Research Article

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Real-world evidence on clinical outcomes in immune thrombocytopenia treated with thrombopoietin receptor agonists

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Aim: Eltrombopag and romiplostim are US FDA approved for treatment of immune thrombocytopenia in patients with insufficient response to other treatments. Clinical or real-world data comparing outcomes of the two drugs are limited. **Methods:** This retrospective cross-sectional study sought information on bleeding-related episodes (BREs), adverse events (AEs) and other outcomes of eltrombopag or romiplostim treatment in immune thrombocytopenia. **Results:** Patients receiving eltrombopag experienced significantly reduced BREs, severe BREs, rescue medication use and platelet transfusions. Diarrhea and headache were significantly less frequent in patients receiving eltrombopag; other AEs occurred equally in both groups. **Conclusion:** There may be a potential advantage for the use of eltrombopag versus romiplostim in the practice settings studied, based on rates of BREs and AEs and rescue medication utilization.

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Keywords: adverse events • bleeding episodes • eltrombopag • immune thrombocytopenia • romiplostim • treatment outcomes

Chronic immune thrombocytopenia (ITP) is an immune-mediated disease characterized by persistent low platelet counts that place patients at risk of uncontrolled bleeding [1]. The incidence of ITP in adults is between 16 and 39 cases per million adults per year, translating to 3900 to 9500 adults diagnosed with ITP in the USA each year [2,3]. The less severe symptoms of ITP include bruising, mucosal bleeding, petechiae and fatigue, all of which have an impact on health-related quality of life (HRQoL) [4,5]. More severe symptoms include serious bleeding-related episodes (BREs), such as gastrointestinal bleeding, intracranial hemorrhage (ICH) and intra- or post-operative hemorrhage, which are associated with morbidity, mortality and diminished HRQoL [4,6,7]. Patients with severe BREs may require whole blood transfusions and hospitalization, in addition to pharmacologic therapies, which can lead to substantial costs [8]. The risk of bleeding increases with age [9].

Population-based studies have found excess mortality in patients with ITP, with hazard ratios of death of 1.5 and 1.6 in two recent reports [10,11]; reasons include severe BREs, infection, cardiovascular disease and hematologic cancer [10–12]. Risk of ICH in ITP patients has been estimated at 1.5% for adults and 0.5% in children, and risk of severe (non-ICH) bleeding is estimated at 3–20% in children and approximately 10% in adults [9]. The risk of fatal hemorrhage has been estimated at 0.4% per year in patients <40 years, and 13% per year in patients >60 years [13].

The primary goal of ITP therapy is to lower the risk of bleeding or prevent recurrence. While bleeding risk is not strictly correlated with platelet count, and other variables (e.g., age, comorbidity, genetic factors) influence risk, practice guidelines from the American Society of Hematology recommend treatment initiation with first-line corticosteroids (longer courses preferred over shorter) with or without intravenous immune globulin (IVIG; depending on the desired rate of platelet increase), to prevent bleeding in patients with platelet count

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$<30 \times 10^9$/l. However, it is also recognized that the risk of severe bleeding is much more substantial at platelet counts $<10 \times 10^9$/l [14,15].

Newly diagnosed ITP patients receive corticosteroids and/or immunoglobulins, which are also used in chronic ITP to control emergent bleeding events [15]. Response to first-line corticosteroids can be variable, with initial response rates between 60 and 80%, but with relapses occurring after drug tapering in up to 80% of patients [16]. Prolonged treatment with corticosteroids is not advisable in many cases due to severe side effects [17]. First-line IVIG produces a rapid (1–3 days) response in 90% of patients, with response typically lasting for 2–4 weeks [15]. IVIG is usually considered a rescue treatment rather than therapy for patients with severe bleeding, as long-term IVIG is also inadvisable due to costs, inconvenience associated with infusions and debilitating headaches post infusion [16,18]. For patients with chronic ITP who do not respond to or tolerate first-line treatment, or who stop responding within 6 months, second-line treatment options include splenectomy, rituximab and thrombopoietin receptor agonists (TPO-RAs) [18]. Despite the potential for long-term remission with splenectomy, up to 20% of patients do not respond, and up to 20% will later relapse; risks include surgical complications, infections from long-term immunosuppression and thromboembolism [18–20]. Rituximab is an off-label option that depletes the B-cell pool, producing autoreactive antibodies that target platelets for destruction [21,22]. Eltrombopag and romiplostim are TPO-RAs that stimulate platelet production. Eltrombopag is a once-daily oral therapy, and romiplostim is subcutaneously injected [19,23]. In a recent US retrospective observational cohort study, in 2047 patients initiating second-line treatment between 2009 and 2016, rituximab was the most common treatment (72.7%), followed by splenectomy (12.7%), romiplostim (9.2%) and eltrombopag (5.4%) [24].

