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Efficacy and safety of eltrombopag in combination with rituximab in the treatment of immune thrombocytopenic purpura: A multicentre, randomised, open-label, prospective study

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Abstract: This study aimed to evaluate the efficacy and safety of eltrombopag plus rituximab in the treatment of patients with immune thrombocytopenic purpura (ITP). Sixty ITP patients treated from September 2022 to September 2023 were recruited for this study, and were randomly divided into a control group and a treatment group. The former was given eltrombopag, and the later was given eltrombopag plus rituximab. The treatment efficacy, platelet levels, coagulation function, sustained effective SR, progression-free-survival, and incidence of adverse reactions and adverse events were compared in both groups using SPSS 22.0 statistical software. After nine months of treatment, the platelet level of the treatment group was significantly better than that of the control group ($P<0.05$). The platelet levels of the treatment group were better than those of the control group at discharge and 6 months after discharge ($P<0.05$). After treatment, the levels of PT and APPT in the treatment group were lower than those in the control group ($P<0.05$). There was no difference in the incidence of adverse reactions and adverse events between 2 groups after treatment ($P>0.05$). In conclusion, eltrombopag combined with rituximab can effectively improve the efficacy of treatment in ITP patients, with high safety.

Keywords: Adverse event; eltrombopag; rituximab; immune thrombocytopenic purpura; efficacy.

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INTRODUCTION

Primary immune thrombocytopenia (ITP) is an acquired autoimmune hemorrhagic disease characterized by isolated thrombocytopenia in peripheral blood, and the annual incidence of ITP is (2-10)/100,000 (Bolton-Maggs *et al.*, 2021). The bleeding symptoms of patients with ITP largely depend on the severity of thrombocytopenia, and a platelet count of <20-30 × 10^9/L is the greatest risk of major bleeding in clinical practice (Liu *et al.*, 2023). More importantly, patients with platelet counts < 30 × 10^9/L have a mortality rate due to bleeding as high as 3.9% per year (Kochhar *et al.*, 2021). Therefore, the main strategy for treating ITP is to achieve a platelet count sufficient for hemostasis and minimize the risk of clinically significant bleeding in patients.

The first-line drug for the treatment of ITP is glucocorticoid and intravenous immunoglobulin (IVIG) (Sandal *et al.*, 2021). However, approximately 11% of the patients have no response to this treatment or the therapeutic effect cannot be maintained (DeSouza *et al.*, 2021). For patients who fail to respond to first-line treatment or relapse, second-line treatment is preferred, and eltrombopag and rituximab are common second-line agents (Hamed *et al.*, 2023). Eltrombopag is a non-peptide thrombopoietin (TPO) receptor agonist that stimulates megakaryocytes to produce platelets by activating protein tyrosine kinase (JAK)/ signal transducer and transcriptional activator (STAT) signals (Oliva *et al.*, 2023). The main adverse reactions of eltrombopag include liver function injury, and thrombosis (Patel *et al.*, 2022). Foreign studies have shown that the effective rate of eltrombopag in the treatment of ITP patients is 72.3% (Will, 2022). Rituximab is a chimeric mouse/human monoclonal antibody drug, and it promotes the immune response of B cell lysis and exerts the effect of reducing platelet destruction by specifically binding to the CD20 antigen (Werth *et al.*, 2021). It has been reported that the effective rate of rituximab in treating TP is approximately 50%, and the long-term effective rate is 20% to 25% (Beltrami-Moreira *et al.*, 2022). The Chinese Guidelines for the Diagnosis and Treatment of Primary Immune Thrombocytopenia in Adults (2020 Edition) recommend rituximab and recombinant human thrombopoietin as a second-line treatment option ("[Chinese guideline on the diagnosis and management of adult primary immune thrombocytopenia (version 2020)]," 2020).

Therefore, this study evaluated the efficacy and safety of eltrombopag combined with rituximab in the treatment of ITP.

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MATERIALS AND METHODS

Study design

This study was approved by the Ethics Committee of Siyang Hospital on January 1, 2024 and the approval number was KS2024001. This is a multicentre, randomised, open, prospective study of immune thrombocytopenic purpura. This clinical trial followed the Declaration of Helsinki, the Good Practice for the Administration of Drug Clinical Trials (GCP) issued by the State Drug Administration, and related regulations.

Sample size

The sample size was calculated using a G-Power statistical sample size calculation (Kang, 2021). For F tests with a medium effect size, with an error probability of 0.05 and power of 0.95 the total sample required was 60.

Participants

Sixty patients with immune thrombocytopenic purpura treated from September 2022 to September 2023 were recruited for the study.

