Thrombosis Research 220 (2022) 5–11

Contents lists available at ScienceDirect

Thrombosis Research

journal homepage: www.elsevier.com/locate/thromres

Full Length Article

Treatment patterns and outcomes of second-line rituximab and thrombopoietin receptor agonists in adult immune thrombocytopenia: A Canadian retrospective cohort study

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ARTICLE INFO

Keywords:
Immune thrombocytopenia
Rituximab
Thrombopoietin receptor agonists
Health service utilization
Bleeding
Mortality

ABSTRACT

Background: The optimal choice of second-line treatment for immune thrombocytopenia (ITP) is unclear. Guidelines recommend either rituximab, splenectomy, or thrombopoietin receptor agonists (TPO-RA). There is, however, scarce data comparing treatment patterns, outcomes and resource utilization across second-line treatments. Despite Canada's universal healthcare system, publicly funded access to second-line ITP therapies is highly variable across provinces/territories.

Objectives: To describe treatment patterns and compare health service utilization and outcomes among recipients of second-line rituximab and TPO-RA for ITP.

Methods: In this multicentre retrospective cohort study, we included adults who received second-line ITP therapies rituximab, eltrombopag and romiplostim (2012-2020) in Alberta, Canada. Patients were identified through a provincially-funded special drug access (STEDT) program. We examined treatment patterns, predictors of second-line treatment, hospitalizations, blood product utilization, and outcomes. Kaplan-Meier survival curves were used to estimate the cumulative incidence of ITP-related hospitalizations (bleeding or infections), overall survival (OS) and relapse-free survival (RFS). Cox proportional hazards regression was used to examine the impact of second-line therapy on OS.

Results: 223 patients received rituximab (67 %), eltrombopag (29 %), and romiplostim (4 %). TPO-RA recipients experienced significantly longer time from ITP diagnosis to second-line therapy compared with rituximab recipients (15.9 vs 6.7 months, $P < 0.0001$), accompanied by significantly higher platelet and IVIG utilization prior to second-line therapy. Age (adjusted odds ratio [aOR] 1.04, 95 % CI 1.02–1.07, $P < 0.0001$) and prior intracranial hemorrhage (aOR 12.7, 95 % CI 1.6–272.8, $P = 0.03$) were significant predictors of second-line TPO-RA. TPO-RA is associated with a trend towards longer median RFS (6.3 vs 3.8 years, $P = 0.06$) compared with rituximab, and similar rates of ITP-related hospitalizations, major bleeding, and thromboembolism. Age, time period, and Charlson comorbidity index, but not second-line ITP therapy, were significant predictors of OS.

Conclusions: Our study identified older age and intracranial hemorrhage as predictors of second-line TPO-RA prescription in a real-world practice. There were no significant differences in hospitalizations and outcomes between second-line rituximab and TPO-RA, although delayed initiation of TPO-RA was associated with higher blood product utilization.

1. Introduction

Immune thrombocytopenia (ITP) is characterized by increased platelet clearance and reduced megakaryopoiesis, and is associated with increased risk of bleeding [1]. Adults with chronic ITP often relapse after first-line therapy with corticosteroids. For second-line treatment of corticosteroid-dependent or refractory ITP, international guidelines recommend either medical therapies including rituximab,

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https://doi.org/10.1016/j.thromres.2022.09.021
Received 13 July 2022; Received in revised form 19 September 2022; Accepted 22 September 2022
Available online 29 September 2022

thrombopoietin receptor agonists (TPO-RA) or fostamatinib, or surgical splenectomy, guided by shared decision-making and available resources [2,3]. There are no head-to-head comparisons between these treatment options [4]. In addition, real-world data describing treatment patterns in the second-line setting, healthcare utilization and outcomes are scarce [5–7]. In this multicentre retrospective cohort study, we sought to describe treatment patterns of second-line medical therapies (rituximab, eltrombopag, and romiplostim) in adults with ITP and predictors of second-line TPO-RA use in a large Canadian province over the past decade. We also compared health service utilization, and outcomes in patients who received second-line rituximab and TPO-RA.

2. Methods

2.1. Patients

Adult patients (aged 18 years or older) diagnosed with ITP who received either rituximab, eltrombopag, or romiplostim as second-line therapies between February 2012 and December 2020 in the province of Alberta, Canada (population 4.4 million) were included in the study. Avatrombopag and fostamatinb were unavailable during the study period, and thus not evaluated. ITP is primarily diagnosed and managed by hematologists affiliated with tertiary academic centres in Edmonton and Calgary. In Alberta, rituximab, eltrombopag and romiplostim are available through a publicly funded provincial special drug access (STEDT) program upon meeting pre-specified criteria. Access to TPO-RA in our province is currently available for chronic ITP with lack of response or contraindications to rituximab. This contrasts with most other Canadian provinces which have more stringent funding criteria for TPO-RAs, often requiring failure of three or more lines of treatment, including failure or contraindications to splenectomy [8].

