Int J Clin Exp Med 2021;14(2):1133-1139
www.ijcem.com /ISSN:1940-5901/IJCEM0122430

Original Article

Therapeutic effectiveness of eltrombopag in hematologic diseases

Ling Song, Yue Hu, Youwei Yang, Li Xu

Department of Hematology, Anhui No. 2 Provincial People's Hospital, Hefei, Anhui Province, China

Received September 15, 2020; Accepted October 14, 2020; Epub February 15, 2021; Published February 28, 2021

Abstract: Objective: This study aimed to explore the effectiveness of eltrombopag in the treatment of hematological disorders. Methods: A total of 55 patients with hematological disorders admitted to our hospital were enrolled and divided into a study group (n = 27) and a control group (n = 28) according to treatment options. Patients in the control group only received conventional treatment for hematologic diseases, while patients in the study group were additionally treated with eltrombopag. The clinical efficacy, the levels of peripheral blood cytokines and B lymphocytes before and after treatment, the dynamic changes in platelet count (PLT), and the incidence of adverse reactions during the treatment were compared between the two groups. Results: The effective rate of patients in the study group reached 88.89% (24/27), higher than that of 67.86% (18/28) in the control group ($P < 0.05$). The levels of the cytokines IL-2, IL-4, and INF-γ showed little significant difference between the two groups before treatment ($P > 0.05$), but the levels of the above cytokines in the study group were significantly lower than those in the control group after intervention ($P < 0.05$). There was no significant difference in the $CD3^+$ and $CD4^+$ levels of B lymphocytes between the two groups ($P > 0.05$), but the levels of the above B lymphocytes in the study group were significantly higher than those in the control group after treatment ($P < 0.05$). The PLT of the study group was significantly higher than that of the control group at 30, 60 and 90 d after treatment ($P < 0.05$). The incidence of adverse reactions showed no significant difference in the two groups of patients ($P > 0.05$). Conclusion: Eltrombopag is effective in treating patients with hematologic diseases, which can greatly improve the patients' inflammatory state and immune status with high safety.

Keywords: Eltrombopag, hematologic diseases, treatment, effectiveness

Introduction

Platelets are small pieces of cytoplasm that are detached from mature megakaryocytes, which play a crucial role during hemostasis. Studies have found that when an individual experiences blood loss, platelets will quickly coagulate at the wound site. Platelets can also rupture to produce fibrin, which along with red blood cells, platelets and other substances forms thrombus to block the wound site and exert a hemostatic effect. Platelet count (PLT) is one of the key indices of blood test and ranges (125-320)×10^9/L, and lower level is defined as thrombocytopenia [1-3]. Thrombocytopenia can be caused by a variety of factors, and targeted treatments or regulation of the expressions of related cytokines are effective means to control thrombocytopenia [4].

Eltrombopag induces the proliferation and differentiation of megakaryocytes, thereby increasing platelet levels [5]. Eltrombopag has been validated in several clinical practices and has shown good efficacy in the treatment of immune thrombocytopenia (ITP), aplastic anemia (AA) and other hematologic disorders, and currently eltrombopag has been recommended as the first-line drug for immune thrombocytopenia [6, 7]. A multicenter study found that eltrombopag exhibited good effects on different types of ITP [8]. In addition, studies have found that eltrombopag is a thrombopoietin analog, which could promote the proliferation of blood cells such as platelets, and its inhibitory effect on myelofibrosis is also worthy of recognition [8, 9].

The aim of this study was to investigate the feasibility of intervention with eltrombopag in patients with hematologic disorders, analyze its clinical efficacy and safety as well as the changes in blood and immune indicators, so as

to provide a more detailed theoretical basis for the clinical application of eltrombopag.

Materials and methods

General information

Fifty-five patients with hematologic disorders admitted to our hospital from January 2019 to December 2019 were divided into a study group (n = 27) and a control group (n = 28) according to the differences in their treatment modalities.

Inclusion criteria: (1) patients aged 18-78 years; (2) those with platelet count < 50×10^9/L and clinical symptoms of thrombocytopenia; (3) those with duration of ITP > 6 months; (4) those with clear consciousness and good compliance. This study was approved by hospital ethics committee. Patients signed the informed consent form.