The end point to assess treatment effects in patients with ITP is often defined as a transient and/or sustained increase in platelet counts, while bleeding and quality of life have been assessed as secondary end points [9]. Thus, platelet counts may not capture the full burden of ITP for many patients who have reduced quality of life despite improvements in platelet count. Serious bleeding leading to hospitalization diminishes patients' quality of life [4,25–27]. In the real-world practice setting, prevention or treatment of bleeding-related episodes (normal and severe), use of rescue medications, rates of AEs, quality of life, mortality and avoidance of other ITP agents are common factors included in clinical decision-making [9]. Despite growing use of these TPO-RAs, no large clinical studies have directly compared clinical outcomes with eltrombopag and romiplostim. A recently published meta-analysis of 13 randomized clinical trials (RCTs) analyzed data on any or severe bleeding events from ten of the included studies; pooled analysis of TPO-RAs indicated a significant reduction in incidence of any bleeding events compared with placebo [28]. Subgroup analysis indicated that eltrombopag, but not romiplostim, significantly reduced any or severe bleeding events compared with placebo [28]. To complement the meta-analysis approach with real-world evidence, here we provide data from US healthcare organizations (HCOs) that places into perspective clinical outcomes and risk of AEs associated with TPO-RA treatment of ITP.

Methods

Study setting & data

This study utilized a federated electronic health record (EHR) network of >39 million patients from 32 US HCOs (TriNetX), at the time the EHR network was accessed (3 April 2018). The HCOs contributing to the TriNetX data consisted at that time mostly of large academic health centers comprised main and satellite hospitals and outpatient clinics. TriNetX EHR data are aggregated results from de-identified patient records and can be queried in real time with an average of 5–6 years of retrospective data available from the time of query. The TriNetX EHR network provides information on patient demographics, International Classification of Diseases, Ninth Revision and Tenth Revision, Clinical Modification (ICD-9-CM; ICD-10-CM), procedure codes (ICD-9-CM, ICD-10-Procedure Coding systems, Current Procedural Terminology), medications, labs, oncology data, genomics and vital signs. Details on this network have previously been described [21,29]. When the network was accessed, the technology behind this approach had been primarily developed and used to facilitate real-time large-scale extraction of patient clinical data from HCO databases to help streamline enrollment in clinical trials. The technology and the various means used to ensure patient privacy using de-identified aggregated data thus allow access to patient characteristics and clinical features associated with different treatment groups, in this instance, patients with ITP who received either eltrombopag or romiplostim.

Table 1. Patient characteristics.

Characteristic	Eltrombopag n = 1617	Romiplostim n = 1140	p-value
Age (mean ± SD)	53 (23)	56 (22)	0.1196
Gender (male %)	49%	51%	0.3011
Splenectomy	67 (4)	85 (7)	0.0002†
Co-morbidities, n (%)			
Acute hepatitis B without δ-agent with hepatic coma	10 (1)	10 (1)	0.4305
Acute hepatitis B without δ-agent and without hepatic coma	21 (1)	20 (2)	0.3305
Acute hepatitis C without mention of hepatic coma	35 (2)	21 (2)	0.5546
Acute hepatitis C with hepatic coma	10 (1)	0 (0)	0.0079†
Chronic viral hepatitis C	183 (11)	112 (10)	0.2120
Unspecified viral hepatitis B without hepatic coma	31 (2)	30 (3)	0.2093
Unspecified viral hepatitis B with hepatic coma	10 (1)	10 (1)	0.4305
Unspecified viral hepatitis C without hepatic coma	183 (11)	102 (9)	0.0443
Prothrombin gene mutation	31 (2)	36 (3)	0.0374†
Other primary thrombophilia	60 (4)	44 (4)	0.8397
Lupus anticoagulant syndrome	37 (2)	40 (4)	0.0556
Systemic lupus erythematosus	41 (3)	53 (5)	0.0026†
Cachexia	39 (2)	27 (2)	0.9414
Essential (hemorrhagic) thrombocythemia	59 (4)	71 (6)	0.0017†
Myelodysplastic syndrome	283 (18)	149 (13)	0.0017†
Thrombotic microangiopathy	26 (2)	19 (2)	0.9046
Defibrination syndrome	51 (3)	44 (4)	0.3173
Acquired hemolytic anemias	153 (9)	105 (9)	0.8234
Hemolytic-uremic syndrome	10 (1)	10 (1)	0.4305
HIV disease	17 (1)	14 (1)	0.6648
Asymptomatic HIV infection status	14 (1)	10 (1)	0.9747
Malignant neoplasm of lymphatic and hematopoietic tissue	83 (5)	56 (5)	0.7943
Malignant neoplasm	641 (40)	487 (43)	0.1057
Malignant neoplasm of ill-defined, other secondary	167 (10)	134 (12)	0.2370
Malignant neoplasm of digestive organs	88 (5)	78 (7)	0.1283
Malignant neoplasm of breast	46 (3)	43 (4)	0.1752
Malignant neoplasm of lymphoid, hematopoietic and related tissue	447 (28)	298 (26)	0.3815
Malignant neoplasm of respiratory and intrathoracic organs	30 (2)	30 (3)	0.1691
Malignant neoplasm of male genital organs	37 (2)	35 (3)	0.2050
Malignant neoplasm of female genital organs	26 (2)	21 (2)	0.6400