Patients were identified from the provincial STEDT special drug access database; only those who received rituximab, eltrombopag or romiplostim as second-line therapies were included. ITP secondary to human immunodeficiency virus (HIV), viral hepatitis, rheumatologic and other autoimmune disorders were included. Among patients with lymphoproliferative disorders (LPD), only cases who received second-line treatment for ITP were included. Patients who received rituximab as part of chemoimmunotherapy or maintenance therapy, drug-induced thrombocytopenia, inherited thrombocytopenia and Evan's syndrome were excluded. The year 2012 was used as the inception year as this was when ITP therapies were publicly funded through the STEDT program. Chart reviews collecting patient demographics, disease characteristics, comorbidities, treatment course, and outcomes were performed using a standardized case report form. The study was approved by the University of Alberta research ethics board (Pro00097263; September 2021).

2.2. Treatment patterns of second-line therapy

Treatment patterns of rituximab and TPO-RAs were examined, focusing on the median time from ITP diagnosis to initiation of second-line therapy, the sequence of second- and third-line therapies, rates of TPO-RA discontinuation among responders, and temporal trends of prescription patterns over time. We also examined potential predictors of second-line TPO-RA, including age, sex, socioeconomic status (using the Pampalon material deprivation index as a proxy), Charlson comorbidity index, rural residence, underlying ITP etiology, time frame (2012–2014, 2015–2017, 2018–2020), treatment centre (Edmonton vs Calgary), and intracranial hemorrhage (ICH) or gastrointestinal (GI) bleeding prior to second-line therapy [9].

2.3. Health service utilization and outcomes

The following measures of health service utilization that occurred following initiation of second-line therapy were collected: ITP-related hospitalizations (defined as hospitalizations for bleeding or infections), intensive care unit (ICU) admissions, and hospital length of stay. We also examined the utilization of blood products and components, including packed red blood cells, platelets and intravenous immunoglobulins (IVIG), before and after initiation of second-line therapy. Relevant clinical outcomes included platelet response, major bleeding events (ICH or GI bleeding), infections, arterial and venous thrombosis, and all-cause mortality. Response rates and duration of response were assessed using international consensus guidelines [10]. Overall response was defined as platelet count $\geq 30 \times 10^9$/L and at least a 2 fold increase from baseline without need for other ITP treatments. Complete response (CR) was defined as platelet count $\geq 100 \times 10^9$/L [10]. Platelet counts confirmed on at least 2 separate occasions ($\geq$7 days apart) were used to ascertain overall response and CR. Relapse was defined as platelet count $< 30 \times 10^9$/L in patients who had achieved response.

2.4. Statistical analysis

Descriptive analysis was performed using median and interquartile range (IQR) for continuous variables, frequencies and percentages for categorical variables. Differences between groups were assessed using *t*-test for continuous variables and the Chi-square test for categorical variables. No imputation was performed for missing data. Response rates, blood product utilization, ITP-related hospitalizations, major bleeding, and thromboembolism were compared between second-line therapies. Due to small numbers of patients who received second-line romiplostim, eltrombopag and romiplostim were combined into one group for analysis. Univariate and multivariable logistic regression analyses were used to examine factors associated with the choice of second-line TPO-RA. Kaplan-Meier survival curves were used to estimate the cumulative incidence of ITP-related hospitalization, overall survival (OS), and relapse-free survival (RFS), stratified by second-line therapy. Log-rank test was used to assess for significant differences between groups. OS was calculated from initiation of second-line therapy to death or last follow-up. RFS was calculated from initiation of second-line therapy to relapse. Patients alive without relapse at last follow-up were censored. Cumulative incidence of ITP-related hospitalization was calculated from initiation of second-line therapy to first hospitalization for bleeding or infection. Patients were censored at time of subsequent lines of therapy. Cox proportional hazards regression models were used to examine the impact of second-line ITP therapy on OS. Variables with $P < 0.20$ on univariate analysis were included on multivariable Cox proportional hazards regression. A 2-sided *P*-value <0.05 was considered statistically significant. R statistics software (R Foundation for Statistical Computing, Vienna, Austria) was used for analysis.

3. Results

3.1. Patient demographics

A total of 361 ITP patients were identified from the STEDT special drug access database, who received approval for rituximab, eltrombopag, or romiplostim (Fig. 1). Thirty-five were excluded due to: second-line therapies approved for funding but not prescribed ($n = 12$), childhood diagnosis of ITP ($n = 9$), TPO-RA prescription for chemotherapy- or hematopoietic cell transplantation-associated thrombocytopenia ($n = 4$), and other diagnoses ($n = 10$). Of the 326 adults who received rituximab or TPO-RAs for ITP, 76 were excluded due to third-line rituximab or TPO-RA use (relapsed post-splenectomy), another 27 were excluded due to $\geq$2 concurrent second-line therapies within one month. A cohort of 223 ITP patients who required second-line medical therapies were included for final analysis. Rituximab was the most commonly prescribed second-line therapy (149; 67 %) followed by eltrombopag (65; 29 %) and romiplostim (9; 4 %), with a trend towards increased second-line TPO-RA use over time (Table 1). The median age at ITP diagnosis was 57 years (interquartile range [IQR], 39–69), 122 (55 %)

