

## Mini-review

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# Pathogenesis-oriented approaches for the management of corticosteroid-resistant or relapsed primary immune thrombocytopenia

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**Abstract:** Primary immune thrombocytopenia (ITP) is a complex autoimmune disorder in which the patient's immune system reacts with platelet autoantigens resulting in immune-mediated platelet destruction and/or suppression of platelet production. Corticosteroids can induce sustained remission rates in 50% to 75% of patients with active ITP. For these patients who are unresponsive to glucocorticoids, or relapsed after an initial response, multiple second-line treatment modalities can be chosen. However, how to make an optimal therapeutic strategy for a specific patient still remains a major challenge. As the pathogenetic heterogeneity of the ITP is increasingly identified, pathogenesis-oriented approach might offer an opportunity to improve the outcome of corticosteroid-resistant or relapsed ITP.

**Keywords:** ITP, Pathogenesis, Management.

## 1 Introduction

Primary immune thrombocytopenia (ITP) is an acquired immune-mediated disorder characterized by transient or persistent decrease of the platelet count (peripheral blood platelet count  $< 100 \times 10^9/L$ ) in the absence of conditions known to cause thrombocytopenia, and increased risk of bleeding depending on the degree of thrombocytopenia [1]. According to population-based studies, the overall incidence of ITP ranges from 3.2 – 12.1 per  $10^5$  adults each

year [2-4], and recent epidemiologic data suggest nearly equal incidence for both sexes, except in women of child-bearing age, when the disease is more prevalent in female [2]. ITP in adults typically has an insidious onset which is usually followed by a chronic course. Manifestations of ITP are very heterogeneous. A large proportion of patients have either no symptoms or minimal bruising, while others may exhibit severe bleeding, such as intracranial hemorrhage (ICH), gastrointestinal hemorrhage (GI), or extensive skin and mucosal hemorrhage. Besides the level of platelet counts, additional factors (life style, age, uremia, etc) affect the risk of bleeding in ITP.

Historically, ITP has been thought as an autoantibody-mediated hemorrhagic disease involving increased platelet destruction by macrophages in the reticuloendothelial system [5]. Aside from humoral immune abnormalities, T-cell-mediated immunity also plays important roles in platelet destruction. Antiplatelet autoantibody production is under the control of platelet-specific T helper (Th) cells, and loss of tolerance to self antigen by T cells is the critical step of the immune dysregulation in ITP [6,7]. Antiplatelet T-cell reactivity in ITP patients has been shown to be enhanced at polyclonal and oligoclonal levels [8-11]. Defects of the apoptotic pathway in T cells could promote the survival of autoreactive T cells in ITP. Additionally, T-cell subset polarization in ITP has been attributed to increased Th1 [12,13], Th17 [14], Th22 cells [15,16] and reduced number or function of CD4<sup>+</sup>CD25<sup>+</sup>Foxp3<sup>+</sup> T-regulatory cells (Tregs) [17,18]. CD8<sup>+</sup> cytotoxic T lymphocyte (CTL)-mediated platelet lysis or apoptosis is another mechanism of platelet destruction [19,20], especially in patients with negative glycoprotein (GP)-specific autoantibodies [21]. Besides the accelerated platelet clearance, the decreased platelet production has been recently identified as an important mechanism contributing to thrombocytopenia in ITP. Autoantibodies may impair megakaryocyte development and maturation, induce apoptosis-like programmed megakaryocyte death, and impede platelet release. CTLs in bone marrow of ITP

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have also been reported to impair platelet production via suppression megakaryocyte apoptosis.

Glucocorticoids, intravenous immunoglobulin (IVIG), and anti-D immunoglobulin (anti-D) are traditional first-line therapy for ITP and most patients achieve a durable response. For patients who fail first-line therapy, splenectomy or second-line drugs such as Rituximab, thrombopoietin-receptor agonists (TPO-RAs) and immunosuppressive agents can be chosen. Management of ITP is dependent on multiple factors such as platelet count, bleeding symptoms, patient age, health-related quality of life, and side effects associated with therapy [22]. Moreover, patients' perspective, anticipated response rates, comorbidities, and compliance should be taken into account when making treatment plans.

## 2 Highlights

Treatment of ITP should always be tailored to the individual patients, and novel pathogenesis-oriented approaches might be potential for the management of corticosteroid-resistance or relapsed ITP.