Exclusion criteria: (1) patients with secondary immune thrombocytopenia (HCV or systemic lupus erythematosus); (2) those with severe cardiovascular disease (congestive heart failure, arrhythmia); (3) pregnant and lactating women; (4) those with abnormal levels of creatinine, muscle enzymes, or neutrophils; (5) those with co-morbid psychiatric disorders; (6) those who had hypersensitivity to the investigated drugs; (7) those with co-morbid thrombophilia.

Elimination criteria: (1) those with poor medication compliance; (2) those who were lost to follow up; (3) those who volunteered to withdraw from the study.

Intervention methods

Patients in the control group were treated with conventional drugs, including glucocorticoids, gammaglobulin, immunosuppressants, etc., and splenectomy could be performed if necessary, while patients in the study group were treated with eltrombopag (Novartis Healthcare Pvt. Ltd., Switzerland, 25 mg/tablet) on the basis of treatments in the control group for 3 months. The initial dose was 50 mg/d (or 25 mg/d for patients with moderate to severe hepatic dysfunction).

Observation indicators

Clinical effectiveness: The outcomes were assessed in both groups after 3 months of treatment as follows: complete response (CR, PLT ≥ 100×10^9/L, and the patient had no bleeding symptoms); partial response (PR, PLT ranged 30×10^9/L-100×10^9/L, or PLT counts increased twofold compared to pre-treatment and the patient had no bleeding symptoms); no response (NR, PLT < 30×10^9/L, or PLT increased less than twice of the basal value, or bleeding symptoms were present). The total effective rate = (CR+PR)/total cases ×100%.

Changes in peripheral blood cytokines: The fasting venous blood samples of the two groups were collected before and at 3 months after treatment, and the serum was centrifuged and stored at -80°C. The levels of IL-2, IL-4 and INF-γ of the two groups before and after treatment were detected using the enzyme-linked immunosorbent assay (ELISA) (Shanghai Xinyu Biotechnology Co., Ltd.).

Changes in B-lymphocyte levels: Blood samples were collected from the two groups of patients before and at 3 months after treatment, and $CD3^+$ and $CD4^+$ levels were determined using flow cytometry (model EPICS-XL, Beckman, USA).

The dynamically monitored PLT levels: Routine blood tests were carried out and the changes in PLT count were analyzed at 30, 60 and 90 d after treatment.

Comparison of the incidence of adverse reactions: The incidence of various adverse events such as petechiae, headache, gastrointestinal reactions, joint pain, and other events occurred during treatment in the two groups was counted separately.

Statistical analysis

The data were entered into the EXCEL table, and analyzed by SPSS22.0. Data conforming to normal distribution were employed. Count data were indicated by [n (%)] and the differences between the groups were examined by Chi-square test. Measurement data (mean ± standard deviation) were compared. GraphPad Prism was used as the drawing software. $P < 0.05$ was considered as statistically significant difference [10].

Results

Differential analysis of baseline data

There was little difference in terms of age, gender, disease duration, and surgical history be-

Table 1. Comparison of baseline data between the two groups ($\bar{x}$ ± sd)/[n (%)]

Baseline data		Study group (n = 27)	Control group (n = 28)	t/X^2	*P*
Gender	Male	14	14	0.019	0.891
	Female	13	14		
Average age (years)		40.39 ± 4.33	40.44 ± 4.29	0.129	0.898
Average weight (kg)		61.28 ± 3.29	61.38 ± 2.38	0.13	0.897
Average duration of illness (years)		1.28 ± 0.11	1.31 ± 0.09	1.109	0.272
Education level	University and above	10	11	0.222	0.887
	Junior school	14	15		
	Lower secondary and below	3	2		
Monthly income	< 1000 Yuan	4	5	0.341	0.781
	1000-5000 Yuan	15	15		
	Over 5000 Yuan	8	8		
Splenectomy	Yes	10	10	0.01	0.919
	No	17	18		

Table 2. Differential analysis of clinical outcomes between the two groups [n (%)]

Grouping	Cases	CR	PR	NR	Total effective rate
Study group	27	20 (74.07)	4 (14.81)	3 (11.11)	24 (88.89)
Control group	28	10 (35.71)	8 (28.57)	10 (35.71)	18 (64.29)
X^2	--	--	--	--	4.61
P	--	--	--	--	0.032

tween the two groups (*P* > 0.05), which was comparable (**Table 1**).

