



Efficacy and mechanism of intravenous immunoglobulin treatment for immune thrombocytopenia in adults

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Contributions: (I) Conception and design: DR Branch; (II) Administrative support: None; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Abstract: Intravenous immunoglobulin (IVIg) has been used for almost 40 years as a biologic therapeutic for the treatment of immune thrombocytopenia (ITP). Originally found to ameliorate ITP in pediatric patients, IVIg is now used to treat adult patients with acute and chronic ITP and has become a first-line therapy for this autoimmune disease. Treatment in adult ITP usually consists of high-doses of IVIg, usually 1–2 g/kg given as one bolus dose or over 4 to 5 days. Success rates vary but in adults with acute ITP, response rates are around 60% but often the response is transient. In chronic ITP, IVIg is not as efficacious and is often used in combination with other therapeutics, such as glucocorticoids or rituximab or, rarely, these patients will undergo splenectomy. Despite its many years of use, the mechanism of action of IVIg in ITP remains controversial. Although IVIg has a good record of low toxicity in adult patients, most products contain anti-A and anti-B iso-agglutinins, which can cause hemolysis in non-blood group O patients, sometimes life-threatening, with blood group AB patients being at highest risk for a severe hemolytic episode. In addition, IVIg is expensive and is susceptible to world-wide shortages due to its human source material and expanding use to treat various autoimmune/inflammatory diseases. Despite these caveats, IVIg will likely continue to be a first-line therapy for adult ITP, particularly if bleeding.

Keywords: Immune thrombocytopenia (ITP); mechanism; platelets; treatment; intravenous immunoglobulin (IVIg)

Received: 21 October 2020; Accepted: 10 December 2020; Published: 31 March 2021.

doi: 10.21037/aob-20-87

View this article at: <http://dx.doi.org/10.21037/aob-20-87>

Introduction

Immune thrombocytopenia (ITP) is a complex and rare autoimmune disease characterized by reduced platelet counts (peripheral blood platelet count $<100 \times 10^9/L$) that can lead to an increased bleeding risk (1,2). ITP may be a primary condition in the absence of other underlying causes or disorders, or it may be secondary, associated with or caused by other diseases such as an infection, an autoimmune disease, or malignancy (2). ITP can be further classified according to The International ITP Working

Group (IWG) as newly diagnosed ITP (acute; up until 3 months), persistent ITP (lasting 3–12 months, more prevalent in children), chronic ITP (lasting >12 months, more prevalent in adult patients) (2-4). This classification is important because patients with newly diagnosed and persistent ITP have significantly higher remission rates than patients with chronic ITP (2,5-8). Therefore, physicians usually recommend a more rigorous treatment plan for patients with chronic ITP, which is more predominant in adult patients (2).

Signs and symptoms, mainly hemorrhagic symptoms,

are widely variable. While the predominant symptom is bleeding, and increased risk of bleeding poses the major clinical problem for ITP, bleeding symptoms may not always be present as the clinical presentation varies among ITP patients (2,5-10). Most of ITP patients are asymptomatic at presentation or show mild skin bruising and mucocutaneous bleeding (e.g., sporadic bruises or epistaxis), while only few patients present with severe, life-threatening bleeding, such as gastrointestinal bleeding and rarely, intracranial hemorrhage (4,11,12). Noteworthy, it has been shown that the risk of severe bleeding is not necessarily correlated with platelet counts unless the absolute platelet count is lower than $20 \times 10^9/L$, as other factors such as age, lifestyle and other clinical condition of the patient may play a role (12-17). Noteworthy, while there are similarities between children and adults with ITP, there is increased evidence that highlight several distinctive characteristic of adult ITP, such as higher rates of comorbidities and chronicity compared to children with ITP (18-20), and which can be valuable characteristics to further improve and personalize the diagnosis and treatment of this disease.

The diagnosis of ITP is one of exclusion (6). Thus, and in the absence of a “gold standard” diagnostic test for ITP, the diagnosis for this disorder remains clinical where history, physical examination, and laboratory testing are necessary to exclude other causes of thrombocytopenia (1,6,21,22). Currently, there are no clear cut-off diagnostic tools or laboratory tests to diagnose ITP, to predict the treatment response, or to identify the best treatment option for ITP patients. Therefore, the International Working Group and the American Society for Hematology published guidelines for the diagnosis and management of ITP (5,6,9,10). However, the existing guidelines are based on opinion of professionals and experts more than on the evidences of the studies (23,24).

