First-Line Therapy for Immune Thrombocytopenia

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Abstract

Immune thrombocytopenia (ITP) is an autoimmune disease affecting blood platelets that causes thrombocytopenia and an increased risk of bleeding. First-line therapy is indicated for patients with bleeding complications or who are at increased risk of bleeding, and the decision to initiate therapy depends not only on the platelet count, but also on other endpoints including quality of life. The choice of first-line therapy depends primarily on how quickly a platelet count response is required, with intravenous immune globulin providing the more rapid response, followed by high-dose dexamethasone and prednisone. In this narrative review, we discuss key issues with first-line therapy in ITP including when to initiate therapy, treatment options and special considerations for children. Evidence-based guidelines are lacking for the emergency management of patients with ITP who present with significant bleeding; we provide our approach to this critical situation.

Keywords

- platelet
- autoimmune diseases
- paediatric

Introduction

Immune thrombocytopenia (ITP), formerly immune thrombocytopenic purpura, is a disorder of platelet number characterized by thrombocytopenia and an increased risk of bleeding. The International Working Group defined primary ITP as a platelet count less than 100×10^9/L in the absence of other causes or underlying conditions.[1,2] Although ITP is a heterogeneous syndrome with diverse pathological mechanisms,[3,4] it remains a diagnosis of exclusion and misdiagnosis is common, even among experienced haematologists.[5]

Newly diagnosed patients with ITP who are at low risk of bleeding can be safely managed with observation, while those with severe thrombocytopenia or at higher risk of bleeding require urgent treatment. This review explores common questions about first-line therapy for ITP, including when to treat/when not to treat, efficacy and safety of first-line therapies, management of ITP bleeding emergencies and unique treatment considerations for paediatric patients.

When to Treat/When Not to Treat ITP

The platelet count is the most important measure of disease activity in patients with ITP. As a surrogate marker, the platelet count inversely correlates with morbidity from bleeding,[6,7] but is only one of many factors that influence the bleeding risk of an individual patient.[8] Patients with severe bleeding almost invariably have severe thrombocytopenia, but most patients with severe thrombocytopenia do not bleed.

Reported rates of severe bleeding vary depending on the population studied and the instrument used to measure bleeding. In a systematic review of 118 studies ($n = 10{,}908$ patients with ITP), the rate of intracranial haemorrhage (ICH) was 1.0% overall (95% confidence interval [CI]: 0.7–1.3), 1.4% in adults (95% CI: 0.9–2.1) and 0.4% in children (95% CI: 0.2–0.7).[9] Among 29 studies that reported this outcome, the overall rate of non-ICH major bleeding was 15.0% (95% CI: 4.1–17.1).[9] A more recent study that measured bleeding prospectively using a validated ITP bleeding assessment tool[6] reported that 56% of patients had severe bleeding at some point during their disease course, and 2% had ICH.[5]

Deaths due to bleeding are rare, and overall mortality among patients with ITP is only slightly higher than age- and sex-matched controls. In a cohort study of 152 adults with ITP, the relative mortality risk was 1.5 (95% CI: 1.1–2.2), which was not significantly higher than the general population after patients with secondary ITP were excluded

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(relative risk [RR]: 1.3; 95% CI: 0.89–2.0).[10] Biologically, patients with ITP tend to have less bleeding complications compared with patients with non-ITP and similar platelet counts (e.g. chemotherapy-induced thrombocytopenia) likely because in ITP, the platelets are generally 'younger' and more haemostatically active.[11]

Besides the platelet count and bleeding, health-related quality of life (HRQoL) and fatigue are other endpoints that should be considered when deciding on treatment. HRQoL has been shown to be reduced in patients with chronic ITP compared with matched controls, specifically in the domains of physical and mental wellbeing.[12] Fatigue is reported in 20 to 40% of patients with ITP and has been associated with female sex and severe thrombocytopenia in one cross-sectional study ($n = 653$).[13] Treatment with eltrombopag,[14] romiplostim[15] and other therapies[16] has been shown to improve HRQoL among adults and children.

