BMC Pharmacology and Toxicology

RESEARCH

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Safety analysis of romiplostim, eltrombopag, and avatrombopag post-market approval: a pharmacovigilance study based on the FDA Adverse Event Reporting System

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Abstract

Background Romiplostim, eltrombopag, and avatrombopag, as new-generation thrombopoietin receptor agonists (TPO-RAs), have been widely used in the treatment of immune thrombocytopenia (ITP). Given their similar efficacy, a comprehensive evaluation of their safety is crucial for optimizing treatment choices. This study aims to explore the potential safety issues of three major drugs for treating ITP: romiplostim, eltrombopag, and avatrombopag, thereby providing references and research directions for subsequent high-quality clinical studies.

Methods We retrieved data from the FDA Adverse Event Reporting System (FAERS) database from the first quarter of 2018 to the second quarter of 2023. Using reporting odds ratio (ROR), proportional reporting ratio (PRR), bayesian confidence propagation neural network (BCPNN), and multiple gamma poisson shrinkage (MGPS), we mined and analyzed adverse events (AEs) associated with romiplostim, eltrombopag, and avatrombopag. The Designated Medical Event (DME) list from the European Medicines Agency (EMA) was used to screen out the DME of three drugs. Venn analysis was used to screen the specific AEs of each drug.

Results The study included 2,851 cases of romiplostim, 10,297 cases of eltrombopag, and 973 cases of avatrombopag. Venn analysis revealed nine common AEs across the three drugs. The number of significant specific AEs associated with romiplostim, eltrombopag, and avatrombopag were 58, 98, and 15 respectively. DMEs for romiplostim included autoimmune haemolytic anaemia (ROR = 6.1, $n = 3$), haemolytic anaemia (ROR = 8.13, $n = 7$), sudden hearing loss (ROR = 5.24, $n = 3$), haemolysis (ROR = 3.89, $n = 3$). DMEs for eltrombopag included hepatic infection (ROR = 9.56, $n = 6$), granulocytopenia (ROR = 2.91, $n = 4$), autoimmune haemolytic anaemia (ROR = 3.03, $n = 5$), haemolytic anaemia (ROR = 3.46, $n = 10$), haemolysis (ROR = 4.65, $n = 12$), hepatic failure (ROR = 2.51, $n = 23$). Not a single DME was found for avatrombopag.

Conclusion This study indicates that eltrombopag manifests significant safety signals within the hepatic system. This implies that monitoring liver function during treatment is advisable. Avatrombopag shows relatively lower

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hepatotoxicity signals; however, further large-scale studies are needed to validate these observations. Moreover, both romiplostim and eltrombopag therapies may be linked to a risk of sudden hearing loss or deafness, which merits clinical attention. These findings offer crucial safety references for clinical drug use. Nevertheless, the causal relationship between the drugs and AEs necessitates further in-depth investigation.

Keywords Thrombocytopenia, Drug safety, Romiplostim, Eltrombopag, Avatrombopag, FDA Adverse Event Reporting System

Introduction

Immune thrombocytopenia (ITP), which may result from reduced platelet production or accelerated platelet clearance, is common in various medical conditions, including immune-mediated thrombocytopenia, liver cirrhosis, and myelodysplastic syndromes [1]. Clinical manifestations vary, with bleeding events ranging from asymptomatic thrombocytopenia to mucocutaneous bleeding and severe visceral or fatal intracranial hemorrhage [2]. Thrombopoietin receptor agonists (TPO-RAs), including the peptide drug romiplostim and the second-generation non-peptide small molecules eltrombopag and avatrombopag, stimulate platelet production by binding and activating thrombopoietin (TPO) receptors, promoting the proliferation and differentiation of megakaryocytes in the bone marrow. Romiplostim and eltrombopag have been widely approved for treating chronic ITP and severe aplastic anemia in adults and children unresponsive to corticosteroids and immunoglobulins [3], while avatrombopag is used for ITP in adults with chronic liver disease scheduled for surgery. TPO-RAs show high response rates in promoting platelet production and reducing bleeding risk [3]. Eltrombopag and romiplostim have been on the market for over a decade, while avatrombopag, approved in 2018, offers an oral TPO-RA option without dietary restrictions and no known hepatotoxicity signals [4]. study suggests no significant differences in severe Adverse Events (AEs) among patients treated with different TPO-RAs [5]. Multiple Phase III clinical trials have confirmed the efficacy and safety of romiplostim and eltrombopag in chronic ITP patients [6–9]. research also reported that the efficacy and safety of these two TPO-RAs align with clinical trial results [10]. However, large-scale safety studies on these three drugs in real-world settings remain underexplored.

Pharmacovigilance research provides ongoing support for drug safety in real-world. Spontaneous reporting systems play a crucial role in collecting and recording drug-related AEs [11]. FDA Adverse Event Reporting System (FAERS), one such system, is a readily available data source for early identification of drug-related safety issues in large populations [12].

The main objective of this study is to use the FAERS database to analyze the real-world safety data of eltrombopag, romiplostim, and avatrombopag, especially visualizing their associated AEs and the risk of DMEs (EMA/326038/2020) [13].

Methods

Data source

The data for this study was obtained from the publicly accessible FAERS database, which has been updated quarterly since 2008. We downloaded adverse reaction data for avatrombopag as the primary suspect from the first quarter of 2018 to the second quarter of 2023, along with corresponding data for eltrombopag and romiplostim during the same period (Q1 2018 to Q2 2023). Data was imported into SAS 9.4 for cleaning and analysis. The data source included seven tables: demographic and administrative data (DEMO), drug information (DRUG), details on adverse drug reac-tions (REAC), report source information (RPSR), indications for use/diagnosis (INDI), and drug therapy information (THER). The tables were linked by Primaryid and Caseid.