Inclusion criteria

(1) Age >18 years. (2) According to the 2020 Chinese Guidelines for Primary Immune Thrombocytopenia and Treatment in Adults ("[Chinese guideline on the diagnosis and management of adult primary immune thrombocytopenia (version 2020)]," 2020), the following 4 were met: a. At least 2 consecutive routine blood tests showed a reduced platelet count, and there was no obvious abnormality in the morphology of haematocytes on microscopic examination of the peripheral blood smears; b. Spleen was generally not enlarged; c. Bone marrow cell morphology in patients with ITP was characterized by megakaryocytes increased or normal with impaired maturation; d. Other secondary thrombocytopenia needed to be excluded. (3) Platelets less than 30×10^9/L at screening. (4) No prior treatment with eltrombopag and rituximab. (5) No severe cardiac, hepatic or renal insufficiency. (6) Patients understood the purpose and risks of the trial, abided by the trial procedures, and signed the informed consent form.

Exclusion criteria

(1) Arterial or venous thrombotic event within 6 months prior to screening. (2) Patients with severe cardiovascular disease (NYHA Cardiac Function Score III-IV) and cardiac arrhythmias (e.g., atrial fibrillation) that increase the risk of thrombosis after coronary stenting, angioplasty, and coronary artery bypass grafting. (3) Clinical evidence of severe bleeding (e.g., gastrointestinal bleeding) within 2 weeks prior to screening. (4) Abnormal liver function (TBL > 3 × ULN; alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 3 × ULN). (5) Abnormal renal function with serum creatinine > 1.5 × ULN or creatinine clearance < 60 ml/min using the Cockcroft-Gault estimate. (6) Females who are pregnant or preparing for pregnancy or breastfeeding. (7) Participation or ongoing participation in a clinical trial of another drug within the past 3 months. (8) Those whom the researchers considered unsuitable to participate in the study.

Treatment program

The study was divided into two periods: a baseline period and a treatment observation period, with the treatment period set at 12 months and the observation period at six months. The patients were randomly divided into a control group and a treatment group at a ratio of 1:1. The control group was given eltrombopag, and the treatment group was given eltrombopag plus rituximab.

Procedures

Patients in the control group took a single dose of eltrombopag tablets orally on an empty stomach as described previously (Peffault de Latour *et al.*, 2022). The initial dose was 25 mg/d, and then it was increased to 50 mg/d (the maximum dose was 75 mg/d) for 2 weeks. Individualized medication adjustments were made to maintain a platelet count of $\geq 50 \times 10^9$/L. Whether the patient continued to take the medicine or discontinues it depended on the response of subsequent subjects to the treatment.

Patients in the treatment group were administered oral eltrombopag tablets (same as the control group) in combination with rituximab. Rituximab treatment was mentioned as previously described (Li *et al.*, 2025): 100 mg intravenous drip, once a week, for a total of 4 times. It was recommended that the initial infusion rate be 50 mg/h. If there was no infusion reaction, 50 mg/h could be increased every 30 minutes until the maximum was 400 mg/h.

Indications for dose adjustment and discontinuation

As mentioned earlier (Kaur *et al.*, 2022), the dose adjustments of eltrombopag were implemented strictly according to the requirements of table 1. The indications for discontinuation were as follows: After 4 weeks of treatment with this product, the dose was 75 mg once daily. If the platelet count did not rise to a level sufficient to avoid clinically significant bleeding, the use of this product was discontinued. If the patient showed obvious liver abnormalities, drug withdrawal was also considered. For the subjects who responded to the treatment, when their platelet count was $\geq 100 \times 10^9$/L and maintained at approximately 100×10^9/L (all platelet count evaluations $\geq 70 \times 10^9$/L) for 2 months, dose reduction and drug withdrawal would be considered. The duration of dose reduction varied from individual to individual, depending on the initial dose and the patient's response: 25 mg every two weeks. If the platelet count was stable, the next dose reduction would start within two weeks, taking 25 mg every other day for two weeks until the drug was

completely discontinued. For patients whose dose was increased to 75 mg/dose, as long as complete remission (CR) was achieved and the platelet count was maintained at approximately 100 $\times 10^9$/L (all platelet count evaluations $\geq 70 \times 10^9$/L), the dosage could be gradually reduced and the drug discontinued for up to 2 months.

The indications for discontinuing rituximab were as follows: Patients with severe reactions, especially those with severe breathing difficulties, bronchospasm and hypoxemia, should immediately discontinue the intravenous drip.