†Patients with co-morbidities that were distributed significantly differently ($p < 0.01$) were excluded from further analysis.
SD: Standard deviation.

Design & study population

In this cross-sectional observational study, the inclusion and exclusion criteria were built into the data extraction parameters. Patients were included if they had any diagnosis code of ITP defined with an ICD-10-CM of D69.3, D69.4, D69.5 or D69.6 (Supplementary data) and were ≥18 years of age at the time of extraction (3 April 2018). Once adult ITP patients were identified, medication data were queried to identify ITP patients on eltrombopag or romiplostim. To ensure the eltrombopag and romiplostim patient groups were mutually exclusive (i.e., no patients counted in both treatment groups), we excluded romiplostim patients with any prior history of eltrombopag, and eltrombopag patients with any prior history of romiplostim from each treatment group. Therefore, patients in the eltrombopag group had no prior history of romiplostim use, and patients in the romiplostim group had no prior use of eltrombopag. In building an initial set of patients, age and gender were captured in the query search, as well as splenectomy and co-morbidities related to hepatitis virus B and C, HIV, severe aplastic anemia, myelodysplastic syndrome and myelofibrosis, among others. The initial patient characteristics from this set are listed in Table 1.

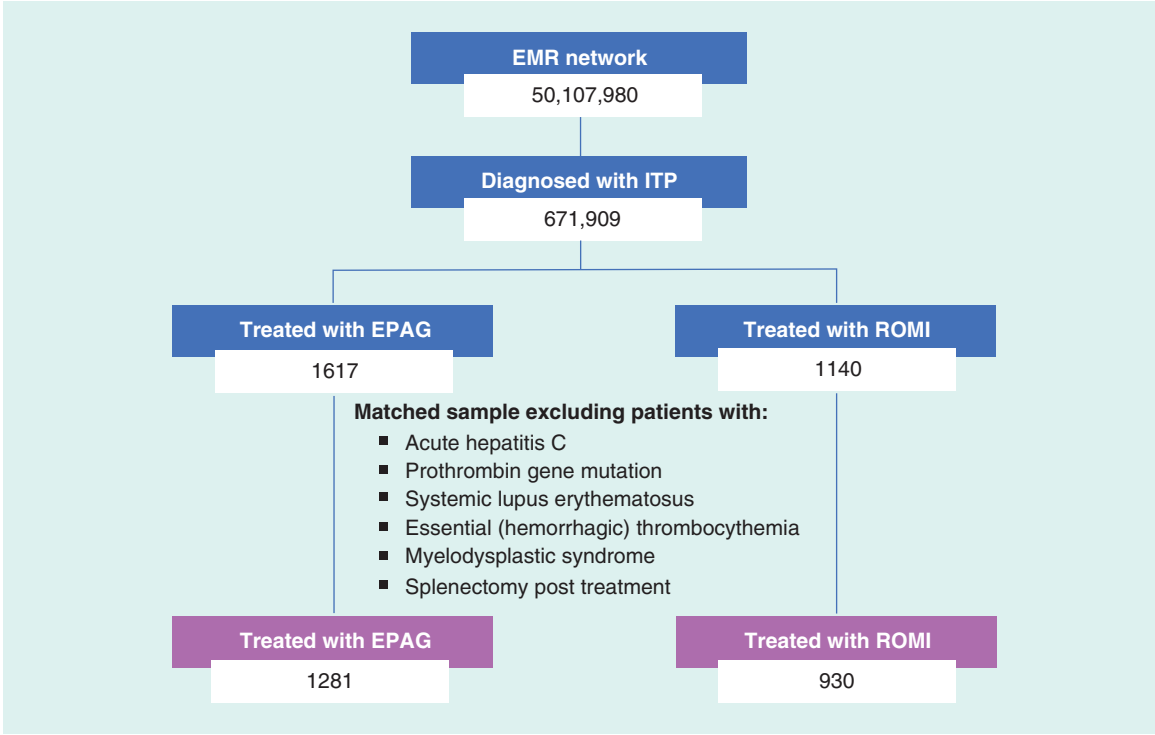

Figure 1. Patient flow.
EMR: Electronic medical record; EPAG: Eltrombopag; ITP: Immune thrombocytopenia; ROMI: Romiplostim.

