İzmir Eğitim ve Araştırma Hastanesi Tıp Dergisi (Medical Journal of İzmir Hospital) 15 (1-4): 5-11, 2009

İDİYOPATİK TROMBSİTOPENİK PURPURA'YA YAKLAŞIM VE TEDAVİ

MANAGEMENT AND TREATMENT OF IDİOPATHİC THROMBOCYTOPENİC PURPURA

Oktay BİLGİR* Ferda BİLGİR**

*Izmir Training and Research Hospital, 2nd Clinic of Internal Medicine, 35380, Izmir, Turkey
**Buca State Hospital, Clinic of Internal Medicine, Buca, Izmir, Turkey

Anahtar Sözcükler: İmmunglobulin, ortalama trombosit volümü, diyabetik komplikasyonlar
Key Words: Purpura trombositopenik,idiyopatik

ÖZET

Idiopathic thrombocytopenic purpura (ITP) is a disease known to have medical and surgical treatments. Although ITP is a benign disease, it is associated with high morbidity and mortality, especially in refractory cases. With the advent of thrombopoietic agents in recent years (AMG 531 and eltrombopag), it is appropriate to re-evaluate the management and treatment of ITP. Ideally, treatment of ITP should be based on the underlying pathophysiology.

SUMMARY

Idiopatik trombositopenik purpura(ITP) medikal veya cerrahi olarak tedavi edilebilen bir hastalıktır.ITP genellikle selim gidişli bir hastalık olmasına karşın özellikle dirençli olgularda yüksek morbidite ve mortalite nedeni olmaktadır.Son yıllarda yeni trombopoietik ajanların(AMG 531 ve eltrombopag) kullanılması nedeniyle ITP'nin yeniden değerlendirilme ve tedavisi gereksinimi doğmuştur..ITP'nin ideal tedavisi altta yatan patolojiye yönelik olmalıdır.

BACKGROUND

Idiopathic thrombocytopenic purpura (ITP) is defined as the condition of having a low platelet count after the exclusion of other causes of thrombocytopenia and isolated thrombocytopenia [1]. In 1916, splenectomy was first used for the treatment of ITP, and in the 1950s corticosteroid therapy was introduced [2]. ITP is not rare in adults (annually, 1.6-3.3/100,000). While female gender is predominant in patients < 60 years of age, an equal gender distribution occurs in the elderly population [3]. ITP diagnosis can be established after a detailed differential diagnosis [1]. As the first-line therapy, oral prednisone or prednisolone, intravenous immunoglobulin (IVIG), or anti-D therapy is administrated [4-6]. If there is no response to first-line therapy, splenectomy is performed, and if splenectomy is not curative, rituximab, immunosuppressive agents, danazol, dapsone, immunoadsorption, and peripheral stem cell transplantation are considered [7-10]. Recently, thrombopoietic agents, such as AMG 531 and eltrombopag, have been introduced for the treatment of ITP [11,12].

PATHOPHYSİOLOGY

Platelet autoantibodies that damage platelets are thought to involve in the pathophysiology of ITP. The best characterized antigenic targets of these autoantibodies are glycoproteins located on the platelet surface (GpIIb-IIIa and GpIb/IX) [13]. However, these autoantibodies are detected in only 50% of patients, and the autoantibodies persist during remission [14]. Besides the fact that B lymphocytes are

involved in the formation of these autoantibodies, T lymphocytes reactive against GpIIb-IIIa are also activated; however, the reason is not clear [15]. In addition, an increase in the number of soluble interleukin-2 receptors and an increase in the Th1/Th2 ratio are well-known immunologic findings in ITP. Moreover, during acute ITP episodes, cell-mediated cytotoxicity against platelets has been demonstrated with an increase in cytotoxic T lymphocytes [16]. In healthy individuals, the presence of autoreactive T cells against GpIIb-IIIa supports the hypothesis that immunologic tolerance is impaired in patients with ITP [17]. In addition, an interaction between T and B lymphocytes is required for the activation of platelets, and the cellular interaction is mediated by an increase in CD40-CD40L. In patients with ITP, an increase in CD40 levels has been detected [18].