Although treatment for patients with ITP should always be personalized to the individual patient (5,25), glucocorticoids (steroids) and intravenous immunoglobulin (IVIg), which are the most common therapeutic options, having replaced splenectomy, remain the initial ITP treatment for both newly diagnosed patients and chronic patients needing immediate rescue therapy (5,6). Glucocorticoids (GCs) are the conventional front-line therapy for ITP patients, typically either as prednisone or dexamethasone (5,6). Prednisone, the standard treatment recommended in practical guidelines for ITP, administrated at 1 mg/kg daily until the platelet level increases ($\geq 50 \times 10^9/L$;

can require several days to weeks) is considered the most common treatment strategy (5,26,27). GCs are an inexpensive treatment option, and it has been observed that about 70% of patients respond to the treatment within 1–2 weeks (28). Unfortunately, it has been indicated that about 70–90% of patients treated with GCs relapse when the treatment is stopped or even reduced (29). In addition, it has been revealed that GCs are associated with potentially severe side effects, and the detrimental effects of corticosteroids can create significant complications and reduce the quality of life of patients (6). Although IVIg is more expensive than GCs, it is better tolerated and is generally considered to be a safe therapy due to the minimal side effects (6,30,31). In addition, in contrast to conventional GCs treatment, it has been shown that IVIg induces recovery of platelet counts within a couple of days (32), demonstrating its therapeutic advantage when a rapid increase in the number of platelets is required, such as patients with a high risk of critical bleeding (6,23,29,33). IVIg is a blood product enriched with IgG antibodies that is obtained via collection and pooling of human plasma from several thousands of donors (34-38). IVIg is generally recommended for ITP patients under critical bleeding condition, as an emergency rescue procedure, and even for those not responding to GCs or cannot tolerate glucocorticoids (6,23,33). Several clinical trials have shown that IVIg (up to 1 g/kg) is an effective treatment in 70–80% of patient with ITP (39-42). The aim of this review is to focus on the efficacy and the general mechanisms of IVIg therapy used to treat adults with primary ITP. However, first we will provide an introduction into the pathogenesis of ITP to better understand the rationale of this important treatment.

Pathophysiology of ITP

ITP is an autoimmune hemorrhagic disease and its pathophysiology involves both excessive platelet destruction in the spleen and liver and insufficient platelet production in the bone marrow, resulting in low platelet counts (43-45).

Increased peripheral platelet destruction

Traditionally, platelet destruction in the spleen and/or liver, and less so in the periphery, is the main cause for low platelet counts in ITP. Antibody-coated platelets are destroyed by macrophages in the spleen and/or liver through interaction with Fc-gamma receptors

(Fc γ R) (46) (*Figure 1A*). In the 1950s, Harrington infused blood from ITP patients to healthy volunteers, one of which was himself, and showed that most recipients demonstrated profound thrombocytopenia/low platelet counts (47). The transmissible causative factor in the blood serum was subsequently identified as an immunoglobulin, primarily immunoglobulin G (IgG), which was the first proof that a humoral factor is involved in ITP pathogenesis (48). Noteworthy, while the antiplatelet antibodies in ITP are primarily IgG, other immunoglobulin isotypes (IgA and IgM) can also be found (49). Anti-platelet antibodies are directed against platelet membrane glycoprotein (GP) or GP complexes mainly GPIIb/IIIa and GPIb/IX/V, and less against GPIa/IIa, IV or VI (49-52). As a result, anti-platelet antibodies targeting GPIIb/IIIa participate in platelet destruction when the platelets are opsonized by the attachment of autoantibodies to the GP, then bound to Fc γ Rs expressed on macrophages, and phagocytosed (43,44). Following the phagocytosis, these macrophages present a platelet-derived antigen that stimulates CD4⁺ T cells, which can contribute in the activation of B cells (53). This activation leads to the differentiation of auto-reactive B cells into plasma cells to produce anti-platelet antibodies (53,54). While autoantibodies against platelet GP remains a major mechanism in the ITP pathogenesis, it is important to mention that these autoantibodies are not detected in almost half of patients with ITP, which suggest the involvement of other mechanisms (55). For instances, it has been shown that the immune platelet destruction in ITP is also associated with wide range of B-cell and T-cell involvement (46,56,57). In addition to removal of platelets by Fc γ R-mediated mechanisms, anti-GPIb/IX has an unusual activity where the antibody binds to platelets and removes sialic acid (58,59). These desialylated platelets are then removed through interaction with the Ashwell-Morell receptor on hepatocytes in the liver (60). This interaction results in production of the platelet growth factor, thrombopoietin (TPO), likely as a feed-back mechanism in an effort to produce more platelets. CD8⁺ cytotoxic T lymphocytes (CTLs) also plays a role in ITP and can directly kill platelets and megakaryocytes and/or induce desialylated platelets (61,62) (*Figure 1A*).

