MANAGEMENT OF IMMUNE THROMBOCYTOPENIA

Dr. Touseef Anwar
M.B.B.S, F.C.P.S
Assistant Professor of Medicine
Independent University Hospital
Faisalabad.

Correspondence Address:
Dr. Touseef Anwar
M.B.B.S, F.C.P.S
Assistant Professor of Medicine
Independent University Hospital
Faisalabad.

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Key Concepts
- Definition of immune thrombocytopenia
- First line of therapy for immune thrombocytopenia
- Second line drugs for immune thrombocytopenia
- Surgical treatment for immune thrombocytopenia
- Complications of immune thrombocytopenia

Abstract: Immune thrombocytopenia (ITP) is an immune-mediated disease characterized by transient or persistent decrease of the platelet count to less than 100 × 10⁹/liter. The major therapeutic goal for ITP is to use minimal treatment to maintain platelet counts that are sufficient to reduce bleeding symptoms with the least amount of side effects. Intravenous immunoglobulin (IVIG) and anti-D are effective in raising the platelet counts but the effects are usually transient. For patients with chronic ITP whose condition failed to respond to corticosteroids or who have severe adverse effects from corticosteroids, splenectomy is the second-line therapy in many centers.

Key words: Immune thrombocytopenia, splenectomy, Eltrombopag, platelet transfusion.

Immune thrombocytopenia (ITP) is an immune-mediated disease characterized by transient or persistent decrease of the platelet count to less than 100 × 10⁹/liter. The term ‘newly diagnosed ITP’ is used to describe all cases at diagnosis. Persistent ITP is defined as ITP lasting between 3 and 12 months from diagnosis while chronic ITP is defined as the presence of ITP for more than 12 months. Secondary ITP includes all forms of immune-mediated thrombocytopenia except primary ITP.

The major therapeutic goal for ITP is to use minimal treatment to maintain platelet counts that are sufficient to reduce bleeding symptoms with the least amount of side effects. Since most fatal bleeding in adult ITP occurs with platelet counts lower than 30 × 10⁹/liter, current guidelines suggest that treatment should only be considered in symptomatic patients with counts less than 30 × 10⁹/liter. Corticosteroids are the standard initial treatment. Prednisolone 0.5–2 mg/kg/day is the common starting dose for patients with ITP. After the platelet count increases to more than 50 × 10⁹/liter, prednisolone should be tapered off to the minimal effective dose required to maintain a platelet count over 30–50 × 10⁹/liter. If no significant increase in platelet count is observed after 4 weeks of treatment with high-dose prednisolone, the drug should be tapered off quickly.
One to four cycles of dexamethasone 40 mg/day for 4 days is the preferred corticosteroid regimen in some centers, with response rates of 50–80% in newly diagnosed adult patients with ITP. Some patients had prolonged response after treatment with high-dose dexamethasone. However, a recent study suggested that dexamethasone was not more effective than conventional doses of prednisolone. According to the International Consensus Report on investigation and management of ITP, prednisolone, dexamethasone, or methylprednisolone are all acceptable first-line treatments.

Intravenous immunoglobulin (IVIG) and anti-D are effective in raising the platelet counts but the effects are usually transient. They are recommended as first-line treatments, especially in emergency situations.

For patients with chronic ITP whose condition failed to respond to corticosteroids or who have severe adverse effects from corticosteroids, splenectomy is the second-line therapy in many centers. However, about 15–20% of patients do not respond to splenectomy and another 15–20% of responders relapse weeks, months, or years later. In addition, many patients with chronic ITP are reluctant to have splenectomy because of fear of complications such as bleeding, infection, thrombosis, and the reported mortality rates of 0.2–1.0%.

In patients who were refractory to or relapsing after splenectomy or when splenectomy was contraindicated, a variety of immunosuppressive or cytotoxic drugs such as vincristine, cyclophosphamide, azathioprine, dapsone, cyclosporine A, mycophenolate mofetil and rituximab were used with a response rate of 20–80%. However, most of the studies with immunosuppressive agents were not randomized clinical trials and patients may have serious infection complications from prolonged use.

In a prospective phase II trial patients with ITP were given rituximab at doses of 375 mg/m2 weekly for 4 weeks. One-third of the patients had a platelet count of 50 × 10^9/liter or higher without any additional treatment after 2 years of observation. Most patients with a durable (> 1 year) complete response will respond to repeat treatment if they relapse. A combination of rituximab with high-dose dexamethasone as initial therapy may result in an even higher response rate. However, after 3 years of follow up, around 25% of the patients with ITP had platelet counts over 50 × 10^9/liter.

Rituximab is currently not registered for the treatment of chronic ITP and can cause fulminant hepatitis in hepatitis B carriers. Therefore, rituximab is contraindicated in patients with active hepatitis B infection and prophylaxis with lamivudine is required in patients who carry hepatitis B without active infection. Also, more than 50 cases of progressive multifocal leukoencephalopathy associated with rituximab treatment have been reported in patients with lymphoma and systemic lupus erythematosus. Additional long-term safety data are required before rituximab can be recommended as a frontline therapy.

