CODEN [USA]: IAJPBB ISSN : 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

SJIF Impact Factor: 7.187
https://doi.org/10.5281/zenodo.7565603

Available online at: http://www.iajps.com *Review Article*

A REVIEW ON TREATMENT OF PRIMARY IMMUNE THROMBOCYTOPENIA

J.S. Venkatesh[1], Mr.Vinuth Chikkamath[2], Mahin M G[3*], Neethu Samuel[4*], Nimmy Babu[5*]and Nimmy P George[6*]

[1]Professor, Head, Department of Pharmacy Practice,
S.C.S College of Pharmacy, Harapanahalli

[2]Lecturer, Department of Pharmacology, S.C.S College of Pharmacy, Harapanahalli

[3-6]Pharm D Interns, CG Hospital, Davangere Department of Pharmacy Practice,
S.C.S College of Pharmacy, Harapanahalli

Article Received: December 2022 **Accepted:** December 2022 **Published:** January 2023

Abstract:

An autoimmune disease called immune thrombocytopenic purpura (ITP) affects roughly 1 in 10,000 people worldwide. A platelet count of less than 100 x 109L has historically been used to describe it, however symptoms are more often used to guide treatment than the actual platelet count. Corticosteroids have traditionally been the first line of treatment for patients with primary idiopathic ITP, with intravenous immune globulin (IVIG) or Rho(D) immune globulin (anti-RhD) being added for steroid-resistant instances. Second-line treatment options for ITP include splenectomy or rituximab, a monoclonal antibody that targets the CD20 antigen (anti-CD20).. The diagnosis of "chronic refractory ITP" is warranted in patients who continue to experience severe thrombocytopenia and symptomatic bleeding despite first- and second-line therapies, and third-line therapies are considered.

Corresponding author:

J.S. Venkatesh,
Professor, Head, Department of Pharmacy Practice,
S.C.S College of Pharmacy, Harapanahalli

QR code

Please cite this article in press J.S. Venkatesh et al, ***A Review On Treatment Of Primary Immune Thrombocytopenia.,*** *Indo Am. J. P. Sci, 2023; 10(01).*

INTRODUCTION:

A low platelet count of fewer than 100 x 10^9 L is a haematological symptom of immune thrombocytopenia (ITP), also known as idiopathic thrombocytopenia. Autoantibodies to glycoproteins expressed on megakaryocytes, the progenitor cell to platelets, are primarily responsible for this platelet deficiency, which can also be brought on by decreased synthesis, immune-mediated destruction, or an increase in splenic sequestration of platelets [1]. ITP symptoms can vary, but they frequently mirror those of thrombocytopenia generally, including petechiae, purpura, mucosal bleeding like epistaxis, and in the most serious circumstances, deadly cerebral haemorrhage [2]. In 80% of instances, ITP is idiopathic, and primary ITP is frequently thought of as an autoimmune disorder [3].However, 20% of ITP cases may manifest as a result of other disorders [2]. ITP, for instance, is frequently observed after infection. Two-thirds of ITP cases in children, who make up half of all cases diagnosed each year, are preceded by a fever infectious illness [3,4]. ITP has been linked to specific cases of Helicobacter pylori, cytomegalovirus, varicella-zoster virus, hepatitis C virus, and human immunodeficiency virus. ITP has also been associated to several other autoimmune and rheumatologic diseases, including chronic lymphocytic leukaemia (CLL), which affects 1-5% of CLL patients [3].ITP has a broad and complex epidemiology. Adults with primary ITP had a prevalence of 9.5:100,000 and an annual incidence of 3.3:100,000 [2]. Although there are many different clinical presentations, bleeding is the most common sign, and the intensity of presentation can range from asymptomatic to intractable bleeding. Acute presentations last less than three months, persistent presentations last between three and twelve months, and chronic presentations last longer than twelve months [3].Childhood ITP often resolves on its own, hence the treatment parameters outlined below are typically only used for primary ITP, while secondary ITP care is depending on the underlying condition [4]. However, some of the recommendations for primary ITP can be utilised to stabilise the patient in severe and resistant cases of secondary ITP while therapy for the underlying illness is started [5]. Those with symptomatic ITP are often the only ones who receive treatment. Although this varies from person to person, the objective is to reach a hemostatic platelet count, which is usually between 20 and 30 x10 ^{9}L. The 1996 American Society of Hematology (ASH) evidence-based practise guidelines for managing ITP state that any newly diagnosed patients who have platelets less than 30 x 10^9 L should get treatment. According to the 2011 recommendations, this objective threshold is still a helpful value, but whether or not to treat should ultimately depend on the patient's preferences, the severity of their symptoms, and any potential for bleeding [6].