Since this study used a real-time EHR network, we applied additional criteria to help mitigate the confounding factors arising from patient selection bias. Prevalence of acute hepatitis C with hepatic coma, prothrombin gene mutation, systemic lupus erythematosus, essential (hemorrhagic) thrombocythemia and myelodysplastic syndrome was significantly different ($p < 0.01$) between the two treatment groups (Table 1), Therefore, patients with these co-morbidities were excluded to prevent imbalance due to these characteristics. Patients with a history of rituximab treatment and those with ongoing (i.e., not rescue) corticosteroid treatment during the study period were excluded.

Prevalence of splenectomy was also significantly different between eltrombopag (4%) and romiplostim (7%; $p = 0.0017$) treatment groups; we did not, however, initially exclude these patients because splenectomy is a procedure indicated in some ITP patients. Instead, we conducted an exploratory analysis to determine the descriptive rates of splenectomy prior to treatment initiation with TPO-RAs, and rates following treatment initiation. There was a significant difference between patients who underwent splenectomy after eltrombopag initiation (2%) versus after romiplostim initiation (4%; $p = 0.0039$); these patients were further excluded from both the treatment groups to prevent imbalance due to splenectomy following TPO-RA treatment initiation. After applying this exclusion, the two treatment groups selected for further analysis were eltrombopag (n = 1281) and romiplostim (n = 930; Figure 1). The two patient groups were well balanced and not significantly different with respect to age, proportion of males and platelet volumes.

Outcomes

Clinical outcomes related to benefit and risks were identified retrospectively in the TriNetX patient records within a 6-month period following treatment initiation with eltrombopag or romiplostim. While data were collected for a 6-month period from treatment initiation, the availability of 6 months of data was not a specific inclusion criterion, that is, if <6 months of data were available for a patient, then <6 months of data were used.

Treatment outcomes: rescue medications & BREs

Key treatment outcomes in ITP included use of rescue medications (intravenous immunoglobulin, corticosteroid injections or platelet transfusions) and occurrence of BREs. BREs were identified using ICD-10 diagnosis codes,

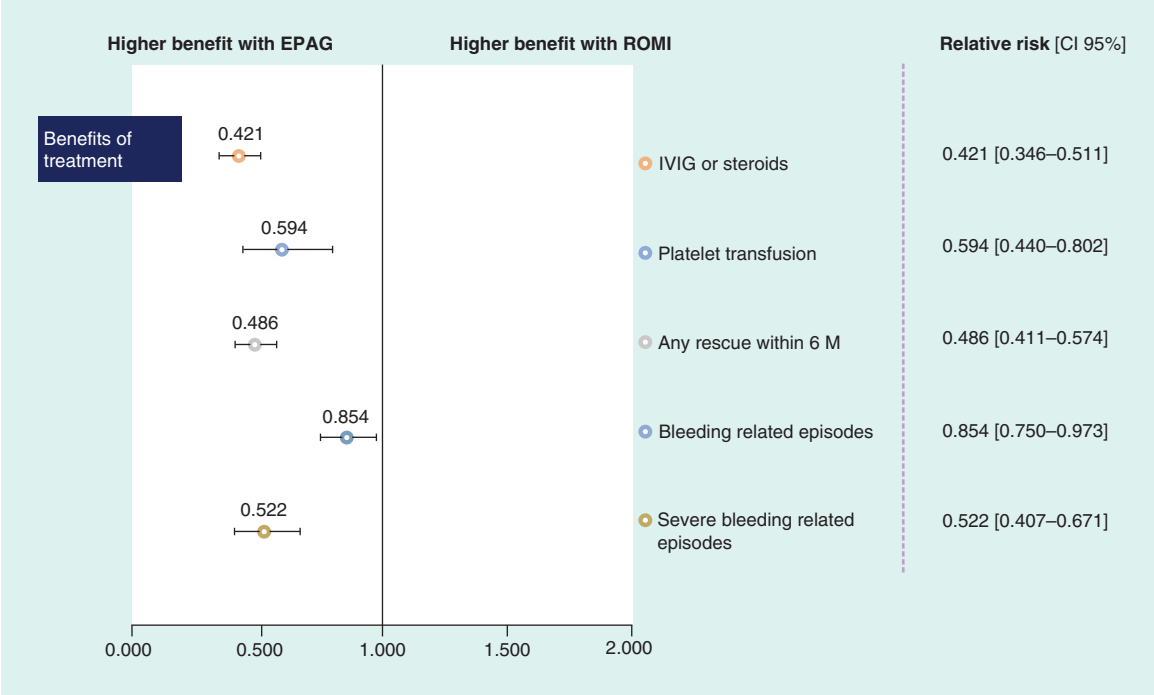

Figure 2. Forest plot comparing outcomes of treatment between eltrombopag and romiplostim.
EPAG: Eltrombopag; IVIG: Intravenous immune globulin; ROMI: Romiplostim.

and severe BREs were defined as having a BRE plus rescue medication use. The ICD-10 codes used to identify these outcomes are provided in Supplementary data.