Differential analysis of the clinical outcomes

In the study group, there were 20 cases (74.07%) of CR, 4 cases (14.01%) of PR, and 3 cases (11.11%) of NR, with the total effective rate of 88.89%. In the control group, there were 10 cases (35.71%) of CR, 8 cases (28.57%) of PR, and 10 cases (35.71%) of NR, with the total effective rate of 64.29%. The total effective rate in the study group was significantly higher than that in the control group (*P* < 0.05) (**Table 2**).

Changes in peripheral blood cytokines

There was little difference in the levels of IL-2 [(4.28 ± 0.32) vs (4.31 ± 0.29)], IL-4 [(2.71 ± 0.21) vs (2.69 ± 0.27)] and INF-γ [(11.29 ± 1.29) vs (11.31 ± 1.31)] between the study group and the control group before treatment (*P* > 0.05). The levels of these cytokines were significantly reduced after treatment, and the difference of each cytokine before and after treatment was statistically significant (*P* < 0.05). Meanwhile, the levels of these cytokines after treatment in the study group were significantly lower than those in the control group, indicating statistically significant difference (*P* < 0.05) (**Figure 1**).

Changes of B-lymphocyte levels in the two groups

Blood samples were collected from both groups before and after treatment, and B lymphocyte levels were analyzed. The results showed that there was little difference between the $CD3^+$ and $CD4^+$ levels of the two groups before treatment (*P* > 0.05). At 3 months after treatment, the $CD3^+$ and $CD4^+$ levels in the study group were improved compared with those before treatment, showing significant difference (*P* < 0.05). However, the levels of $CD3^+$ and $CD4^+$ in the control group were only slightly improved after treatment compared with those before treatment, and the difference was not statistically significant before and after treatment (*P* > 0.05). After treatment, the levels in the study group were significantly higher than those in the control group, indicating significant difference (*P* < 0.05) (**Figure 2**).

The dynamically monitored PLT levels

The PLT level was dynamically monitored for 90 days in both groups. The overall assessment

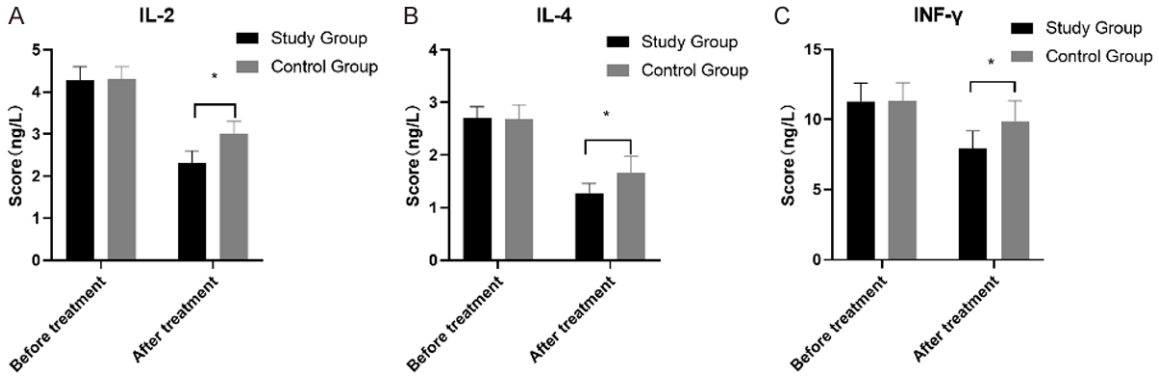

Figure 1. Changes in peripheral blood cytokines in the two groups of patients before and after treatment. IL-1 (A), IL-4 (B) and INF-γ (C). *$P < 0.05$ compared with the control group.