FIRST LINE TREATMENTS

Corticosteroids are the main treatment for ITP in adults. Prednisone and dexamethasone have been demonstrated to alter B-cell and dendritic cell activation, resulting in a reduction in the immune system's ability to destroy platelets [2]. Up to 80% of patients benefit with steroid treatment, however many of them relapse after the medication is tapered off. Prednisone has long been the cornerstone of therapy, often 1 mg/kg/d for two to four weeks, but several recent trials have indicated that high dose dexamethasone is much more beneficial. A single short course of dexamethasone, 40 mg per day for four days, resulted in a stable platelet count greater than 50 x 10^9/L in 50% of responders, and this level remained stable six months later, according to a study conducted in Hong Kong on 125 patients with initial platelet counts of less than 20 x 10^9/L [7].Additionally, a number of Italian studies demonstrated that four to six cycles of dexamethasone administered every two weeks resulted in a response rate of 80 to 90% after 15 months [8]. According to a retrospective analysis of 100 patients, high-dose dexamethasone had a response rate of 42.7% compared to 28.4% for prednisone [9]. Similar outcomes were seen in a prospective trial involving 26 patients. Although both prednisone and dexamethasone had 100% initial response rates (platelet count > 50 x 109 per litre), long-term remission was significantly more common with pulsed dexamethasone (77% vs. 22% with daily prednisone) [10]. For ITP patients who are pregnant and require treatment, corticosteroids are regarded as safe [6]. It is undeniable that corticosteroids, more specifically high-dose dexamethasone, are a successful first-line therapy for ITP. Although certain individuals may have issues with the corticosteroid adverse effect profile, which includes weight gain, hypertension, and diabetes, corticosteroids are still an usually safe and simple treatment, making them a viable first-line option [11]. Intravenous immunoglobulin (IVIG) or Rho (D) immune globulin (anti-RhD) can be utilised to boost the therapeutic impact in steroid-resistant patients. Additionally, these two therapies can be used to patients in cases where corticosteroids are not advised [6]. In addition, IVIG is recommended when platelet counts need to rise quickly, such as when there is current bleeding that is severe, and it can be used with corticosteroids in some patients. The usual dosage is an infusion of 1 g/kg/day over one to two days, though regimens can change depending on the

doctor's preference [12]. In a trial of 19 patients with chronic ITP, there was a 75% response rate to IVIG, with active bleeding stopping if IVIG was given within 12 hours of active bleeding and platelet counts rising in 53% of patients within an hour [13]. Following IVIG, a review of 28 trials revealed that 64% of patients had peak platelet counts >100,000/mm3 and 83% had peak platelet counts >50,000/mm3 [14]. However, long-lasting remission is rare. Additionally, IVIG is costly and has side effects such allergy, renal failure, and pulmonary insufficiency [4]. When used with corticosteroids, anti-RhD can be helpful for patients who are RhD positive. One study claims a patient efficacy of 50–70%, whereas other studies report a patient efficacy of 37% [11,12].However, some individuals have reported side symptoms like severe hemolysis, nausea, fever, and headaches, therefore caution should be exercised [11,12].