The importance of the platelet count level in deciding on treatment depends on the population. For children, acute severe thrombocytopenia often resolves spontaneously and the toxicities of treatments often outweigh their benefits.[1] For adults, severe thrombocytopenia is much less likely to improve spontaneously.[17] Furthermore, patients with additional bleeding risks (e.g. those who require anti-coagulation or anti-platelet agents), patients undergoing invasive procedures or patients at increased risk of trauma (e.g. contact sports) may need a higher platelet count threshold for treatment.[18] Treatment guidelines from the American Society of Hematology[1] recommend treatment for adults with newly diagnosed ITP and a platelet count $<30 \times 10^9$/L (Grade 2C) since above 30×10^9/L, clinically significant bleeding is rare.[9] Recommendations for children place less emphasis on the platelet count number, and more emphasis on clinical evidence of haemostatic impairment.[1]

The decision to initiate treatment should be based on the platelet count level and other factors that influence the bleeding risk in individual patients. In addition, HRQoL and the toxicities of treatment are also important considerations. While estimating the bleeding risk of an individual patient is imprecise, predictors of bleeding include severe thrombocytopenia (defined as a platelet count $<10 \times 10^9$/L or $<20 \times 10^9$/L), chronic ITP, history of major bleeding and older age (>60 years).[9,19] A platelet count response to intravenous immune globulin (IVIG) or corticosteroids can be useful to differentiate ITP from other thrombocytopenic disorders.[20] Most non-bleeding adults with ITP can be treated in the outpatient setting with close follow-up. Hospital admission should be considered for patients with newly diagnosed ITP and severe thrombocytopenia, or for patients at increased risk for bleeding (e.g. those who are taking an anti-coagulant[7]).

Choice of First-Line Therapy for ITP

ITP treatments are prescribed to achieve one of three main goals: (1) to rapidly but transiently raise the platelet count level; (2) to maintain a stable, haemostatic platelet count or (3) to achieve remission.[4] Traditional first-line treatments with corticosteroids, IVIG or Rh(D) immune globulin (RhIg) are directed at the first goal of rapidly raising the platelet count. A more recent concept for first-line therapy is to consider the goal of achieving remission without the need for maintenance therapy, as has been recently reported in a subgroup of patients who received thrombopoietin (TPO) receptor agonist (TPO-RA) medications.[21,22] While previous reports had suggested that high-dose corticosteroids[23] or IVIG[24] may improve long-term disease control, more recent studies have found that neither improves response rates at 6 months.[25,26]

Guidelines from the American Society of Hematology[1] recommend corticosteroids, IVIG or RhIg as first-line therapy for a newly diagnosed adult with ITP. The urgency of a platelet count response, and the patient's comorbidities and preferences should guide which treatment should be prescribed. The fastest platelet count responses can be achieved with IVIG (12–48 hours), followed by high-dose dexamethasone (1–2 days) and standard-dose prednisone (2–4 days).[2,27] Thus IVIG (or RhIg) is preferred when a rapid rise in the platelet count is required. Concerns about toxicities with RhIg have limited its use in recent years (see below).

Corticosteroids

Commonly prescribed corticosteroid regimens include high-dose dexamethasone and standard-dose prednisone. Dexamethasone is most commonly administered as one or more cycles of 40 mg orally once daily for 4 days, with no taper usually 4 weeks apart.[28] Prednisone is administered 1 to 2 mg/kg orally per day for 1 to 2 weeks, with a gradual taper and discontinuation by 6 to 8 weeks.[26] Lower starting doses of prednisone may also be effective.[29,30] As in other autoimmune diseases,[31] there is no evidence supporting a specific corticosteroid tapering regimen in ITP. Up to 80% of patients with ITP will have an initial response to corticosteroids[26]; however, long-term responses are less common and have been observed in only 20 to 40% of newly diagnosed patients,[26,28] which may be related to the treatment or to the natural history of the disease. In a meta-analysis of five randomized trials ($n = 533$ patients), high-dose dexamethasone increased the likelihood of a platelet count response by day 14 (79 vs. 59%; RR: 1.22; 95% CI: 1.00–1.49) when compared with standard-dose prednisone, but did not lead to more long-term remissions.[26]