Furthermore, while genetic predispositions in ITP are uncommon, there are genetic polymorphisms in cytokines and Fc γ Rs that may increase the risk of developing the disease in some people by participating in the initiation of the autoimmune process (63-68). Molecular mimicry may

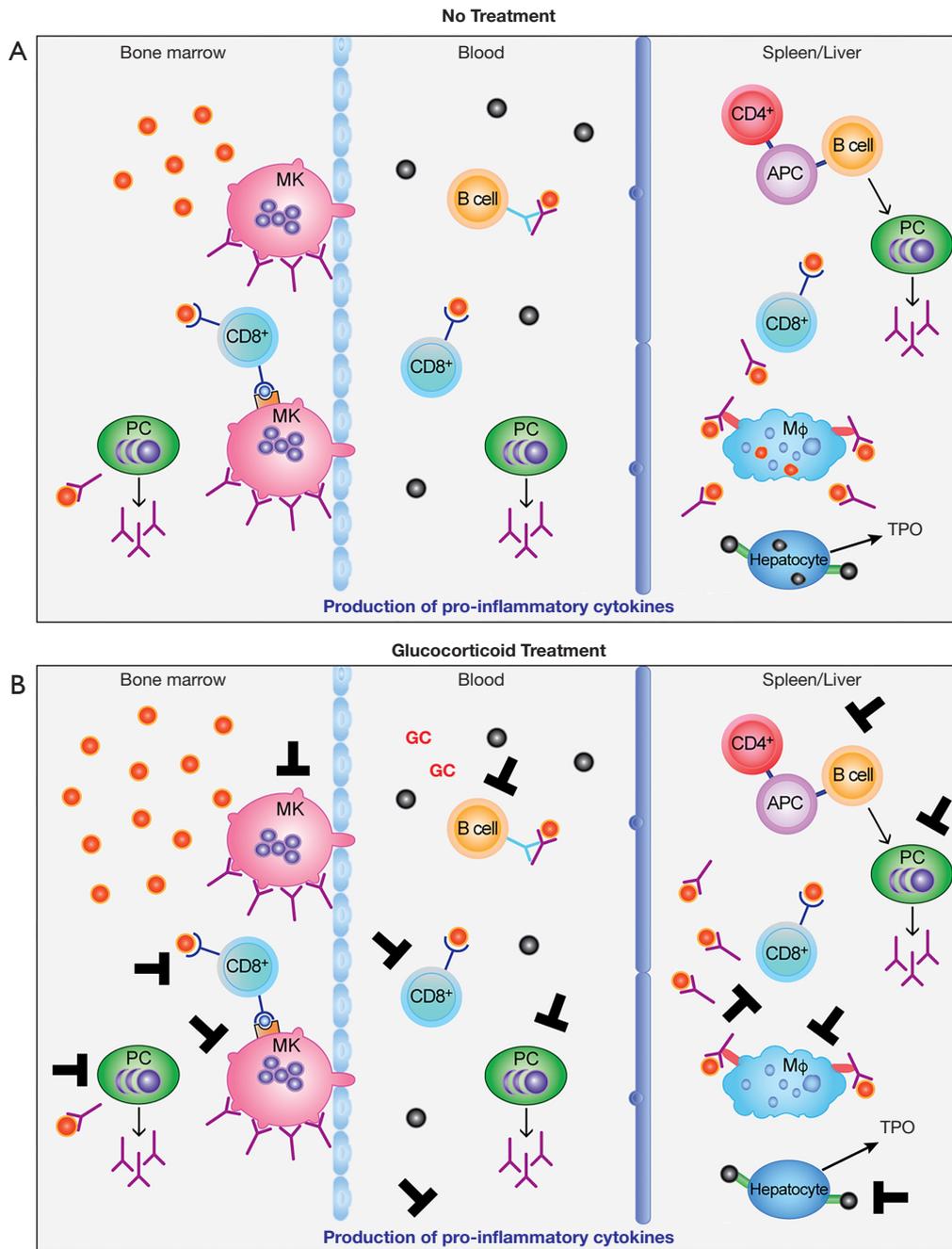
play a role in the development of cross-reactive platelet auto-antibodies as certain viral and bacterial pathogens such as human immunodeficiency virus (HIV), hepatitis C virus (HCV), varicella-zoster virus (VZV) and *Helicobacter pylori* (*H. pylori*), may express antigens/proteins that are similar to platelet GPIIIa (69-72). Interestingly, it has been shown that some peptides from these viral proteins are recognized by anti-platelet antibodies *in vitro* due to the similarities between the sequences of these viral proteins and platelet GPs (22). Although the absence of these bacterial and viral infections leads to remission in most patients with ITP, there is still a high variation in response rates in patients infected with *H. pylori* (73).