SECOND LINE TREATMENTS

Splenectomy, or the removal of the spleen to reduce splenic sequestration of platelets, has traditionally been the second-line treatment for patients who do not respond to initial medication and do not experience complete remission, which occurs in up to 70%–90% of individuals [15]. In fact, the ASH 2011 guidelines still suggest splenectomy as the next line of treatment after corticosteroids, IVIG, and anti-RhD fail to induce remission [6]. Theoretically, a splenectomy could stop the spleen from prematurely destroying the defective platelets in people with ITP. According to some research, there is a 60–70% long-term response rate and a 6–70% complete response (defined as the absence of substantial bleeding.[12,16,17]. According to a retrospective research, 60% of patients experienced long-lasting remission after splenectomy [11]. Eighty eight percent of patients in a retrospective analysis of 174 patients had an excellent response to medication, although 20 percent of those patients relapsed. The study also discovered that patients who were younger and dependent on corticosteroids appeared to have a higher chance of responding to splenectomy [18]. In children with ITP, splenectomy is typically postponed as long as feasible because the majority of cases recover on their own and because the infection with encapsulated bacteria after splenectomy tends to be severe. Surgery is still an option, though, in situations that are severe and symptomatic and persist for more than a year. Children had similar response rates to adults, with complete remission occurring in 70–80% of cases [4]. Splenectomy procedures can be done laparoscopically or openly. The two response rates are comparable. Although laparoscopic surgery takes longer to perform, it often results in shorter hospital stays, less post-operative pain, and quicker recovery times [19]. Even in patients with extremely low platelet counts, splenectomy has been demonstrated to be safe, and prophylactic platelet infusion is typically not recommended [20]. Splenectomy hazards include those related to the procedure itself, infections, bleeding, thrombosis, and relapse[12]. One novel approach for the treatment of chronic and persistent ITP is rituximab, a monoclonal antibody against the CD20 antigen (anti-CD20). Rituximab is often administered intravenously (IV) at a dose of 375 mg/m2/week for four weeks to treat ITP [5]. The effectiveness of splenectomy and rituximab in treating ITP has been compared in numerous studies. When compared to the rituximab group, the splenectomy group had better outcomes in one retrospective trial of 105 patients with primary ITP, with full response rates of 82.8% versus 39.5% at three months and 81.0% versus 35.9% at 12 months, respectively [21]. There was no discernible difference in the response rate between patients who underwent splenectomy versus rituximab therapy, according to a quasiexperimental analysis of 143 patients [22].According to a retrospective analysis of 222 patients conducted in the United States, those who underwent splenectomy had a higher five-year relapse-free rate than those who received rituximab, at 53.7% versus 14.96%, respectively [15]. According to one study, 50% of patients experienced an initial response to rituximab, which was maintained in 20% of cases after five years and lasted at least six months in 30% of cases [2]. In another study, rituximab and high-dose dexamethasone were discussed as an alternative first-line treatment for ITP. It was found that the combination had higher remission rates than monotherapy, 63% versus 35% at six months and 53% versus 33% at one year. This rise in remission was, however, accompanied with a rise in the frequency of severe toxicity.The effectiveness of rituximab used alone was also discussed in this study, which noted initial response rates of 40–60% with a sustained response rate of 20–% at five years [5]. Rituximab can cause infusion responses, serum sickness, and cardiac arrhythmias in the short term [12]. According to a review of many research, 3.7% of patients had serious events, 2.9% of patients died, and 21.6% of patients experienced mild or moderate adverse effects, usually infusion responses. This implies that rituximab is a potentially harmful medication and should only be taken under strict supervision [23]. These studies also demonstrate that, despite rituximab's promise as a new treatment, patients who can tolerate splenectomy still benefit from it more. Rituximab is still a viable treatment for people for whom splenectomy is not

appropriate, as well as for kids with persistent and severe ITP [6].

THIRD LINE THERAPY

"Chronic refractory ITP" is the term used to describe patients who fail first-line therapy and continue to show no improvement following splenectomy [4]. Only when there is a serious bleeding danger are these individuals treated. Although long-term use of corticosteroids is uncomfortable because to the numerous side effects discussed above, many of these individuals are retreated with prednisone [4]. The range of treatments for chronic refractory ITP has increased in recent years as a result of the release of numerous new medications. Additionally, in people for whom splenectomy is contraindicated or has a higher risk, such as children and pregnant patients, these medications may be an option. There is evidence of platelet response following treatment with azathioprine, cyclophosphamide, cyclosporin A, danazol, dapsone, mycophenolate mofetil, vinblastine, vincristine, and the TPO-RA medications eltrombopag and romiplostim [6]. Studies are still ongoing. Unless specified, side effects from these treatments were generally manageable. Before any impartial assessment of efficacy can be made, results from several of these trials should be redone due to their age and small sample sizes.