Precaution

Any medication other than the trial medication used from the time the subject signs the informed consent until withdrawal from the study was considered as a co-medication, and a detailed record of all co-medications used by the subject were required. At each follow-up, the subjects were asked about their combined medication situation. If the subject experienced adverse event, active treatment was carried out and detailed information on all the drugs used was recorded in the original medical record. The drugs that the subjects had used within 7 days before administration were collected, including prescription drugs, over-the-counter drugs, Chinese herbal medicines and other research drugs. The researchers verified the inclusion/exclusion criteria of the patients based on their previous medication history.

Adverse event

An adverse event (AE) is an adverse medical event that occurs after patients or clinical trial subjects receive drug treatment, but they do not necessarily have a causal relationship with the treatment. All adverse events that occurred after the patient signed the informed consent form were fully recorded in the original medical record. Adverse event records included: (1) Descriptions of all symptoms related to adverse events; (2) The time of occurrence and duration of adverse events; (3) The severity of adverse events; (4) Investigation and treatment due to adverse events; (5) The results and basis for judging whether adverse events were related to the investigational drug. When adverse events occurred, researchers could determine the measures to be taken based on the situation. The methods adopted included: (1) Continuous observation without medication; (2) Without corresponding treatment, observation and drug withdrawal; (3) Discontinued the test drug and provided corresponding treatment. All adverse events were tracked and investigated, with detailed records of treatment and outcomes until the subjects were properly addressed or their conditions were stable. Abnormalities in laboratory tests were also followed up until they returned to normal or pre-dose levels. Follow-up was conducted until the condition was appropriately resolved or stabilized. The methods of follow-up could be in the form of hospitalization, outpatient visits, and telephone calls, depending on the severity of the adverse events.

Methodology for checking indicators

Fasting blood was collected at each test time point to evaluate hematological parameters, including PLT, PT and APPT. Bleeding events were evaluated at each visit and adverse events were recorded.

Outcomes

(1) The primary endpoint was to compare the post-treatment complete response (CR) between the two groups: post-treatment platelet counts $\geq 100 \times 10^9$ /L and no bleeding manifestations. The secondary endpoints were mainly assessed as follows: (1) comparing the post-treatment partial response (PR) of the two groups: post-treatment platelet count $\geq 30 \times 10^9$ /L, at least 2-fold increase over the basal platelet count, and no bleeding manifestations; (2) Comparison of the post-treatment no response (NR) of the two groups: post-treatment platelet count $< 30 \times 10^9$ /L, or platelet count increase less than 2-fold of the basal value, or bleeding; (3) Comparison of the proportion of subjects who remained SR in the two groups: patients maintained CR or PR status for at least 6 months or more after treatment; (4) Statistics on the changes in coagulation indexes before and after treatment; (4) Statistics on the progression-free-survival (PFS) rate during the observation period; (5) Types of adverse reactions and adverse events during the observation period.

STATISTICAL ANALYSIS

Epidate was used for data double entry, and SPSS 22.0 statistical software was applied for statistical processing. Count data were described by frequency and percentage, and comparisons between groups were made using the $\chi 2$ test or Fisher's exact probability method; measurement data were expressed as mean ± standard deviation, and were tested for normality by the independent samples t-test for comparisons between groups if they met the normal distribution, and by the rank-sum test (Mann-Whitney U-test) for comparisons between groups if they did not meet the normal distribution.

RESULTS

Patient demographics and baseline characteristics

As shown in table 2, there was no statistically significant difference between the demographic and baseline characteristics of the patients ($P>0.05$). More than 50% of the 60 patients had chronic ITP, all of whom had been diagnosed for more than 1 year. More than 20% of these patients were on eltrombopag at 75 mg/kg. PT and APTT levels were suggestive of poor coagulation.

Assessment of treatment efficacy

We measured PLT at admission and discharge, observed the bleeding manifestations and counted the treatment efficacy of the patients. table 3 listed the CR, PR and NR of the two groups of patients, and calculated overall response (OR) = CR + PR.

The results found that there was no statistically significant difference between the OR of the two groups of patients, and there was a tendency for the OR to increase in the treatment group (P>0.05). The statistical details of the efficacy at different periods were shown in fig. 1.

Comparison of PLT levels before and after treatment

We counted the PLT before treatment, after treatment and 6 months after drug withdrawal. In both groups, PLT increased significantly after one month of treatment (P<0.05), and the PLT level of the treatment group was significantly better than that of the control group after nine months of treatment (P<0.05, fig. 2A). As shown in fig. 2B, the PLT levels of patients in both groups improved significantly at the time of discharge (P<0.05), but there was a downward trend in PLT six months after discharge. However, there was no statistically significant difference in the PLT levels at discharge and 6 months after discharge (P>0.05). More importantly, the PLT levels of the treatment group were better than those of the control group at discharge and 6 months after discharge (P<0.05).

