.1%)	-413	0.18
Sensitivity analyses				
All medication cost included (ITP	and non-ITP)			
Eltrombopag	8424 ± 5202	30 (78.9%)		
IVIG	9525 ± 6082	22 (61.1%)	-1101	0.18
Surgery-related costs excludedt				
Eltrombopag	5476 ± 3592	30 (78.9%)		
IVIG	6000 ± 3253	22 (61.1%)	-524	0.18
Unplanned ER visits and hospitali	ization costs excluded			
Eltrombopag	7597 ± 4804	30 (78.9%)		
IVIG	7752 ± 3898	22 (61.1%)	-155	0.18
Lowest published cost for eltrom	bopag (CAD 1.87)			
Eltrombopag	6518 ± 4481	30 (78.9%)		
IVIG	8156 ± 4255	22 (61.1%)	-1638	0.18
Highest published cost for eltrom	bopag (CAD 7.03)			
Eltrombopag	15178 ± 8154	30 (78.9%)		
IVIG	8156 ± 4255	22 (61.1%)	7022	0.18
IVIG 1 g/kg only				
Eltrombopag	7743 ± 4897	30 (78.9%)		
IVIG: 1 g/kg (n = 24)	7181 ± 4306	14 (58.3%)	562	0.21
IVIG 2 g/k only				
Eltrombopag	7743 ± 4897	30 (78.9%)		
IVIG: 2 g/kg (n=12)	10457 ± 4897	8 (66.6%)	-2714	0.12
IVIG per-gram cost varied by -\$	10 (CAD 40.84)			
Eltrombopag	7743 ± 4897	30 (78.9%)		
IVIG	7171 ± 3895	22 (61.1%)	572	0.18
IVIG per-gram cost varied by +\$	10 (CAD 60.84)			
Eltrombopag	7743 ± 4897	30 (78.9%)		
IVIG	9142 ± 4624	22 (61.1%)	-1399	0.18
IVIG per-gram cost varied by -\$	20 (CAD 30.84)			
Eltrombopag	7743 ± 4897	30 (78.9%)		
IVIG	6185 ± 3570	22 (61.1%)	1558	0.18
IVIG per-gram cost varied by +20	0 (CAD 70.84)			
Eltrombopag	7743 ± 4897	30 (78.9%)		
IVIG	10128 ± 5017	22 (61.1%)	-2385	0.18
Physician visit cost of \$51.95				
Eltrombopag	7743 ± 4897	30 (78.9%)		
IVIG	7854 ± 3860	22 (61.1%)	-111	0.18

All numbers are rounded to the nearest whole number. CAD, Canadian dollar; ITP, immune thrombocytopenia; IVIG, intravenous immunoglobulin; SD, standard deviation. *Incremental effect is the difference in the rate of achieving platelet count without rescue therapy in eltrombopag and IVIG. tIncludes costs associated with transfusion of blood product during surgery and during postoperative hospitalization.

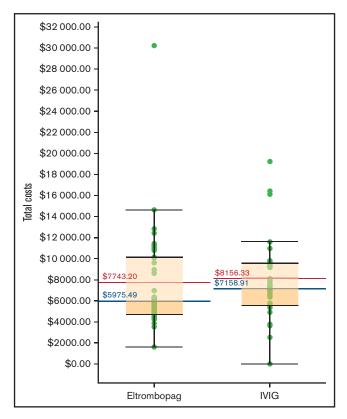


Figure 1. Total cost associated with perioperative eltrombopag and intravenous immunoglobulin (IVIG) for patients with ITP.

Sensitivity analyses

When surgery costs were excluded, eltrombopag was \$524 less expensive per patient than IVIG (Table 2). When the lowest published cost of eltrombopag (\$1.87 per milligram) was used, eltrombopag was \$1638 less expensive per patient; however, when the highest published cost of eltrombopag was used (\$7.03 per milligram), the cost in the eltrombopag group was \$7022 higher per patient than IVIG. Patients on the trial received IVIG 1 g/kg (n = 24) or IVIG 2 g/kg (n = 12). We found that when 1 g/kg of IVIG was used, 58% of patients in the IVIG group achieved preoperative platelet count targets, and eltrombopag had a higher mean cost of \$562 per patient, whereas when 2 g/kg of IVIG was used, 66% patients in the IVIG group achieved preoperative platelet count targets and eltrombopag saved \$2714 per patient. When the IVIG per-gram cost were reduced by \$10 and \$20 from the cost used in base case analysis (\$50.84), IVIG group had cost savings of \$572 and \$1558, respectively. However, when the costs were increased by \$10 and \$20, the eltrombopag was found to save \$1399 and \$2385, respectively. When a conservative estimate of the cost of physician visit for IVIG (\$51.95) was used, eltrombopag remained superior in terms of cost-effectiveness and was associated with cost saving of \$111.

