Immune Thrombocytopenia: Pathogenesis and Treatment Approaches

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Abstract

Immune thrombocytopenia (ITP) is a common hematologic disorder affecting both adult and pediatric patients. Pathogenesis of ITP involves 2 major mechanisms: increased platelet destruction by the immune system and abnormalities in megakaryocytopoiesis with impaired platelet production. This disease is conventionally treated using a unilateral approach, i.e., and immunosuppression. However, in many patients, immunosuppressive treatments are not tolerable or do not provide a sustained, durable response, suggesting the need for a more comprehensive treatment approach to improve outcomes in these patients. Thrombopoietin receptor agonists (TPO-RAs) target reduced platelet production, unlike conventional treatment options in ITP, thereby filling an important clinical need. Clinical data demonstrate that TPO-RAs have very high efficacy and good tolerability in patients with ITP, including patients who were refractory to multiple previous treatments. When used in combination with immunosuppression, TPO-RAs can help fully address both aspects of the bipartite ITP pathology, often leading to improved treatment response rates. TPO-RAs may also help reduce the need for conventional treatments and thus decrease treatment-associated morbidity and mortality. In addition, recent data suggest that TPO-RAs may enable durable remissions, in which no ITP therapy, including TPO-RAs themselves, are needed.

The advent of TPO-RAs fully equipped clinicians to comprehensively treat the underlying pathology of ITP. Personalized treatment strategies devised with knowledge of pathogenic processes within an individual may help achieve the best treatment outcomes with the current armamentarium.

ABBREVIATIONS

ALPS: Autoimmune Lymphoproliferative Syndrome; ASH: American Society of Hematology; IgG: Gamma Immunoglobulin; ITP: Immune Thrombocytopenia; IVIG: Intravenous Immunoglobulin; MMF: Mycophenolate Mofetil; mTOR: mechanistic Target of Rapamycin; TPO-RA: Thrombopoietin Receptor Agonist; Treg: Regulatory T cell.

INTRODUCTION

Platelet physiology overview: function, normal levels, half-life

Thrombocytes, more commonly referred to as platelets, are nonnucleated cellular discs of approximately 2 to 3 µm in diameter that contain mitochondria and express various surface receptors for signaling and intracellular trafficking [1,2]. Although platelets contribute to various important functions and processes such as inflammation, atherosclerosis, antimicrobial host defense, angiogenesis, and tumorigenesis [3], they are most widely recognized for their role in hemostasis ( clotting) [2].

Normal platelet count in healthy individuals is defined as 150 to 450 × 10^9/L of blood [4,5]. Platelets have a rapid turnover rate: typically 5 to 9 days after their production, they are eliminated via phagocytosis in the spleen and liver by Kupffer cells [2]. Thrombopoiesis is the process by which new platelets are formed from megakaryocytes in the bone marrow. An average of 1 × 10^11 platelets must be created daily to maintain circulating platelet numbers [6], but platelet production can increase up to 20-fold during periods of high demand [7].

Peptide cytokine thrombopoietin (TPO) is the principal regulator of thrombopoiesis [8] and is also involved in the differentiation of megakaryocytes [8] and erythroid and myeloid progenitors [9,10]. The level of TPO is controlled by its removal from the plasma by internalization into target cells acting as a negative feedback mechanism [10]. TPO was first discovered in 1958 based on the homology to another peptide cytokine, erythropoietin, which promotes red blood cell formation [11].

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• Eltrombopag
• Romiplostim

and the cDNA of human TPO was first cloned in 1994 [12-15].

TPO is a 353-amino acid polypeptide [14] primarily generated in the liver, with some production in the kidney and skeletal muscles [16,17]. It consists of 2 domains: 152-154-amino acid amino-terminal domain, which contains erythropoietin homology and receptor-binding sites [18], and unique carboxyl-terminal domain, which promotes stability and protein folding [19,20].