Adverse events

AEs were defined from a list of ICD-10 diagnosis codes (Supplementary data). Relevant AEs were selected based on FDA prescribing information for eltrombopag and romiplostim, with input from clinical experts [30,31]. AEs included arthralgia, confusion, diarrhea, epistaxis, fatigue, headache, pain in extremities, petechiae and upper respiratory tract infection.

Statistical analysis

Incidence proportions of patient characteristics and outcomes were compared using unadjusted descriptive statistics; 95% CIs were compared for each outcome using two-tailed Z-tests with α of 0.05. Risk ratios were calculated using probabilities of observing a given event in each group: risk ratios = (probability with eltrombopag)/(probability with romiplostim). Probabilities were derived from incidence proportions of events in each group. Forest plots graphically display results obtained for each event measured in this study (Figures 2 & 3).

Results

Of 671,909 patients (≥18 years) diagnosed with ITP in the EHR network on 3 April 2018, 1617 patients were on eltrombopag (with no prior romiplostim) and 1140 patients were on romiplostim (with no prior eltrombopag) (Table 1). The patient flow is displayed in Figure 1. To analyze patient outcomes from matched samples, we excluded patients with the following co-morbidities/characteristics as there were significant differences ($p < 0.01$) in prevalence between the two groups: acute hepatitis C, prothrombin gene mutation, systemic lupus erythematosus, essential (hemorrhagic) thrombocythemia, myelodysplastic syndrome and splenectomy post treatment. Following these exclusions, there were 1281 patients treated with eltrombopag and 930 patients treated with romiplostim available for analysis. Mean ages of patients included in the subsequent analysis of clinical outcomes and AEs were: eltrombopag, 50 years (standard deviation: 23) and romiplostim, 55 years (standard deviation: 23). There were 48% males in the eltrombopag group and 51% in the romiplostim group, and mean platelet volumes were

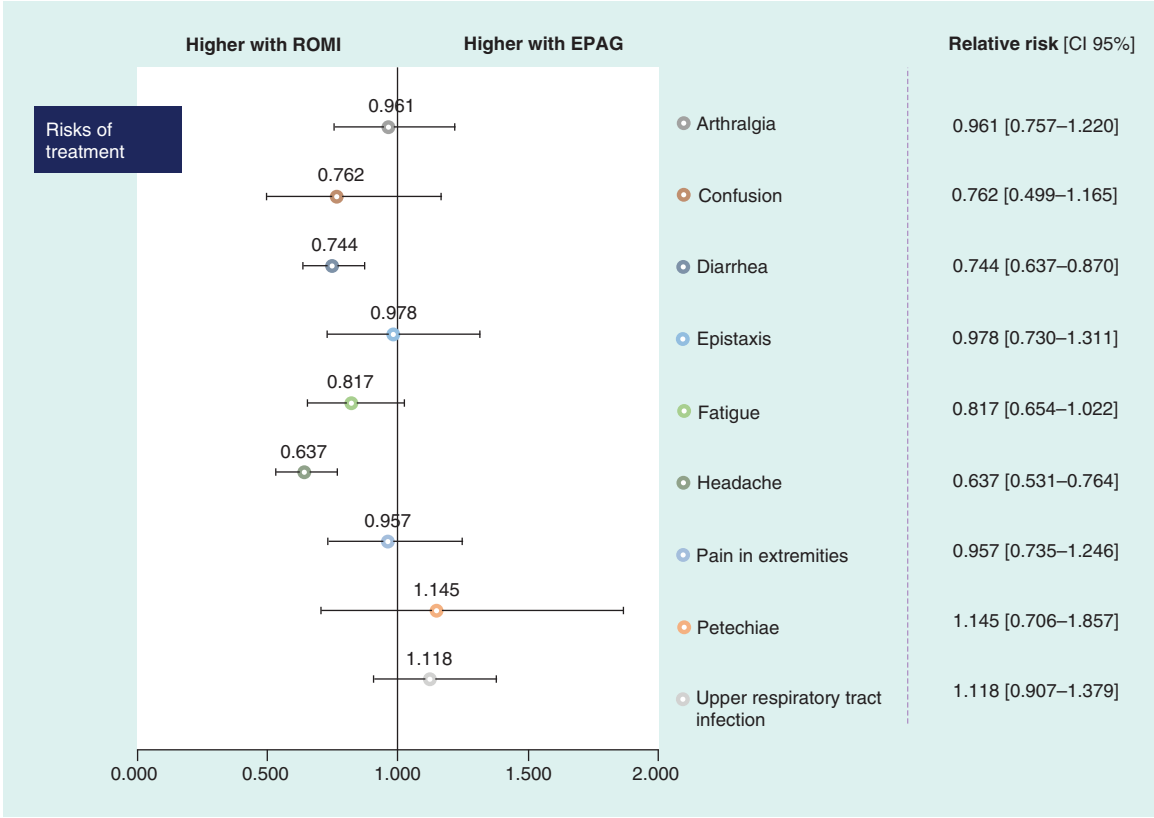

Figure 3. Forest plot comparing adverse events between eltrombopag and romiplostin.
EPAG: Eltrombopag; ROMI: Romiplostim.