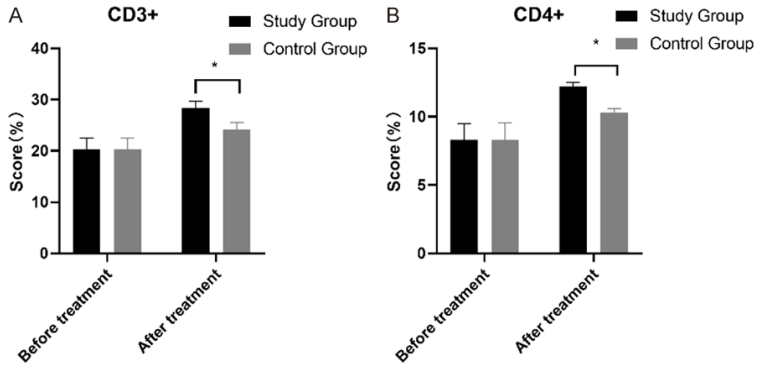

Figure 2. Changes in the levels of B lymphocytes in the two groups of patients before and after treatment. $CD3^+$ (A) and $CD4^+$ (B). *$P < 0.05$ compared with the control group.

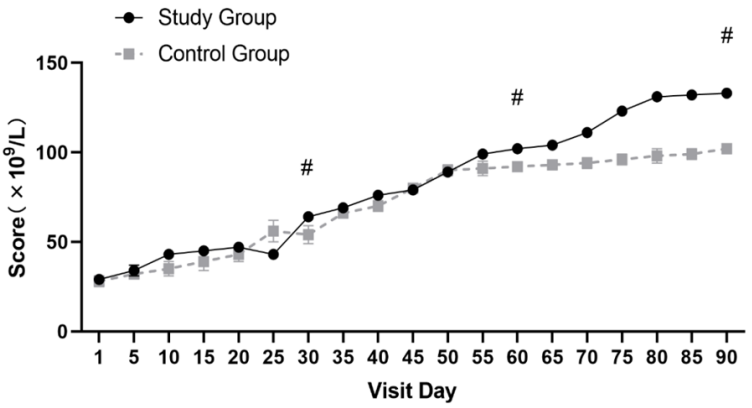

Figure 3. Changes in PLT levels in the two groups of patients during treatment. #$P < 0.05$ compared with the control group.

revealed that the PLT level of patients in both groups showed a gradually increasing trend after treatment. The PLT level at 90 days after treatment was compared with that at 0 day after treatment, and the difference was statistically significant ($P < 0.05$). Three time points, i.e. 30, 60 and 90 days, were selected to conduct inter-group difference comparison. The PLT levels in the study group were significantly higher than those in the control groups at 30, 60 and 90 days after treatment, showing statistically significant difference ($P < 0.05$) (**Figure 3**).

Comparison of the incidence of adverse effects

In the study group, there were 2 cases of ecchymosis, 1 case of headache and 2 cases of joint pain, with the incidence rate of 18.52%, while in the control group, there were 2 cases of ecchymosis, 1 case of headache, 1 case of joint pain and 1 case of gastrointestinal reactions, with the incidence rate of 17.86%. There was no significant difference in incidence of adverse reactions between the two groups ($P > 0.05$) (**Table 3**).

Discussion

Thrombocytopenia is a group of diseases characterized by decreased platelet count and patients present with bleeding from mucous membranes of the skin, petechiae, oral and nasal bleeding, *etc*. In severe cases, massive bleeding may occur in the gastrointestinal tract and central nervous system, endangering the life of the patient [11,

Table 3. Comparison of the incidence of adverse events between the two groups [n (%)]

Grouping	Cases	Ecchymosis	Headaches	Joint pain	Gastrointestinal reactions	Total incidence rate
Study group	27	2 (7.41)	1 (3.70)	2 (7.41)	0 (0.00)	5 (18.52)
Control group	28	2 (7.14)	1 (3.57)	1 (3.57)	1 (3.57)	5 (17.86)
X^2	--	--	--	--	--	0.004
P	--	--	--	--	--	0.949

12]. Primary ITP and AA are the common types of thrombocytopenia, in which ITP is present with a significant increase in the level of antiplatelet antibodies in the blood circulation, resulting in excessive platelet destruction, purpura, and skin ecchymosis [13]. AA is a group of bone marrow hematopoietic failure syndromes with multiple etiologies, characterized by hypoplasia of bone marrow hematopoietic cells and decreased peripheral whole blood cells, with anemia, hemorrhage and infection as the common clinical manifestations.