Data cleaning and standardization

Since FAERS is a spontaneous reporting system, duplicate reports might exist. In this study, we de-duplicated the raw data by selecting PRIMARYID, CASEID, and FDA_DT fields from the DEMO table, sorting by CASEID, FDA_DT, and PRIMARYID, and retaining the most recent FDA_DT when CASEID was the same, and the highest PRIMARYID when both CASEID and FDA_DT were the same.

To ensure stability in data analysis, this study included only data involving three or more reports. Reports marked as product issues, aplastic anaemia, immune thrombocytopenia, social environment, no AEs, various congenital familial genetic disorders, surgeries, medical operations, injuries, poisonings, and operation complications were excluded from further analysis.

AEs in the FAERS database are recorded using Medical Dictionary for Regulatory Activities (MedDRA) preferred terms (PTs), which also provides system organ classification (SOC) terms to map PTs, facilitating the aggregation of overall clinical syndrome-related terms for specific AEs. This study used MedDRA version 26.0, categorizing, aggregating, and standardizing AE names from FAERS data with different levels of PT and SOC terms.

Data analysis

In this study, we employed the reporting odds ratio (ROR), proportional reporting ratio (PRR), bayesian confidence

Table 1 The fourfold table of disproportionality measurement

Drug	Number of Reports of Target AEs	Number of Reports of Other AEs	Total
Target Drug	a	b	a+b
Other Drugs	c	d	c+d
Total	a+c	b+d	a+b+c+d

propagation neural network (BCPNN), and multi-item gamma poisson shrinker (MGPS) to conduct frequency analysis. The specific criteria for determining a safety signal were as follows: a safety signal was generated if any one of the following four conditions was met: [$ROR_{025}>1$ (95% CI), $N\geq3$], [PRR ≥ 2, $\chi^2\geq4$, $N\geq3$], [$IC_{025}\geq0$ (95% CI)], and [$EBGM_{05}\geq2$]. methods were employed for data mining (Table 1) [14]. Detailed algorithms and formulas are available in Table 2. ROR identifies potential drug-related signals by comparing the ratio of specific AE reports to background data. This approach effectively distinguishes true signals from false ones, reducing the likelihood of false positives. PRR assesses the proportion of AE reports for a target drug relative to all drugs. By utilizing relative frequencies, PRR provides an unbiased evaluation of drug-AEs associations, thereby minimizing false positives. BCPNN integrates neural network models with Bayesian inference to account for complex multifactorial relationships. This method filters out spurious associations caused by data variability or random factors, significantly reducing false positives. MGPS employs a Poisson distribution-based model to analyze multi-level data structures, such as reporting sources and regions. By estimating parameters at various levels, MGPS identifies reporting biases and other external factors that may lead to false positive signals, enhancing detection accuracy and reducing false positives. In this study, the situation where all four methods have statistical significance is regarded as producing a safety signal, in order to reduce the generation of false positive signals.

In the FAERS database, AEs may include symptoms and disease progression. To reduce the bias from disease-related events, Venn analysis was used to screen common and drug-specific AEs. The analysis tool used was https://bioinfogp.cnb.csic.es/tools/venny/index.html.

Results

Characteristics of cases

We extracted and analyzed case reports related to romiplostim, eltrombopag, and avatrombopag, totaling 2,851, 10,297, and 973 cases, respectively. Specifically, the analysis showed that for romiplostim-related cases, there were 7,311 AE reports, among which 58 AEs exhibited significant safety signals. For eltrombopag-related cases, there were 24,561 AE reports, with 98 AEs exhibited significant safety signals. For avatrombopag-related cases, there were 2,332 AE reports, with 15 AEs exhibited significant safety signals. The basic characteristics of the cases (Table 3). In the AE reports for romiplostim, eltrombopag, and avatrombopag, the reporters were primarily clinicians, consumers, nurses, or pharmacists, and the reports mainly originated from the United States, Japan, and Europe.

Gender-based SOC signal intensity analysis

A gender-based differential analysis of SOC signal intensities was conducted separately for romiplostim, eltrombopag, and avatrombopag. The results indicated that the number of reports and ROR values for romiplostim, eltrombopag, and avatrombopag were similar between males and females.

Disproportionality analysis of romiplostim AEs

Among all confirmed AEs related to romiplostim, the top 10 AEs signals of romiplostim ranked by number of cases (Table 4) and the top 10 AEs signals of romiplostim ranked by ROR are shown in Table 5. DMEs include autoimmune hemolytic anemia, hemolytic anemia, sudden hearing loss, and hemolysis, all of which exhibit high

Table 2 Calculation formulas and detection standards of signal mining

Method	Computational formula	Threshold value
ROR	$\mathrm{ROR}=\frac{(a/c)}{(b/d)}=\frac{ad}{bc}$	$ROR_{025}>1$, $N\geq3$
	$95\%\mathrm{CI}=\mathrm{e}^{\ln(\mathrm{ROR})\pm1.96\sqrt{(\frac{1}{a}+\frac{1}{b}+\frac{1}{c}+\frac{1}{d})}}$	
PRR	$\mathrm{PRR}=\frac{a/(a+b)}{c/(c+d)}$	PRR ≥ 2, $\chi2\geq4$, $N\geq3$
	$\chi2=\frac{(\mathrm{ad}-\mathrm{bc})^2(\mathrm{a+b+c+d})}{(\mathrm{a+b})(\mathrm{a+c})(\mathrm{c+d})(\mathrm{b+d})}$	
BCPNN	$\mathrm{IC}=log_2\frac{p(x,y)}{p(x)p(y)}=log_2\frac{a(a+b+c+d)}{(a+b)(a+c)}$	$IC_{025}>0$
	$\mathrm{IC025}=\mathrm{e}^{\ln(\mathrm{IC})\pm1.96\sqrt{(\frac{1}{a}+\frac{1}{b}+\frac{1}{c}+\frac{1}{d})}}$	
MGPS	$\mathrm{EBGM}=\frac{a(a+b+c+d)}{(a+c)(a+b)}$	$EBGM_{05}>2$
	$\mathrm{EBGM05}=\mathrm{e}^{\ln(\mathrm{EBGM})\pm1.96\sqrt{(\frac{1}{a}+\frac{1}{b}+\frac{1}{c}+\frac{1}{d})}}$	