The spleen is not only the primary site of antibody production but also the primary site of IgG-coated platelet elimination. Therefore, splenectomy provides successful results in patients with refractory ITP. In addition, the antibodies which are generated against platelets reduce platelet formation by interacting with megakaryocyte development [19].

Table 1: Management of refractory ITP

Possible causes	Required investigations
Accessory spleen	Spleen scintigraphy, abdominal USG, MRI
Infection	EBV, CMV, HIV, HCV, HPV
Drugs (valproic acid, quinine)	Drug levels
Hematologic malignant diseases (CLL, lymphoma)	Peripheral smear, bone marrow aspiration, and cytogenetic analysis
Collagen tissue diseases (SLE)	ANA, dsDNA, p-ANCA, c-ANCA
Hemolytic diseases (MDS, PNH, TTP)	CD55, CD59, ADAMTS13 and inhibitors, peripheral smear, bone marrow, and FISH
Autoimmune hemolytic anemia and Evans syndrome	Reticulocyte count, Coombs tests
Hereditary thrombocytopenia	Family history, peripheral smear

USG: Ultrasonography; MRI: Magnetic resonance imaging; EBV: Epstein-Barr virus; CMV: Cytomegalovirus; HIV: Human immunodeficiency virus; HCV: Hepatitis C virus; HPV: Human papillomavirus; CLL: Chronic lymphocytic leukemia; SLE; Systemic lupus erythematosus; ANA: Antinuclear antibodies; dsDNA: Double-stranded DNA; p-ANCA: Protoplasmic-staining antineutrophil cytoplasmic antibodies; c-ANCA: Classical antineutrophil cytoplasmic antibodies; MDS; Myelodysplastic syndrome; PNH: Paroxysmal nocturnal hemoglobinuria; TTP: Thrombotic thrombocytopenic purpura; FISH: Fluorescence in situ hybridization.

THERAPEUTIC APPROACH

Prioritizing treatment of patients with ITP is important. As a general consensus, a platelet count < 20,000/L, a platelet count between 20,000 and 50,000/L with cutaneous and subcutaneous hemorrhage, or a need to maintain a platelet count > 50,000/L for a patient who will undergo splenectomy necessitates treatment to prevent a life-threatening hemorrhage. Patients with a platelet count < 20,000/L should be hospitalized before treatment. In patients with a platelet count < 5,000/L, treatment should be planned immediately, if focal hemorrhage is detected. In such emergent cases, platelet transfusions, IVIG, or a pulsed regimen of methylprednisolone can be administrated. Based on a meta-analysis, it has been shown that overall mortality due to ITP is increased with age, and the mortality rate among patients 40, 40-60, and > 60 years of age is 0.004, 0.012, and 0.130, respectively [20].

During first-step therapy, glucocorticoids are administered to patients at a dose of 1 mg/kg/day for 4 to 6 weeks, and thereafter are discontinued by a gradual taper in dose. In this step, a single or intermittent high dose of dexamethasone (40 mg/day) or anti-D therapy would be appropriate. As thrombocytopenia may recur after discontinuation of the drug, low-dose corticoid therapy may be extended for up to 1 year; however patients must be closely monitored for drug-related side effects [21]. It has been suggested that in patients with ITP, anti-D antibody binds to the fragment crystallizable receptors (FcRs) on macrophages in the spleen, and thereby decreases the destruction of platelets.