Conventional therapeutic measures for thrombocytopenia are glucocorticoids, high-dose intravenous administration of human immunoglobulin, danazol, and immunosuppressive drugs, aiming to maintain the patient's platelet count at a safe level by inhibiting platelet destruction and reduce the occurrence of serious bleeding events [14, 15]. Although the above interventions have been clinically proven to be effective, the side effects are also pronounced, for example, administration of hormones can cause bone loss and diabetes in individuals, and the immunoglobulins could increase the chances of infection and liver damage. In addition, other second-line treatments such as splenectomy and immunosuppressants tend to have a lower efficiency as well as significant adverse effects [16]. Eltrombopag is a second-generation thrombopoietin receptor agonist, which promotes the differentiation and proliferation of macrophages as well as platelet production. The drug was approved for adult chronic immune thrombocytopenia after being marketed in the United States in 2008, and has been clinically proven to have satisfactory short-term and long-term therapeutic effects [17]. A multicenter, randomized, double-blind study of 100 patients with ITP showed that 59% of patients achieved a platelet count of 50×10^9/L after 43 days of treatment, compared with 16% in the placebo group [18]. It was also found that platelet counts reached 50×10^9/L in 20%, 27% and 30% of patients at 12.5 mg/d, 25 mg/d and 50 mg/d respectively after 2 weeks of treatment, and 42% of patients had met the target of platelet counts after 6 weeks of treatment [19, 20]. All the above studies indicate that eltrombopag has a good efficacy for the treatment of ITP and AA.

This study was conducted to analyze the clinical effects of eltrombopag in the treatment of ITP and AA by grouping 55 patients with hematologic disorders according to treatment options, and the results showed that the total effective rate of treatment was 88.89% in the study group and 64.29% in the control group, with a significant difference between the two groups. The results of a double-blind, controlled trial on 117 patients with ITP showed that the proportion of patients with platelet counts > 50×10^9/L at the 4th day of treatment reached 81%, and 80% of them had platelet counts of 50×10^9/L after 15 d of intervention at 50 mg/d, suggesting that eltrombopag is effective in improving platelet counts in ITP patients, which is similar to the results of this study [21]. Eltrombopag is a non-peptide thrombopoietin receptor agonist, which can bind to the surface thrombopoietin receptor on megakaryocyte lines and induce myeloid differentiation by activating MAPK, JAK and other signaling pathways, thus promoting platelet production [22] which is evidenced by the changes in PLT count in the study group, indicating that eltrombopag is significantly more effective in increasing PLT counts than regular prescribed hormones.

The results showed that the IL-2, IL-4, and INF-γ levels were significantly lower in the study group than those in the control group, and the $CD3^+$ and $CD4^+$ levels were significantly higher in the study group than those in the control group. The results of a controlled study carried out on eltrombopag suggest that patients treated with eltrombopag had a significant increase in numbers of $CD19^+$ lymphocyte and a significant decrease in IL-4 and IL-5 levels,

similar to the results in this study [23, 24]. The reason may be that eltrombopag could stimulate the conversion of bone marrow $CD34^+$ cells into megakaryocytes $CD41^+$, and that patients with thrombocytopenia often had obvious immune regulatory abnormalities, such as loss of regulatory T-cells, leading to abnormal expression of cytokines and related lymphocytes, while eltrombopag could modify the secretion of different cytokines by regulating the proliferation of T cells and B cells, thereby affecting the biological behavior of lymphocytes [25, 26]. Finally, the incidence of adverse events was 18.52% in the study group and 17.86% in the control group respectively, suggesting that the eltrombopag does not significantly increase the incidence of adverse events in patients, proving its safety.