In addition, anti-platelet antibodies can mediate complement-dependent cytotoxicity, inhibit megakaryocyte function, and induce desialylation-induced platelet destruction (74-78). It has been shown that the destruction of platelets in ITP patients results in a shorter life span compared to healthy humans as confirmed by different groups using Chromium-51 labeled platelets or Indium-111 labelled platelets (79-83). This may be a result of an activated mononuclear phagocyte system in ITP patients. Noteworthy, the theory of increased platelet destruction in the spleen was also supported by the effectiveness of splenectomy in raising platelet counts in patients with ITP (81,84-86).

Decreased platelet production

Besides the platelet destruction in the circulation, mechanisms leading to inadequate platelet production in the bone marrow due to an immune response against megakaryocytes is also involved in the pathogenesis of ITP (87-90). While the immune mechanisms of insufficient platelet production in ITP remain not very well-known, there are some indications in some studies.

It has been shown that megakaryopoiesis is strongly affected in ITP as evidenced by an increase in the proportion of premature megakaryocytes and impaired development, which can be characterized by a decrease in the granularity, ploidy, cytoplasmic vacuolization and nuclear condensation, leading to significant reduction in platelet production (86,88,91). The results of radiolabeled platelet studies have revealed that the megakaryocytes in healthy individuals were able to produce 10 \times as many platelets as the megakaryocytes from patients with ITP during states of blood loss (45,86). A decrease in megakaryocyte maturation, abnormalities in thrombopoiesis, and inadequate platelet production rely on