Azathioprine

Chronic refractory ITP has been shown to respond well to azathioprine doses of 150mg/day [24,25]. A six-month retrospective analysis found a response rate of 71.4%, with 38% of patients experiencing a full recovery [24]. A 64% response was seen in a prospective analysis of 53 individuals, and 40% of those responses persisted after a year [25]. According to a French study, response rates were 40%, with 29% of those remaining responsive after stopping azathioprine [26]. Only 2% of patients in a second retrospective trial of 96 patients had a durable response to azathioprine, while 54% of patients responded to the drug [11]. Alopecia, gastrointestinal issues, leukopenia, transaminase elevations, and an elevated risk of cancer, notably lymphoma, were also noted [24,25].However, because many of these studies had small sample sizes, more research is required to confirm the efficacy and safety of azathioprine.

Cyclophosphamide

A 65% complete response was seen in a prospective study of 20 patients receiving high-dose pulsed IV cyclophosphamide. Neutropenia was the most typical adverse reaction, but acute deep vein thromboses and a psoas abscess were also reported [27]. A full response was documented in 55% of individuals with refractory ITP following splenectomy and in 50% of patients who had not undergone a splenectomy in another prospective analysis of 30 patients [28].

Cyclosporine A

Cyclosporin A was found to be efficient in a retrospective analysis of 30 children under the age of 18, showing a 57% complete response rate and a 23% maintained response after the end of therapy. Hirsutism was one of the side effects, however it was usually mild and treatable [29].

Danazolin

A prospective trial of 47 patients with persistent ITP and refractory disease following splenectomy found that danazol therapy resulted in a 22% response rate. A smaller prospective research with nine patients found an 11% response, and 67% of patients experienced adverse symptoms like weight gain, arthralgias, headaches, rashes, amenorrhea, breast soreness, and weakness [30]. A third prospective analysis of 10 patients with refractory ITP found that only 10% of patients experienced a temporary increase in platelets, while 60% of patients experienced side effects.

Dapsone

Dapsone was shown to have a 49% response rate and 41% complete response in a retrospective analysis of 38 individuals (including 12 children), however sustained response after six months was only seen in 5% of patients (alladults). In 13% of those patients, there were side effects, and 5% of those patients had to stop taking the medication because of skin rashes [32]. Another retrospective analysis of 42 patients had a response rate of 55%, with a full response in 38% of patients. Skin rash, methemoglobinemia, sulfa allergy, neuropathy, and other side events were recorded in 31% of patients, with 22% of those needing drug discontinuation [33].

Mycophenolate Mofetil

An 80% response with a 45% complete response rate was seen after therapy in a prospective study of 20 patients with refractory ITP [34]. A 62% response rate with a 24% complete response was found in another prospective study of 21 individuals. 14% of the participants in this trial experienced minor diarrhoea and nausea [35]. Retrospective analysis of 46 patients revealed a response rate of 52% with a full response rate of 33%. In this study, 8% of the patients reported experiencing nausea, vomiting, abdominal discomfort, or myalgias [36].

Vinblastine

A 13% response to continuous IV vinblastine was reported in a prospective investigation of 13 individuals [26]. Another prospective research of 43 ITP patients revealed a 53% complete response to slow IV vinblastine infusion in individuals with acute ITP and a 32% response maintenance following one-to two-year follow-up. 17% of patients with chronic ITP experienced a full recovery that lasted for at least six months [37]. A third prospective research with 16 patients found that 67% of the patients responded, and 17% had a complete recovery [38]. Vinblastine side effects included peripheral neuropathy and leukopenia [37].