Discussion

We evaluated the cost-effectiveness of eltrombopag and IVIG in the perioperative setting from a Canadian public health care payer perspective. Compared with IVIG, eltrombopag was both noninferior and less costly at achieving perioperative platelet count targets during the time horizon of the study. The cost of the treatment itself and postoperative hospitalizations were associated with the highest cost burden in our analysis, followed by the cost of investigating or managing adverse events (ie, emergency department visits and unplanned hospital admissions). A higher proportion of patients in the IVIG group received blood product transfusion (including red blood cells, platelets, and plasma) or had hospitalizations that were unrelated to the treatments compared with the eltrombopag group. When the cost of unrelated hospitalization and emergency department visits were excluded, eltrombopag was still associated with lower cost. In a sensitivity analysis of IVIG dosing, eltrombopag was \$562 more costly per patient when 1 g/kg IVIG was used, whereas eltrombopag was -\$2714 less costly when 2 g/kg of IVIG was used.

The majority of the randomly drawn incremental cost-effect pairs fell in the "southeast quadrant" of the cost-effectiveness plane, where eltrombopag was both more effective and less costly than IVIG. This indicates low uncertainty in the cost-effectiveness profile of eltrombopag in comparison with IVIG as only 2% of the pairs fell into the "northwest quadrant," where IVIG was more effective and less costly, which was likely caused by a few resource-intensive cases and the small sample size. The high resource utilization in few patients was primarily due to the type of surgical procedure, days spent in the hospital, or concomitant medications, none of which was directly related to the intervention. The wide confidence intervals on the costs reflect skewed cost data distribution and the small sample size; nevertheless, the differences in the mean per-patient cost and the total cost between groups can inform policy for determining overall budget impact associated with alternative treatments.

This study used patient-level data to estimate the cost-effectiveness of eltrombopag and IVIG from randomized controlled trial data in the perioperative setting. Previous studies have examined the cost of eltrombopag either alone or in comparison with the watch-and-rescue approach,¹⁷ other TPO-RAs drugs,¹⁷⁻²¹ and rituximab¹⁹⁻²² for chronic ITP or patients with hepatitis C virus infection. A substantial variation is noted in the lifetime costs for eltrombopag for chronic ITP patients based on modeling studies ranging from \$440 000 US to \$1.5 million US,^{17,18,20,21} including costs for managing bleeding or other adverse events. Five^{17-20,22} of the 6 studies¹⁷⁻²² concluded that eltrombopag was cost-effective compared with romiplostim, another TPO-RA medication, over 6 months and lifetime due to lower cost of acquiring and administering the drug and lower bleeding episode rates.

Eltrombopag was the dominant intervention in our study (ie, both clinically noninferior and cost saving) even after the costs of surgery were excluded from the analysis. With regard to the cost of eltrombopag itself, the cost in this study was \$2.6 per mg, which is within the range of values reported in the literature and by the Canadian Agency for Drugs and Technologies in Health.²⁷ Based on the published literature, the costs for eltrombopag were lowest in Europe and United Kingdom (approximately \$1.87 to \$2.27 per mg).²⁰⁻²² and highest in the United States (\$5.12 to \$7.03 per mg).¹⁸ When the highest reported eltrombopag cost (\$7.03) was used, eltrombopag was adjusted to approximately \$2.83 per gram (from \$2.60 per gram), the cost would be very similar between the 2 treatments (mean cost eltrombopag, \$8129, and mean cost IVIG, \$8,156). An important

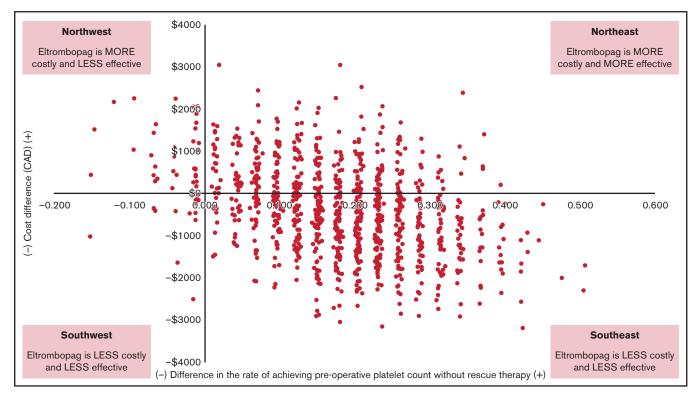


Figure 2. Incremental cost-effectiveness plane comparing eltrombopag with intravenous immunoglobulin.

but expected trend was that as the cost of IVIG increased, the cost savings associated with eltrombopag also increased. Recent data suggests that immunoglobulin costs have increased exponentially in the past decade, making it the third highest drug category for private payers in the United States and fourth under Medicare.²⁸ With the rising costs of immunoglobulin, it is imperative that cost-effective alternatives are carefully considered for those who require it.