Comparison of coagulation indices

After treatment, the levels of PT and APPT in the treatment group were lower than those in the control group (P<0.05), as shown in fig. 3.

Assessment of sustained effective SR at 6 months post-treatment

A total of 22 people in the control group were treated effectively and 3 people had a decrease in PLT within 6 months and turned ineffective. A total of 25 people in the treatment group were treated effectively and 1 turned ineffective. There was no statistical difference in SR between the two groups (P>0.05), as shown in table 4.

Assessment of PFS after treatment

Three patients in the control group experienced deterioration after 6 months of treatment, at months 2, 5, and 6 of treatment. One patient in the treatment group deteriorated in the 5th month after 6 months of treatment. There was no statistical difference in PFS between the two groups (P=0.25), as shown in fig. 4.

Assessment of adverse events and adverse reactions

Adverse reactions in patients after administration of the drug mainly included gastrointestinal discomfort, skin itching, headache, nausea and fatigue, liver damage, fever, etc., and the adverse event was the occurrence of thromboembolism. There was no statistically significant difference in the incidence of adverse reactions and adverse events between 2 groups after the administration of the drug (P>0.05), as shown in table 5.

DISCUSSION

ITP is a relatively common autoimmune disease, and several studies have suggested that the main pathogenesis of ITP is the loss of platelet autoantigen immune tolerance, leading to abnormal activation of humoral and cellular immunity, jointly mediating megakaryocytes to accelerate platelet destruction and insufficient platelet production (Delshad *et al.*, 2024).

Eltrombopag is a novel non-peptide small molecule compound, which can activates platelet receptors, binds to the transmembrane domain of non-peptide TPO receptors, catalyzes the differentiation and proliferation of bone marrow progenitor cells, and simultaneously increases the number of megakaryocyte lineage cells, thereby increasing platelet production and raising platelet levels (Oliva *et al.*, 2023). Rituximab, a chimeric monoclonal antibody against CD20, was initially used for the treatment of malignant lymphoma, and recent studies have demonstrated its efficacy in autoimmune diseases such as ITP (Vianelli *et al.*, 2022). Several studies have revealed the therapeutic efficacy of rituximab in combination with eltrombopag in ITP. For instance, a case report discovered by Zhang *et al*. suggested that early treatment of rituximab combined with eltrombopag was beneficial to patients with refractory ITP in rheumatoid arthritis (Zhang *et al.*, 2022). Zhou *et al*. systematically reviewed 19 randomized controlled trials (including 2615 participants) from January 1, 2015, to April 20, 2021, and found that rituximab plus eltrombopag had the best efficacy (Zhou *et al.*, 2022). Therefore, our study performed a multicentre, randomised, open-label, prospective study to measure the efficacy and safety of eltrombopag plus rituximab in the treatment of ITP.

The results of our study indicated that the PLT levels increased significantly after one month of treatment in both groups, and the PLT level of the treatment group was significantly better than that of the control group after nine months of treatment. Besides, the PLT levels of patients in both groups improved significantly at the time of discharge, and the PLT levels of the treatment group were better than those of the control group at discharge and 6 months after discharge. All these results suggested that eltrombopag plus rituximab could improve the PLT levels of ITP patients. Consistent with our findings, Witkowski *et al*. suggested that TPO receptor agonist and rituximab combination therapy could increase the PLT level in patients with refractory ITP (Witkowski *et al.*, 2024).

Besides, our study also indicated that after treatment, the levels of PT and APPT in the treatment group were lower than those in the control group, suggesting that eltrombopag plus rituximab could improve the coagulation function of ITP patients. We speculate that the reason might be that eltrombopag has certain effects on the human hematopoietic system and blood, which can increase platelet proliferation, increase fibrinogen concentration, and shorten coagulation time. However, the combined treatment not only induces the proliferation and differentiation of megakaryocytes but also plays a crucial role in promoting platelet production.