Vincristine

A slow-infusion of vincristine was found to be beneficial for 70% of the 24 patients in a prospective study with refractory ITP [39]. In a later prospective study with 10 patients, the response rate was 72% [40]. In a more recent research, vincristine treatment for refractory thrombocytopenia caused by ITP, autoimmune hemolytic anaemia, and Evan's syndrome resulted in a 100% response rate and a 60% complete remission [41]. A retrospective analysis of 62 patients found that vincristine therapy resulted in a 75% response after two months and a 51% response retention after a year [42]. Another retrospective analysis revealed a 20% sustained response rate after two years and an initial response rate of 86% [43]. One of the often mentioned side effects is peripheral neuropathy [20,43].

Thrombopoietin receptor Agonists (TPO-RA)

The introduction of thrombopoietin receptor agonists is one of the most recent clinical advancements that has altered the landscape of chronic resistant ITP therapy (TPO-RA). Eltrombopag, a naphthalenesulfonic acid that also enhances platelet synthesis, and romiplostim, an Fc peptide fusion peptibody that stimulates megakaryopoiesis, are the two medications that are utilised the most frequently [44]. Eltrombopag is licenced for use in children with chronic ITP, whereas romiplostim is approved by the US Food and Drug Administration (FDA) for use in adults. To investigate this novel treatment, several research have been carried out. Eltrombopag significantly increased platelet counts with a relative risk of 3.4 compared to untreated groups, and it significantly decreased the incidence of bleeding with a relative risk of 0.56, according to a recent meta-analysis that looked at the drug's effects on chronic ITP in adults and children. The results also showed that ITP required fewer later rescue treatments [45]. A long-term, single-arm, open-label study of 292 people with chronic ITP found that romiplostim helped maintain a platelet count between 50 and 200 x 10^9/L on average and that 95% of patients at least once saw a platelet response greater than 50 x 10 ^{9}/L [46]. A platelet response of greater than 50 x 109/L was initially observed in 74% of patients and was maintained two years later in 65% of patients in a long-term study of 80 patients with chronic ITP treated with romiplostim [47]. Romiplostim produced a 78% response in a retrospective study of 52 patients, however none of the patients had a sustained response [11]. In a prospective study of 70 patients, 93% of those who received romiplostim experienced a peak platelet count greater than 50 x 109/L, with 32% experiencing remission after 24 weeks [48]. These new medicines' side effect profile is still up for debate. Minor side effects like headaches, nasopharyngitis, upper respiratory infections, and exhaustion are mentioned in some cases, while more severe adverse events like hepatotoxicity, arthralgias, visual abnormalities, and severe exhaustion have also been mentioned [49]. Studies are now being undertaken to determine the effects of spleen tyrosine kinase inhibitors (Syk inhibitors) such as fostamatinib, anti-CD40 ligand, antihuman CD16 (FcRIII) monoclonal antibody (GMA161), daclizumab, alemtuzumab, and avatrombopag on chronic disease. ITP that is resistant to treatment, with a greater rate of total and long-lasting remission and few side effects [5,44].

CONCLUSION:

ITP treatment is complicated and should be tackled gradually. We conducted a thorough literature search and discovered that corticosteroid usage is still the best first-line treatment for ITP. Switching to or supplementing corticosteroids with IVIG or anti-RhD demonstrated comparable high response rates in patients with steroid-refractory ITP. The use of rituximab or a splenectomy are examples of second-line treatments. Although many patients respond to the conventional first- and second-line medications, the need for new and better treatment alternatives is still present due to chronic and refractory situations. Although a number of therapy alternatives have been discussed above, a third line treatment that is both widely acceptable and successful is still lacking in current clinical practise. In the interim, the doctor's decision for third-line therapy may be influenced by patient- and institution-specific circumstances.

