Positioning New Treatments in the Management of Immune Thrombocytopenia

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Abstract

Immune thrombocytopenia (ITP) is a syndrome characterized by low platelet counts and an increased risk of bleeding. For most children, ITP is a self-limiting disease; however, for some children and most adults, thrombocytopenia can become chronic. Newer therapies for ITP include rituximab and thrombopoietin (TPO) receptor agonists. Rituximab is a useful second-line therapy and may be splenectomy-sparing. Thrombopoietin receptor agonists have demonstrated large treatment effects with respect to increasing platelet levels; however, they require maintenance dosing. This review summarizes how these new agents might be positioned in the management of patients with chronic ITP.

Keywords

bleeding; clinical trials; platelets; thrombopoietin

NORMAL PLATELET HOMEOSTASIS

The number of circulating platelets is tightly regulated. Platelet production from bone marrow megakaryocytes is balanced against platelet removal by the spleen after their normal 7–10 day lifespan in circulation. Thrombopoietin (TPO), a hormone secreted by the liver constitutively, acts on hematopoietic progenitor cells and bone marrow megakaryocytes to stimulate platelet production and binds to circulating platelets. The feedback mechanism for TPO is primitive but effective: when platelet levels are low, free TPO levels are high and more platelets are produced. Conversely, when platelet levels are high, TPO levels are low and platelet production is not further stimulated (Fig. 1). A cross-sectional population-based study of 12,142 participants suggested that mean platelet counts controlled for covariates, decreased by only 9% from late adolescence to over 70 years of age [1]. Although these aggregate data do not necessarily reflect changes within individuals, they suggest that platelet counts remain remarkably stable over time.

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Immune mediated thrombocytopenia is caused by platelet reactive antibodies that bind to platelet glycoproteins. These autoantibodies bind to circulating platelets and cause accelerated destruction in the reticuloendothelial system [2]. In addition, platelet-reactive autoantibodies have also been shown to bind to cultured megakaryocytes and interfere with their normal growth [3], which may explain why platelet production is impaired in immune thrombocytopenia (ITP). Other mechanisms of ITP pathogenesis include cytotoxic T-cells [4] and abnormal T-regulatory function [5]. Thus, ITP is characterized by humoral and cellular immune disruption of platelet homeostasis at multiple levels which leads to the development of thrombocytopenia.

CLINICAL FEATURES OF IMMUNE THROMBOCYTOPENIA

For the majority of children, ITP presents acutely and resolves within weeks often without any intervention. A viral prodrome is common in children, which may explain the seasonal variability observed in longitudinal studies [6]. The incidence of childhood ITP is approximately 4 per 100,000/year [7], and the prevalence is approximately 8 per 100,000 [8]. The incidence is lower in adults, estimated at approximately 3 per 100,000; however the prevalence is higher, approximately 12 per 100,000, reflecting the longer disease duration.

ITP remains a diagnosis of exclusion and should be considered in any patient with isolated thrombocytopenia. A platelet count below $100 \times 10^9/L$ has been proposed as the diagnostic threshold for ITP [9], recognizing that mild thrombocytopenia ($100\text{--}150 \times 10^9/L$) often does not worsen and may be normal for certain ethnic groups and during pregnancy. Investigations of patients are aimed at excluding non-immune causes of thrombocytopenia and determining whether thrombocytopenia is primary or secondary to an underlying infection such as *Helicobacter pylori*, HIV, hepatitis C, or Epstein-barr virus; drugs; lymphoproliferative disease or immune deficiency.

THERAPIES TO RAISE PLATELET COUNTS

Guidelines for the diagnosis and management of ITP have recently been updated [10] to incorporate new treatments including rituximab and the TPO receptor agonists. The following section will outline several key recommendations about management and highlight areas of controversy.

Conventional Management of ITP

Conventional treatments for ITP include careful observation, corticosteroids, intravenous immune globulin (IVIG) or anti-D, and splenectomy.

Many children with ITP will improve without therapy. Several randomized trials comparing corticosteroid-based therapy to observation or placebo [11] suggest that observation may be safe for children with platelet counts above $10 \times 10^9/L$ without signs of bleeding, even though corticosteroids may shorten the duration of thrombocytopenia [12]. Up to 80% of childhood ITP will resolve with no treatment after 6 months. For adults, a period of observation may also be reasonable provided that bleeding is absent; however, most adults will eventually require treatment.

Corticosteroids are accepted as first line therapy for ITP for adults and children. A common regimen is prednisone, 1–2 mg/kg for 2–4 weeks with taper once a platelet count response is achieved. In adults, an initial platelet count response can be expected in 60–70% of patients [13]; however most will relapse by 6 months. In children, response rates are even higher and most will achieve sustained remission. Low-dose prednisone and high dose dexamethasone have been evaluated with promising results; however controlled trials are needed to compare platelet count response, bleeding, and tolerability associated with various regimens.