Table 3 Basic characteristics of Romiplostim, Eltrombopag, and Avatrombopag case reports

Characteristic	Romiplostim(*n* = 2,851)	Eltrombopag(*n* = 10,297)	Avatrombopag(*n* = 973)
SEX			
Female	1235(43.32)	5256(51.04)	513(52.72)
Male	1001(35.11)	4259(41.36)	385(39.57)
NA	615(21.57)	782(7.59)	75(7.71)
AEs Reports number	7,311	24,561	2,332
Reporter role			
Physician	1277(44.79)	2948(28.63)	248(25.49)
Other health-professional	586(20.55)	595(5.78)	58(5.96)
Consumer	443(15.54)	5782(56.15)	384(39.47)
Pharmacist	538(18.87)	539(5.23)	21(2.16)
NA	7(0.25)	433(4.21)	262(26.93)
Reporter_country			
United States	1756(61.59)	5781(56.14)	917(94.24)
Japan	245(8.59)	472(4.58)	0(0)
Europe	178(6.24)	135(1.31)	2(0.21)
Others	670(23.50)	1148(11.15)	51(5.24)
NA	2(0.07)	2761(26.81)	3(0.31)
Yearsgroup			
< 18	22(0.77)	6(0.04)	2(0.21)
18–65	53(1.86)	82(0.49)	17(1.74)
≥ 65	45(1.58)	118(0.71)	25(2.57)
NA	2731(95.79)	10,091(98.76)	929(95.48)
Reported year			
2018–2023	2851	10,297	973

Table 4 AEs signals of Romiplostim ranked by number of cases (Top 10)

PT	*n*	ROR(95%CI)	PRR(χ^2)	IC^2(IC_{025})	EBGM($EBGM_{05}$)
Platelet count decreased	323(25.63)	26.44(23.64–29.57)	25.31(7501.34)	4.65(2.99)	25.14(22.89)
Platelet count abnormal	240(19.05)	331.99(290.27–379.70)	321.13(70110.30)	8.20(6.53)	294.01(262.76)
Thrombocytopenia	139(11.03)	11.48(9.70-13.58)	11.28(1300.17)	3.49(1.83)	11.25(9.77)
Thrombocytosis	121(9.60)	303.38(251.60-365.80)	298.37(33023.57)	8.10(6.43)	274.82(234.99)
Therapy non-responder	111(8.81)	16.23(13.45–19.59)	16.00(1555.59)	3.99(2.33)	15.93(13.62)
Therapeutic product effect decreased	80(6.35)	6.85(5.49–8.54)	6.79(394.60)	2.76(1.09)	6.78(5.63)
Platelet count increased	77(6.11)	47.54(37.92–59.60)	47.05(3424.85)	5.54(3.87)	46.43(38.43)
Haemorrhage	63(5.00)	5.70(4.45–7.31)	5.66(241.78)	2.50(0.83)	5.65(4.59)
Deep vein thrombosis	53(4.21)	10.69(8.16–14.02)	10.62(460.97)	3.41(1.74)	10.59(8.45)
Pulmonary embolism	53(4.21)	6.48(4.94–8.49)	6.44(243.17)	2.68(1.02)	6.43(5.12)

Table 5 AEs signals of romiplostim ranked by ROR (Top 10)

PT	*n*	ROR(95%CI)	PRR(χ^2)	IC^2(IC_{025})	EBGM($EBGM_{05}$)
Reticulin increased	3(0.73)	946.61(264.03-3393.86)	946.23(2225.68)	9.54(7.71)	743.68(255.50)
Neutralising antibodies positive	9(2.19)	359.35(180.84-714.07)	358.91(2911.11)	8.35(6.65)	325.36(183.16)
Bone marrow reticulin fibrosis	7(1.70)	357.50(164.15-778.58)	357.15(2254.07)	8.34(6.64)	323.91(168.88)
Anti-platelet antibody positive	3(0.73)	347.09(105.90-1137.57)	346.95(940.78)	8.30(6.56)	315.50(116.85)
Platelet count abnormal	240(58.39)	331.99(290.27–379.70)	321.13(70110.30)	8.20(6.53)	294.01(262.76)
Mucocutaneous haemorrhage	8(1.95)	330.79(160.12-683.38)	330.43(2398.98)	8.24(6.54)	301.78(164.45)
Thrombocytosis	121(29.44)	303.38(251.60-365.80)	298.37(33023.57)	8.10(6.43)	274.82(234.99)
Evans syndrome	7(1.70)	155.83(73.05-332.41)	155.68(1029.63)	7.22(5.54)	149.04(79.07)
Thrombocytopenia neonatal	7(1.70)	155.83(73.05-332.41)	155.68(1029.63)	7.22(5.54)	149.04(79.07)
Marrow hyperplasia	6(1.46)	99.68(44.26–224.50)	99.60(569.34)	6.60(4.92)	96.85(49.10)

signal strength [ROR (95% CI): 6.10 (1.96–18.92), $n = 3$; 8.13 (3.87–17.07), $n = 7$; 5.24 (0.74–37.27), $n = 3$; 3.89 (1.25–12.07), $n = 3$].