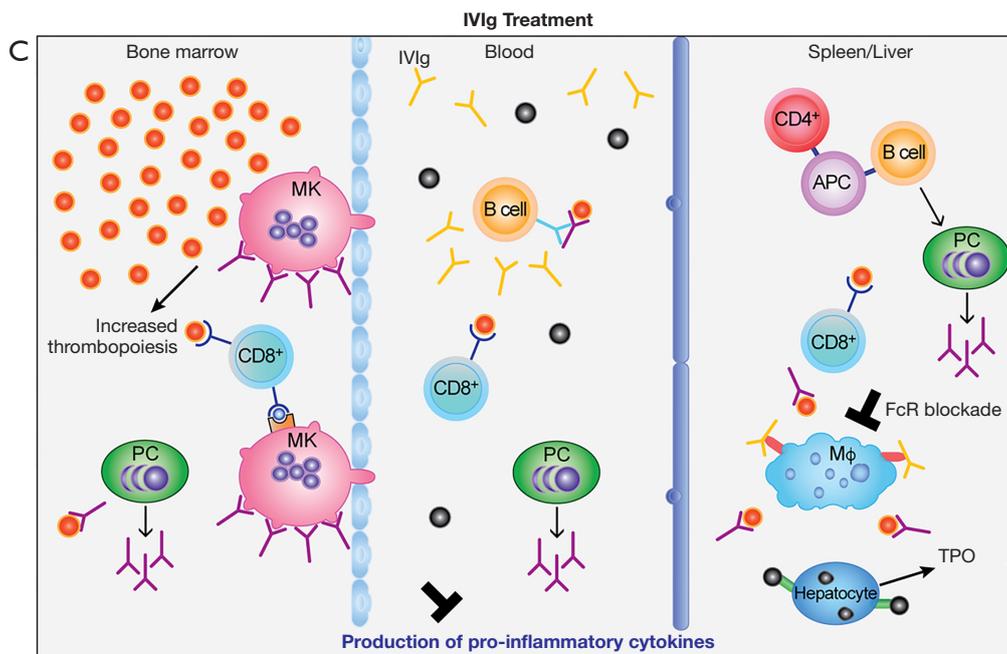


Figure 1 The pathophysiology of ITP and how first-line therapies ameliorate the disease. (A) No treatment. Platelets (orange) are produced by megakaryocytes (MK) located in the bone marrow. Autoantibodies (purple) to platelet glycoproteins can be produced by plasma B-cells (PC) in the bone marrow, but predominantly are produced within the spleen. These autoantibodies are produced as a result of loss of immune tolerance and require antigen presenting cells (APCs), CD4⁺ helper T-cells and B-cells. The autoantibodies recognize and bind to platelet glycoproteins and interact with monocyte-macrophages (Mφ) in the spleen and/or liver through binding to Fcγ receptors (FcγRs; salmon pink), resulting in their removal from the circulation due to phagocytosis. Furthermore, platelets can lose sialic acid and these desialylated platelets (black) can be removed in the liver by hepatocytes (dark blue) expressing the Ashwell-Morell receptor (green). This results in the production of thrombopoietin (TPO) but also increased clearance of the desialylated platelets. In addition to receptor-mediated increased platelet clearance, CD8⁺ T-cells (cytotoxic T-lymphocytes, CTLs), can also recognize platelet glycoproteins and destroy circulating platelets or induce desialylated platelets. As platelet glycoproteins are found on the surface of megakaryocytes, both platelet antibodies and CD8⁺ CTLs can attack the megakaryocytes causing apoptosis and a reduction in platelet production. ITP patients also have increased production of pro-inflammatory cytokines. (B) Glucocorticoid (GC) treatment. First-line therapies to ameliorate ITP include the primary class of drugs known as glucocorticoids. GCs are small-molecule, powerful immunosuppressive agents used to treat a myriad of autoimmune diseases. GCs (red) in the blood enter various cell compartments and then, once inside the cell, bind to glucocorticoid receptors, disrupting signal transduction which affects most aspects of the immune response. Mφ phagocytosis of autoantibody-coated platelets and hepatic cell clearance of desialylated platelets is inhibited (⊥). GCs also down-regulate autoantibody production in the spleen by inhibiting the CD4⁺ T-helper cell compartment resulting in inhibition of the immune response and CD8⁺ CTL killing (⊥). GCs also result in inhibition (⊥) of pro-inflammatory cytokine production. (C) IVIg treatment. IVIg is first-line therapy if a patient is bleeding, as its ability to increase platelet numbers is more rapid than that of GCs. The mechanism of action of IVIg amelioration of ITP when it enters the blood is less understood than that of GCs. Mouse models reveal that IVIg (yellow) likely can bind to free Fc receptors on Mφ; thus, blocking their interaction with antibody-coated platelets, increasing the numbers of circulating platelets. In addition, IVIg induces thrombopoiesis in megakaryocytes, increasing production of platelets which also increases circulating platelets. Like GCs, IVIg is an anti-inflammatory agent and has been shown to reduce pro-inflammatory cytokines in ITP, similar to GCs, and its effects on cytokine profiles likely also affects T- and B-cell responses.

a specific immune response caused by autoantibodies and/or T-cell mediated megakaryocyte inhibition and destruction (46,92-94).

Additionally, it has been shown that inappropriate levels of TPO contribute to inadequate platelet production in ITP (53,95,96). TPO, the main growth factor of megakaryocytes, is predominantly and constitutively synthesized in the liver to regulate thrombopoiesis via binding and activation of its receptor, cMPL, on the megakaryocyte and platelet (97,98). Thus, the higher number of platelets released into the circulation, the lower TPO level required to stimulate the megakaryocytes to produce more platelets (99). Therefore, levels of TPO increase in the serum as an automatic compensatory response to thrombocytopenia, which has been observed by several studies (95,100-105). However, this is not the case in ITP as despite the low number of platelets in the circulation, the TPO concentration is not elevated and, instead, remains within the range of healthy individuals, which is not enough to bind to cMPL on megakaryocytes to increase platelet production in the bone marrow (53,96,104-106). Moreover, studies using electron microscopy showed that megakaryocytes from patients with ITP frequently undergo apoptosis (107,108), which may further contribute to the insufficient platelet production in these patients.

Finally, ITP has been found to present a skewed cytokine profile (109). Pro-inflammatory cytokines such as IL-2/IL-17 produced by Th1/Th17 T-cells have been documented, which can have a profound effect on T-regulatory cells and Th2 anti-inflammatory cells.

While an increase in platelet destruction and a decrease in platelet production are central aspects in the pathophysiology of ITP, patients with ITP vary with the degree of these two processes with several abnormalities and multiple components of the immune system involved (58-62,109). Therefore, this complexity and variations have led to different approaches and opened different ways for the design of specific immunotherapies to treat patients with ITP based on a case-by-case basis.