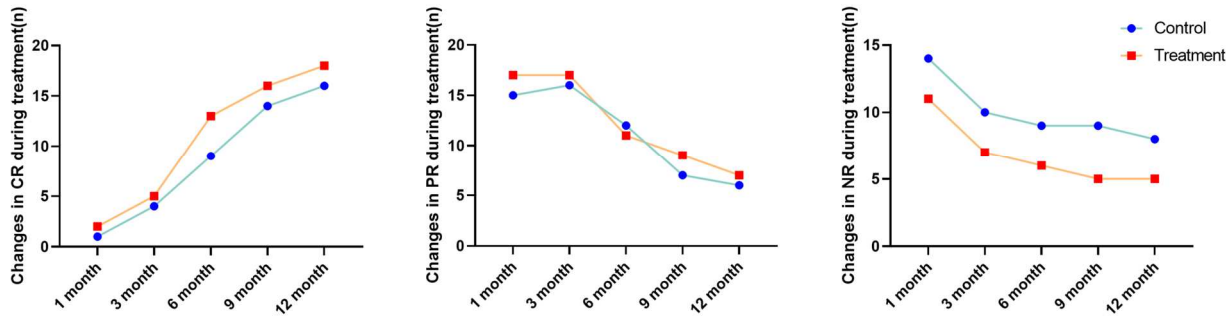

Fig. 1: Trend graphs of SR, PR and NR during treatment (n).

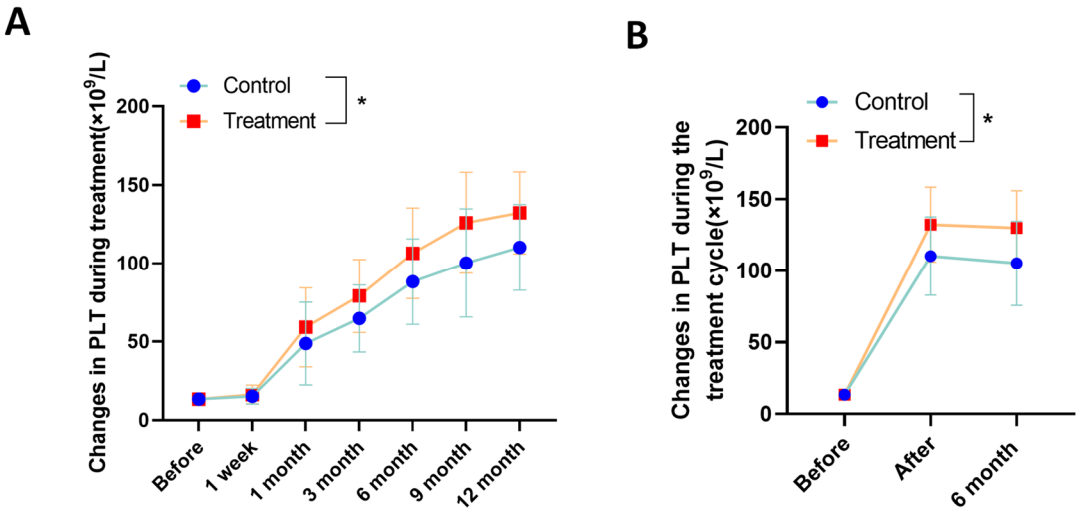

Fig. 2: Comparison of PLT levels during treatment cycles. *P<0.05, vs before treatment; #P<0.05, vs control group.

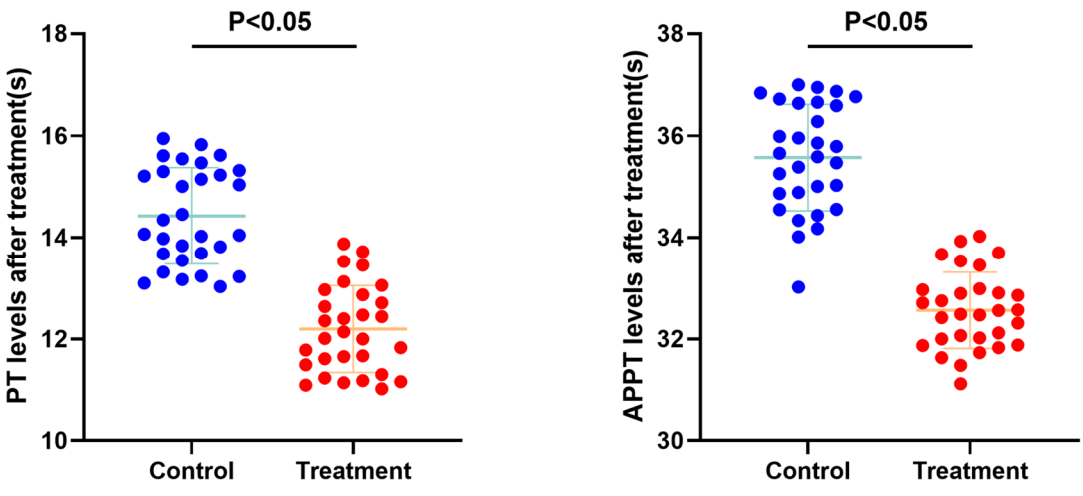

Fig. 3: Comparison of PT and APTT levels during the treatment cycle.