Disproportionality analysis of eltrombopag AEs

Among all confirmed AEs related to eltrombopag, the top 10 AEs signals of eltrombopag ranked by number of cases (Table 6) and the top 10 AEs signals of eltrombopag ranked by ROR are shown in Table 7. DMEs include hepatic infection, granulocytopenia, autoimmune hemolytic anemia, hemolytic anemia, hemolysis, and hepatic failure, all of which exhibit high signal strength [ROR (95% CI): 9.56 (4.28–21.36), $n = 6$; 2.91 (1.09–7.75), $n = 4$; 3.03 (1.26–7.28), $n = 5$; 3.46 (1.86–6.43), $n = 10$; 4.65 (2.63–8.19), $n = 12$; 2.51 (1.67–3.78), $n = 23$].

Disproportionality analysis of avatrombopag AEs

Among all confirmed AEs related to avatrombopag, the top 10 AEs signals of avatrombopa ranked by number of cases (Table 8) and the top 10 AEs signals of eltrombopag ranked by ROR are shown in Table 9. Not a single DME was found for avatrombopag.

Comparison of significant safety signals among romiplostim, eltrombopag, and avatrombopag AEs

Using Venn analysis (Fig. 1), nine common AEs were identified across all three drugs. Additionally,

Table 6 AEs signals of eltrombopag ranked by number of cases (Top 10)

PT	*n*	ROR(95%CI)	PRR(χ^2)	IC^2(IC_{025})	EBGM($EBGM_{05}$)
Platelet count decreased	1883(35.89)	49.19(46.89–51.61)	45.50(78627.96)	5.45(3.78)	43.62(41.90)
Death	1806(34.42)	5.65(5.39–5.93)	5.31(6372.00)	2.40(0.74)	5.29(5.08)
Platelet count increased	532(10.14)	107.43(98.17-117.55)	105.12(49805.35)	6.58(4.91)	95.50(88.56)
Haemorrhage	187(3.56)	5.05(4.37–5.83)	5.01(599.08)	2.32(0.65)	5.00(4.43)
Haemoglobin decreased	176(3.35)	4.81(4.15–5.58)	4.78(524.87)	2.25(0.59)	4.76(4.21)
Platelet count abnormal	163(3.11)	63.42(54.12–74.32)	63.01(9375.24)	5.89(4.23)	59.44(52.05)
Thrombosis	146(2.78)	4.82(4.10–5.68)	4.80(437.93)	2.26(0.59)	4.78(4.17)
Hypoacusis	145(2.76)	6.73(5.71–7.93)	6.70(698.91)	2.74(1.07)	6.66(5.81)
Epistaxis	111(2.12)	3.98(3.30–4.80)	3.97(245.91)	1.98(0.32)	3.96(3.39)
Therapy non-responder	98(1.87)	4.21(3.45–5.14)	4.20(238.24)	2.07(0.40)	4.19(3.55)

Table 7 AEs signals of eltrombopag ranked by ROR (Top 10)

PT	*n*	ROR(95%CI)	PRR(χ^2)	IC^2(IC_{025})	EBGM($EBGM_{05}$)
Reticulin increased	4(0.49)	412.89(129.48-1316.58)	412.82(1173.78)	8.21(6.38)	295.16(111.86)
Serum colour abnormal	3(0.37)	344.06(93.14-1270.98)	344.02(769.55)	8.01(6.16)	258.26(86.54)
Clonal evolution	15(1.85)	281.64(159.11-498.54)	281.47(3293.79)	7.79(6.09)	221.37(137.28)
Bone marrow reticulin fibrosis	14(1.73)	237.00(132.57–423.70)	236.86(2674.38)	7.59(5.89)	192.84(118.60)
Paroxysmal nocturnal haemoglobinuria	14(1.73)	123.56(70.97-215.12)	123.49(1519.24)	6.79(5.10)	110.40(69.42)
Platelet count increased	532(65.76)	107.43(98.17-117.55)	105.12(49805.35)	6.58(4.91)	95.50(88.56)
Platelet count abnormal	163(20.15)	63.42(54.12–74.32)	63.01(9375.24)	5.89(4.23)	59.44(52.05)
Bone marrow myelogram abnormal	4(0.49)	60.72(22.15-166.46)	60.71(221.85)	5.84(4.14)	57.39(24.68)
Red blood cell morphology abnormal	3(0.37)	59.55(18.60-190.69)	59.54(163.26)	5.82(4.11)	56.35(21.28)
Platelet disorder	57(7.05)	52.79(40.44–68.90)	52.67(2748.86)	5.65(3.98)	50.16(40.13)

Table 8 AEs signals of avatrombopag ranked by number of cases (Top 10)

PT	*n*	ROR(95%CI)	PRR(χ^2)	IC^2(IC_{025})	EBGM($EBGM_{05}$)
Platelet count decreased	128(31.45)	32.85(27.48–39.27)	31.11(3725.24)	4.95(3.29)	31.02(26.71)
Headache	107(26.29)	4.97(4.09–6.03)	4.79(323.44)	2.26(0.59)	4.78(4.07)
Platelet count increased	81(19.90)	159.97(127.96-199.98)	154.45(12172.01)	7.25(5.58)	152.22(126.28)
Platelet count abnormal	39(9.58)	152.83(111.12–210.20)	150.29(5702.28)	7.21(5.54)	148.17(113.49)
Thrombosis	10(2.46)	3.46(1.86–6.43)	3.45(17.38)	1.78(0.12)	3.45(2.05)
Portal vein thrombosis	9(2.21)	91.01(47.16-175.63)	90.66(791.22)	6.49(4.82)	89.89(51.86)
Deep vein thrombosis	9(2.21)	5.79(3.01–11.14)	5.77(35.47)	2.53(0.86)	5.76(3.33)
Pulmonary embolism	9(2.21)	3.48(1.81–6.69)	3.47(15.81)	1.79(0.13)	3.47(2.00)
Full blood count abnormal	8(1.97)	5.11(2.55–10.23)	5.09(26.32)	2.35(0.68)	5.09(2.85)
Laboratory test abnormal	7(1.72)	5.52(2.63–11.60)	5.51(25.83)	2.46(0.79)	5.51(2.96)