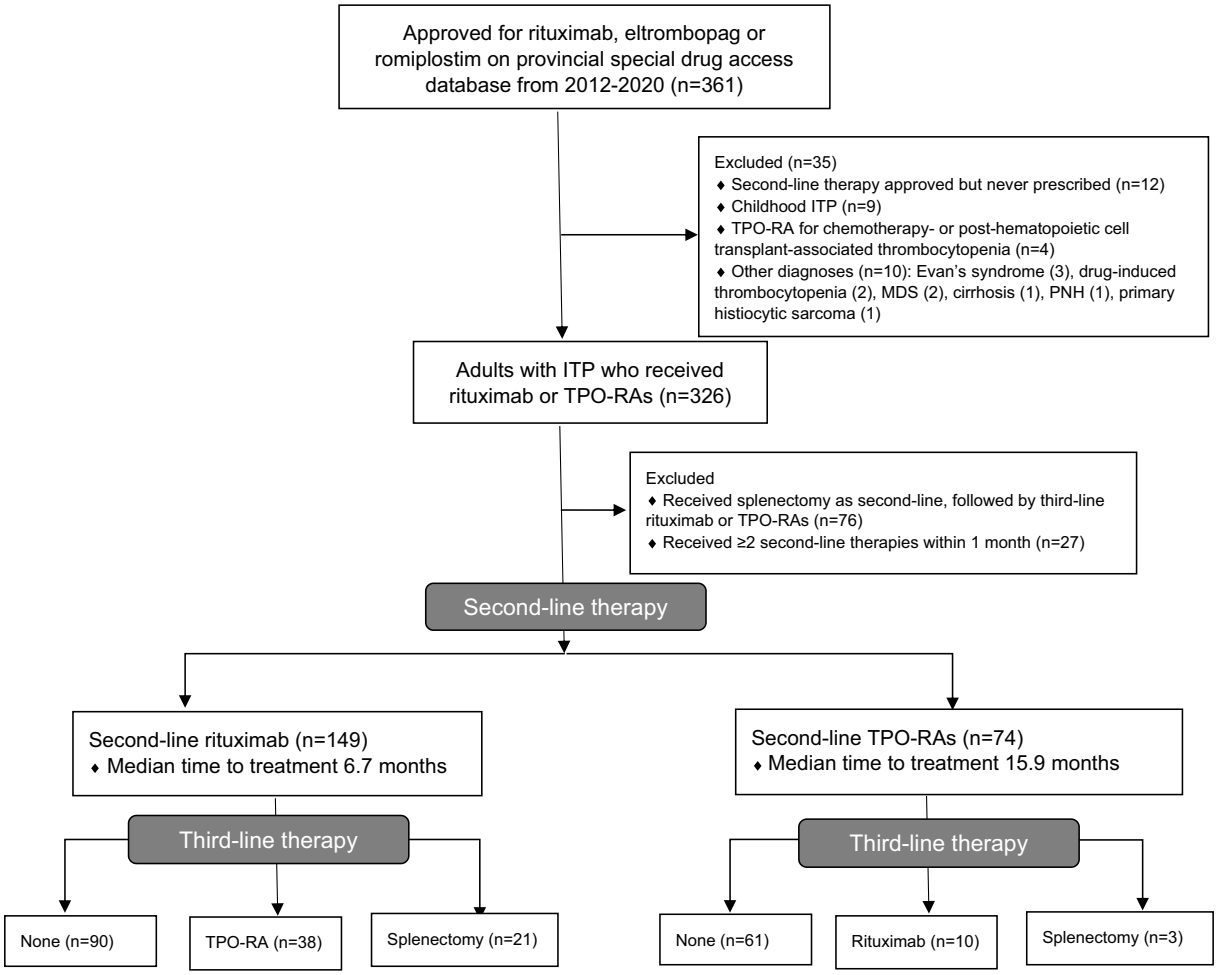

Fig. 1. Flow diagram of treatment sequences in adults with chronic immune thrombocytopenia.

were female, and 31 (14 %) lived in a rural setting. The majority (216; 97 %) were managed by a hematologist, with the remainder managed by internal medicine or oncology. Over half (129; 58 %) of the cases were primary ITP, whereas the remaining had secondary ITP from autoimmune disorders (73; 33 %), LPD or monoclonal gammopathy of undetermined significance (MGUS, 19; 9 %), and viral infections (2; 1 %). GI bleeding and ICH occurred in 23 (10 %) and 4 (2 %) individuals prior to second-line medical therapies. Atherosclerotic risk factors were prevalent in this population: hypertension in 102 (46 %), dyslipidemia in 67 (30 %), diabetes in 41 (18 %), chronic kidney disease in 28 (13 %), and active smokers in 22 (10 %).