Corticosteroids should be tapered rapidly and discontinued in non-responding patients. Short courses of dexamethasone (which has an anti-inflammatory effect that is 7.5 times more potent than prednisone)[32] may prevent toxicities associated with prolonged corticosteroid exposure, including weight gain and osteoporosis, but result in acute toxicities including cognitive impairments, hypertension and hyperglycaemia. Notably, most studies of high-dose dexamethasone in ITP excluded patients with uncontrolled diabetes, hypertension or cardiovascular disease.[23,33]

Intravenous Immune Globulin

IVIG is usually administered as 1 to 2 g/kg in divided doses. Treatment guidelines from the American Society of Hematology[1] recommend that IVIG should be given initially as a single dose of 1 g/kg and repeated in non-responding patients. In a

randomized trial of 37 adults with ITP and a platelet count $<50 \times 10^9$/L, patients who received a single IVIG dose of 1 g/kg were more likely to have a platelet count response by day 4 compared with patients who received lower initial doses of 0.5 g/kg (67 vs. 21%, $p = 0.005$).[34] Patients who had no response by day 4 received a second dose of IVIG (either 1.5 or 1 g/kg depending on the initial dose given), which resulted in an excellent cumulative response rate of 78% that was similar between groups. These results suggest that an initial IVIG dose of 1 g/kg is preferred for most patients with the possibility of repeating a second dose the next day. Common side effects of IVIG include headache in 10 to 25% of patients,[35] aseptic meningitis[36] and acute kidney injury.[37,38] Haemolysis from passive transfer of anti-A and anti-B haemagglutinins is an uncommon complication that can occur in non-blood group O patients, with IVIG preparations containing high-titre anti-A or anti-B antibodies and large cumulative doses of IVIG (>100 g over 2–4 days).[39]

IVIG has been associated with an increased risk of thrombosis, which led to a boxed warning from the U.S. Food and Drug Administration in 2013.[40] The risk has been estimated at 1% per year for arterial or venous thrombosis for patients who are regularly treated with IVIG.[41,42] Risk estimates vary depending on a patient's underlying risk factors for thromboembolism, the specific product used and the indication for treatment. In contrast to the findings of observational studies, a recent systematic review of 31 randomized trials ($n = 4{,}129$ patients) did not demonstrate an increased risk of thromboembolism with IVIG for a variety of indications (odds ratio [OR]: 1.10; 95% CI: 0.44–2.88).[43]

IVIG raises the platelet count more rapidly than corticosteroids.[44] In a multicentre, randomized 2 × 2 trial of 122 adults with newly diagnosed ITP[27] and a platelet count $\leq 20 \times 10^9$/L, patients were randomized to IVIG at a dose of 0.7 g/kg daily for 3 days or high-dose methylprednisolone at a dose of 15 mg/kg daily for 3 days (first randomization). Patients then received either oral prednisone (1 mg/kg per day) or placebo from days 4 to 21 (second randomization). IVIG was more effective at raising the platelet count by day 5 than corticosteroids (79 vs. 60% response rate, $p = 0.04$). Long-term responses were similar between patients who initially received IVIG or methylprednisolone (64 vs. 60%, $p = 0.80$). In total, 24% of the patients experienced transient, mostly mild, side effects from therapy and there were no deaths.

Rh(D) Immune Globulin

The mechanism of action of RhIg is to bind and occupy Fc receptors in the reticuloendothelial system with antibody-coated Rh(D)-positive red blood cells, thus preventing antibody-coated platelets from being destroyed.[45] RhIg is usually given at a dose of 50 to 75 mcg/kg intravenously[46] and is reserved for patients with Rh(D)-positive blood type with an intact spleen. RhIg can cause mild infusion reactions such as headache, nausea, chills, fever and mild to moderate haemolysis.[47] Life-threatening episodes of severe intravascular haemolysis associated with RhIg administration have been rarely reported.[48,49] These observations led to a warning on the product monograph[50] and withdrawal from European markets.