Finally, we found that the dose of IVIG impacted the cost-analysis: 1 g/kg IVIG was associated with cost-savings with IVIG, whereas 2 g/kg IVIG was associated with cost-savings with eltrombopag. When results from randomized trials and this cost-effectiveness are triangulated, it suggests that clinicians who prescribe 1 g/kg IVIG routinely may continue to favor IVIG without any health care resource or patient outcome-related implications. Clinicians who prescribe 2 g/kg IVIG could consider 1 g/kg IVIG or eltrombopag. However, due to the small sample size, this finding is hypothesisgenerating and should be explored in future studies.

The use of clinical data from a randomized, controlled trial and comprehensive data on cost are strengths of this study. The results are timely as many health care providers struggle with IVIG shortages for the treatment of ITP, and, at the same time, limited access to TPO receptor agonist medications. The comprehensive reporting of unit costs and resources used in this study will be useful to compare groups across different settings and countries. The small sample size (n = 74) limits the certainty around the cost-effectiveness estimates; thus, although the cost associated with the use of (non-IVIG) blood products was higher in the IVIG group, the small number of outcome events limited inferences about the effects of the intervention on blood product transfusions. This study did not include patient-reported outcomes such as quality of life, fatigue, or functional assessments, which may have significant impact on patients with ITP.²⁹⁻³³ In addition, other factors besides cost contribute to treatment decisions, including confidence in the diagnosis of ITP and previous response to therapies, which were not directly captured in this study. Another limitation was the omission of overhead and indirect costs incurred by patients or their caregivers. We reasoned that including these costs would have made an even stronger case for eltrombopag because patients who receive IVIG

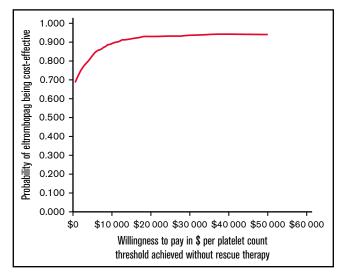


Figure 3. Cost-effectiveness acceptability curve showing the probability that eltrombopag is cost-effective compared with intravenous immunoglobulin over a range of willingness-to-pay values per rescue treatment averted.

spend more time in the outpatient hospital or medical day unit, which results in added costs to the health care system and hours lost from work. Most patients on the trial (\sim 85%) were from Ontario, Canada; therefore, Ontario-based costs were applied to all patients. Results of this study should be interpreted in the context of a high resource setting in a publicly insured health system.

Cost-effectiveness analyses are especially important for interventions that are clinically noninferior, as is the case for eltrombopag and IVIG for the perioperative management of ITP. Our study demonstrates that eltrombopag was less costly than IVIG from a public health care payer's perspective in Canada. These data could help inform policies on drug accessibility.

Acknowledgments

M.N.K. is supported by the Canadian Institutes of Health Research Fellowship Award (2020-23). The views herein do not necessarily reflect the views of Canadian Blood services or the federal, provincial, or territorial governments of Canada.

Funding support for this article was provided by the GlaxoSmithKline and Novartis. Programme funding for the McMaster Center for Transfusion Research was provided by Canadian Blood Services, the Federal Government of Canada (Health Canada), and provincial and territorial ministries of health.

Authorship

Contribution: M.N.K., D.M.A., and F.X. had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis; D.M.A., F.X., M.N.K., E.J., N.L., Y. Liu, and J.C. are responsible for the concept and design of the study, acquiring and interpreting the data; D.M.A., C.H., M.B.,

M.S., Y. Lin, J.K., L.L., N.M.H., R.J.C., and A.T. acquired and/or analyzed primary source data from the Bridging ITP trial for this economic analysis; M.N.K. and F.X. are responsible for drafting the manuscript and performed statistical analysis; D.M.A. and F.X. supervised the work; and all authors critically revised the manuscript for important intellectual content.