3.2. Treatment patterns of second- and subsequent-lines of ITP therapy

The sequence of second-line and subsequent lines of ITP therapy is shown in Fig. 1. The most common treatment sequences were 1) second-line rituximab followed by no further therapies (n = 90, 40 %), 2) second-line TPO-RA followed by no further therapies (n = 61, 27 %), 3) rituximab followed by TPO-RA (n = 38, 17 %). The median time from ITP diagnosis to second-line therapy was significantly longer for patients who received TPO-RA compared to rituximab (15.9 vs 6.7 months, $P <$ 0.0001; Table 1). Patients received a median of 1 (IQR 1–2) course of corticosteroids (IQR 1–2), 1.6 g/kg of IVIG (IQR 0–3.0), and 0 (IQR 0–1) dose of adult platelets prior to initiation of second-line therapy. Only a small proportion of patients received ≥3 courses of corticosteroids (32; 14 %) or ≥ 3 doses of platelets (28; 13 %) prior to second-line therapy. Second-line TPO-RA was associated with significantly higher utilization of IVIG (P = 0.007) and platelet transfusions ($P <$ 0.0001) from the time of ITP diagnosis to initiation of second-line therapy compared with second-line rituximab (Table 1).

The mean age at the time of second-line therapy was significantly older in recipients of TPO-RA compared to rituximab (65.2 vs 55.3 years, P = 0.0004; Table 1). On univariate logistic regression, age at second-line therapy (odds ratio [OR] 1.04, 95 % confidence interval [CI] 1.02–1.05, $P <$ 0.0001), Charlson comorbidity index ≥3 (OR 1.9, 95 % CI 1.1–3.3, P = 0.02), ICH prior to second-line therapy (OR 12.8, 95 % 1.9–252.6, P = 0.02) were significantly associated with second-line TPO-RA prescription. Sex, socioeconomic status, ITP etiology, rural residence, treatment centre, and time frame were not significant predictors of choice for second-line TPO-RA. On multivariable logistic regression, age at second-line therapy (adjusted OR 1.04, 95 % CI 1.02–1.07, $P <$ 0.0001) and prior ICH (aOR 12.7, 95 % CI 1.6–272.8, P = 0.03) remained as significant predictors of second-line TPO-RA. Male sex had a trend towards higher odds of receiving second-line TPO-RA on univariate (OR 1.6, 95 % CI 1.0–2.8, P = 0.06) and multivariable logistic regression (aOR 1.6, 95 % CI 0.9–2.8, P = 0.09), albeit non-statistically significant. Over the years, there was no significant difference in the time from diagnosis to second-line therapy or the number of corticosteroids courses prior to second-line therapy. The doses of IVIG ($P <$ 0.0001) and platelet transfusions (P = 0.03) prior to second-line therapy, however, declined over time.

Among the 99 patients who achieved a response to any of the TPO-RA (used as second- or subsequent lines), 27 (27 %) successfully discontinued TPO-RA without relapse. Of the responders to eltrombopag and romiplostim, 33 % and 30 % were weaned off their TPO-RA at a median of 9.4 (IQR 5.0–17.1) months and 15.7 (IQR 11.2–18.5) months,

Table 1
Baseline characteristics of patients who received rituximab and TPO-RA as second-line therapy for chronic ITP.

	Rituximab (*n* = 149)	TPO-RA (*n* = 74)	P-value
Mean age at time of second-line therapy, years (SD)	55.3 (20.1)	65.2 (18.8)	0.0004
Female sex, n (%)	86 (58)	36 (49)	0.26
Rural residence, n (%)	21 (14)	10 (14)	0.99
CCI, n (%)			0.03
0	39 (26)	8 (11)	
1–2	37 (25)	19 (26)	
3–4	22 (15)	19 (26)	
≥5	51 (34)	28 (38)	
Year of second-line			0.005
2011 or earlier	6 (4)	0	
2012–2014	36 (24)	11 (15)	
2015–2017	45 (30)	39 (53)	
2018–2020	62 (42)	24 (45)	
ITP etiology, n (%)			0.90
- Primary ITP	86 (58)	43 (58)	
- Autoimmune	48 (32)	25 (34)	
- LPD	8 (5)	2 (3)	
- MGUS	6 (4)	3 (4)	
- Viral infection	1 (1)	1 (1)	
ITP duration at time of second-line therapy, months			<0.0001
Median (IQR)	6.7 (1.8–24.9)	15.9 (1.7–79.9)	
Mean (SD)	28.9 (59.4)	45.5 (58.0)	
Mean courses of prior corticosteroids therapy (SD)	1.6 (0.9)	1.4 (0.8)	0.56
Platelet transfusion pre-second line, doses, mean (SD)	1.1 (3.7)	2.0 (5.4)	<0.0001
IVIG pre-second line, g/kg, mean (SD)	2.3 (3.4)	5.2 (14.3)	0.007
Other immunosuppressive therapy, n (%)	14 (9)	7 (9)	0.99
Major bleeding prior to second-line therapy, n (%)			
CNS bleeding	0	4 (5)	0.01
GI bleeding	17 (11)	6 (8)	0.12
Comorbidities, n (%)			
Hypertension	54 (36)	48 (65)	<0.0001
Dyslipidemia	34 (23)	33 (45)	0.001
Diabetes	24 (16)	17 (23)	0.29
Active smoker	16 (11)	6 (8)	0.70
Obesity, BMI >30	32/93 (34)	25/51 (49)	0.09
Atrial fibrillation/flutter	23 (15)	14 (19)	0.64
History of myocardial infarction	4 (3)	6 (8)	0.09
History of stroke or TIA	9 (6)	4 (5)	0.99
Chronic kidney disease	18 (12)	10 (14)	0.93
Liver cirrhosis	10 (7)	4 (5)	0.82
Malignancy			
Active within 6 months	13 (9)	12 (16)	0.12
Any	37 (25)	21 (28)	0.63
Psychiatric condition	27 (18)	17 (23)	0.50
Depression	20 (13)	8 (11)	0.73
Psychosis	3 (2)	3 (4)	0.66
Dementia	6 (4)	6 (8)	0.34