Can Some First-Line Therapies Induce Long-Term Remission?

Several early observational studies showed encouraging effects of high-dose dexamethasone on rates of long-term remission in adults, with studies reporting 6-month response rates between 40 and 80%.[23,51] Randomized trials, however, did not show a difference in long-term benefits with high-dose dexamethasone or prednisone, as demonstrated in a recent meta-analysis ($n = 533$ patients).[26] Rates of long-term responses at 6 months were 54% with high-dose dexamethasone and 43% with prednisone ($p = 0.44$); however, 79% of patients in the dexamethasone group achieved a platelet count response at 14 days compared with 59% of patients in the prednisone group (RR: 1.22; 95% CI: 1.00–1.49; $p = 0.048$).

Early use of IVIG in children was initially thought to reduce the risk of chronic ITP.[24,44] In a systematic review of nine randomized trials ($n = 596$ patients) comparing IVIG with corticosteroids in children with newly diagnosed ITP, 25% of children treated with corticosteroids and 18% of children treated with IVIG went on to develop chronic ITP ($p = 0.04$).[44] A case–control study of 449 matched pairs of children with ITP showed that patients who received IVIG were more likely to have a normal platelet count 6 months after diagnosis than patients who did not receive IVIG (OR: 1.81; 95% CI: 1.25–2.64).[24] In contrast, a recent randomized trial did not show a difference in long-term benefit with IVIG compared with observation alone in children with ITP, although there was a trend towards improved disease control at 6 months.[25] In this trial, 206 children (aged 3 months to 16 years) with newly diagnosed ITP, platelets $<20 \times 10^9$/L and mild to moderate bleeding were randomized to receive either a single dose of IVIG 0.8 g/kg or observation. Chronic ITP occurred in 18.6% of patients in the IVIG arm compared with 28.9% in the observation arm (RR: 0.64; 95% CI: 0.38–1.08).

Treatment intensification in the first-line setting is hypothesized to increase the likelihood of achieving long-term disease remission.[3] Two randomized trials of rituximab showed a higher rate of sustained platelet count response at 6 months (58–63%) compared with standard of care.[52,53] Two other placebo-controlled trials, one in newly diagnosed or relapsed patients[54] and one in corticosteroid-unresponsive patients[55] showed no difference in response rates at 6 months or longer. A meta-analysis of non-splenectomized patients ($n = 463$) showed slightly higher rates of complete response with rituximab (47% vs. 33%; RR: 1.42; 95% CI: 1.13–1.77; $p = 0.0020$).[56] Two-single arm studies have evaluated the use of TPO-RAs in the first-line setting[21,22] based on observational studies that reported remission rates of up to 30% after drug discontinuation.[57] In one study, romiplostim was given to 75 adults with newly diagnosed ITP to target a platelet count of 50–200 × 10^9/L.[22] At the end of 12 months, patients with a platelet count above 50 × 10^9/L gradually tapered and discontinued romiplostim. Twenty-four patients (32%) had long-term disease remission. In another study, 12 adults received a 4-day course of high-dose dexamethasone followed by a 28-day course of eltrombopag (50 mg orally daily).[21] Nine patients (75%) had a

platelet count $\geq 30 \times 10^9$/L at 6 months and eight patients (67%) had a response at 12 months off therapy. These encouraging data require further confirmation.