## 3 Discussion

Recent years have witnessed major progress in the management of ITP as several novel agents have been developed. Based on the mechanism of action, available second-line treatment modalities for ITP can be broadly classified into those that target to decrease the destruction of platelets, and those that aim to increase the production of platelets. The major site of platelet destruction is spleen in which autoantibody-opsonized platelets are phagocytosed by macrophages in a Fc $\gamma$  receptor (Fc $\gamma$ )-dependent manner. Fc $\gamma$ R blocking treatment with IVIG has been used for a long time. Our group recently found that the efficacy of IVIG or dexamethasone in ITP was associated with autoantibody species, and GPIIb $\alpha$ -autoantibody-positive patients were demonstrated to be less responsive to IVIG or dexamethasone therapy comparing with GPIIb $\alpha$ -autoantibody-negative patients [23,24]. Splenectomy removes both the mechanism of platelet destruction and a large source of autoantibody production. Standard medical treatment modalities that aim to decrease platelet destruction in ITP include a variety of immunosuppressive or immunoregulatory agents. For instance, B-cell depletion therapy with rituximab has been successfully used in inducing remission

of ITP [25,26]. Other immunosuppressants, such as cyclosporine A (CsA), cyclophosphamide (CTX), azathioprine, mycophenolatemofetil (MMF), and vinca alkaloids have been shown to be clinically effective in ITP management. Rather than modulating the immune system, another therapeutic approach is to stimulate platelet production. TPO is the primary factor regulating platelet production. Along these lines, the TPO-RAs, eltrombopag [27,28], romiplostim [29,30], and recombinant human thrombopoietin (rhTPO) launched in China [31], have been shown to be effective, with comparatively high response and low toxicity. Before administering these drugs, possible side effects and methods of administration should be considered to ensure a safe environment for drug use.

ITP is a very heterogeneous condition and it is unlikely that a single pathogenetic mechanism underlies all cases. Experimental treatment using combination therapy with different drugs targeting diverse mechanisms of action has yielded encouraging outcomes. Two groups recently reported identically that dexamethasone plus rituximab could induce higher response rates and longer time to relapse than dexamethasone monotherapy, with non-overlapping toxicities in previously untreated adult ITP [32,33]. However, compared with dexamethasone monotherapy, dexamethasone plus rituximab therapy showed increased incidences of grade 3 to 4 adverse events (AEs), including pneumonia, fever, transaminase increase, et al [32,33]. In order to reduce serious AEs, combination therapy should avoid overlapping toxicities of drugs as much as possible. rhTPO in combination with CsA was reported to be effective for the management of corticosteroid-resistant ITP, with a relative short time to response and low recurrence rate [34]. Our recently published results from a multicenter clinical trial showed that the combination therapy with rituximab and rhTPO which targeted both increased platelet destruction and insufficient platelet production, could overcome the long time to response (TTR) of rituximab and short duration of response of rhTPO, thus yielded a shorter TTR and a longer time to relapse compared with rituximab monotherapy in the treatment of corticosteroid-resistant or relapsed ITP [35]. A triple-therapy regimen combining romiplostim with CsA and IVIG were demonstrated to be effective to manage patients with refractory ITP. These 3 agents target different mechanisms of ITP pathobiology: inhibition of T cell activation (CsA), stimulation of platelet production (romiplostim), and Fc $\gamma$ R blockade (IVIg), and were well tolerated in most patients [36]. Nevertheless, it is notable that the abstract presented by Leven E, et al. at the 54th ASH annual meeting was a retrospective study, and only 9 patients were included. Furthermore, dosages

of CsA, IVIg and romiplostim in the study were individually adjusted, lacking a unified criterion [36], and further perspective studies are needed to evaluate the effectiveness and safety of the therapeutic modality [36]. Recently, our group showed that exogenous rhBAFF could not only promote the survival of CD19+ B cells and CD8+ T cells, but also increase the apoptosis of platelets *in vitro*. Moreover, it is noteworthy that effect of rhBAFF could be neutralized by BAFF-R-Fc fusion protein (BR3-Fc) [37]. Considering the crucial role of elevated B-cell activating factor (BAFF) in the maintenance of autoreactive B-cell development [37-40], blockade of BAFF signaling with BAFF-receptor-Fc fusion protein (BR3-Fc) or belimumab might be potential in ITP treatment [40,41]. In line with that, rituximab in combination with BAFF inhibitors might be a novel promising therapeutic strategy for ITP management as additional BAFF blockade could antagonize the strengthened BAFF signaling which was a feedback of B-cell loss induced by rituximab. Further clinical trials are needed to evaluate the effect of those novel therapeutic modalities in ITP.

During the past few years, a growing body of emerging evidence has advanced our appreciation of the pathophysiology of ITP and improved our understanding of the heterogeneity of the disease. Further exploration of the pathogenesis of ITP would help to identify disease features and predictors of treatment response, thus facilitating the decision-making process for ITP management. Taking together, the potential mechanisms of ITP are multiple, and novel pathogenesis-oriented approaches could act as potential therapeutics for the treatment of corticosteroid-resistant or relapsed ITP.

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