In general, the response rate is approximately 70% when a glucocorticoid dose of 50-75 µg/kg is administered [6]. However, several investigators have reported anti-D antibody administration leads to disseminated intravascular coagulation associated with acute hemoglobinemia or hemoglobinuria [22]. IVIG may be administered to patients with severe hemorrhage who are unresponsive to glucocorticoid therapy or as a pre-operative regimen for splenectomy. A number of mechanisms of action have been proposed for IVIG; these include a decrease in platelet degradation via blockade of FcγRII and FcγRIII, which are active in spleen cells and reticuloendothelial system (RES), elimination of pathogenic autoantibodies via competitive inhibition of

neonatal immunoglobulin FcR, and neutralization of autoantibodies (anti-idiotypic antibodies) [5,23]. Although the precise mechanism is not known, it is considered that IVIG and anti-D antibody exert their therapeutic effects via blockade of RES function and modulation of the immune system. The standard IVIG dose is 1 g/kg for 2 days.

Second-step therapy is classic or laparoscopic splenectomy in patients who do not respond to glucocorticoid therapy. Recently, despite the use of new therapeutic agents in the treatment of ITP, the importance of splenectomy in the treatment of ITP has been maintained [24]. The mortality rates of surgery are 1% and 0.2% for classic and laparoscopic splenectomies, respectively. In a recent systematic review, it was reported that 66% of patients who underwent splenectomy had a complete response, and that despite the increased risk for surgical complications (12.9%), splenectomy is a well-established treatment with high response rates, and without any alternative treatment regarding complete responses [7]. Approximately 30% of the patients who undergo splenectomy have an incomplete response and are diagnosed with chronic refractory ITP. The rate of patients unresponsive to splenectomy has been reported to be 34% [25].

REFRACTORY İMMUNE THROMBOCYTOPENİC PURPURA

While ITP is generally considered unresponsiveness to treatment in patients who undergo splenectomy, despite the other treatments in the context of this definition, a platelet count ≤ 20,000/L as a resistance may be added as well. Particularly in the elderly population, myelodysplastic syndrome should be excluded to establish the diagnosis of ITP as these two conditions are frequently confounded. Although the drugs leading to this condition such as heparin are well-defined, drugs like estrogen preparations and valproic acid should be investigated in patients with secondary ITP [26]. Furthermore, infections may lead to an exacerbation of thrombocytopenia in some chronic ITP patients. It has been shown that in patients with hepatitis C virus infections and human immunodeficiency virus (HIV)-induced thrombocytopenia, thrombocytopenia is resolved by the treatment of these conditions [27,28]. If there is a suspicion of HIV, PCR analysis should be performed when required. Besides, cytomegalovirus, Epstein-Barr virus, and parvovirus should be further investigated, which are the most frequently encountered pathogens in ITP [29]. In addition, Helicobacter pylori infection may be considered as a cause for refractory thrombocytopenia. It has been shown that eradication of H. pylori improves thrombocytopenia [30].

In addition, refractory thrombocytopenia is also encountered in immunodeficiency syndromes (variable immunodeficiency), immune hemolytic anemia and Evans syndrome. In some hematologic conditions (paroxysmal nocturnal hemoglobinuria and thrombotic thrombocytopenic purpura) or patients with malignancies (chronic lymphocytic leukemia), thrombocytopenia is resolved by the treatment of the underlying primary disease.

TREATMENT IN REFRACTORY IMMUNE THROMBOCYTOPENIC PURPURA

If the platelet count remains low after splenectomy, patients should be investigated for the presence of an accessory spleen (Table 1). If the scan for an accessory spleen is negative, further investigations as specified in Table 1 should be performed. If the refractory ITP persists after all the probable causes are eliminated, third-line therapies (azathioprine, mycophenolate mofetil, vinca alkaloids, cyclosporine A, dapsone, danazol, cyclophosphamide, and immunoadsorbents) should be planned. On the other hand, chronic low-dose glucocorticoids, IVIG, and anti-D antibody infusions (repeated more than once) may be repeated after the splenectomy. During this period, if there is no response to the treatment, rituximab and thrombopoietin receptor agonists may be used for treatment

Rituximab is a monoclonal anti-CD20 antibody and was first used for the treatment of hematologic malignancies, B-cell lymphomas in particular. Rituximab has been used in patients with refractory ITP and has been reported to be efficient. Preliminary data has shown that approximately one-third of the patients treated with rituximab achieve a complete response and remission persists for > 1 year [9]. In a systematic review of the efficacy and safety of rituximab, complete remission was reported to be 46.3% [31]. In another study, the patients with chronic ITP who did or did not undergo splenectomy received rituximab, and in both conditions the initial response was 60% (25%-75%), while the long-term response was 15%-20% [32]. This treatment is quite expensive and the long-term results are overestimated.