IVIG is associated with a platelet count response in approximately 90% of patients and it occurs quickly, usually within 48 hours [14]. The effect typically lasts 2–4 weeks and a platelet count response generally indicates an immune cause of the thrombocytopenia. Several small randomized trials have shown that anti-D produces similar platelet count responses using high dose (75 µg/kg [15]) or standard dose (50 µg/kg [16]) anti-D; however, the concern about severe intravascular hemolysis [17] led to a black box warning. The mechanism of action for both agents is likely through reticuloendothelial blockade and competition for Fc-receptor binding with antibody-coated platelets. Other mechanisms have been proposed including anti-idiotypic antibodies; stimulation of cytokines; up or down regulation of Fc receptors; and the formation of soluble immune complexes. IVIg-primed dendritic cells have been shown to recapitulate the effect of IVIG in a mouse model of ITP [18], an observation that in time may lead to the development of more specific IVIG products.

Splenectomy has been associated with a platelet count response in approximately 60–70% of patients with chronic ITP. In a systematic review involving 2,623 patients who were followed for up to 12.5 years, only younger age was identified as a predictor of splenectomy success [19]. The biggest concern after splenectomy is overwhelming infection, which has been estimated to occur in approximately 3% of patients [20]. A population-based cohort study of 3,812 splenectomized patients suggested that the risk of infection following splenectomy in patients with ITP was only slightly higher than non-splenectomized ITP patients, with an odds ratio of 2.6 [95% confidence interval (CI), 1.3–5.1] in the first 90 days; hazard ratio of 1.0 (95% CI, 0.5–2.0) from 91 days to 1 year; and hazard ratio of 1.4 (95% CI, 1.0–2.0) beyond 1 year [21]. Vaccinations against encapsulated bacteria and penicillin prophylaxis in high risk patients can reduce the risk.

Newer Agents for ITP

Rituximab—Rituximab is an anti-CD20 monoclonal antibody that targets and destroys CD20⁺ B-lymphocytes. Although ITP is not a licensed indication, ITP guidelines recommend rituximab for patients who have failed splenectomy and possibly as an alternative to splenectomy [9]. In a systematic review of 19 observational studies enrolling 313 splenectomized or non-splenectomized adult ITP patients, rates of complete response (platelet count $\geq 150 \times 10^9/L$) and overall response (platelet count $\geq 50 \times 10^9/L$) with rituximab were 43.6% (95% CI, 29.5–57.7%) and 62.5% (95% CI, 52.6–72.5%), respectively, after a median follow up of 9.5 months [22]. Response rates were similar for splenectomized and non-splenectomized patients [23]. The typical dose was 375 mg/m² by intravenous infusion weekly for 4 consecutive weeks although lower doses have been used.

Median time to response was 5.5 weeks. In children, a systematic review of observational studies (n = 323 patients) reported response rates that were similar to adults: rates of complete response (platelets $100 \times 10^9/L$) and overall response (platelets $30 \times 10^9/L$) were 39% (95% CI, 30–49%) and 68% (95% CI, 58–77%), respectively.

Two randomized trials examining rituximab in ITP compared with other treatments have been completed. In adults, a randomized trial of adjuvant rituximab or placebo in 60 non-splenectomized patients receiving standard of care therapy reported no difference in the composite endpoint of platelet count above $50 \times 10^9/L$, significant bleeding or rescue treatment after 6 months [24]. Another randomized trial of 103 newly diagnosed adults, reported that 31/49 (63%) patients receiving rituximab plus dexamethasone achieved a platelet count of $50 \times 10^9/L$ or higher after 6 months without rescue treatment compared with 19/52 (36%) patients receiving dexamethasone alone (absolute risk reduction 27%; 95% CI, 8–46%) [25].

The duration of response after rituximab without continued dosing is a key issue. Across most studies, platelet count responses lasted 10.5–11.3 months [22,23]. In a recent long-term follow up study, the 1-year response rate from children who achieved an initial response to rituximab (n = 66) was 33% and the estimated 5-year response rate was 26% [26]. Among 72 adults with an initial response to rituximab, the rate of a continued response at 1 year and 5 years was 38% and 21%, respectively [26].

Infusion-related side effects with rituximab include hypotension, rash, sore throat, fever, and rigors and occur in approximately 30% of patients with ITP. Serum sickness may be more frequent in children. Treatment has been rarely linked to progressive multifocal leukoencephalopathy (PML), a rapidly fatal neurological syndrome caused by reactivation of latent JC virus in the brain [27].

Thrombopoietin receptor agonists—Perhaps the most important advance in the management of ITP since the discovery of IVIG was the introduction of TPO receptor agonists. The impact of this discovery has been just as important for the advancement of current understanding of pathophysiology as it has for expanding treatment options for patients with refractory disease.

Initial studies with recombinant forms of human TPO were halted abruptly 2 decades ago when cross-reactive antibodies that neutralized endogenous TPO were observed in a few patients and healthy volunteers [28]. Subsequent drug development was aimed at capitalizing on the platelet-raising effect of TPO while minimizing the potential for cross reactive antibodies. As a result, two drugs have been developed and are currently approved for adult patients with ITP: romiplostim and eltrombopag. Both bind to different sites of the TPO receptor c-Mpl and neither have structural homology with endogenous TPO (Fig. 2).