Pediatric versus adult ITP

ITP is a disorder that occurs in both adults and children with considerable differences between these two populations (110). For instance, the incidence rate of primary ITP is approximately 1.9–6.4/100,000 in children per year, and about 3.3–3.9/100,000 adults per year (2-4,111). Noteworthy, research studies and the

epidemiologic data suggest that ITP that occurs in adults under the age of 65 years is more prevalent in women (ratio ~2:1) (2,4,112-117). One of the most well-documented distinctions between adult and children is that ITP in most pediatric patients tends to be acute/transient and more likely resolved eventually without any treatment. Most children undergo spontaneous remission and rarely experience active bleeding, although most of these patients still experience skin bruising and bleeding (5,6,18,19). Chronic ITP, however, is more prevalent in adult patients (~ 70–80%) and difficult to treat, as adults with ITP tend to have a higher risk of bleeding and a lower spontaneous remission rate (4,23,118). Therefore, current treatment protocols and practice guidelines for ITP are considered and developed in relationship with the clinically relevant differences between children and adult patients (5,6,23,24).

The current goals of treatment for patients with ITP are to prevent or minimize serious risk of bleeding, improve quality of life, and to achieve a safe hemostatic platelet count (generally considered to be around $20\text{--}30 \times 10^9/\text{L}$), which can vary between patients (119,120). Thus, considering the nature of the disease and symptoms, it has been shown that adults with ITP often undergo pharmacological therapy and splenectomy more than children (5,6,117). For newly diagnosed patients with ITP, observation and waiting without treatment is a standard approach for children whose platelet counts are above $20 \times 10^9/\text{L}$ with no or mild bleeding, while treatment is incorporated as standard clinical practice for adults with a platelet count below $30 \times 10^9/\text{L}$, which is more likely influenced by the higher risk of bleeding in adults (5,6,117,121-123). According to the American Society of Hematology 2011 evidence-based guidelines and the International Consensus Report, Glucocorticoids, IVIg, or Rh immune globulin (RhIg) (anti-D) are recommended as first-line treatments for ITP, and they are used in both children and adults with ITP (1,5,6) (see *Table 1*). In this review article the focus will be on IVIg therapy used to treat ITP in adult patients.

IVIg efficacy in adults with ITP

IVIg is a blood product enriched with IgG antibodies that is obtained via collection and pooling of human plasma from several thousands of donors (34-38). The manufacturing processes of IVIg include several steps such as precipitation, chromatography techniques and viral inactivation steps to purify the products, maximize tolerability and efficacy, and to minimize side effects (124,125). While the serum IgG is

Table 1 Comparison of treatment regimens for pediatric versus adult with immune thrombocytopenia (ITP)

Variables	Pediatric	Adult
Trigger→	Often secondary (viral)	Usually primary/idiopathic
Course→	Spontaneous remissions common	Low (up to 20%) spontaneous remission rate
1 st line→	IVIg; Rhlg; or glucocorticoids +/- IVIg	Glucocorticoids; IVIg*; Rhlg**; IVIg + glucocorticoids
2 nd line→	TPO receptor agonists, rituximab, splenectomy (less likely to be used in children), others (immunosuppressant medications, etc.)	TPO receptor agonists, rituximab, splenectomy, others (immunosuppressant medications, Syk inhibitors, combination therapy)

*, IVIg is appropriate first-line therapy in adult ITP patients with bleeding, or at high risk for bleeding, who require a surgical procedure, or who are unresponsive to glucocorticoids. **, Rhlg (anti-D) can be used in adults, but it is uncommon because of the black box warning from the FDA about potential hemolytic anemia and disseminated intravascular coagulation (DIC). IVIg, intravenous immunoglobulin; Rhlg, Rh immune globulin (anti-D); TPO, thrombopoietin; Syk, spleen tyrosine kinase.

the dominant fraction in all the prepared IVIg, IVIg also contains small amounts of other proteins and components such as albumin, IgA, IgE, IgM, sugars, salts, solvents and buffers, which vary from batch to batch depending on the preparation and manufacturing processes (34,36). These variabilities may contribute to tolerability complications and side effects post infusion (34,36). Therefore, these variables should be carefully considered in relation to the clinical and physiologic conditions of the recipient. In general, IVIg is considered safe and well tolerated with minimal mild and transient side effects (most commonly; headache, fever, chills and nausea) and rare serious adverse events (AEs) such as thrombosis and hemolysis (6,31,36,126) (see below).