The receptors for TPO (TPO-R) are primarily expressed by mature platelets and megakaryocytes [8]. When activated by TPO, TPO-R initiates mitogen-activated protein kinase (MAPK)/ERK 1/2, STAT-p3/5, and AKT pathways, which ultimately induce cell proliferation and differentiation from bone marrow progenitor cells [8].

Apart from TPO-mediated regulation of platelet production, platelet counts may also be affected by changes in platelet sequestration or destruction. Platelet destruction may occur via immune or nonimmune processes [21] and is typically increased by drugs, vaccination, alloimmunity, or autoimmunity [21]. Under steady-state conditions, approximately 30% of platelets are sequestered in the spleen at any given time, and these platelets may be released to circulation when there is a need [6,21,22]. Nevertheless, an increase in platelet sequestration, which can be observed secondary to splenomegaly, typically does not cause pathological changes in platelet counts by itself [21] and thus will not be further discussed here.

**Immune thrombocytopenia**

**Definition/characteristics:** Thrombocytopenia is a severe reduction in circulating platelet levels, leading to disruption of platelet-mediated processes. International guidelines define thrombocytopenia as a peripheral blood platelet count < 100 × 10^9/L [23]. Immune thrombocytopenia (ITP) is a condition that typically presents with purpura, petechiae, hematoma, nosebleeds, bleeding from the gums, and blood in urine or stool [24] and occurs due to immunologic destruction and/or inadequate generation of platelets [25]. When ITP is a result of a known condition, such as an autoimmune disease (eg, antiphospholipid antibody syndrome), viral infection (eg, HCV or HIV), or treatment for other conditions (vaccinations, bone marrow transplant, certain drugs), the disease is called secondary ITP [25]. Primary ITP (hereafter ITP) is a diagnosis of exclusion.

In the United States, the prevalence rates of ITP in adults and children are 66 and 50 per million individuals per year, respectively [26], while the overall incidence is about 3-4 per 100,000 people [27]. Females are more frequently affected, but the sex difference is less pronounced in ITP compared with most autoimmune diseases, indicating possible involvement of other disease mechanisms in addition to autoimmunity [28].

**Pathophysiology**

As aforementioned, 2 major processes contribute to ITP: decreased platelet production and increased platelet destruction (Figure 1) [29]. These processes may be affected by multiple pathogenic changes, and they contribute at varying extents to ITP pathogenesis in each patient; these variations may account for the heterogeneity in response to different treatment strategies.

**Increased platelet destruction:** Abnormally accelerated platelet destruction is a characteristic of ITP [30,31]. Current evidence suggests involvement of a 3-step mechanism. Firstly, immune tolerance is lost due to pathological regulatory and inflammatory T-cell function. Secondly, T-follicular helper cells located primarily in the spleen trigger differentiation of B cells to autoreactive cells [32] that produce antiplatelet antibodies [30,31]. Finally, antiplatelet antibodies target glycoproteins, primarily glycoprotein IIb/IIIa, on platelets [33–35] and cause platelet destruction by macrophages or cytotoxic T cells.

Immune mechanisms that lead to increased platelet destruction may be triggered by many factors. There are over 100 drugs that cause drug-induced thrombocytopenia...
In addition, vaccines, particularly measles, mumps, and rubella (MMR), and infections have also been associated with thrombocytopenia [21,30,37]. There may be common mechanisms by which these factors generally induce accelerated platelet destruction. For instance, the foreign factor (drug or inactivated/live pathogen) may bind to the surface of the platelet and act as an adapter recruiting anti-foreign factor antibodies, thereby triggering a temporary immune response to platelets [38]. Thrombocytopenia could be more persistent if anti-foreign factor antibodies cross-react with platelet antigens [39], or if platelet/foreign factor complexes induce internalization and presentation of platelet antigens by antigen presenting cells, leading to development of anti-platelet antibodies [40].