REFERENCES:

1. Kistangari G, McCrae KR: Immune thrombocytopenia. Hematol Oncol Clin North Am. 2013, 27:495-520. 10.1016/j.hoc.2013.03.001

2. Zufferey A, Kapur R, Semple JW: Pathogenesis and therapeutic mechanisms in immune thrombocytopenia (ITP). J Clin Med. 2017, 6:16. 10.3390/jcm6020016
3. Cines DB, Bussel JB, Liebman HA, Luning Prak ET: The ITP syndrome: pathogenic and clinical diversity . Blood. 2009, 113:6511-6521. 10.1182/blood-2009-01-129155
4. Cines DB, Blanchette VS: Immune thrombocytopenic purpura. N Engl J Med. 2002, 346:995-1008. 10.1056/NEJMra010501
5. Lambert MP, Gernsheimer TB: Clinical updates in adult immune thrombocytopenia . Blood. 2017, 129:2829- 2835. 10.1182/blood-2017-03-754119
6. Neunert C, Lim W, Crowther M, Cohen A, Solberg L, Jr., Crowther MA: The American Society of Hematology 2011 evidence-based practice guideline for immune thrombocytopenia. Blood. 2011, 117:4190-4207. 10.1182/blood-2010-08-302984
7. Cheng Y, Wong RS, Soo YO, et al.: Initial treatment of immune thrombocytopenic purpura with high-dose dexamethasone. N Engl J Med. 2003, 349:831-836. 10.1056/NEJMoa030254
8. Mazzucconi MG, Fazi P, Bernasconi S, et al.: Therapy with high-dose dexamethasone (HD-DXM) in previously untreated patients affected by idiopathic thrombocytopenic purpura: A GIMEMA experience. Blood. 2007, 109:1401-1407. 10.1182/blood-2005-12-015222
9. Sakamoto K, Nakasone H, Tsurumi S, et al.: Prednisone versus high-dose dexamethasone for untreated primary immune thrombocytopenia. A retrospective study of the Japan Hematology & Oncology Clinical Study Group. J Thromb Thrombolysis. 2014, 37:279-286. 10.1007/s11239-013-0939-3
10. Matschke J, Muller-Beissenhirtz H, Novotny J, et al.: A randomized trial of daily prednisone versus pulsed dexamethasone in treatment-naive adult patients with immune thrombocytopenia: EIS 2002 study. Acta Haematol. 2016, 136:101-107. 10.1159/000445420
11. Depre F, Aboud N, Mayer B, Salama A: Efficacy and tolerability of old and new drugs used in the treatment of immune thrombocytopenia: results from a long-term observation in clinical practice. PLoS One. 2018, 13:0198184. 10.1371/journal.pone.0198184
12. Nomura S: Advances in diagnosis and treatments for immune thrombocytopenia . Clin Med Insights Blood Disord. 2016, 9:15-22. 10.4137/CMBD.S39643
13. Mayer B, Depre F, Ringel F, Salama A: New aspects on the efficacy of high-dose intravenous immunoglobulins in patients with autoimmune thrombocytopenia. Vox Sang. 2017, 112:64-69. 10.1111/vox.12467
14. Bussel JB, Pham LC: Intravenous treatment with gammaglobulin in adults with immune thrombocytopenic purpura: review of the literature. Vox Sang. 1987, 52:206-211. 10.1111/j.1423-0410.1987.tb03029.x
15. Hammond WA, Rodriguez EM, Li Z, Dholaria B, Shreders A, Vishnu P, Rivera CE: Splenectomy or rituximab in steroid-refractory immune thrombocytopenia (ITP): the Mayo Clinic experience. Blood. 2016, 128:3735- 3735.
16. Rodeghiero F, Michel M, Gernsheimer T, et al.: Standardization of bleeding assessment in immune thrombocytopenia: report from the International Working Group. Blood. 2013, 121:2596-2606. 10.1182/blood-2012-07-442392
17. Vianelli N, Galli M, de Vivo A, et al.: Efficacy and safety of splenectomy in immune thrombocytopenic purpura: long-term results of 402 cases. Haematologica. 2005, 90:72-77.
18. Guan Y, Wang S, Xue F, Liu X, Zhang L, Li H, Yang R: Long-term results of splenectomy in adult chronic immune thrombocytopenia. Eur J Haematol. 2017, 98:235-241. 10.1111/ejh.12821
19. Cordera F, Long KH, Nagorney DM, McMurtry EK, Schleck C, Ilstrup D, Donohue JH: Open versus laparoscopic splenectomy for idiopathic thrombocytopenic purpura: clinical and economic analysis. Surgery. 2003, 134:45-52. 10.1067/msy.2003.204
20. Cines DB, McMillan R: Management of adult idiopathic thrombocytopenic purpura. Annu Rev Med. 2005, 56:425-442. 10.1146/annurev.med.56.082103.104644
21. Moulis G, Sailler L, Sommet A, Lapeyre-Mestre M, Derumeaux H, Adoue D: Rituximab versus splenectomy in persistent or chronic adult primary immune thrombocytopenia: an adjusted comparison of mortality and morbidity. Am J Hematol. 2014, 89:41-46. 10.1002/ajh.23580
22. Al Askar AS, Shaheen NA, Al Zahrani M, et al.: Splenectomy vs. rituximab as a second-line therapy in immune thrombocytopenic purpura: a single center experience. Int J Hematol. 2018, 107:69-74. 10.1007/s12185-017-2325-y
23. Arnold DM, Dentali F, Crowther MA, et al.: Systematic review: efficacy and safety of rituximab for adults with idiopathic thrombocytopenic purpura. Ann Intern Med. 2007, 146:25-33. 10.7326/0003-4819-146-1-200701020-00006
24. Chang H, Tang TC, Hung YS, Li PL, Kuo MC, Wu JH, Wang PN: Immune thrombocytopenia:

effectiveness of frontline steroids and comparison of azathioprine, splenectomy, and rituximab as second-line treatment. Eur J Haematol. 2018, 101:549-555. 10.1111/ejh.13144

25. Quiquandon I, Fenaux P, Caulier MT, Pagniez D, Huart JJ, Bauters F: Re-evaluation of the role of azathioprine in the treatment of adult chronic idiopathic thrombocytopenic purpura: a report on 53 cases. Br J Haematol. 1990, 74:223-228. 10.1111/j.1365-2141.1990.tb02569.x
26. Bourgeois E, Caulier MT, Delarozee C, Brouillard M, Bauters F, Fenaux P: Long-term follow-up of chronic autoimmune thrombocytopenic purpura refractory to splenectomy: a prospective analysis. Br J Haematol. 2003, 120:1079-1088. 10.1046/j.1365-2141.2003.04211.x
27. Reiner A, Gernsheimer T, Slichter SJ: Pulse cyclophosphamide therapy for refractory autoimmune thrombocytopenic purpura. Blood. 1995, 85:351-358.
28. Verlin M, Laros RK, Jr., Penner JA: Treatment of refractory thrombocytopenic purpura with cyclophosphamine. Am J Hematol. 1976, 1:97-104. 10.1002/ajh.2830010111
29. Liu AP, Cheuk DK, Lee AH, et al.: Cyclosporin A for persistent or chronic immune thrombocytopenia in children. Ann Hematol. 2016, 95:1881-1886. 10.1007/s00277-016-2791-y
30. Almagro D: Danazol in idiopathic thrombocytopenic purpura. Acta Haematol. 1985, 74:120. 10.1159/000206184
31. Mazzucconi MG, Francesconi M, Falcione E, Ferrari A, Gandolfo GM, Ghirardini A, Tirindelli MC: Danazol therapy in refractory chronic immune thrombocytopenic purpura. Acta Haematol. 1987, 77:45-47. 10.1159/000205948
32. Patel AP, Patil AS: Dapsone for immune thrombocytopenic purpura in children and adults . Platelets. 2015, 26:164-167. 10.3109/09537104.2014.886677
33. Esteve C, Samson M, Guilhem A, et al.: Efficacy and safety of dapsone as second line therapy for adult immune thrombocytopenia: a retrospective study of 42 patients. PLoS One. 2017, 12:0187296. 10.1371/journal.pone.0187296.
34. Zhang WG, Ji L, Cao XM, et al.: Mycophenolate mofetil as a treatment for refractory idiopathic thrombocytopenic purpura. Acta Pharmacol Sin. 2005, 26:598-602. 10.1111/j.1745-7254.2005.00088.x
35. Hou M, Peng J, Shi Y, et al.: Mycophenolate mofetil (MMF) for the treatment of steroid-resistant idiopathic thrombocytopenic purpura. Eur J Haematol. 2003, 70:353-357. 10.1034/j.1600-0609.2003.00076.x
36. Taylor A, Neave L, Solanki S, et al.: Mycophenolate mofetil therapy for severe immune thrombocytopenia . Br J Haematol. 2015, 171:625-630. 10.1111/bjh.13622
37. Fenaux P, Quiquandon I, Caulier MT, Simon M, Walter MP, Bauters F: Slow infusions of vinblastine in the treatment of adult idiopathic thrombocytopenic purpura: a report on 43 cases. Blut. 1990, 60:238-241. 10.1007/BF01728791