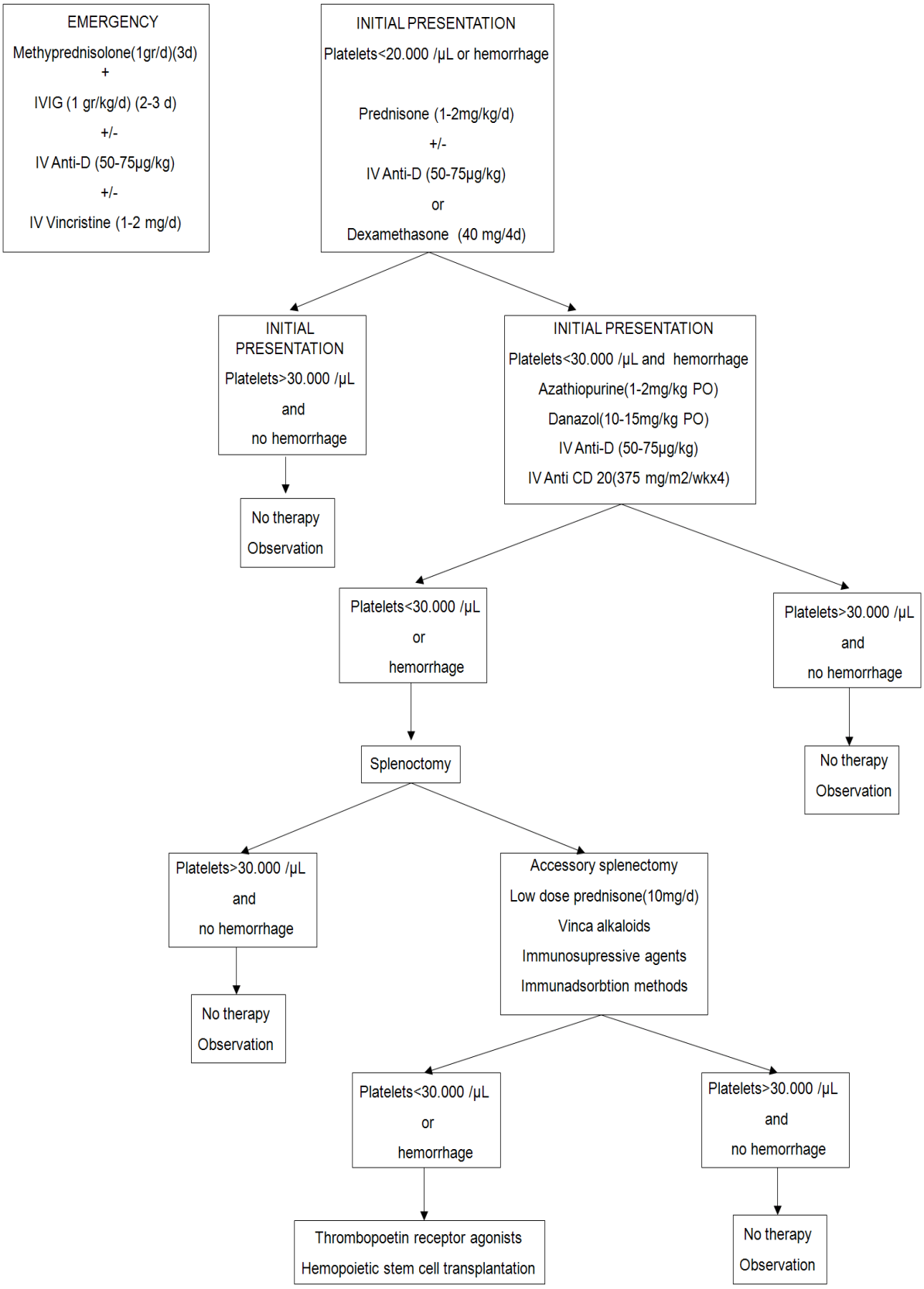

Figure 1: Treatment algorithm for management of adult ITP.