**Decreased platelet production:** In patients with ITP, platelet production may not be sufficient to replace the platelets that are destroyed. Since megakaryocytes and platelets share common surface antigens, most anti-platelet antibodies may also target megakaryocytes [41,42]. Thus, decreased platelet production may be a secondary result of the factors leading to increased platelet destruction, which were discussed above. Other potential causes of decreased platelet production include impaired function of megakaryocytes [43,44], altered megakaryocyte morphology [45], or abnormal T-cell response in the bone marrow microenvironment [46]. In addition, insufficient TPO levels are considered to be involved in pathogenesis of ITP because increased serum TPO, a typical compensatory response to thrombocytopenia, is not observed in ITP [47,48].

**Treatments for ITP**

Until the last decade, immunosuppression has been the only chronic disease patients with refractory/chronic disease can be discussed in detail later in this review, use the TPO pathway to increase platelet counts while not interfering with immune function. TPO-RAs have been specifically developed to treat thrombocytopenia and are recommended for patients with chronic ITP under current guidelines [23,25,52]. However, as compared with the conventional treatment approaches, TPO-RAs are relatively newer treatments that have been in clinical use for less than 10 years.

**Platelet transfusion**

Platelet transfusions are often ineffective in ITP due to the short half-life of platelets which is further shortened by increased immune response in ITP [21]. This treatment should be reserved for patients with very low platelet counts and life-, organ-, or limb-threatening bleeding, in which case platelets should be maintained above 50 × 10^9/L. In the rare circumstances when platelet transfusion is required in the management of ITP, other therapies such as corticosteroids and/or intravenous immunoglobulin should be given at the same time to enhance platelet survival.

**Immune modulation**

**First-line, rapid response treatments:** The treatments discussed in this section can recover platelet counts very quickly and are commonly used as emergency treatments. In contrast,

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Typical Use in ITP</th>
<th>Advantages</th>
<th>Challenges</th>
<th>Abbreviations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelet transfusion</td>
<td>Low platelet emergency, rescue treatment</td>
<td>• Immediate response</td>
<td>• Responses are temporary Complications are relatively common [7] Risk of alloimmunization [7,21]</td>
<td>ITP: Immune Thrombocytopenia; IVIG: Intravenous Immunoglobulin</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>First-line treatment, rescue treatment</td>
<td>• Rapid response</td>
<td>Long-term adverse effects [55] Responses are not durable [53]</td>
<td></td>
</tr>
<tr>
<td>IVIG</td>
<td>First-line treatment, rescue treatment</td>
<td>• Rapid response</td>
<td>Responses are not durable [53] Serious adverse events in patients with risk factors Potential risk of virus transmission [49]</td>
<td></td>
</tr>
<tr>
<td>Anti-D</td>
<td>Alternative to IVIG</td>
<td>• Rapid response</td>
<td>Inconclusive evidence regarding recommended starting dose and efficacy as compared with IVIG [23,25] Reported cases of fatal intravascular hemolysis [25]</td>
<td></td>
</tr>
<tr>
<td>Rituximab</td>
<td>Second-line treatment</td>
<td>• Acceptable short-to medium-term efficacy</td>
<td>Low long-term efficacy [51] May not be effective in all patients populations with ITP</td>
<td></td>
</tr>
<tr>
<td>Older agents</td>
<td>Alternative or supplementary to other ITP treatments</td>
<td>• Low cost</td>
<td>Insufficient clinical data supporting safety and efficacy Long duration of treatment needed for a response Increased need for screening and monitoring [25,52]</td>
<td></td>
</tr>
<tr>
<td>Other treatments</td>
<td>Experimental/ supplementary</td>
<td>• Unique MOA</td>
<td>Clinical data supporting safety and efficacy is limited to autoimmune disease</td>
<td></td>
</tr>
<tr>
<td>Splenectomy</td>
<td>Long-term treatment in patients with refractory/chronic disease</td>
<td>• Sustained long-term remission in the majority of patients</td>
<td>Invasive and irreversible [68] Potential risk of long-term adverse events, including increased risk of infections [67] Often not preferred by patients or parents/caregivers [52]</td>
<td></td>
</tr>
</tbody>
</table>

**Table 1: Summary of the Conventional Treatments of ITP.**
they are not usually considered for long-term use for chronic disease due to limited duration of response and long-term toxicity [53].