38. Simon M, Jouet JP, Fenaux P, Pollet JP, Walter MP, Bauters F: The treatment of adult idiopathic thrombocytopenic purpura: infusion of vinblastine in ITP. Eur J Haematol. 1987,
39:193-196. 10.1111/j.1600-0609.1987.tb00756.x 39. Ahn YS, Harrington WJ, Mylvaganam R, Allen LM, Pall LM: Slow infusion of vinca alkaloids in the treatment of idiopathic thrombocytopenic purpura. Ann Intern Med. 1984, 100:192-196. 10.7326/0003-4819-100-2-192
40. Ries CA: Vincristine for treatment of refractory autoimmune thrombocytopenia . N Engl J Med. 1976, 295:1136. 10.1056/nejm197611112952014
41. Shvidel L, Sigler E, Shtalrid M, Berrebi A: Vincristine-loaded platelet infusion for treatment of refractory autoimmune hemolytic anemia and chronic immune thrombocytopenia: rethinking old cures. Am J Hematol. 2006, 81:423-425. 10.1002/ajh.20632
42. Park YH, Yi HG, Lee MH, Kim CS, Lim JH: Clinical efficacy and tolerability of vincristine in splenectomized patients with refractory or relapsed immune thrombocytopenia: a retrospective single-center study. Int J Hematol. 2016, 103:180-188. 10.1007/s12185-015-1903-0
43. Stirnemann J, Kaddouri N, Khellaf M, et al.: Vincristine efficacy and safety in treating immune thrombocytopenia: a retrospective study of 35 patients. Eur J Haematol. 2016, 96:269-275. 10.1111/ejh.12586
44. Provan D, Newland AC: Current management of primary immune thrombocytopenia . Adv Ther. 2015, 32:875-887. 10.1007/s12325-015-0251-z
45. Elgebaly AS, Ashal GE, Elfil M, Menshawy A: Tolerability and efficacy of eltrombopag in chronic immune thrombocytopenia: meta-analysis of randomized controlled trials. Clin Appl Thromb Hemost. 2017, 23:928- 937. 10.1177/1076029616663849
46. Kuter DJ, Bussel JB, Newland A, et al.: Long-term treatment with romiplostim in patients with chronic immune thrombocytopenia: safety and

efficacy. Br J Haematol. 2013, 161:411-423. 10.1111/bjh.12260

47. Khellaf M, Michel M, Quittet P, et al.: Romiplostim safety and efficacy for immune thrombocytopenia in clinical practice: 2-year results of 72 adults in a romiplostim compassionate-use program. Blood. 2011, 118:4338-4345. 10.1182/blood-2011-03-340166
48. Newland A, Godeau B, Priego V, Viallard JF, Lopez Fernandez MF, Orejudos A, Eisen M: Remission and platelet responses with romiplostim in primary immune thrombocytopenia: final results from a phase 2 study. Br J Haematol. 2016, 172:262-273. 10.1111/bjh.13827
49. Depre F, Aboud N, Ringel F, Salama A: Thrombopoietin receptor agonists are often ineffective in immune thrombocytopenia and/or cause adverse reactions: results from one hand. Transfus Med Hemother. 2016, 43:375-379. 10.1159/000446195