10.24 ± 1.94 fL (eltrombopag) and 10.43 ± 1.84 fL (romiplostim). Differences in distribution between the two groups for these three parameters were nonsignificant.

Treatment patterns & clinical outcomes

Significantly fewer eltrombopag patients received IVIG or corticosteroids compared with romiplostim patients within 6 months of treatment initiation (eltrombopag 11% vs romiplostim 25%; $p < 0.0001$; Table 2 & Figure 2).

Platelet transfusions were also significantly lower in the eltrombopag group compared with romiplostim (eltrombopag 6% vs romiplostim 9%; $p = 0.0006$; Table 2 & Figure 2). Eltrombopag patients also experienced significantly fewer BREs (eltrombopag 27% vs romiplostim 32%; $p = 0.0186$) and fewer severe BREs (eltrombopag 7% vs romiplostim 14%; $p < 0.0001$; Table 2 & Figure 2). Risks were also evaluated within 6 months of treatment initiation, using selected AEs. Eltrombopag and romiplostim patients experienced similar rates of AEs, except for diarrhea and headache, which were significantly different in prevalence (Table 2 & Figure 3). Diarrhea was reported in 19% of eltrombopag-treated patients compared with 26% of romiplostim-treated patients ($p = 0.0002$), and headache was reported in 14% of eltrombopag-treated patients compared with 22% of romiplostim-treated patients ($p < 0.0001$; Table 2 & Figure 3).

Discussion

The use of TPO-RAs for treatment of ITP has expanded over the past decade and improved therapeutic options for patients in whom first-line treatment fails to provide clinical improvement, namely reductions in bleeding risk based on improved platelet counts [14,35]. The original indications for these treatments were limited to adult patients who had relapsed after splenectomy (and those in whom splenectomy was contraindicated) and those in whom first-line treatments were ineffective [36]. The RCT data that initially led to approval of both the treatments included patient populations in which 34–67% had previously undergone splenectomy [37–41]. One RCT included no splenectomized patients [42] and one RCT examined safety and efficacy of romiplostim versus placebo separately in splenectomized

Table 2. Clinical outcomes and adverse events within 6 months of treatment initiation.

Clinical outcome	Eltrombopag n = 1281	Romiplostim n = 930	p-value
Treatment outcomes (n, %)			
IVIG or corticosteroids	135 (11)	233 (25)	0.0000†
Platelet transfusion	72 (6)	88 (9)	0.0006†
Any rescue within 6 months	182 (14)	272 (29)	<0.0001†
Bleeding-related episodes	346 (27)	294 (32)	0.0186†
Severe bleeding-related episodes	95 (7)	132 (14)	0.0000†
Selected adverse events (n, %)			
Arthralgia	139 (11)	105 (11)	0.7448
Confusion	42 (3)	40 (4)	0.2094
Diarrhea	247 (19)	241 (26)	0.0002†
Epistaxis	97 (8)	72 (8)	0.8821
Fatigue	143 (11)	127 (14)	0.0774
Headache	179 (14)	204 (22)	<0.0001†
Pain in extremities	116 (9)	88 (9)	0.7442
Petechiae	41 (3)	26 (3)	0.5836
Upper respiratory tract infection	191 (15)	124 (13)	0.2952

† Statistically significant difference ($p < 0.05$).
IVIG: Intravenous immunoglobulin.

and nonsplenectomized patients [23]. Both eltrombopag and romiplostim are now FDA approved in the USA for ITP patients who have had an insufficient response to corticosteroids, immunoglobulins or splenectomy (i.e., patients who may or may not have had a splenectomy) [30,31]. These improved responses reported in clinical trials are known to translate into reduced bleeding and decreased necessity of providing concomitant or rescue medication [32,35].