Abbreviations: BMI, body mass index; CCI, Charson comorbidity index; GI, gastrointestinal; ICH, intracranial hemorrhage; g/kg, grams per kilogram body weight; IQR, interquartile range; ITP, immune thrombocytopenia; LPD, lymphoproliferative disorder; MGUS, monoclonal gammopathy of undetermined significance; TIA, transient ischemic attack; TPO-RA, thrombopoietin receptor agonists.

respectively. Among those who were maintained on TPO-RA, the median dose was eltrombopag 50 mg (IQR 25–75 mg) daily and romiplostim 2 μg/kg (IQR 1–4 μg/kg) weekly at last follow-up.

3.3. Health services utilization following second-line therapy

Overall, 143 (64 %) patients underwent a total of 274 ITP-related hospitalizations, and 6 (3 %) underwent ITP-related ICU admissions from the time of second-line therapy to last follow-up. Among these, 35 (16 %) required 3 or more hospitalizations. There were no significant differences in the rates of hospitalizations or ICU admissions across second-line therapies, although second-line TPO-RA was associated with a longer length of stay ($P < 0.0001$; Table 2). The 3-year cumulative incidence of hospitalizations for bleeding/infections was comparable between patients who received second-line TPO-RA (30.8 %, 95 % CI 17.1–42.3 %) and rituximab (26.8 %, 95 % CI 16.3–36.1 %) (log-rank $P = 0.10$; Fig. 2). Second-line rituximab and TPO-RA also had comparable cumulative incidence of hospitalizations for bleeding ($P = 0.50$) or infections ($P = 0.09$).

Recipients of second-line TPO-RA received significantly fewer IVIG and packed red cells, but more platelet transfusions, during the period from second-line therapy to next treatment compared with recipients of rituximab (Table 2). The absolute difference, however, was low between groups.

3.4. Treatment response and outcomes

Response rates were comparable between second-line rituximab and TPO-RA: overall response was achieved in 102 (68 %) and 53 (72 %), while CR was achieved in 78 (52 %) and 40 (54 %) in the rituximab and TPO-RA groups. Response rates were similar between eltrombopag and romiplostim. Among responders, 38/102 (37 %) patients relapsed following rituximab at a median of 1.5 years (IQR 0.6–2.2), whereas 13/53 (25 %) patients relapsed following TPO-RA at a median of 0.7 years (IQR 0.4–1.2). There was a trend towards longer RFS in second-line TPO-RA compared to rituximab (median RFS 6.3 vs 3.8 years, log-rank $P = 0.06$; Fig. 3). There was no significant difference in the rates of ICH, GI bleeding, arterial or venous thromboembolism across second-line therapies (Table 2).

At a median follow-up of 4.8 years, 58 (26 %) patients died. The most

Table 2
Health services utilization and outcomes in adults with chronic immune thrombocytopenia, based on second-line therapy.

	Rituximab (*n* = 149)	TPO-RA (*n* = 74)	P-value
Clinical response			
Any response, n (%)	102 (68)	53 (72)	0.43
Complete response, n (%)	78 (52)	40 (54)	0.81
Relapse, n (%)	38/102 (37)	13/53 (25)	0.11
Health services utilization			
ITP-related hospitalizations, n (%)	94 (63)	49 (66)	0.76
Median length of stay, days (IQR)	5.0 (3.0–11.0)	8.0 (4.0–16.0)	<0.0001
ICU admission, n (%)	3 (2)	3 (4)	0.40
Platelet transfusions from second-line therapy[a], doses, mean (SD)	0.4 (2.0)	0.8 (2.7)	<0.0001
IVIG utilization[a], g/kg, mean (SD)	0.9 (2.7)	0.4 (1.4)	<0.0001
Red cell transfusions[a], units, mean (SD)	0.6 (2.2)	0.4 (1.3)	<0.0001
Outcomes			
Major bleeding events, n (%)			
- ICH	4 (3)	4 (5)	0.45
- GI bleeding	3 (2)	5 (7)	0.12
Myocardial infarction, n (%)	5 (3)	5 (7)	0.31
Ischemic stroke/TIA, n (%)	6 (4)	5 (7)	0.51
Venous thromboembolism, n (%)	8 (5)	5 (7)	0.76

GI, gastrointestinal; ICH, intracranial hemorrhage; ICU, intensive care unit; g/kg, grams per kilogram body weight; IQR, interquartile range; ITP, immune thrombocytopenia; IVIG, intravenous immunoglobulins; TIA, transient ischemic attack; TPO-RA, thrombopoietin receptor agonists.