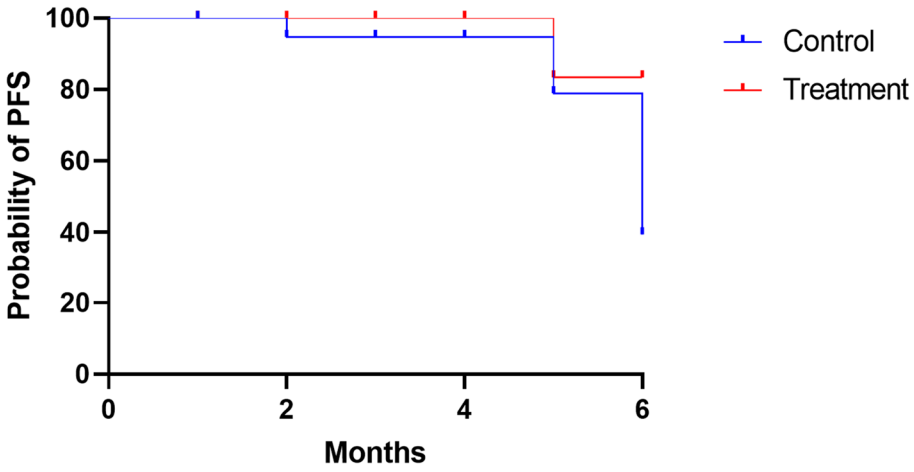

Fig. 4: Statistics of patients' PFS.

Table 1: Dosage adjustment of eltrombopag

Platelet level	Dosage adjustment
Patients take 75 mg of eltrombopag daily with platelets <100 × 10^9/L	Continue eltrombopag 75 mg/day until month 6
Patients who achieve CR (platelets ≥100 × 10^9/L) but whose platelets cannot be maintained around 100 × 10^9/L (i.e. platelets <70 × 10^9/L) for 2 months	Increase dose to a maximum of 75 mg/day until CR is again achieved and platelets are maintained at around 100×10^9/L (platelets must not fall below 70× 10^9/L)
Patients with relapse (< 30 × 10^9/L) during the tapering phase of eltrombopag	Use of doses prior to reduction
Patients with relapse (< 30 × 10^9/L) after stopping eltrombopag	Restart treatment with a starting dose of 25 mg/day

Table 2: Demographics and baseline characteristics of 60 patients (mean ± SD) or n (%)

Parameter		Control	Treatment	X2(t)	P
Number		30	30		
Age(years)		48.9±12.55	50.13±13.86	0.36	0.72
Gender, n (%)	Female	19 (63.33)	16 (53.33)	0.79	0.43
	Male	11 (36.67)	14 (46.67)		
Time since diagnosis, n (%)	<3 months	4 (13.33)	7 (23.33)	-	0.16
	3-12 months	10 (33.33)	4 (13.33)		
	>1 years	16 (53.33)	19 (63.33)		
Baseline Platelet Count	<10 ×10^9/L	12 (40.00)	10 (33.33)	-	0.39
	10-20 ×10^9/L	9 (30.00)	14 (46.67)		
	20-30 ×10^9/L	9 (30.00)	6 (20.00)		
Concomitant ITP medication at baseline, n (%)		8 (26.67)	7 (23.33)	0.3	0.77
Eltrombopag dose, mg/day		57.3±21.36	58.5±20.88	0.22	0.82
Patients with at least 1 dose of 75 mg/day, n (%)		6 (20.00)	8 (26.67)	0.61	0.54
PT(s)		18.13±2.11	18.24±2.05	0.2	0.84
APTT(s)		41.17±5.38	40.26±5.14	0.67	0.51

Table 3: Statistics on treatment efficacy n (%)

Groups	CR	PR	NR	OR
Control (n=30)	16 (53.33)	6 (20.00)	8 (26.67)	22 (73.33)
Treatment (n=30)	18 (60.00)	7 (23.33)	5 (16.67)	25 (83.33)
P value				0.35

Table 4: Comparison of sustained effective SR after treatment n (%)

Groups	CR	PR	SR
Control(n=22)	16 (72.73)	6 (27.27)	19 (83.36)
Treatment (n=25)	18 (81.81)	7 (31.82)	24 (96.00)
P value			0.24

Table 5: Incidence of adverse events and adverse reactions [n (%)]