Table 2: Characteristics of thrombopoietin receptor agonists

	Romiplostim	Eltrombopag
Route of administration	IV, SC	Oral
Dosage	1-3 µg/kg	50-75 mg
Side effects		
- Elevated risk for hematologic malignancy	+	-
- Rebound thrombocytopenia	+	+
- Elevated reticulocyte count	+	-
- Thrombosis	+,-	+,-

IV: Intravenous; SC: Subcutaneous.

In patients with refractory ITP, it has been reported that if there is a response to a single agent, concomitant use of more than one drug leads to a greater response [33]. In 35 patients with ITP who had previously been refractory to single agent therapy, IVIG (1 g/kg), IV methylprednisolone (30 mg/kg), vinca alkaloids (0.03 mg/kg), and/or anti-D antibody (50-75 µg/kg) were given as acute induction therapy and a response rate of 71% was observed; 18 of these patients received oral danazol (10-15 mg/kg) and azathioprine (2 mg/kg) as maintenance therapy. During maintenance therapy, two-thirds of cases were responsive and there were no reported serious toxicities.

The use of thrombopoietin receptor agonists (TPO) in patients with ITP arose from the hypothesis that the autoantibodies against platelets induce apoptosis in megakaryocytes via binding to glycoprotein complexes located on megakaryocytes, and thus thrombopoietin levels is markedly reduced resulting in the inhibition of platelet formation [34]. In one of the first studies involving first-generation thrombopoietic growth factors (unmodified recombinant human TPO rHuTPO-pegylated recombinant human megakaryocyte growth and development factor PEG-rHuMGDF), platelet counts were improved in 4 of 5 patients; in another study, severe refractory thrombocytopenia in 13 of 538 healthy individuals occurred [35,36].

A recent breakthrough in ITP treatment is second-generation thrombopoietic growth factors. Romiplostim, which was formerly called AMG 531, is a TPO peptide agonist. One study in Europe and one study in the US have been conducted with romiplostim. In the European study (phase 1-2), 13 patients achieved an increase in platelet count by 73% with a dose of 1-10 µg/kg [11]. In the study conducted in the USA (phase 2), 75% of 16 patients achieved a platelet response [37]. The outcomes were similar for each of these studies. While romiplostim is administrated subcutaneously weekly, another second-generation TPO agonist, eltrombopag, is administered orally daily. In a multicenter, placebo-controlled study on 118 patients with ITP who received 50 and 75 mg of eltrombopag during an average period of 43 days, a response of 75%-81% was reported [12]. In 2 parallel trials, efficacy of romiplostim as measured by a persistence of high platelet count during 6 or more of the last 8 weeks of treatment was investigated in splenectomized and non-splenectomized patients with ITP, and the persistence was 38% in splenectomized patients and 61% in non-splenectomized patients [38]. Currently, there are ongoing studies being carried out on long-term administration of romiplostim and eltrombopag, but no data have been published. Although both drugs are generally considered well-tolerated, there are reported side effects, including thrombosis, formation of autoantibodies, hematologic malignant cell stimulation, an increase in reticulin or collagen levels in bone marrow, and stem cell depletion [39] (Table 2). In patients with refractory ITP, a curative therapy model can be constructed after obtaining the long-term results of the ongoing studies. However, further studies with different patient populations (splenectomized and non-splenectomized) are warranted to achieve a persistent effect following discontinuation of the drug.