Table 9 AEs signals of avatrombopag ranked by ROR(Top 10)

PT	*n*	ROR(95%CI)	PRR(χ^2)	IC^2(IC_{025})	EBGM($EBGM_{05}$)
Platelet count increased	81(29.03)	159.97(127.96-199.98)	154.45(12172.01)	7.25(5.58)	152.22(126.28)
Platelet count abnormal	39(13.98)	152.83(111.12–210.20)	150.29(5702.28)	7.21(5.54)	148.17(113.49)
Renal vein thrombosis	3(1.08)	145.55(46.54-455.18)	145.36(424.23)	7.16(5.49)	143.39(55.23)
Portal vein thrombosis	9(3.23)	91.01(47.16-175.63)	90.66(791.22)	6.49(4.82)	89.89(51.86)
Platelet disorder	6(2.15)	55.37(24.80-123.64)	55.23(317.83)	5.78(4.11)	54.95(28.06)
Platelet count decreased	128(45.88)	32.85(27.48–39.27)	31.11(3725.24)	4.95(3.29)	31.02(26.71)
Ammonia increased	3(1.08)	19.23(6.19–59.72)	19.20(51.68)	4.26(2.59)	19.17(7.43)
Petechiae	4(1.43)	11.18(4.19–29.84)	11.17(36.99)	3.48(1.81)	11.16(4.91)
Hepatic encephalopathy	3(1.08)	9.93(3.20-30.83)	9.92(24.04)	3.31(1.64)	9.91(3.84)
General physical condition abnormal	3(1.08)	9.62(3.10-29.86)	9.61(23.12)	3.26(1.60)	9.60(3.72)

romiplostim and eltrombopag had 58 specific AEs, had 98, and avatrombopag had 15 (Fig. 1A). These common AEs span categories such as vascular and lymphatic, hepatobiliary, hematologic and lymphatic, various neurological diseases, abnormal laboratory findings, and skin and subcutaneous tissue diseases (Fig. 1B).

Specific significant AEs of romiplostim include neutralising antibodies positive [ROR (95% CI), 359.35(180.84-714.07), $n=9$], anti-platelet antibody positive [ROR (95% CI), 347.09(105.90-1137.57)), $n=3$], mucocutaneous haemorrhage [ROR (95% CI), 330.79(160.12-683.38), $n=8$], marrow hyperplasia [ROR (95% CI), 99.68(44.26–224.50), $n=6$], monocytosis [ROR (95% CI), 54.52(17.42-170.58), $n=3$] etc.

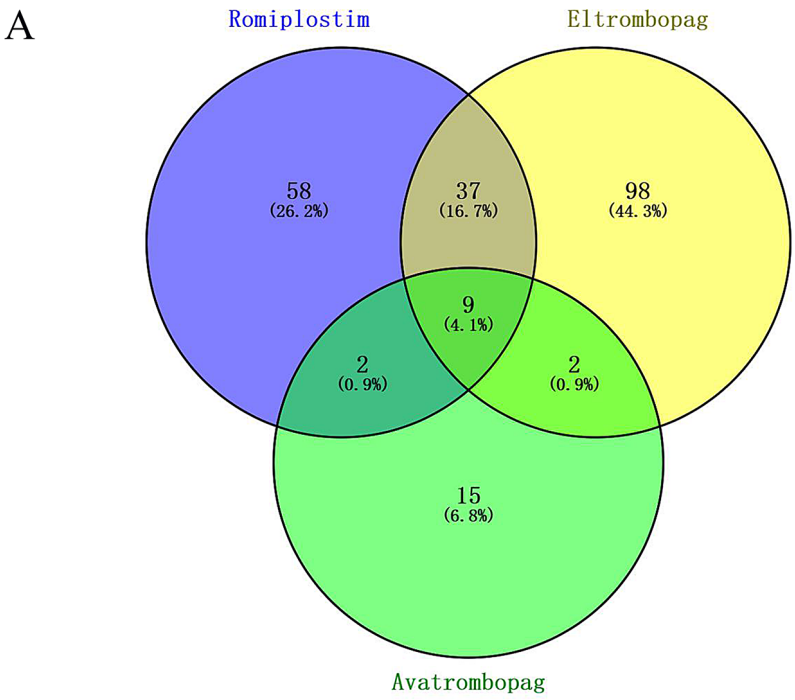
Specific significant AEs of eltrombopag include serum colour abnormal [ROR (95% CI), 344.06(93.14-1270.98), $n=3$], clonal evolution [ROR (95% CI), 281.64(159.11-498.54), $n=15$], paroxysmal nocturnal haemoglobinuria [ROR (95% CI), 123.56(70.97-215.12), $n=14$], hypoacusis [ROR (95% CI), 6.73(5.71–7.93), $n=145$], deafness [ROR (95% CI), 2.98(2.10–4.25), n=31] etc.