We sought to quantify the responses – clinical outcomes and AEs – to TPO-RAs in a real-world setting utilizing de-identified aggregated patient data from a federated EHR network with access to multiple US HCOs. In this study of 2211 ITP patients, eltrombopag's use was associated with subsequent significantly lower rates of BREs (including severe BREs), decreased use of rescue medications (including IVIG or corticosteroid injections) and platelet transfusions compared with romiplostim. We sought to avoid potential sources of bias that might affect our results; notably, the patient populations included here were mutually exclusive and comparable with respect to TPO-RA treatment. Patients on romiplostim at the time of data capture were excluded if they had previously been on eltrombopag, and vice-versa. Second, we assessed 20 co-morbidities for imbalances between the two patient groups. Five of these, acute hepatitis C with hepatic coma, prothrombin gene mutation, systemic lupus erythematosus, essential (hemorrhagic) thrombocythemia and myelodysplastic syndrome, had significantly different ($p < 0.01$) prevalence rates between the two treatment groups. Consequently, all patients with these co-morbidities were excluded. Third, although a minority of patients were reported to have undergone splenectomy, either before or after treatment initiation, we found that higher rates of patients treated with romiplostim subsequently underwent splenectomy (4%) compared with eltrombopag-treated patients (2%; $p = 0.0039$). To prevent bias, patients from both the groups were excluded if they underwent splenectomy following TPO-RA initiation. As for exclusion of patients who previously underwent splenectomy, this was considered not necessary, given the indications for both the treatments and given that the majority of clinical trials for TPO-RA enrolled patients both with and without prior splenectomy. Data from clinical trials are not uniformly consistent with respect to splenectomy prior to treatment. For example, multivariate analysis from one study that separately analyzed patients with and without splenectomy showed baseline weight <70 kg ($p = 0.0106$) and no splenectomy ($p = 0.0306$) were the only two variables significantly associated with increased rates of durable response [23]. In a separate study, previously splenectomized patients responded equally well to romiplostim compared with non-splenectomized patients [38].

The results presented here are comparable with a recently published meta-analysis of 13 RCTs that analyzed data on any or severe bleeding events from ten of the included studies. Pooled analysis of TPO-RAs indicated a significant reduction in incidence of any bleeding events compared with placebo [28]. Subgroup analysis indicated that eltrombopag, but not romiplostim, significantly reduced any or severe bleeding events compared with placebo [28].

In this real-world evidence study, we also captured data on selected nonbleeding AEs in both the patient groups. AEs, which are arthralgia, fatigue, headache and diarrhea, with >10% prevalence were the same in both the groups. In this study, the latter two AEs were present at a significantly lower rate in eltrombopag-treated patients compared with romiplostim. These AE results are in contrast with results obtained from a French Pharmacovigilance database indicating higher risk of gastrointestinal and hematologic AEs with romiplostim versus eltrombopag [50]. The reasons for differences in AE patterns between these two studies are not immediately clear but may involve a susceptibility to under-reporting in such databases, along with lower power to detect differences in AE signals between treatments [50].

While current US guidelines include TPO-RAs as appropriate second-line treatment options for ITP, it is recognized that not all patients will have a clinically meaningful response to TPO-RA treatment, and some patients discontinue TPO-RA because of the lack of response [15,43]. For example, in the EXTEND study of eltrombopag treatment, of the 302 patients enrolled, 14% withdrew from the study due to AEs, 13% due to patient decision, 11% due to lack of efficacy and 17% due to other reasons [44]. In one long-term romiplostim study, 8.5% of the 292 enrolled patients discontinued because of withdrawn consent, 3.8% due to AEs or alternative therapy, and 24% for other reasons [45].

In this respect, it is quite interesting that the recognized benefits of TPO-RAs have led to studies where switching from one to the other has proven beneficial following inadequate response to initial romiplostim or eltrombopag [46–49]. A retrospective pooled analysis of 18 switching studies (including 401 patients) estimated a relatively high response rate (improved platelet counts) of 65% when patients switched due to lack of efficacy with the first TPO-RA [49]. These differential effects of TPO-RAs in different patients demonstrating a lack of cross-resistance are consistent with known differences in activation of downstream signaling pathways between eltrombopag and romiplostim [35]. These studies raise the theoretical possibility that molecular and/or genetic markers may eventually be identified to personalize treatment decisions to select the most appropriate TPO-RA option for each patient.

Differential effects between TPO-RAs were also noted in a recent study that compared response rates (defined as platelet counts $\geq 50 \times 10^9$/l and $\geq 20 \times 10^9$/l higher than the pretreatment baseline) as a function of baseline TPO levels [51]. This retrospective chart review of patients on eltrombopag (n = 37) or romiplostim (n = 46) concluded that patients with normal (or lower) baseline TPO were equally likely to benefit from either TPO-RA, and those with moderate TPO levels were more likely to benefit from romiplostim than eltrombopag, whereas those with more substantial elevated baseline TPO were unlikely to respond to TPO-RA [51].