IVIg has been used for more than 40 years to treat ITP, initially used to treat primary immunodeficient patients and then later approved to be used to treat several autoimmune diseases and other conditions, including ITP (127-133). In ITP, IVIg is generally considered an effective and safe treatment option as high-quality evidences showed its favorable immunomodulatory effects (134,135). Although the mechanisms of actions of IVIg are complex and still unclear, there are several mechanisms that have been proposed and extrapolated (discussed in further detail below); but most of these mechanisms are extrapolated based on animal models. Nevertheless, in humans, it has been revealed that IVIg plays a role in increasing the platelet lifespan *in vivo* by reducing the splenic clearance of platelets (136), via Fc-dependent mechanism (6,137).

IVIg was initially shown to be effective in the treatment for ITP when Imbach and colleagues, early in the 1980s, showed an immediate increase in platelet counts in patients with ITP post infusion with IVIg (127). In their study, high-dose IVIg was given at 400 mg/kg over 5 consecutive days.

This was the first breakthrough study describing the use of IVIg to treat ITP. Subsequent studies by the same group showed that more than 80% of ITP patients positively responded to IVIg shortly after treatment (138). Later studies confirmed the effectiveness of IVIg in the treatment of ITP in adult populations, with a comparable clinical response rate, leading to the widespread use of IVIg as an immunomodulatory therapy (6,139-141).

As the immunomodulatory effects of IVIg in ITP depend on the administered dose, the efficacy of different IVIg doses was studied to evaluate and establish the optimal IVIg dose for adults with ITP (142,143). As a result, the original/historical dose of IVIg (administered at 0.4 g/kg daily for 5 days) has been replaced by using a higher initial dose (0.8–1 g/kg) for a short course of treatment, with the possibility to repeat the treatment based on platelet response. A randomized, multicenter trial showed that a 1 g/kg dose of IVIg was more effective in adults with ITP than a 0.5 g/kg regimen, as the results clearly demonstrated a greater increase in platelet count ($106 \times 10^9/L$ versus $55 \times 10^9/L$) and platelet response rate (67% versus 24%; day 4) in the higher-dose group compared with the lower-dose group (142). In this study, they also showed that additional IVIg doses for a total dose of 2 g/kg for non-responders lead to a response rate of 78% in the entire population in the study. To date, numerous studies and clinical trials have demonstrated that high-dose IVIg (1–2 g/kg) has become an effective first-line therapy in up to 80% of adult patients with ITP (37,40,131,134,144-146). On the basis of these studies, the current dosing guidelines by the American Society of Hematology is administration of 1 g/kg IVIg as an initial single dose, repeated as needed based on platelet response (5).

Noteworthy, while several studies have demonstrated the effectiveness of IVIg (up to 1 g/kg) in patients with ITP with a response rate around 80%, most of those studies used only 5% IVIg (146-148). Within the past few years, however, higher concentrations of IVIg (10%) products have been developed and introduced as a new therapeutic choice to improve treatment outcomes (17,40). In comparison to 5% IVIg formulation, the 10% IVIg product was associated with shorter infusion time, which resulted in decreasing the patients' length of stay in hospitals (40,41). Indeed, a number of studies have now been performed to assess the efficacy and safety of several novel human IVIg 10% such as Panzyga[®] (Octapharma; ready-to-use) (40), 10% IVIG-SN (Green Cross Pharma) (39), Octagam[®] (Octapharma; ready-to-use) (149) and Privigen[®] (CSL Behring) (42). Ten percent IVIg is now the standard product used to treat ITP; however, 20% IVIg has recently come onto the market for subcutaneous administration (SCIg) (150-153). Although not currently used to treat ITP, this product shows promise to replace intravenous IVIg administration in the future and further studies will show if this therapeutic approach has efficacy in adult ITP (150). Even though the current IVIg products have a good safety profile and have been shown to be effective treatment for patients with ITP, there are challenges associated with product production, access and availability. Therefore, introduction of new or better products is also needed to maintain a steady and adequate supply and to provide additional options for patients.

While IVIg administered at a dose of 1–2 g/kg typically leads to rapid increases in platelet counts (within 24 to 48 hours) in over 80% of patients, it has been found that the remission post IVIg treatment lasts no longer than 3 to 4 weeks, indicating that this response may be transient (142,154,155). Accordingly, once a patient relapses, particularly when platelet counts fall below $30 \times 10^9/L$, repeat IVIg administration or additional therapy, such as combination therapy using IVIg plus glucocorticoids or second-line therapy such as rituximab, may be necessary as maintenance therapy or to achieve a stable clinical condition for adult patients with ITP (6,139-141,143,155-157). Therefore, a better understanding of the properties and mechanism(s) of action of IVIg, may not only improve the current products but also may influence the future of immunoglobulin-based therapeutics.