Specific significant AEs of avatrombopag include renal vein thrombosis [ROR (95% CI), 145.55(46.54-455.18), $n=3$], drug effect less than expected [ROR (95% CI), 16.80(8.39–33.66), $n=8$], hepatic encephalopathy [ROR (95% CI), 9.93(3.20-30.83), $n=3$], seasonal allergy [ROR (95% CI), 6.17(2.31–16.47), $n=4$], hypersomnia [ROR (95% CI), 4.00(1.50-10.67), $n=4$] etc.

Discussion

This study evaluated the safety profiles of romiplostim, eltrombopag, and avatrombopag using a large real-world adverse event reporting database, rather than directly comparing their safety profiles. The findings are expected to provide valuable reference and research directions for subsequent high-quality clinical studies.

Firstly, the primary AEs of eltrombopag include headache, nausea, vomiting, and diarrhea, consistent with clinical trial findings [8, 15, 16]. DMEs related to eltrombopag included hepatic infection, granulocytopenia, autoimmune hemolytic anemia, hemolytic anemia, hemolysis, and hepatic failure. To comprehensively investigate the potential hepatotoxicity risk associated with eltrombopag, we employed Standardized Medical Queries to systematically screen the FAERS database for hepatic toxicity-related AEs. Through meticulous filtering, 44 PTs were ultimately identified. Eltrombopag-associated hepatotoxicity was [ROR (95% CI), 2.08(1.52–2.84)), $n=607$]. An ROR greater than 1 indicates a positive association, suggesting that exposure to eltrombopag is associated with an increased risk of hepatotoxicity-related AEs compared to non-exposure. Hepatotoxicity is common, with 18% of aplastic anemia patients experiencing severe transaminase and/or bilirubin elevations [17]. Mild liver function abnormalities occur in 7-10% of patients, typically resolving with continued therapy or discontinuation [6, 18, 19]. Eltrombopag's hepatotoxic hydroxybiphenyl group may cause severe liver injury, particularly in pediatric patients [20, 21]. A clinical trial reported a fatal case of liver enzyme elevation exacerbated by underlying cardiopulmonary disease [22]. Eltrombopag is primarily metabolized in the liver, with 40% biliary excretion [23]. Plasma Area Under Curve (AUC) increases by 41% in mild hepatic impairment and 80-93% in moderate to severe impairment [16]. In liver injury, AUC rises by 111-183% [16]. Pharmacogenomic analysis suggests that the hepatotoxicity of atripopar may be related to impaired drug elimination. Especially involved in drug metabolism [CYP2C8, and UDP glucuronosyltransferase (UGT) 1A1 (UGT1A1)] and the allele ATP-binding cassetteG2 (ABCG2) for drug transport such as breast cancer resistance protein (BCRP) was associated with variation [20]. It is recommended to conduct liver function testing as per in the black box warning. Pediatric patients may require additional monitoring of coagulation markers, ammonia, and lactate levels. For moderate to severe hepatic impairment, reduced initial doses, drug concentration monitoring, and pharmacogenomic testing are advised for individualized dosing. The mechanism of eltrombopag-induced hepatic infection remains unclear but may involve underlying conditions or prolonged use. While



B

PT	Romiplostim (ROR)	Eltrombopag (ROR)	Avatrombopag (ROR)
Vascular disorders			
Deep vein thrombosis	10.69	3.22	5.78
Hepatobiliary disorders			
Portal vein thrombosis	9.56	7.62	91.01
Blood and lymphatic system disorders			
Immune thrombocytopenia	54.91	28.04	10.97
Platelet disorder	35.89	52.79	55.37
Investigations			
Platelet count increased	47.54	107.42	159.97
Platelet count decreased	26.43	49.19	32.85
Platelet count abnormal	331.99	63.42	152.83
Skin and subcutaneous tissue disorders			
Petechiae	36.19	20.60	11.18
Nervous system disorders			
Cerebral haemorrhage	6.80	4.21	5.17

Low High

Fig. 1 Analysis of significant safety signals for romiplostim, eltrombopag, and avatrombopag. Figures **A** and **B** respectively display (**A**) the common safety signals among the three drugs and (**B**) the Venn analysis for romiplostim, eltrombopag, and avatrombopag

eltrombopag primarily promotes platelet production, it may also impair bone marrow hematopoiesis, leading to granulocytopenia, exacerbated by comorbidities, concomitant medications, or drug interactions, necessitating regular neutrophil monitoring. It is noteworthy that a significant safety signal of paroxysmal nocturnal hemoglobinuria (PNH) has been detected in patients treated with eltrombopag. Studies suggest that the presence of PNH clones may have predictive value for treatment response to eltrombopag, indicating that patients with PNH clones may achieve better therapeutic outcomes [24]. However, PNH patients are also at risk of developing secondary hematological malignancies, with myelodysplastic syndrome and acute myeloid leukemia being

the most common [25]. Further follow-up studies are needed to clarify the mechanisms underlying this adverse event and its clinical implications.

Secondly, romiplostim and eltrombopag signal reticulin increase and bone marrow reticulin fibrosis, Animal studies link it to local TPO levels [26]. In acute myeloid leukemia, GM-CSF(Granulocyte Macrophage-Colony Stimulating Factor) plus rhTPO causes more fibrosis than GM-CSF alone [27]. Some ITP patients had fibrosis in trials [15, 28–30]. Romiplostim's changes are reversible and dose-dependent [31]. As risks are unclear, use the lowest dose and be vigilant [31]. In acute myeloid leukemia, when reticulin features match chronic myeloproliferative disorders, TPO use history matters [27]. Long - term use may worsen conditions. Some studies show high - level fibrosis is rare [19, 32]. A 7-year eltrombopag study (166 patients, 5356 biopsies) and a 2-year prospective study showed most patients had low MF scores, with little change over time [32]. Ghanima W indicated TPO receptor agonists can induce progressive fibrosis [33]. but long-term follow-up is needed. Large-scale trials are required, and regular peripheral blood smear monitoring is key.