Management of ITP Bleeding Emergencies

Severe bleeding in ITP is a rare, life-threatening medical emergency. Goals of treatment are to increase the platelet count to a safe level and to stop the bleeding. This requires a multipronged approach that includes medications, blood transfusions and coordination with other clinical services for appropriate interventions (e.g. endoscopy, neurosurgery, etc.). There are currently no evidence-based guidelines for ITP bleeding emergencies, thus treatment recommendations reflect expert opinion.[1] In our opinion, an ITP bleeding emergency should be considered in a patient with presumed or definite ITP who has a platelet count $<20 \times 10^9$/L and significant bleeding including ICH, pulmonary haemorrhage, abnormal vaginal bleeding, macroscopic haematuria, overt gastrointestinal bleeding and perhaps extensive mucosal purpura.[6,7] This definition is based on the ITP-bleeding score[6] and incorporates criteria for severe bleeding that is beyond skin bruising or petechiae.[7]

Treatment of acute bleeding in adults and children, especially ICH, is highly time-sensitive. Early haematoma growth, the principal cause of neurological deterioration after ICH, occurs in up to 40% of patients within 3 hours of ICH onset and predicts 30-day mortality.[58] Similarly, upper gastrointestinal bleeding should be treated with early endoscopy (<24 hours).[59] Our practice is to treat patients with severe thrombocytopenia (platelet count $< 20 \times 10^9$/L) and limb or life-threatening bleeding with combination therapy that includes corticosteroids, IVIG and platelet transfusions.[1,60,61] High-dose dexamethasone (e.g. 40 mg daily for 4 days) and high-dose methylprednisolone (e.g. 1 g intravenously daily for 3 days) increase the platelet count faster than standard-dose prednisone.[26] Platelet transfusions cause a rapid but temporary increase in platelet count and may be effective at reducing bleeding even in the absence of a platelet count rise. IVIG may also lengthen the lifespan of transfused platelets.[62] Urgent use of TPO-RAs, such as romiplostim, may be sensible but requires further study. These agents would only be expected to work after 1 to 2 weeks with the goal of avoiding severe thrombocytopenia recurrence after initial disease control.[60] Tranexamic acid, recombinant factor VIIa, intravenous vincristine (1–2 mg) or RhIg (75 µg/kg) may be useful adjunctive treatments for severe, refractory bleeding.[1,61] Refractory bleeding may require emergency splenectomy.[1] Patients with bleeding emergencies should be hospitalized until bleeding is controlled. On discharge, close outpatient follow-up should be arranged because responses to urgent treatments may be short-lived.

First-Line Therapy for Children

Most children with ITP are asymptomatic at diagnosis or present with bleeding confined to the skin or oral mucosa.[63] Whether or not to treat such patients depends on the degree of thrombocytopenia, the severity of bleeding and the presence of other risk factors for bleeding.[1,18] Evidence-based treatment guidelines from the American Society of Hematology[1] recommend that children with no bleeding or mild bleeding only (defined as skin bruising or petechiae) be managed with observation alone, regardless of the platelet count (Grade 1B).[1] This strategy is more conservative than in adults because (1) most children with newly diagnosed ITP will remit spontaneously within 3 to 6 months[64,65]; (2) front-line therapies (corticosteroids, IVIG) do not appear to influence rates of long-term disease remission[25] and (3) severe bleeding is rare, occurring in only 3% of children at diagnosis.[65,66] ICH is especially rare in children: 0.4% compared with 1.4% in adults.[9] A variety of corticosteroid dosing regimens have been used in children, including prednisone at a dose of 1 to 2 mg/kg/day or short courses of high-dose dexamethasone (24 mg/m^2/day, maximum 40 mg per day, for 4 days with no taper). There is insufficient evidence to support any one corticosteroid dosing strategy over another.[1] IVIG is typically administered as a single dose of 0.8 to 1 g/kg.[1]