Corticosteroids: Corticosteroids suppress systemic reticuloendothelial phagocytic function and reduce antibody production [54], leading to reduced platelet destruction. Due to their low cost, simple administration, and good initial efficacy, corticosteroids are the standard starting treatment for ITP [25]. However, corticosteroids are often used in the short term only, as their long-term use is associated with significant adverse effects such as osteoporosis, diabetes, weight gain, hypertension, and cataracts [55], and because they do not typically elicit durable responses [49]. Ongoing studies are investigating maintenance with low-dose corticosteroids, which may help manage toxicity while extending the duration of response [56].

Intravenous immunoglobulin G (IVIG): IVIG contains the pooled plasma gamma globulin from > 1000 human donors. IVIG binds and saturates binding partners of endogenous antibodies and may block cellular receptors involved in autoimmune pathology and neutralize autoantibodies and cytokines [57]. IVIG is generally well tolerated, with adverse effects occurring in approximately 5% of patients [30]. However, because IVIG is a plasma-derived product, transmission of viruses remains a theoretical risk, and serious adverse events such as aseptic meningitis have been reported in some patients, particularly those with pre-existing risk factors [49].

Anti-D: Anti-D contains gamma globulin (IgG) fraction, including antibodies to the Rh (D) antigen. Anti-D is believed to block the macrophage system and neutralize autoantibody binding to platelets [58,59]. It is considered an alternative treatment to IVIG Rh(D)-positive and unsplenectomized patients, as some studies suggest anti-D has greater efficacy as compared with IVIG in ITP [60]. However, other studies provided mixed results [25]. Anti-D may also cause significant reductions in hemoglobin levels and has been associated with fatal intravascular hemolysis [25].

**Off-label immune modulators:** The treatments discussed in this section are used off label to treat patients with ITP and often are not supported by sufficient clinical evidence from large randomized trials.

- **Rituximab:** Rituximab is an antibody against the B-cell surface protein CD20, and it is considered to exert its immunosuppressive effects in ITP through depletion of B cells [61]. Rituximab is commonly used in refractory ITP patients in whom multiple previous treatments have failed [61] and has been recommended in the American Society of Hematology (ASH) 2011 clinical treatment guidelines. However, recent data from the first randomized and placebo-controlled long-term study of rituximab may warrant re-evaluation of the role of rituximab in the treatment of ITP, as the long-term results showed no maintained significant benefit of rituximab vs placebo beyond 78 weeks of use [51].

- **Older agents:** Several agents that have been in clinical use for various indications for more than 25 years, including danazol, dapsone, vinca alkaloids, hydroxy chloroquine, and others, have been utilized in ITP as alternative treatments since they are significantly less expensive compared with most other pharmaceutical options [50]. However, clinical data supporting their safety and efficacy in ITP are limited, and thus they are not recommended as monotherapy under current ITP treatment guidelines [25,52].

- **Others:** Other immunosuppressants that are used in a relatively small group of patients with ITP include mycophenolate mofetil (MMF) and rapamycin (also known as sirolimus). MMF is a noncompetitive inhibitor of the de novo purine synthesis pathway, which specifically inhibits proliferation of lymphocytes that are dependent on this pathway [62]. Although clinical studies showed some promise in children with autoimmune lymphoproliferative syndrome (ALPS) complicated by chronic autoimmune cytopenias [63], more data are needed to extrapolate