TPO receptor agonists are indicated for adult patients at risk of bleeding who relapse after splenectomy or who have a contraindication to splenectomy [9]. They may also be considered for second-line therapy in non-splenectomized patients at risk of bleeding. Too few data are available to make specific recommendations for children.

Romiplostim is a synthetic peptibody consisting of four peptides linked to an Fc fragment of an IgG antibody, which increases its half-life in circulation. It is administered as a subcutaneous injection once per week in escalating doses of 1–10 µg/kg. In a recent randomized trial comparing romiplostim to standard of care treatment (n = 234), romiplostim was associated with more frequent platelet count responses, fewer treatment failures (11% vs. 30%), fewer splenectomies (9% vs. 36%), less bleeding, and a higher quality of life [29]. The average dose of romiplostim in most adults was between 2 and 4 µg/kg.

Romiplostim has also been evaluated in a clinical trial of 22 children who had ITP for at least 6 months and who were randomized in a 3:1 ratio to receive either weekly romiplostim or placebo for 12 weeks [30]. Median age was 10 years, baseline platelet count was $13 \times 10^9/L$ and children had received a median of five prior therapies. Of the 17 children who received romiplostim (median dose 5 µg/kg weekly), 15 (88%) achieved a platelet count of $50 \times 10^9/L$ for at least 2 consecutive weeks compared with none of the five patients who received placebo. Platelet counts were maintained above $50 \times 10^9/L$ for a median of 7 weeks for patients receiving romiplostim. The most common adverse events were headaches and epistaxis and no treatment-related serious adverse events were reported. One patient in the romiplostim group experienced significant bleeding.

Eltrombopag is a non-peptide, small molecule that activates c-Mpl by binding to the transmembrane domain; thus eltrombopag, unlike romiplostim, does not compete with circulating TPO for binding. Eltrombopag is administered as an oral pill administered once daily. In randomized placebo-controlled trials, eltrombopag maintenance was associated with a platelet count response in 60–80% of treated patients [31]. Time to response was 1–2 weeks with minimal need for dose titration. Clinical trials in children are ongoing.

In clinical studies, TPO receptor agonists were generally well tolerated. Headache, fatigue, and insomnia were common side effects and severe thrombocytopenia has been observed upon discontinuation of the drug which may predispose to bleeding. A rare association with either drug was the development of bone marrow reticulin deposition; however, long-term follow up data suggest that this is not a major safety concern and when modest increases in bone marrow reticulin were observed, they did not persist once therapy was discontinued [32]. Thromboembolic events have been reported in patients taking these medications, which did not correlate with elevated platelet counts; although the attributable risk has not been well defined [33]. One study of eltrombopag in patients with advanced liver disease and secondary thrombocytopenia was stopped early because of an increase in portal vein thrombosis [34]. Eltrombopag has been associated with serum liver test abnormalities in approximately 11% of patients compared to 7% receiving placebo. In certain patients with myelodysplastic syndrome, especially those with excess blasts, romiplostim has been associated with an increase in bone marrow blast counts and progression to acute leukemia [35]. Currently, TPO receptor agonists are not recommended for this population.

The mechanism of action of TPO receptor agonists in ITP is not fully understood. The effect is at least partially attributable to an increase in platelet production that is sufficient to overwhelm the effect of the autoantibody. Empirical evidence to support this hypothesis

derives from the observation that very high doses of platelet transfusions can yield a platelet count increment in patients with refractory ITP [36]. TPO receptor agonists have also been associated with an improvement in T-regulatory cell function, reduction in interleukin-2-producing CD4(+) cells, and an increase in total circulating transforming growth factor- β 1 (TGF- β 1) levels [37]. These data suggest that stimulation of the TPO receptors may induce immunological mechanisms to restore immune tolerance in ITP.

FUTURE DIRECTIONS

New pharmacological therapies have provided more options for patients with chronic ITP, but have also made treatment decisions more complex. Whether or not rituximab or the TPO receptor agonists should be positioned before splenectomy for the management of chronic ITP is not yet clear and further research evaluating different treatment strategies is needed. In parallel, it is evident that patient and parental preference often drive treatment decisions [38] and a thorough understanding of the determinants of such choices will help incorporate patients' values alongside best research evidence.

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Fig. 1.

Regulation of platelet number by thrombopoietin (TPO). To maintain normal platelet numbers (**left panel**), adequate levels of TPO are free to circulate, bind megakaryocytes and maintaining platelet production. When platelet count levels are reduced (**middle panel**), circulating TPO levels are high, leading to increased platelet production. When platelet count levels are increased (**right panel**), levels of circulating TPO are low and platelet production is reduced (adapted with permission from [39]).

Fig. 2.

The thrombopoietin (TPO) receptor (known as c-Mpl), a transmembrane heterodimer receptor, showing the binding site for endogenous TPO (**A**) and for the TPO receptor agonists, romiplostim and eltrombopag (**B**) (reprinted with permission from [39]).