Groups	Adverse reaction						Adverse events	Total rates
	Gastrointestinal distress	Pruritus	Headache	Nauseating	Liver damage	Fever	Thrombo-embolism	
Control	1(3.33)	2(6.67)	1(3.33)	2(6.67)	1(3.33)	1(3.33)	1(3.33)	9(30.00)
Treatment	1(3.33)	4(13.33)	2(6.67)	1(3.33)	1(3.33)	3(10.00)	1(3.33)	13(43.33)
X^2								1.07
P								0.28

It can also promote the proliferation and differentiation of bone marrow hematopoietic stem cells, thereby improving the hematopoietic function of patients. Similarly, Nusrat *et al*. found that rituximab improved the clinical symptoms of lupus anticoagulant dysplasia hemagglutination syndrome and alleviated hypoprothrombinemia (Nusrat *et al.*, 2023). Furthermore, the incidence of adverse events in the two groups of patients was not statistically significant, suggesting that the treatment of rituximab combined with eltrombopag had a good safety. Consistently, Ata *et al*. conducted a single-center, retrospective study in the Arabic population and found that in chronic refractory ITP, rituximab appeared to have a better clinical response in the Arabic population with minimal toxicity than in other ethnicities (Ata *et al.*, 2022).

Our study has some limitations. First, the sample size is small. Second, the follow-up time is short. Therefore, more large-scale and long-term studies should be performed in the future.

CONCLUSION

Eltrombopag in combination with rituximab can effectively improve the therapeutic efficacy and coagulation function of ITP patients, with a low incidence of important adverse effects. This therapeutic strategy has greater potential for use in the treatment of ITP patients.

Ethical approval

This study was approved by the Ethics Committee of Siyang Hospital on January 1, 2024, and the approval number was KS2024001.

Conflict of interest

The authors declare that they have no competing interests.

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REFERENCES

Ata F, Yousaf Z, Zahir FZ, Mohamed Babiker A, Ali Farooqi A, Ahmad Al Hiyari M, Al Bozom A I, Mohamed AH, Nashwan AJ and Yassin MA (2022). Efficacy and safety of rituximab as second-line therapy in immune thrombocytopenic purpura based on ethnicity: A descriptive study among the Arabic population. *Qatar Med. J.,* **2022**(3): 22.

Beltrami-Moreira M and Bussel JB. (2022). Low-dose rituximab in immune thrombocytopenia: One and done. *Am. J. Hematol.,* **97**(4): 388-389.

Bolton-Maggs PHB and George JN (2021). Immune thrombocytopenia treatment. *N. Engl. J. Med.,* **385**(10): 948-950.

Chinese guideline on the diagnosis and management of adult primary immune thrombocytopenia (version 2020). (2020). *Zhonghua Xue Ye Xue Za Zhi,* **41**(8): 617-623.

Delshad M, Davoodi-Moghaddam Z, Pourbagheri-Sigaroodi A, Faranoush M, Abolghasemi H and Bashash D (2024). Translating mechanisms into therapeutic strategies for immune thrombocytopenia (ITP): Lessons from clinical trials. *Thromb. Res.,* **235**: 125-147.

DeSouza S and Angelini D. (2021). Updated guidelines for

immune thrombocytopenic purpura: Expanded management options. *Cleve. Clin. J. Med.,* **88**(12): 664-668.

Hamed EM, Ibrahim ARN, Meabed MH, Khalaf AM, El Demerdash DM, Elgendy MO, Saeed H, Salem HF and Rabea H (2023). Therapeutic outcomes of high dose-dexamethasone versus prednisolone + azathioprine, rituximab, eltrombopag and romiplostim strategies in persistent, chronic, refractory and relapsed immune thrombocytopenia patients. *Pharmaceuticals (Basel),* **16**(9): 1215.

Kang H (2021). Sample size determination and power analysis using the G*Power software. *J. Educ. Eval. Health Prof.,* **18**: 17.

Kaur MN, Arnold DM, Heddle NM, Cook RJ, Hsia C, Blostein M, Jamula E, Sholzberg M, Lin Y, Kassis J, Larratt L, Tinmouth A, Carruthers J, Li N, Liu Y and Xie F (2022). Cost-effectiveness of eltrombopag vs intravenous immunoglobulin for the perioperative management of immune thrombocytopenia. *Blood Adv.,* **6**(3): 785-792.

Kochhar M and Neunert C (2021). Immune thrombocytopenia: A review of upfront treatment strategies. *Blood Rev.,* **49**: 100822.

Li J, Guo J, Yuan R and Xue L (2025). Rituximab in Immune-mediated thrombotic thrombocytopenic purpura. *Eur J Intern Med*.