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![Figure 2 Pathogenesis of ITP and Treatment Options](image-url)
While romiplostim is still under evaluation in this population, Eltrombopag was recently also approved for pediatric use [70]. Peptide antibody fusion protein (peptibody) romiplostim [69]. Currently 2 TPO-RAs are approved for treatment of ITP in adults: treatments that aim to slow platelet destruction mechanisms. Increase platelet production as opposed to conventional agents; it was stated that data for these agents (azathioprine, the previous ASH guidelines for ITP (1996), ASH 2011 guidelines trials had not been completed at the time of publication. Unlike guidelines recommended corticosteroids, IVIG, or anti-D as first-line treatments; splenectomy or TPO-RAs (if splenectomy is contradicted or not preferred) as second-line treatments; and TPO-RAs or rituximab as third-line treatments. In children who require treatment, corticosteroids, IVIG, or anti-D were recommended as first-line treatments, and splenectomy or high-dose dexamethasone were recommended as second-line treatments. Rituximab was suggested for second-line treatment if splenectomy is contradicted, is not preferred, or had failed, and if there is significant bleeding and need for improved quality of life. TPO-RAs were not recommended in children because pediatric trials had not been completed at the time of publication. Unlike the previous ASH guidelines for ITP (1996), ASH 2011 guidelines no longer recommended alternative immuno-suppressive agents; it was stated that data for these agents (azathioprine, danazol, cyclosporine, etc) were not sufficient to support specific recommendations.

**TPO-RAs for the treatment of ITP**

**Overview:** TPO-RAs interact with the TPO receptor to increase platelet production as opposed to conventional treatments that aim to slow platelet destruction mechanisms. Currently 2 TPO-RAs are approved for treatment of ITP in adults: the oral small-molecule eltrombopag and the subcutaneous peptide antibody fusion protein (peptibody) romiplostim [69]. Eltrombopag was recently also approved for pediatric use [70]. While romiplostim is still under evaluation in this population, current data in pediatric patients are consistent with the efficacy and safety findings in adult patients [71,72].

Whereas romiplostim competes with TPO for the same binding region on the TPO receptor, eltrombopag binds to a unique region on the TPO. Thus, eltrombopag stimulates a distinct set of downstream signaling pathways (MAPK/ERK 1/2 and STAT-p5) vs the pathways stimulated by TPO and romiplostim (MAPK/ERK 1/2, STAT-p3/5, and AKT). These differences may allow an additive or synergistic effect when the target cells are simultaneously exposed to TPO and eltrombopag [70,71,73].

**Efficacy and safety summary:** TPO-RAs are the only treatment option for refractory ITP that has been shown to be effective in randomized clinical trials [23]. They are highly effective in increasing the platelet count in healthy volunteers and adult and pediatric patients with ITP in clinical studies [74–77], with response rates ranging from about 60% to almost 95% [75,77–80]. Notably, a recent retrospective real-world study confirmed these high response rates in clinical trials; an overall response rate of 94.2% was reported with eltrombopag vs 80% with romiplostim [80]. Importantly, TPO-RAs are safe and well tolerated; the adverse events reported were mostly mild or moderate [76,81]. Consequently, increases in health-related quality of life are evident in adult patients with ITP who receive TPO-RAs [78,82,83].

TPO-RAs have been considered as life-long maintenance therapies; although they are well tolerated in long-term use, their relatively high cost remains a concern. However, accumulating data indicate that TPO-RAs may enable long-term remissions that are maintained after discontinuation of all ITP therapies, including the TPO-RA itself, in a significant proportion of patients [84–86]. Emtrombopag-induced remissions were observed as early as the second month of TPO-RA treatment, but they may take years to occur [86]. Thus, the rate of long-term remissions, which is currently estimated at around 30% [84–86], may be increased with an optimal TPO-RA weaning algorithm whereby the dose is gradually decreased with careful monitoring over an extended period of time. It can be speculated that TPO-RAs promote remissions by the restoration of immune tolerance to platelets with persistent antigen exposure or expansion of the megakaryocyte pool in the bone marrow [87]. Characteristics such as autoantibody levels or the bone-marrow megakaryocyte pool may potentially play a role in establishment of durable remissions; however, thus far no association has been detected in clinical trials. In addition, it is not yet known if early use of TPO-RAs in persistent or newly diagnosed ITP would improve the rate of permanent remission.