Conflict-of-interest disclosure: D.M.A. reports grants from GlaxoSmithKline and Novartis during the conduct of the study; grants and personal fees from Novartis and Amgen outside the submitted work; grants from Bristol Myers Squibb outside the submitted work; and personal fees from UCB, Principia, and Rigel outside the submitted work. C.H. reports personal fees from Novartis, Amgen, and GlaxoSmithKline outside the submitted work. E.J. reports personal fees from Novartis outside the submitted work. M.S. reports personal fees from Novartis outside the submitted work. Y. Lin and Y. Liu reports grants from Novartis during the conduction of the study and consulting and advisory board fees from Pfizer outside the submitted work. L.L. reports personal fees from Novartis outside the submitted work. The remaining authors declare no competing interests.

ORCID profiles: M.N.K., 0000-0002-1911-0395; D.M.A., 0000-0003-0943-8853; Y. Lin, 0000-0002-5562-9020; A.T., 0000-0001-8869-389X.

Correspondence: Feng Xie, Health Research Methods, Evidence, and Impact, Faculty of Health Sciences, McMaster University, Hamilton, ON, Canada; e-mail fengxie@mcmaster.ca; and Donald M. Arnold, Medicine, Hematology & Thromboembolism, Health Sciences Center, McMaster University, 3V-50, 1280 Main St West, Hamilton, ON, Canada; e-mail: arnold@mcmaster.ca.

References

- 1. Provan D, Stasi R, Newland AC, et al. International consensus report on the investigation and management of primary immune thrombocytopenia. *Blood.* 2010;115(2):168-186.
- 2. Cines DB, Blanchette VS. Immune thrombocytopenic purpura. N Engl J Med. 2002;346(13):995-1008.
- Neunert C, Noroozi N, Norman G, et al. Severe bleeding events in adults and children with primary immune thrombocytopenia: a systematic review. J Thromb Haemost. 2015;13(3):457-464.
- 4. Neunert CE, Buchanan GR, Imbach P, et al; Intercontinental Childhood ITP Study Group Registry II Participants. Severe hemorrhage in children with newly diagnosed immune thrombocytopenic purpura. *Blood.* 2008;112(10):4003-4008.
- Glance LG, Dick AW, Mukamel DB, et al. Association between intraoperative blood transfusion and mortality and morbidity in patients undergoing noncardiac surgery. Anesthesiology. 2011;114(2):283-292.
- 6. Glance LG, Blumberg N, Eaton MP, et al. Preoperative thrombocytopenia and postoperative outcomes after noncardiac surgery. *Anesthesiology*. 2014;120(1):62-75.
- Bernard AC, Davenport DL, Chang PK, Vaughan TB, Zwischenberger JB. Intraoperative transfusion of 1 U to 2 U packed red blood cells is associated with increased 30-day mortality, surgical-site infection, pneumonia, and sepsis in general surgery patients. J Am Coll Surg. 2009; 208(5):931-937.e1-2.
- 8. Neunert C, Terrell DR, Arnold DM, et al. American Society of Hematology 2019 guidelines for immune thrombocytopenia [published correction appears in *Blood Adv.* 2020;4(2):252]. *Blood Adv.* 2019;3(23):3829-3866.
- 9. Lisman T, Porte RJ. Eltrombopag before procedures in patients with cirrhosis and thrombocytopenia. N Engl J Med. 2012;367(21):2055-2056.
- 10. Arnold DM, Heddle NM, Cook RJ, et al. Perioperative oral eltrombopag versus intravenous immunoglobulin in patients with immune thrombocytopenia: a non-inferiority, multicentre, randomised trial. *Lancet Haematol.* 2020;7(9):e640-e648.
- 11. 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(3):500-507.