In conclusion, eltrombopag is feasible for the treatment of blood system diseases, with high clinical efficacy and safety. The inflammatory state and immune status of patients are significantly improved as well. However, the study has the following shortcomings: (1) there is a lack of analysis on the safety of long-term use; (2) there is a lack of analysis on the differences in efficacy and safety between different doses of eltrombopag, which will be improved in future studies.

Disclosure of conflict of interest

None.

Address correspondence to: Li Xu, Department of Hematology, Anhui No. 2 Provincial People's Hospital, No. 1868 Dangshan Road, North 2nd Ring Road, Yaohai District, Hefei 230000, Anhui Province, China. Tel: +86-0551-64272603; +86-150-56254901; E-mail: songling511511@163.com

References

[1] Cooper N and Ghanima W. Immune thrombocytopenia. N Engl J Med 2019; 381: 945-955.

[2] Di Buduo CA, Currao M, Pecci A, Kaplan DL, Balduini CL and Balduini A. Revealing eltrombopag's promotion of human megakaryopoiesis through AKT/ERK-dependent pathway activation. Haematologica 2016; 101: 1479-1488.

[3] Cines DB and Blanchette VS. Immune thrombocytopenic purpura. N Engl J Med 2002; 346: 995-1008.

[4] Cooper N and Bussel J. The pathogenesis of immune thrombocytopaenic purpura. Br J Haematol 2006; 133: 364-374.

[5] Abbonante V, Di Buduo CA, Malara A, Laurent PA and Balduini A. Mechanisms of platelet release: in vivo studies and in vitro modeling. Platelets 2020; 31: 717-723.

[6] Witkowski M, Witkowska M and Robak T. Autoimmune thrombocytopenia: current treatment options in adults with a focus on novel drugs. Eur J Haematol 2019; 103: 531-541.

[7] Garabet L, Ghanima W, Monceyron Jonassen C, Skov V, Holst R, Mowinckel MC, C Hasselbalch H, A Kruse T, Thomassen M, Liebman H, Bussel JB and Sandset PM. Effect of thrombopoietin receptor agonists on markers of coagulation and P-selectin in patients with immune thrombocytopenia. Platelets 2019; 30: 206-212.

[8] Wu K, Thapar M, Farrell C, Hayes S, Guo H, Hou M and Zhang J. Population pharmacokinetic and pharmacodynamic modeling and effects on platelet counts of different dosages of eltrombopag in Chinese patients with chronic primary immune thrombocytopenia. Clin Ther 2015; 37: 1382-1395.

[9] Gernsheimer T, Stratton J, Ballem PJ and Slichter SJ. Mechanisms of response to treatment in autoimmune thrombocytopenic purpura. N Engl J Med 1989; 320: 974-980.

[10] Townsley DM, Scheinberg P, Winkler T, Desmond R, Dumitriu B, Rios O, Weinstein B, Valdez J, Lotter J, Feng X, Desierto M, Leuva H, Bevans M, Wu C, Larochelle A, Calvo KR, Dunbar CE and Young NS. Eltrombopag added to standard immunosuppression for aplastic anemia. N Engl J Med 2017; 376: 1540-1550.

[11] Taft C, Karlsson J and Sullivan M. Performance of the Swedish SF-36 version 2.0. Qual Life Res 2004; 13: 251-256.

[12] Roth M, Will B, Simkin G, Narayanagari S, Barreyro L, Bartholdy B, Tamari R, Mitsiades CS, Verma A and Steidl U. Eltrombopag inhibits the proliferation of leukemia cells via reduction of intracellular iron and induction of differentiation. Blood 2012; 120: 386-394.

[13] Ghanima W, Cooper N, Rodeghiero F, Godeau B and Bussel JB. Thrombopoietin receptor agonists: ten years later. Haematologica 2019; 104: 1112-1123.