Although TPO-RAs are best suited for chronic treatment for patients with ITP, rapid-responding immunosuppressants are still the treatment of choice in emergencies when an urgent platelet response is needed to stop or prevent critical bleeding events. TPO-RAs usually take approximately 2 weeks to achieve a desired therapeutic effect, whereas corticosteroids and IVIG work within days, rendering them more suitable for emergency use [68,88]. Another consideration with TPO-RAs is that the treatment duration is not clear at the time of treatment initiation. While some patients may achieve long-term remissions after a few months of TPO-RA treatment, others may need maintenance...
Therapy even after years of TPO-RA exposure [86]. Currently, no known biomarkers have been identified to predict whether maintenance therapy will be needed with TPO-RAs, and this uncertainty about treatment duration may affect patient preference and adherence [68].

TPO-RAs are also associated with certain risks in patients with ITP. Some patients may experience rebound or worsening of thrombocytopenia after discontinuation because their elevated platelet levels may have reduced endogenous TPO [89]. Additionally, liver function test abnormalities and bone marrow fibrosis have been observed with TPO-RAs, but these events are most often reversible upon TPO-RA discontinuation or interruption and not associated with clinical symptoms [70,71]. Other suspected risks of TPO-RAs include increased rate of thromboembolic events, cataracts, and the development of anti-TPO antibodies. The risk of such events, particularly in patients with pre-existing susceptibility factors, should be considered while making treatment decisions.

Combination therapies

Because manifold mechanisms are involved in pathogenesis of ITP (Figures 1,2), some ITP patients may not adequately respond to monotherapies that target a single pathogenic step. In treatment-resistant patients, combination treatments targeting multiple disease mechanisms may be more effective than monotherapy. Combinations of immunosuppressive treatments often resulted in improved treatment response as compared with monotherapy; examples include triple therapy with high-dose dexamethasone plus low-dose rituximab and cyclosporine, and low-dose rituximab plus high-dose dexamethasone [90,91]. However, a combination of TPO-RAs plus another immunosuppressive ITP treatment (ie, almost any other ITP treatment) addresses both major pathological mechanisms of ITP and may result in enhanced efficacy [92]. Moreover, the addition of TPO-RAs to ITP treatment regimens may also help reduce the dosage of or eliminate immunosuppressive medications, thereby decreasing treatment burden and morbidity associated with these medications [77,79].

DISCUSSION AND CONCLUSION

Pathogenesis of ITP involves 2 major mechanisms: increased platelet destruction and decreased platelet production. The varying levels of contribution of these processes to ITP pathology in patients may be responsible for the heterogeneity of responses to different treatment strategies. Conventional treatments for ITP address only symptoms or increased platelet destruction (Figure 2), and most of these treatments were originally developed for other indications. Although they have an important role in the management of ITP, they are also associated with undesirable and unpredictable side effects.

TPO-RAs, which improve platelet production, fill an important clinical need and show very high efficacy and good tolerability in patients with ITP. Clinical data demonstrate that patients whose disease is refractory to conventional treatments may benefit from TPO-RAs. It has been suggested that TPO-RAs may also normalize increased platelet destruction by inducing self-tolerance, thereby enabling long-term, treatment-free remissions in some patients. When used in combination with conventional treatments, TPO-RAs can help fully address ITP pathogenesis, which may lead to improved response rates. TPO-RAs may also help reduce the need for conventional treatments and thereby decrease treatment-associated morbidity and mortality.

With the advent of TPO-RAs, clinicians are now fully equipped to comprehensively treat the underlying pathology of ITP. Personalized treatment strategies devised with knowledge of pathogenic processes within an individual may help achieve the best treatment outcomes with the current armamentarium.

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Conflict of Interest

Ashok Raj has been a speaker for Novartis and advisor to Shire, Biogen and Octapharma.

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