- 12. Drummond MF, Sculpher MJ, Claxton K, Stoddart GL, Torrance GW. Cost analysis. In: Methods for the Economic Evaluation of Health Care Programmes. 4th ed. Oxford, United Kingdom: Oxford University Press; 2015:219-262.
- 13. Ontario Ministry of Health and Long-Term Care. Physician Services Schedule of Benefits 2020 [updated 12 June 2020]. Available at: http:// www.health.gov.on.ca/en/pro/programs/ohip/sob/.] Accessed 22 October 2020.
- 14. Ontario Ministry of Health and Long-Term Care. E-Formulary 2020 [updated 21 November 2018]. Available at: http://www.health.gov.on.ca/en/pro/ programs/drugs/odbf_eformulary.aspx. Accessed 28 September 2020.
- Ontario Regional Blood Coordinating Network. Bloody Easy 5: Blood Transfusions, Blood Alternatives and Transfusion Reactions. A Guide to Transfusion Medicine, 4th ed. ORBCON; 2016 [available from https://transfusionontario.org/wp-content/uploads/2020/06/EN_BE4-JULY11_ FINAL.pdf]
- 16. Inflation Calculator. Bank of Canada. Available at: https://www.bankofcanada.ca/rates/related/inflation-calculator/. Accessed 13 November 2020.
- 17. Fust K, Parthan A, Li X, et al. Cost per response analysis of strategies for chronic immune thrombocytopenia. Am J Manag Care. 2018;24(8 Spec No.):SP294-SP302.
- 18. Tremblay G, Dolph M, Roy AN, Said Q, Forsythe A. The cost-effectiveness of eltrombopag for the treatment of immune thrombocytopenia in the United States. *Clin Ther.* 2020;42(5):860-872.e8.
- 19. Tremblay G, Dolph M, Bhor M, et al. Cost-consequence model comparing eltrombopag and romiplostim in pediatric patients with chronic immune thrombocytopenia. *Clinicoecon Outcomes Res.* 2018;10:715-721.
- 20. Allen R, Bryden P, Grotzinger KM, Stapelkamp C, Woods B. Cost-effectiveness of eltrombopag versus romiplostim for the treatment of chronic immune thrombocytopenia in England and Wales. *Value Health.* 2016;19(5):614-622.
- 21. Lee D, Thornton P, Hirst A, Kutikova L, Deuson R, Brereton N. Cost effectiveness of romiplostim for the treatment of chronic immune thrombocytopenia in Ireland. *Appl Health Econ Health Policy*. 2013;11(5):457-469.
- 22. González-Porras JR, Parrondo García FJ, Anguita E. Cost-per-responder analysis for eltrombopag and rituximab in the treatment of primary immune thrombocytopenia in Spain. *Farm Hosp.* 2020;44(6):279-287.
- 23. Piscitelli E, Massa M, De Martino BM, et al. Economic evaluation of subcutaneous versus intravenous immunoglobulin therapy in chronic inflammatory demyelinating polyneuropathy: a real-life study. *Eur J Hosp Pharm Sci Pract.* 2021;28(Suppl 2):s115-s119.
- 24. Le Masson G, Solé G, Desnuelle C, et al. Home versus hospital immunoglobulin treatment for autoimmune neuropathies: a cost minimization analysis. *Brain Behav.* 2018;8(2):e00923.
- 25. Soares MO, Welton NJ, Harrison DA, Peura P, Hari MS, Harvey SE, Madan JJ, Ades AE, Palmer SJ, Rowan KM. An evaluation of the feasibility, cost and value of information of a multicentre randomised controlled trial of intravenous immunoglobulin for sepsis (severe sepsis and septic shock): incorporating a systematic review, meta-analysis and value of information analysis. *Health Technol Assess.* 2012;16(7)1-186.
- Blackhouse G, Xie F, Levine MA, et al. Canadian cost-utility analysis of intravenous immunoglobulin for acute childhood idiopathic thrombocytopenic purpura. J Popul Ther Clin Pharmacol. 2012;19(2):e166-e178.
- Canadian Agency for Drugs and Technologies in Health. CDEC Final Recommendation Eltrombopag Olamine (Revolade GlaxoSmithKline Inc.) [updated 18 March 2015]. Available at: https://www.cadth.ca/sites/default/files/cdr/complete/cdr_complete_SR0377_Revolade_Mar-23-2015_e. pdf. Accessed 12 February 2021.
- 28. Vaughan LJ. Managing cost of care and healthcare utilization in patients using immunoglobulin agents. *Am J Manag Care.* 2019;25(6 Suppl): S105-S111.
- 29. Trotter P, Hill QA. Immune thrombocytopenia: improving quality of life and patient outcomes. Patient Relat Outcome Meas. 2018;9:369-384.
- Signorovitch J, Brainsky A, Grotzinger KM. Validation of the FACIT-fatigue subscale, selected items from FACT-thrombocytopenia, and the SF-36v2 in patients with chronic immune thrombocytopenia. Qual Life Res. 2011;20(10):1737-1744.
- 31. Sestøl HG, Trangbæk SM, Bussel JB, Frederiksen H. Health-related quality of life in adult primary immune thrombocytopenia. *Expert Rev Hematol.* 2018;11(12):975-985.
- 32. Sanz MA, Aledort L, Mathias SD, Wang X, Isitt JJ. Analysis of EQ-5D scores from two phase 3 clinical trials of romiplostim in the treatment of immune thrombocytopenia (ITP). Value Health. 2011;14(1):90-96.
- 33. Cooper N, Kruse A, Kruse C, et al. Immune thrombocytopenia (ITP) World Impact Survey (I-WISh): impact of ITP on health-related quality of life. *Am J Hematol.* 2021;96(2):199-207.