Liu X G, Hou Y and Hou M (2023). How we treat primary immune thrombocytopenia in adults. *J. Hematol. Oncol.,* **16**(1): 4.

Nusrat S, Tewari S and Khan O (2023). Successful treatment of lupus anticoagulant hypoprothrombinemia syndrome with rituximab. *Thromb. J.,* **21**(1): 77.

Oliva EN, Riva M, Niscola P, Santini V, Breccia M, Giai V, Poloni A, Patriarca A, Crisà E, Capodanno I, Salutari P, Reda G, Cascavilla N, Ferrero D, Guarini A, Tripepi G, Iannì G, Russo E, Castelli A, Fattizzo B, Beltrami G, Bocchia M, Molteni A, Fenaux P, Germing U, Ricco A, Palumbo G A, Impera S, Di Renzo N, Rivellini F, Buccisano F, Stamatoullas-Bastard A, Liberati A M, Candoni A, Delfino IM, Arcadi MT, Cufari P, Rizzo L, Bova I, D'Errigo M G, Zini G and Latagliata R (2023). Eltrombopag for low-risk myelodysplastic syndromes with thrombocytopenia: Interim results of a phase ii, randomized, placebo-controlled clinical trial (EQOL-MDS). *J. Clin. Oncol.,* **41**(28): 4486-4496.

Patel BA, Groarke EM, Lotter J, Shalhoub R, Gutierrez-Rodrigues F, Rios O, Quinones Raffo D, Wu CO and Young NS. (2022). Long-term outcomes in patients with severe aplastic anemia treated with immunosuppression and eltrombopag: A phase 2 study. *Blood,* **139**(1): 34-43.

Peffault de Latour R, Kulasekararaj A, Iacobelli S, Terwel SR, Cook R, Griffin M, Halkes CJM, Recher C, Barraco F, Forcade E, Vallejo J C, Drexler B, Mear JB, Smith AE, Angelucci E, Raymakers RAP, de Groot MR, Daguindau E, Nur E, Barcellini W, Russell N H, Terriou L, Iori A P, La Rocca U, Sureda A, Sánchez-Ortega I, Xicoy B, Jarque I, Cavenagh J, Sicre de Fontbrune F, Marotta S, Munir T, Tjon JML, Tavitian S, Praire A, Clement L, Rabian F, Marano L, Hill A, Palmisani E, Muus P, Cacace F, Frieri C, van Lint MT, Passweg JR, Marsh JCW, Socie G, Mufti GJ, Dufour C and Risitano AM (2022). Eltrombopag added to immunosuppression in severe aplastic anemia. *N. Engl. J. Med.,* **386**(1): 11-23.

Sandal R, Mishra K, Jandial A, Sahu KK and Siddiqui AD (2021). Update on diagnosis and treatment of immune thrombocytopenia. *Expert Rev. Clin. Pharmacol.,* **14**(5): 553-568.

Vianelli N, Auteri G, Buccisano F, Carrai V, Baldacci E, Clissa C, Bartoletti D, Giuffrida G, Magro D, Rivolti E, Esposito D, Podda GM and Palandri F (2022). Refractory primary immune thrombocytopenia (ITP): current clinical challenges and therapeutic perspectives. *Ann. Hematol.,* **101**(5): 963-978.

Werth VP, Joly P, Mimouni D, Maverakis E, Caux F, Lehane P, Gearhart L, Kapre A, Pordeli P and Chen DM. (2021). Rituximab versus mycophenolate mofetil in patients with pemphigus vulgaris. *N. Engl. J. Med.,* **384**(24): 2295-2305.

Will B (2022). Effects of eltrombopag on mesenchymal stem cells in immune thrombocytopenia purpura. *Br. J. Haematol.,* **197**(2): 137-138.

Witkowski M, Ryżewska W and Robak T (2024). Thrombopoietin receptor agonist and rituximab combination therapy in patients with refractory primary immune thrombocytopenia. *Blood Coagul. Fibrinolysis.,* **35**(3): 108-114.

Zhang N, Ji C, Bao X and Yuan C (2022). Early treatment of rituximab combined with eltrombopag for secondary thrombocytopenic purpura in rheumatoid arthritis: A case report. *Medicine (Baltimore),* **101**(2): e28417.

Zhou H, Fan J, He J and Hu S (2022). Comparative efficacy of 19 drug therapies for patients with idiopathic thrombocytopenic purpura: A multiple-treatments network meta-analysis. *Ann. Hematol.,* **101**(5): 953-961.