Thirdly, hemolytic anemia is another shared designated medical event between romiplostim and eltrombopag, exhibiting a multifactorial pathogenesis that includes genetic factors, environmental influences, and other factors [34]. Research [35] indicates a strong association between severe autoimmune hemolytic anemia and eltrombopag; however, the exact mechanism remains unclear and may be related to specific disease contexts [17]. Additionally, specific significant AEs of eltrombopag may cause serum colour abnormal, such as plasma discoloration (red or pink), It is important to differentiate this phenomenon from acute hemolysis. long-term high-dose use of eltrombopag can cause discoloration of the sclera, skin, and plasma, leading to a "jaundiced-like" appearance, "dusky" or "graying" skin, and yellow to reddish-brown plasma, depending on pH. These changes can interfere with visual inspection of plasma for hemolysis and other laboratory analyses (e.g., spectrophotometry). Discontinuation of eltrombopag typically reverses both plasma and skin discoloration [36]. Additionally, High-dose eltrombopag can interfere with bilirubin measurement, which is particularly relevant given its potential hepatotoxicity. This interference may mask signs of hepatotoxicity [37]. Acute hemolysis is usually accompanied by typical clinical symptoms, including fever, chills, headache, soreness in the lower back and extremities, and pallor. Moreover, laboratory tests may reveal morphological changes in peripheral blood smears, decreased haptoglobin levels, and significant increases in lactate dehydrogenase, bilirubin, and free 'asma hemoglobin [36]. In contrast, cases presenting only with serum discoloration generally lack these typical symptoms, and relevant laboratory parameters do not show significant abnormalities. Which should be distinguished from true hemolysis. If patients exhibit clinical symptoms related to hemolysis during treatment, the possibility of drug-induced hemolysis should be considered.

Fourthly, the study observed that the main adverse reactions associated with romiplostim were headache, epistaxis, and arthralgia, consistent with the adverse reactions reported in clinical trials [15, 38]. Additionally, DMEs such as autoimmune hemolytic anemia, hemolytic anemia, and sudden hearing loss were identified. Both romiplostim and eltrombopag have been associated with safety signals related to hearing impairment. including sudden hearing loss, hearing decline, and deafness. This phenomenon may be linked to the following factors and mechanisms: (1) Impact of underlying diseases: Large-scale cohort studies have shown that when platelet counts are at the lower end of the normal range, there is a significant correlation with the incidence of high-frequency hearing impairment. Platelets may play a critical role in the development of hearing impairment, with potential mechanisms possibly related to dysfunction of the stria vascularis in the cochlea. However, the exact biological pathways connecting platelets to hearing impairment still require further in-depth research [39]. (2) Association with anemia: Some patients using romiplostim and eltrombopag have concurrent anemia. Relevant studies indicate that iron deficiency anemia is significantly associated with hearing loss [40]. Numerous clinical cases suggest that anemia is likely an important factor contributing to hearing loss in patients [41]. (3) Vascular endothelium and microcirculation: Chronic inflammatory conditions, such as sickle cell anemia, can damage vascular endothelium, leading to microcirculatory disturbances in the inner ear and ultimately resulting in sensorineural hearing loss [42]. Romiplostim and eltrombopag promote platelet production, causing a significant increase in platelet count. Excessive platelet elevation may lead to local vascular occlusion, resulting in vascular endothelial dysfunction. However, it remains unclear whether romiplostim and eltrombopag induce hearing impairment through similar mechanisms. Rigorous studies are still needed to clarify the potential risks and mechanisms of action. Given the safety signals associated with hearing impairment for romiplostim and eltrombopag, clinicians need to remain vigilant. During patient treatment, hearing changes should be closely monitored. If abnormalities or potential risks are detected, a comprehensive hearing assessment should be conducted promptly to enable early and effective intervention measures [40]. Avatrombopag has not yet detected a safety signal for hearing loss and may be a potential alternative

for these patients. However, it is not ruled out that the short time to market such AEs is not fully exposed.

Fifthly, in this study, the main adverse reactions associated with avatrombopag were headache, thrombosis, fatigue, consistent with clinical trial results [43]. Avatrombopag was generally well toleratedin all of these clinical studies. There has been no evidence for increased hepatotoxicity reported in these studies [44]. No significant hepatotoxicity was observed with avatrombopag, and its metabolism primarily occurs via CYP3A and CYP2C9, indicating minimal impact on liver function [45]. Avatrombopag is specifically approved for the treatment of thrombocytopenia in patients with chronic liver disease prior to surgery, whereas romiplostim and eltrombopag are indicated for chronic ITP. This difference in target populations fundamentally limits the number of patients treated with avatrombopag, thereby reducing the overall number of AE reports. Additionally, compared to romiplostim and eltrombopag, which have been widely used for over a decade, avatrombopag has been on the market for a shorter period. This difference in market availability significantly impacts cumulative exposure, which in turn affects the number of AE reports. Although the relatively low number of AE reports for avatrombopag may raise concerns about false-negative bias, this is primarily due to its specific indications, shorter time on the market, and limited patient exposure, rather than a true reflection of its safety profile. Specific safety signals associated with avatrombopag included seasonal allergies and hypersomnia. The underlying pathogenesis of seasonal allergic reactions requires further clinical investigation to elucidate potential drug-related mechanisms. Regarding hypersomnia, studies have indicated that approximately one-third of patients with ITP may experience comorbid hypersomnia. Importantly, the observed hypersomnia signal appears less likely to be directly attributable to avatrombopag administration, given that this symptom was frequently documented in the baseline characteristics of this patient population prior to pharmacological treatment [46].