[a] Platelet and IVIG utilization from the time of second-line therapy to the time of third-line therapy or last follow-up.

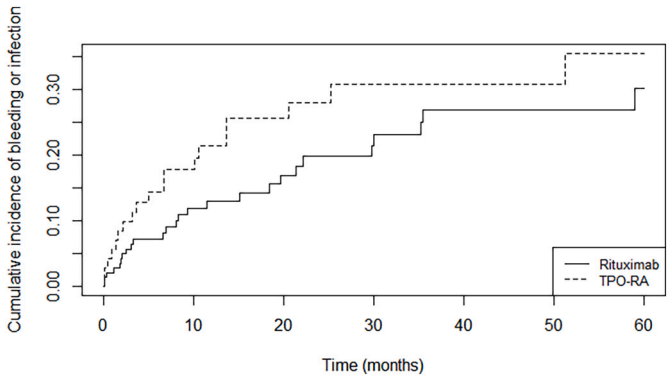

Fig. 2. Kaplan-Meier curve of cumulative incidence of hospitalizations for bleeding or infection in adults with immune thrombocytopenia, stratified by second-line rituximab vs thrombopoietin receptor agonists.

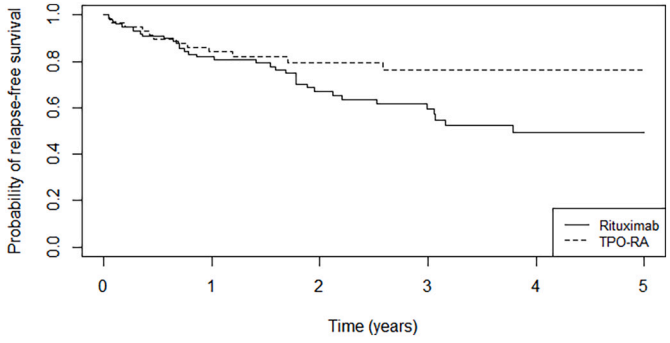

Fig. 3. Kaplan-Meier curve of relapse-free survival in adults with immune thrombocytopenia, stratified by second-line rituximab vs thrombopoietin receptor agonist.

common causes included cardiovascular diseases (13; 22 %), infections (13; 22 %) and malignancy (11; 19 %), followed by bleeding (7; 12 %). Of the 13 cardiovascular deaths, 2 (15 %) had prior splenectomies, and 5 (38 %) were on TPO-RA at time of death. In contrast, none of the 7 hemorrhagic deaths was on TPO-RA at last follow-up. Second-line TPO-RA had a significantly worse 5-year OS (63 %, 95 % CI 51–77 %) compared with second-line rituximab (74 %, 95 % CI 65–84 %) (log-rank $P = 0.03$; Fig. 4). Age (aHR 1.03, 95 % CI 1.01–1.05, $P = 0.001$), Charlson comorbidity index ≥5 (aHR 8.1, 95 % CI 4.2–15.5, $P < 0.0001$), and earlier time period (2015–2017 vs 2012–2014: aHR 0.45, 95 % CI 0.26–0.78, $P = 0.004$; 2018–2020 vs 2012–2014: aHR 0.43, 95 % CI 0.23–0.80, $P = 0.007$) were significant independent predictors of death on multivariable Cox regression analysis (Table 3). Second-line

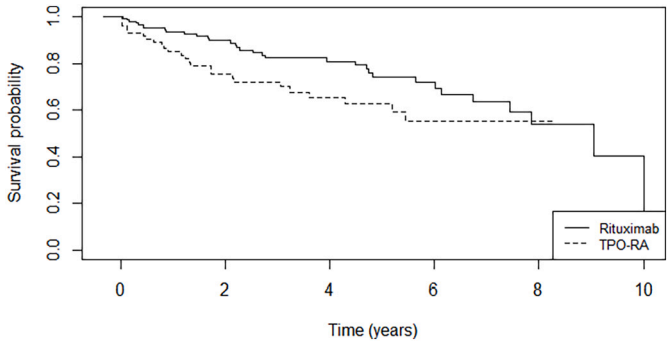

Fig. 4. Kaplan-Meier curve of overall survival in adults with immune thrombocytopenia, stratified by second-line rituximab vs thrombopoietin receptor agonist.

Table 3
Predictors of overall survival on univariate and multivariable Cox proportional hazards regression.