Recently, impaired platelet production was observed in many patients with ITP. Therefore, stimulation of megakaryopoiesis by thrombopoietin or thrombopoietin-mimetic agents may be useful in the treatment of ITP. Recombinant thrombopoietin had been shown to increased platelet counts in patients with ITP but was associated with
production of autoantibodies that crossreact with and neutralize endogenous thrombopoietin, leading to severe thrombocytopenia. Recently, two thrombopoietin-receptor (TPO-R) agonists, romiplostim (AMG-531, Nplate; Amgen, Thousand Oaks, CA, USA) and eltrombopag (Revolade, Promacta; GlaxoSmithKline, Brentford, UK) have been licensed for the treatment of chronic ITP. They have no sequence homology with native thrombopoietin and should not stimulate production of antithrombopoietin antibodies. The current indications of TPO-R agonists are for relapsed splenectomized adult patients with chronic ITP who are refractory to other treatments or adult nonsplenectomized patients in whom splenectomy is contraindicated.

This article reviews data on the pharmacology, clinical efficacy, and safety profile of eltrombopag in the treatment of ITP.

Eltrombopag is an orally administered small-molecule nonpeptide TPO-R agonist. It has been shown to effectively increase platelet counts and reduce bleeding symptoms in patients with chronic ITP with overall response rate of 60–80%. Eltrombopag is well tolerated and has a good safety profile. It is recommended for splenectomized patients with ITP who are refractory to other treatments (e.g. corticosteroids, immunoglobulins). It may also be considered as second-line treatment for adult nonsplenectomized patients who refused surgery or in whom surgery is contraindicated.

The recommended starting dose of eltrombopag is 50 mg once daily. For patients of East Asian ancestry, eltrombopag should be initiated at a reduced dose of 25 mg once daily. After initiating eltrombopag, if no significant increase in platelet counts is observed after 2–3 weeks of treatment, the dose may be increased. After achieving a stable platelet count on a specific dose, the dose should be further adjusted to the lowest dose sufficient to maintain a platelet count of around 50 × 109/liter with minimal bleeding symptoms. In the EXTEND study, 13 of 301 patients (4.5%) had prolonged remission (median 50 weeks) without ITP therapy following discontinuation of eltrombopag [Cheng et al. 2001a]. The median time from diagnosis of ITP was 24 months (range 6–73 months) and the median duration of eltrombopag therapy was 237 days (range 14–1014 days). Therefore, in some patients with chronic ITP, it may be possible to gradually taper and eventually discontinue eltrombopag. If the disease relapses, eltrombopag can be restarted at the previous effective dose. According to data from the REPEAT study, such patients will still be responsive to eltrombopag.

In most responding patients, platelet counts start to increase after the first week of therapy and peak at the second week. Therefore, eltrombopag may be used in the preparation of patients with chronic ITP for elective surgery. Patients can start taking eltrombopag at home 2 weeks before the scheduled surgery, thus avoiding presurgical admission for IVIG infusion, which is common practice.

Eltrombopag should be taken at least 4 h before or after any products such as antacids, dairy products (or other calcium-containing food products), or mineral supplements containing polyvalent cations (e.g. iron, calcium, magnesium, aluminum, selenium, and zinc).

Eltrombopag is not recommended for use in children and adolescents below the age of 18 years due to insufficient data on safety and
efficacy.

Even though no increased incidence of thromboembolic events, myelofibrosis, or irreversible hepatic damage was reported in follow up over 4 years, patients on eltrombopag should still be monitored closely for such adverse events.

Experience with intravenous anti-D in pregnancy to treat ITP has been limited. This is likely because of concerns of possible fetal hemolysis from transplacental passage of the IgG molecules. Significant fetal hemolysis from maternal antepartum prophylaxis has not been reported; however, doses of intravenous anti-D used for prophylaxis to prevent Rh disease are much lower than those used to treat ITP. Thus, IVIG tends to be used more commonly in pregnancy.

Platelet transfusions should be used sparingly because maternal antiplatelet antibodies result in rapid destruction of transfused platelets. Administer platelet transfusions to women with hemorrhage or platelet counts less than 10,000/µL. Generally, at time of delivery or just prior to cesarean delivery, 6-10 units of platelets are administered if the maternal platelet count is less than 50,000/µL to prevent intrapartum or postpartum bleeding.

The safety and efficacy of thrombopoietin mimetics is not established in pregnant women with ITP. In one case report, in which romiplostim was used during pregnancy in addition to steroids and IVIG, the newborns still manifested intraventricular hemorrhage, although there was no developmental delay at 10 months. Rituximab crosses the placenta, and data are insufficient to recommend use in ITP during pregnancy.

Cyclophosphamide, mycophenolate, vincristine, and danazol are contraindicated during pregnancy.

References


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