Improving platelet count is the most practical clinical end point in randomized trials, but the other key goal of treatment is to prevent bleeding, as this feature of ITP is the most worrisome for patients and clinicians [52,53], and associated costs for treatment of BREs are high. Factoring in fear of bleeding, fatigue, restriction in daily activities, altered immune responses and treatment-related side effects, there is the potential for diminished HRQoL in ITP patients [16]. Though our results did not include formal HRQoL assessments, our real-world findings suggest that patients may have fewer disruptions on eltrombopag compared with romiplostim, based on the potential reduction in platelet transfusions, fewer BREs and fewer severe BREs, along with lower rates of diarrhea and headache. Recent analyses directly link higher rates of BREs to increased healthcare resource use and elevated costs [33,34]. Reducing BREs is critical to the cost–effectiveness of ITP treatment [32].

In this respect, the type of real-world evidence presented in this study is directly relevant to potential cost savings and potential improved QoL attributable to TPO-RAs in general, and further research is warranted to investigate these issues in ITP patients on TPO-RA treatments.

Limitations

This study utilized a federated EHR network (TriNetX) incorporating data from various HCOs providing statistical results, that is, aggregated data and frequency calculations, on variables of interest. Without access to individual patient-level data, regression-aided matching of cohorts cannot be carried out, and patient characteristics cannot be identified with date or time. Regression is preferred when a researcher wants to make inferences about causal relationships and predictions (e.g., using the regression coefficients to predict how changes in the covariates affect the outcome of interest); therefore, this is an important limitation. The imbalances and potential confounding factors introduced by the nonrandomized nature of the study were thus not fully accounted for. However, we believe the methods employed in this analysis are reasonable for the goals of the analysis.

While our inclusion criteria used codes for primary ITP, and we excluded patients with codes for secondary ITP, we cannot exclude the possibility that some patients had ITP secondary to malignancy, infection or other conditions. The co-morbidities (Table 1) suggest that there was a fraction of patients receiving either of the drugs who had co-morbid malignancies or infections.

As romiplostim is administered as a weekly injection and eltrombopag is an oral suspension or tablet, the difference in therapeutic setting may have contributed to differences in documentation. This may especially be applicable to the AEs of diarrhea and headache as typical outpatient complaints; likewise, minor bleeding events that do not require additional follow-up may be more likely to be recorded for patients who have more frequent clinic visits. Unlike adjudicated or audited claims, data from EHR are subject to change as patients progress through episodes of care, and this process introduces an opportunity for error as new data and older conflicting data should ideally be reconciled. This cross-sectional method does not capture duration of disease, duration of therapy, or various other clinical details that may provide additional insights. This study examined events from treatment initiation and the ensuing 6 months, while perhaps a longer duration of follow-up would identify more clinical outcomes. However, since bleeding episodes are severe occurrences, these incidences are mostly captured in the hospital setting, suggesting that there may be minimal impact to the underestimation of these clinical outcomes.

Conclusion

This is the first direct (real-world evidence based) comparison of clinical outcomes and AEs in patients with ITP treated with eltrombopag or romiplostim that suggests there may be a potential advantage for the use of eltrombopag, based on lower rates of BREs (normal and severe), lower utilization of rescue medications and fewer AEs versus romiplostim in the practice settings studied. Further research is warranted in more patients, and in a variety of different settings to arrive at more definitive understanding of the real-world relative risks and benefits of the two TPOs.

Summary points

- Chronic immune thrombocytopenia is an immune-mediated disease characterized by persistent low platelet counts that place patients at risk of uncontrolled bleeding.
- Eltrombopag is a US FDA-approved second-line treatment for immune thrombocytopenia.
- A retrospective cross-sectional study was conducted to examine treatment outcomes and adverse events associated with eltrombopag or romiplostim treatment in immune thrombocytopenia patients.
- In the practice settings studied using electronic health records, patients receiving eltrombopag experienced significantly lower instances of diarrhea and headache – and significantly reduced bleeding-related episodes, rescue medication use and platelet transfusions – compared with those receiving romiplostim.
- Some studies have seen that switching between thrombopoietin receptor agonists after lack of response results in improved platelet counts.
- More research is warranted into the relative risks and benefits of eltrombopag and romiplostim.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.futuremedicine.com/doi/suppl/10.2217/cer-2019-0177. Some preliminary results from this study were presented at the American Society of Hematology 2017 Congress. The associated abstract is available at: http://www.bloodjournal.org/content/130/Suppl_1/3409?sso-checked=true

Author contributions

A Forsythe and A Roy made substantial contributions to study conception/design, data acquisition and critically revising the article for important intellectual content. CS Kwon, J Schneider and A Allepuz substantially contributed to data analyzed and critical article revision. T Pham, M Bhor, Q Said and MSO Portella were substantial contributors to study design and data analysis, as well as to the critical review of the article. All authors approved the final version to be published and agreed to be accountable for all aspects of the work.

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