In a word, early identification and management of the emergence of AEs in clinical practice is critical [47], especially in pediatric patients. This comprehensive data is intended to provide clinicians with valuable advice on the safety profile of these ITP treatments in real-world settings.

In this study, we acknowledge the following limitations. Firstly, the FAERS database primarily relies on spontaneous reports, which may lead to certain adverse reactions being overreported or overlooked, thus affecting the accuracy and completeness of the reports. Secondly, in order to reduce the potential impact of time span and control confounding factors as much as possible, we chose the same time period for analysis. However, the limitation of this method is that it may underestimate the true adverse event risks of romiplostim and eltrombopag. Thirdly, we analyzed data from the same time period, which, although unable to completely eliminate the differences in reporting frequencies among the three drugs, partially narrowed the gap. It should be noted that, given the later market entry of avatrombopag, the risk of false-negative results cannot be entirely ruled out, recommended continuous monitoring in subsequent studies. Fourth, we acknowledge that despite implementing Venn diagram analysis and stringent exclusion criteria to minimize indication bias, there may still remain certain pathological and physiological confounding factors that cannot be fully controlled. Specifically, adult patients with chronic liver disease-related thrombocytopenia scheduled for elective diagnostic procedures or surgeries and patients with chronic ITP exhibit significant differences in disease progression, comorbidities, and treatment backgrounds. These differences may indirectly influence the incidence and reporting rates of AEs. For instance, patients with chronic liver disease often present with complex conditions such as hepatic insufficiency and portal hypertension, whereas ITP patients may have distinct risk profiles due to long-term immunomodulatory therapies. These factors could lead to variations in AE reporting rates, thereby affecting the interpretation of the study results. Fifthly, a direct causal relationship between adverse reactions and specific drugs cannot be established at this stage; only statistical correlations have been revealed, necessitating further validation through larger studies. The Naranjo algorithm could be considered to clarify causality [48]. Sixthly, varying levels of experience and knowledge among reporters may lead to selective reporting, making it impossible to completely avoid bias [11]. Seventh, the identification and interpretation of safety signals associated with these therapeutic agents may be subject to multiple confounding factors. The partial absence of gender-specific data could potentially obscure sex-based patterns in AE reporting, thereby limiting comprehensive safety profile characterization across demographic subgroups. Furthermore, the substantial proportion of missing age-related data precludes robust analysis of age-dependent variations in AE reporting frequencies, consequently restricting our ability to provide clinically relevant, age-stratified safety recommendations. While our current analytical framework suggests no systematic association between data missingness and specific AE categories or severity grading, we must acknowledge that this assessment cannot definitively exclude potential bias in our findings. In summary, the limitations of the FAERS data should be carefully considered when analyzing and interpreting the results, and assessments should be combined with other data sources and methods.

Conclusion

This study indicates that eltrombopag manifests significant safety signals within the hepatic system. This implies that monitoring liver function during treatment is advisable. Avatrombopag shows relatively lower hepatotoxicity signals; however, further large - scale studies are needed to validate these observations. Moreover, both romiplostim and eltrombopag therapies may be linked to a risk of sudden hearing loss or deafness, which merits clinical attention. These findings offer crucial safety references for clinical drug use. Nevertheless, the causal relationship between the drugs and adverse events necessitates further in-depth investigation.

Abbreviations

FDA	Food and Drug Administration
TPO-RA	Thrombopoietin Receptor Agonist
ITP	Immune Thrombocytopenia
FAERS	FDA Adverse Event Reporting System
ROR	Reporting Odds Ratio
BCPNN	Bayesian Confidence Propagation Nneural Network
AE	Adverse Event
DME	Designated Medical Event
EMA	European Medicines Agency
TPO	Thrombopoietin
SAS	Statistical Analysis System
DEMO	Demographic and Administrative data
DRUG	Drug Information
REAC	Details on Adverse Drug Reac-tions
RPSR	Report Source Information
INDI	Indications for Use/Diagnosis
THER	Drug Therapy Information
MedDRA	Medical Dictionary for Regulatory Activities
PT	Preferred Term
SOC	System Organ Classification
AUC	Area Under Curve
UDP	Uridine Diphosphate
UGT1A1	UDP Glucuronosyltransferase Family 1 Member A1
ABCG2	Allele ATP-binding cassette G2
BCRP	Breast Cancer Resistance Protein
PNH	Paroxysmal Nocturnal Hemoglobinuria
GM-CSF	Granulocyte Macrophage-Colony Stimulating Factor
rhTPO	Recombinant Human Thrombopoietin
MF	Myelofibrosis

Acknowledgements

Not applicable.

Author contributions

A: Xiaoling Wang performed the main data analysis and statistics work, and wrote this manuscript.B: Yunsong Li，Wei Zhuang designed and supported this study, critically reviewed and revised the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Funding

This work was supported by the Young and Middle-aged Talent Cultivation Projects of Fujian Province, China [grant number 2024GGB27], the Young and Middle-aged Talent Cultivation Projects of Xiamen city, China [grant number 2024GZL-GG10], the National Natural Science Foundation of China [grant number 82304629], Fujian Provincial Natural Science Foundation of China [grant number 2024J08304], the Natural Science Foundation of Xiamen, China [grant number 3502Z202371048].

Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethical approval

The present pharmacovigilance study was conducted using a public database of spontaneous reports. Given the use of deidentified data, ethical approval was not considered necessary.

Consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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Received: 3 December 2024 / Accepted: 19 February 2025
Published online: 27 February 2025

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