KAYNAKLAR

1. George JN, Woolf SH, Raskob GE, et al. Idiopathic thrombocytopenic purpura: a practical guideline developed by explicit methods for the American Society of Hematology. Blood 1996;88:3-40.
2. Bethel FH, Meyers MC, Millers S, et al. Effects of ACTH and cortisone on idiopathic thrombocytopenic purpura. Trans Assoc Am Physicians 1951;64:199-203.
3. Frederiksen H, Schmidt K. The incidence of idiopathic thrombocytopenic purpura in adults increases with age. Blood 1999;94:909-913.
4. Stasi R, Provan D. Management of immun thrombocytopenic purpura in adults. Mayo Clinic Proc 2004;79:504-522.
5. Lazarus AH, Crow AR. Mechanism of action of IVIG and Anti-D in ITP. Transfus Apher Sci 2003;28:249-255.
6. Scaradavuo A, Woo B, Woloski BM,et al. Intravenous Anti-D treatment of immun thrombocytopenic purpura: experience in 272 patients. Blood 1997;89:2689-2700.
7. Kojouri K, Vesely SK, Terrell DR,et el. Splenectomy for adult patients with idiopathic thrombocytopenic purpura: A systematic review to assess long-term platelet count responses, prediction of response and surgical complications. Blood 2004;104:2623-2634.
8. Stasi R, Stipa E, Masi M,et al. Long-term observation of 208 adults with chronic idiopathic thrombocytopenic purpura. Am J Med 1995;98:436-442.
9. Cooper N, Stasi R, Cunningham-Rundles S, et al. The efficacy and safety of B-cell depletion with anti-CD20 monoclonal antibody in adults with chronic immun thrombocytopenic purpura.Br J Haematol 2004;125:232-239.
10. Bilgir O, Bilgir F, Calan M,et al. Immunoabsorption method using immunoglobulin Adsopak in adult cases with ITP resistant to splenectomy and other medical therapies. Transfus Apher Sci 2008;39:109-113.
11. Newland A, Caulier MT, Kappers-Klunne M,et al. An open label, unit dose-finding study of AMG 531, a novel thrombopoiesis-stimulating peptibody, in patients with immun thrombocytopenic purpura.Br J Haematol 2006;135:547-553.
12. Bussel JB, Cheng G, Saleh MN,et el. Eltrombopag for the treatment of chronic idiopathic purpura NEJM 2007;357:2237-2247.
13. McMillan R, Wang L, Tani P, Prospective evaluation of the immunobead assay for the diagnosis of adult chronic immune thrombocytopenic purpura (ITP). J Thromb Haemost 2003;1:485-491.
14. Stockelberg D, Hou M, Jacobsson S,et al. Detection of platelet antibodies in chronic idiopathic thrombocytopenic purpura (ITP). A comparative study using flow cytometry, a whole platelet ELISA, and an antigen capture ELISA. Eur J Haematol 1996;56:72-77.
15. Kuwana M, Kaburaki J, Kitasato H,et al. Immunodominant epitopes on glycoprotein IIb-IIIa recognized by autoreactive T cells in patients with immune thrombocytopenic purpura.Blood 2001;98:130-139.
16. Olsson B, Andersson PO, Jernas M,et al. T-cell-mediated cytotoxicity toward platelets in chronic idiopathic thrombocytopenic purpura. Nature Med 2003;1123-1124.
17. Filion MC, Proulx C, Bradly AJ,et al. Presence in peripheral blood of healthy individuals of autoreactive T cells to a membran antigen present on bone marrow-derived cells.Blood 1996;88:2144-2150.
18. 18. Solanilla A, Pasquet JM, Viallard JF,et al. Platelet-associated CD154in immune thrombocytopenic purpura. Blood 2005;105:215-218.
19. Chang M, Nakagawa PA, Williams SA,et al. Immune thrombocytopenic purpura (ITP) plasma and purified ITP monoclonal autoantibodies inhibit megakaryocytopoiesis in vitro. Blood 2003;102:887-895.
20. Cohen YC, Djulbegovic B, Shamai-Lubovitz O,et al. The bleeding risk and natural history of idiopathic thrombocytopenic purpura in patients with persistant low platelet counts Arch Intern Med 2000;160:1630-1638.
21. Schiavotto C, Rodeghiero F. Twenty years experience with treatment of idiopathic thrombocytopenic purpura in a single department: Results in 490 cases. Haematologica 1993;78:22-28.
22. Gaines AR. Disseminated intravascular coagulation associated with acute hemoglobinemia or hemoglobinuria following Rh(0) (D) immune globulin intravenous administration for immune thrombocytopenic purpura. Blood 2005;106:1532-1537.
23. Crow AR, Lazarus AH. The mechanisms of action of intravenous immunoglobulin and polyclonal anti-D immunoglobulin in the amelioration of immune thrombocytopenic purpura: what do we really now? Transfus Med Rev.2008;22(2):103-116.
24. Rodeghiero F, Ruggeri M. Is splenectomy still the gold standard for the treatment of chronic ITP? Am J Hematol.2008;83:91.
25. Schwartz J, Leber MD, Gillis S, et al. Long-term follow-up after splenectomy performed for immune thrombocytopenic purpura (ITP).Am J Hematol.2003;72:94-98.
26. Onel K, Bussel JB. Adverse effects of estrogen therapy in a subset of women with ITP J Thromb Haemostasis 2004;2:670-671.