	HR (95 % CI)	P-value	aHR (95 % CI)	P-value
Age at diagnosis	1.06 (1.05–1.08)	<0.0001	1.03 (1.01–1.05)	0.001
Female sex	0.78 (0.45–1.32)	0.36		
Rural residence	2.4 (1.3–4.5)	0.006	1.5 (0.78–2.8)	0.23
Etiology				
Idiopathic	0.71 (0.40–1.25)	0.23	1.5 (0.89–2.6)	0.13
LPD	0.57 (0.14–2.42)	0.45	0.31 (0.07–1.4)	0.12
MGUS	2.5 (1.0–6.0)	0.05	2.6 (0.84–4.6)	0.12
Autoimmune	1 (reference)		1 (reference)	
Second-line therapy				
TPO-RA	1.3 (0.77–2.2)	0.34	1.4 (0.84–2.4)	0.19
Rituximab	1 (reference)		1 (reference)	
Charlson comorbidity index				
0–2	1 (reference)		1 (reference)	
3–4	8.6 (2.3–31.9)	0.001	1.7 (0.77–3.6)	0.19
≥ 5	31.5 (9.6–103.2)	<0.0001	8.1 (4.2–15.5)	<0.0001
Year of second-line				
2012–2014	1 (reference)		1 (reference)	
2015–2017	0.52 (0.28–0.98)	0.04	0.45 (0.26–0.78)	0.004
2018–2020	0.68 (0.34–1.4)	0.28	0.43 (0.23–0.80)	0.007
Major bleeding prior to second-line therapy	2.4 (1.2–4.6)	0.01	1.7 (0.85–3.3)	0.14

Abbreviations: 95 % CI, 95 % confidence interval; CCI, Charson comorbidity index; GI, gastrointestinal; HR, hazard ratio; ITP, immune thrombocytopenia; LPD, lymphoproliferative disorder; MGUS, monoclonal gammopathy of undetermined significance; TPO-RA, thrombopoietin receptor agonists.

medical therapies (TPO-RA vs rituximab) were not a significant predictor of death on univariate or multivariable regression.

During 1363 patient-years of follow-up, arterial and venous thromboembolism occurred in 20 and 13 patients, respectively. The rate of arterial and venous thromboembolism was comparable across second-line medical therapies. Thirty-eight patients experienced 60 serious infections requiring hospitalization. The incidence of serious infections per 100 person-years was 4.4 (95 % CI 3.4–5.6), ranging from 3.8 (95 % CI 2.7–5.9) in patients who received rituximab alone to 6.1 (95 % CI 4.0–9.0) in patients who received TPO-RA alone. Infections occurred at a median of 10.3 months (IQR 7–18) after rituximab exposure. The most common sites of infections included pneumonia (34; 57 %), bacteremia (14; 23 %), skin and soft tissue infection (6; 10 %), and urinary tract infections/pyelonephritis (5; 8 %). There were six opportunistic infections, including three invasive candidiasis, one disseminated herpes zoster, one *Pneumocystis jirovecii* pneumonia, and one miliary TB with TB meningitis. Four opportunistic infections occurred within 12 months post-rituximab, and one occurred following splenectomy.

4. Discussion

While international consensus guidelines recommended the use of either rituximab, TPO-RA or splenectomy as second-line ITP therapy [2,3], and systematic reviews and network meta-analysis have demonstrated indirect evidence of superior efficacy of TPO-RA compared with rituximab [11,12], there are few real-world studies that directly compared patient outcomes and health service utilization among second-line therapies. Likewise, few contemporary studies have

described treatment patterns and sequencing of second-line therapies. In this large provincial cohort study of 326 adults with ITP receiving second-line rituximab, eltrombopag or romiplostim, we described the clinician practice patterns, and evaluated the impact of second-line therapy on health resource utilization and outcomes.

The choice of second-line ITP therapy depends not only on patient and disease characteristics, values and preferences of patients/families and clinicians, but also heavily on access to medications. Although the TPO-RAs romiplostim and eltrombopag were approved by Health Canada in February 2009 and January 2011, respectively, provincial drug funding posed a major access issue for Canadians, with marked inequities across provinces and territories [8]. We showed that the most common treatment sequences were rituximab alone (40 %), TPO-RA alone (27 %), and rituximab followed by TPO-RA (17 %). Our treatment patterns are comparable to a large US electronic health record-based study conducted in a comparable period (2008–2017), which also identified rituximab as the most commonly used second-line therapy (73 %) followed by TPO-RA (16 %) [5]. Our findings are in contrast with those from a single-centre Canadian retrospective cohort study derived from the McMaster ITP registry [13]. Due to more stringent access to TPO-RA in the province of Ontario, which includes failure of two other second-line therapies (including failure after splenectomy or contraindications to splenectomy), splenectomy (41 %) and immunosuppressant agents (23 %; azathioprine, cyclosporine, cyclophosphamide, or mycophenolate mofetil) dominated the initial second-line therapies. While over a third of patients eventually required rituximab and TPO-RAs during the treatment course, only 11 % and 9 % received them as the initial second-line therapy [13]. The low rate of other immunosuppressive therapy (9 %) in our cohort may also be affected by our case selection (patients approved for rituximab and TPO-RAs from provincial drug database).