[14] Kuter DJ, Newland A, Chong BH, Rodeghiero F, Romero MT, Pabinger I, Chen Y, Wang K, Mehta B and Eisen M. Romiplostim in adult patients with newly diagnosed or persistent immune thrombocytopenia (ITP) for up to 1 year and in those with chronic ITP for more than 1 year: a subgroup analysis of integrated data from completed romiplostim studies. Br J Haematol 2019; 185: 503-513.

[15] Bussel JB, Kuter DJ, George JN, McMillan R, Aledort LM, Conklin GT, Lichtin AE, Lyons RM, Nieva J, Wasser JS, Wiznitzer I, Kelly R, Chen

CF and Nichol JL. AMG 531, a thrombopoiesis-stimulating protein, for chronic ITP. N Engl J Med 2006; 355: 1672-1681.
[16] Wong RSM, Saleh MN, Khelif A, Salama A, Portella MSO, Burgess P and Bussel JB. Safety and efficacy of long-term treatment of chronic/persistent ITP with eltrombopag: final results of the EXTEND study. Blood 2017; 130: 2527-2536.
[17] Zufferey A, Kapur R and Semple JW. Pathogenesis and therapeutic mechanisms in immune thrombocytopenia (ITP). J Clin Med 2017; 6: 16.
[18] Kantarjian HM, Fenaux P, Sekeres MA, Szer J, Platzbecker U, Kuendgen A, Gaidano G, Wiktor-Jedrzejczak W, Carpenter N, Mehta B, Franklin J and Giagounidis A. Long-term follow-up for up to 5 years on the risk of leukaemic progression in thrombocytopenic patients with lower-risk myelodysplastic syndromes treated with romiplostim or placebo in a randomised double-blind trial. Lancet Haematol 2018; 5: e117-e126.
[19] Neunert C, Terrell DR, Arnold DM, Buchanan G, Cines DB, Cooper N, Cuker A, Despotovic JM, George JN, Grace RF, Kühne T, Kuter DJ, Lim W, McCrae KR, Pruitt B, Shimanek H and Vesely SK. American society of hematology 2019 guidelines for immune thrombocytopenia. Blood Adv 2019; 3: 3829-3866.
[20] Lau JL and Dunn MK. Therapeutic peptides: historical perspectives, current development trends, and future directions. Bioorg Med Chem 2018; 26: 2700-2707.
[21] Jenkins JM, Williams D, Deng Y, Uhl J, Kitchen V, Collins D and Erickson-Miller CL. Phase 1 clinical study of eltrombopag, an oral, nonpeptide thrombopoietin receptor agonist. Blood 2007; 109: 4739-4741.
[22] Saleh MN, Bussel JB, Cheng G, Meyer O, Bailey CK, Arning M and Brainsky A. Safety and efficacy of eltrombopag for treatment of chronic immune thrombocytopenia: results of the long-term, open-label EXTEND study. Blood 2013; 121: 537-545.
[23] Godeau B, Porcher R, Fain O, Lefrère F, Fenaux P, Cheze S, Vekhoff A, Chauveheid MP, Stirnemann J, Galicier L, Bourgeois E, Haiat S, Varet B, Leporrier M, Papo T, Khellaf M, Michel M and Bierling P. Rituximab efficacy and safety in adult splenectomy candidates with chronic immune thrombocytopenic purpura: results of a prospective multicenter phase 2 study. Blood 2008; 112: 999-1004.
[24] Cheng G, Saleh MN, Marcher C, Vasey S, Mayer B, Aivado M, Arning M, Stone NL and Bussel JB. Eltrombopag for management of chronic immune thrombocytopenia (RAISE): a 6-month, randomised, phase 3 study. Lancet 2011; 377: 393-402.
[25] Audia S, Mahévas M, Samson M, Godeau B and Bonnotte B. Pathogenesis of immune thrombocytopenia. Autoimmun Rev 2017; 16: 620-632.
[26] Castelli R, Lambertenghi Delilliers G, Gidaro A, Cicardi M and Bergamaschini L. Complement activation in patients with immune thrombocytopenic purpura according to phases of disease course. Clin Exp Immunol 2020; 201: 258-265.