27. Kaslow RA, Phair JP, Friedman HB, et al. Infection with the human ımmunodeficiency virus:clinical manifestations and their relationship to immune deficiency. A report from the Multicenter AIDS Cohort Study.Ann Intern Med 1987;107:474-480.
28. McHutchison JK, Dusheiko G, Shiffman ML,et al. Eltrombopag for thrombocytopenia in patients with cirrhosis associated with hepatitis C.NEJM 2007;357:2227-2236.
29. Levy AS, Bussel JB. Immune thrombocytopenic purpura: investigation of the role of cytomegalovirus infection. Br J Haematol.2004;126:622-623.
30. Kuwana M, Ikeda Y. Helicobacter pylori and immun thrombocytopenic purpura: unsolved questions and controversies. Int J Hematol.2006;84:309-315.
31. Arnold D, Dentali F, Crowther M,et al. Systematic review: efficacy and safety of rituximab for adults with idiopathic thrombocytopenic purpura.Ann Intern Med.2007;146:25-33.
32. Godeau B, Fain O, Porcher R,et al. Rituximab is an alternative to splenectomy in adults with chronic immune thrombocytopenic purpura: Results of a multicenter prospective phase 2 study. Blood 2006;108:Abstract 478.
33. Boruchov DM, Gururangan S, Driscoll MC et al. Multiagent induction and maintenance therapy for patients with refractory immune thrombocytopenic purpura (ITP) Blood 2007;110:3526-3531.
34. McMillan R, Wang L, Tomer A,et al. Suppression of in vitro megakaryocyte production by antiplatelet autoantibodies from adult patients with chronic ITP. Blood 2004;103:1364-1369.
35. Nomura S, Dan K, Hotta T, et al. Effect of pegylated recombinant human megakaryocyte growth and development factor in patients with idiopathic thrombocytopenic purpura. Blood 2002;100:728-730.
36. Li J, Yang C, Xia Y,et al. Thrombocytopenia caused by the development of antibodies to thrombopoietin. Blood 2001;98:3241-3248.
37. Bussel JB, Kuter DJ, George JN,et al. AMG 531 a thrombopoiesis-stimulating protein, for chronic ITP. NEJM 2006;355:1672-1681.
38. Kuter DJ, Bussel JB, Lyons RM et al. Efficacy of romiplostim in patients with immune thrombocytopenic purpura: a double-blind randomised controlled trial. Lancet 2008;371:395-403.
39. Kuter DJ. New thrombopoietic growth factors.Blood 2007;109:4607-4616.