Our study highlighted markedly longer delays from ITP diagnosis to initiation of second-line therapy among recipients of second-line TPO-RA compared with recipients of rituximab (16 vs 7 months). It is unclear if the delay reflects physician practice, drug access, or patient factors. Alarmingly, this delay was accompanied by not only higher platelet and IVIG utilizations in the second-line TPO-RA group, but also a significantly higher risk of ICH (5 %) during the period prior to second-line therapy. In fact, we identified both older age and prior ICH as independent predictors of second-line TPO-RA prescription. Given high morbidity and mortality associated with ICH, preferential use of TPO-RAs in patients with a history of ICH is a rational choice given their superior efficacy compared with rituximab. While we did not record all bleeding events prior to second-line ITP therapy, data from the CARMEN-France registry demonstrated a very high incidence of bleeding (84 %) prior to eltrombopag initiation even among patients who had early TPO-RA initiation within 6 months of ITP diagnosis [14]. Timing to initiation of TPO-RA has changed over time. Previously, the use of eltrombopag in the first 6-months following ITP diagnosis was off-label in Europe [14]. Updated international ITP guidelines and the COVID-19 pandemic likely contributed to earlier adoption of TPO-RA [2,3,15]. The CARMEN-France prospective registry demonstrated over a similar period (2013–2019) that eltrombopag was the most commonly used second-line therapy, with a median time from diagnosis to eltrombopag initiation of 3.3 months [14]. Earlier adoption of TPO-RA may not only reduce the risk of major bleeding events during windows of critically low platelet counts and prevent prolonged exposure to corticosteroids, but also delay or obviate the need for splenectomy. It is reassuring to note that, in keeping with other studies, 26 % of our TPO-RA responders were able to discontinue therapy without relapse, and only 3/74 (4 %) patients receiving second-line TPO-RA eventually required splenectomy [16–18]. While this may be affected by short follow-up time and confounding by indication, our findings highlight the importance of sequencing of ITP therapies. Considering that the ability to offer long-term remission (82–90 %), efficacy in bleeding reduction (86–87 %), safety (76–86 %), and avoiding immunosuppression (61–72 %) have been identified as key factors affecting patient and physician treatment choices in the ITP World Impact Survey (I-WISh), advocacy for earlier and equitable access to TPO-RA is critical [19].

Few studies reported on differences in health services utilization or outcomes between different second-line ITP treatments [5–7]. Furthermore, the heterogeneous endpoints used in clinical trials and observational studies create further barriers for comparison of different second-line ITP therapies [20]. Our study demonstrated similar health service utilization between TPO-RA and rituximab groups, including comparable cumulative incidence of bleeding- or infection-related hospitalizations and ICU admissions. While the TPO-RA group experienced a significantly lower IVIG and packed red cell utilization following second-line therapy compared with rituximab, the magnitude of the difference was low, making it unlikely to be clinically significant. In terms of clinical outcomes, we identified a trend towards longer RFS in second-line TPO-RA compared with rituximab. The rates of thromboembolism and major bleeding were comparable following initiation of various second-line treatments. Serious infections requiring hospitalizations are frequent (4.4 per 100 person-years). The high incidence of serious infections observed in the TPO-RA group suggests that additional risk factors (older age, comorbidities, pre-existing immunosuppression such as diabetes, cirrhosis and malignancies) contribute to the probability of infections, beyond immunosuppression from ITP treatment. In fact, a population-based study reported increased risk of serious infections in the 5-year period prior to ITP diagnosis, suggesting that the infections may be related to the underlying ITP pathophysiology [21].

Our study has several limitations. Inherent to the retrospective study design, there are missing data, unadjusted confounding including confounding by indication and by changes in drug access over time. Case identification from the provincial drug access database may have created selection bias, missing patients who achieved long-term remission with other second-line therapies, and a small group of patients who accessed rituximab or TPO-RA via private insurance. We do not have access to ethnicity, private insurance, or physician-level data to assess their association with second-line treatment choice or outcomes. For outcome measures, we elected to focus on health service utilizations, major bleeding, RFS and OS, and did not collect platelet count or non-major bleeding data. Finally, the study may be under-powered to detect a significant difference between groups due to a smaller number of patients receiving second-line TPO-RA. We were also unable to compare outcomes between recipients of eltrombopag and romiplostim due to sample size. Despite these limitations, there are several strengths of this study. We included a large cohort of unselected patients, both primary and secondary ITP. Due to publicly funded access to second-line therapy, we captured all patients who accessed a second-line therapy through the provincial special access drug plan, not just patients followed by tertiary academic centres. This mitigates the risk of referral bias.

In this large provincial cohort study, we demonstrated rituximab as the most commonly used second-line ITP therapy, although the use of TPO-RA is on the rise over the past decade. Compared to rituximab, second-line TPO-RA had a comparable cumulative incidence of ITP-related hospitalizations and a trend towards longer RFS. ICH occurred in 5 % of patients prior to second-line TPO-RA, possibly contributed by delays in TPO-RA initiation and older age in the TPO-RA group. Given that international survey of patients and clinicians recently elicited the chance of long-term remission and bleeding prevention while avoiding immunosuppression as the most important factors affecting physician and patient treatment choices, future efforts to improve earlier TPO-RA access are critical to improve patient outcomes and treatment burden.

Addendum

E. Wall and J. Podstawka collected the data and contributed to data interpretation. H. L. Sun designed the study, collected the data,

performed data analysis and interpretation, and wrote the first draft of the manuscript. All authors critically reviewed the manuscript and provided final approval of the manuscript.

Acknowledgments and funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: M.D.G. and H.L.S. received honorarium from Sobi for advisory board participation.

Other authors have no conflicts of interest to declare.

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