First-Line Therapy in Pregnancy

Indications for treatment of ITP in pregnancy are similar to those in non-pregnant patients. Treatment is indicated for bleeding patients, and should be considered if the platelet count falls below $20–30 \times 10^9$/L. First-line therapies are corticosteroids and IVIG. We prefer prednisone, given at a dose of 0.5 to 1 mg/kg daily for 7 to 14 days, over dexamethasone, which is a synthetic, fluorinated corticosteroid that crosses the placenta.[67,68] A retrospective review compared IVIG and corticosteroids as initial therapy for 91 pregnant ITP patients and showed no differences in maternal outcomes including platelet count responses.[69] Therefore, choosing between corticosteroids and IVIG should depend on the toxicities of treatment and how rapidly a response is needed. IVIG raises the platelet count faster than corticosteroids and may be preferred if delivery is imminent. Corticosteroids are more convenient and inexpensive, but may exacerbate post-partum psychiatric disorders, gestational hypertension and diabetes.[1,70] The safety of rituximab and TPO-RAs in pregnancy is not well established and their use is generally avoided.[71,72] The mode of delivery should be based on obstetrical indications.[1] Recommended platelet count thresholds at delivery are 30×10^9/L for vaginal delivery, 50×10^9/L for cesarean delivery and $80–100 \times 10^9$/L for epidural catheter insertion. The infant's platelet count should be monitored in the first week after delivery, since approximately 10% of infants born to mothers with ITP will have thrombocytopenia.[73]

Recommendations for First-Line ITP Therapy

Although the platelet count is the single most important marker for disease activity in ITP, the decision to initiate therapy should be individualized and take into account patient preferences and risk factors for bleeding. In an asymptomatic adult with ITP, treatment should be considered if the platelet

Table 1 Summary of first-line ITP therapy including when to start, which treatment to use, and how to manage ITP bleeding emergencies

When to start first-line therapy?	Adults: severe thrombocytopenia $< 20–30 \times 10^9$/L, adjust threshold based on individual risk factors for bleeding. Children: platelets $< 20–30 \times 10^9$/L and significant bleeding that is worse than skin bruising or petechiae.
Which first-line therapy should be used?	
Corticosteroids	High-dose dexamethasone (40 mg orally for 4 days, with no taper) or standard dose prednisone (1–2 mg/kg daily for 1–2 weeks with gradual tapering). Time to response is faster with high-dose dexamethasone.
IVIG	Single dose of 1 g/kg and repeated the following day in non-responding patients. Expected time to response is 12–24 h. IVIG should be used to treat patients with bleeding or when a rapid platelet count response is required.
Other treatments	Rituximab: early use of rituximab in combination with high-dose dexamethasone improves long-term remission rates, but with increased risk of grade 3–4 toxicities. TPO-RAs: observational studies suggest increased rates of remission with early use of TPO-RAs.
Managing an ITP bleeding emergency	Patients require hospitalization and combination therapy with high-dose corticosteroids, IVIG and platelet transfusions. Adjunctive treatments may include recombinant factor VIIa, tranexamic acid, and TPO-RAs.

Abbreviation: ITP, Immune thrombocytopenia; IVIG, intravenous immune globulin; TPO-RAs, thrombopoietin-receptor agonists.

count falls below $20–30 \times 10^9$/L.[1] Most children with ITP and no bleeding should be managed by observation alone.[1] Treatment should be given with an aim to rapidly raise the platelet count, maintain a stable platelet count or to achieve long-term disease remission.[4] We do not routinely use ITP therapies to alleviate fatigue, or improve physical or mental wellbeing in the absence of another indication for therapy.

Our approach to fist-line therapy is summarized in ►Table 1. We prefer high-dose dexamethasone (40 mg orally for 4 days with no taper) over standard-dose prednisone because it leads to a faster platelet count response and avoids toxicities associated with prolonged courses of glucocorticoids.[26] If there is no platelet count response, we re-evaluate whether ITP is the most likely diagnosis and consider alternate treatments such as IVIG. IVIG is indicated when a rapid platelet count response is required and should be administered as a single dose of 1 g/kg, and repeated if the platelet count does not respond by day 2. Some evidence suggests that early use of TPO-RAs can increase the likelihood of long-term disease remission, but this requires further confirmation.[21,22] ITP bleeding emergencies should be managed with the combination of high-dose corticosteroids, IVIG and platelet transfusions.[61] Adjunctive treatments in an emergency setting may include tranexamic acid, TPO-RAs and recombinant factor VIIa.

Conflict of Interest

None.

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