IVIg mechanism of action

Following the serendipitous discovery in 1981 by Imbach

et al. (127,158) that high-dose IVIg could ameliorate ITP in secondary immune deficiency pediatric patients with concomitant ITP, studies by Fehr *et al.* (139) showed that following administration of IVIg, clearance of radiolabeled antibody-opsonized red blood cells was inhibited. These observations led to the hypothesis that the mechanism of action of IVIg to ameliorate ITP was through blockade of the Fc receptors (139,159-161) (*Figure 1*). This amazing discovery of the immunomodulation of ITP by high-dose IVIg caused other clinicians to begin to examine the use of IVIg for the treatment of other autoimmune and inflammatory diseases (162). Indeed, both evidence-based and off-label use of IVIg in many studies demonstrated the utility of using IVIg for the treatment of a variety of conditions (163,164). These clinical findings of the broad immunomodulatory properties of IVIg resulted in the expansion of the possible mechanism(s) of action of this biologic to include immunomodulation due to the anti-inflammatory properties of IVIg (165,166).

As scientists became more interested in how IVIg could ameliorate various diseases, animal models were developed (167). The first studies in animal models were in mice given ITP by passive anti-platelet antibody administration (165,167,168). Studies by different investigators in mouse models of ITP and arthritis revealed a number of possible mechanisms (165,166,168-170). One theory developed over time has been repeatedly propagated (171). In this theory, Ravetch and his protégé Nimmerjahn (165,166,171), have proposed that a small fraction (10%) of total IVIg sialylated in the Fc γ domain, engages the cluster of differentiation 209 (CD209) receptor, also known as DC-SIGN on dendritic cells (172). Engagement of DC-SIGN causes dendritic cells to release interleukin-33 (IL-33) (173). IL-33 is a Th2 polarizing cytokine that would then promote the release of IL-4 from basophils at sites of inflammation. IL-4 acts on macrophages to upregulate the expression of the inhibitory Fc γ receptor (Fc γ RIIB), which lowers inflammation (174). This model proposes that the subsequent upregulation of Fc γ RIIB on effector cells raises their threshold for activation, thus allowing for a reduction in phagocytosis of antibody-opsonized platelets and inflammation. Although this model of IVIg action has been touted through numerous publications, it has yet to be supported by other investigators; instead, this model has been refuted by many investigators.

First, passive antibody-induced ITP in mice does not create an inflammatory environment (175) and sialylation of IVIg or a role for Fc γ RIIB, IL-33, IL-4 or basophils

has not been found by other investigators as playing a role in the mechanism of action of IVIg (176-184). However, blockade of FcγR, especially FcγRI and FcγRIII, remains a viable mechanism in ITP. Indeed, studies in humans using an anti-FcγRIII, clone 3G8 or a humanized, deglycosylated variant of 3G8, GMA161, showed improvement in platelet numbers in treatment-refractory ITP patients; however, this amelioration of the ITP was transient (185-187). Recently, it was shown that antibody-coated platelets are removed by macrophages through FcγRI and FcγRIII suggesting that the mechanism of IVIg may be through blockade of both of these receptors (188). Interesting, however, is that it has been shown that it takes about 70–100 times more IVIg than mouse IgG to block *in vitro* phagocytosis of sheep red blood cell (SRBC)/anti-SRBC using mouse monocytes or RAW 264.7 mouse macrophages (189). These findings raise additional questions as to how IVIg can efficiently ameliorate ITP solely through FcγR blockade.

Earlier findings in the mouse ITP model have shown that IVIg can induce thrombopoiesis as part of its mechanism of action (190). IVIg inducing thrombopoiesis has been found in humans with ITP and is likely part of the amelioration process (191,192); although, the mechanism of how IVIg can induce thrombopoiesis is uncertain. Megakaryopoiesis is regulated by TPO and interleukin-11 (IL-11) (193). Recent work has shown that IVIg can induce IL-11 in mice and in humans (170,175,194). Recombinant human IL-11 (rhuIL-11) is also used to ameliorate chemotherapy-induced thrombocytopenia where it is treatment of choice (195,196). An initial pilot study of using rhuIL-11 to treat 6 patients with treatment-refractory ITP failed to show any efficacy and was moderately toxic (197). However, recent studies are suggesting that use of rhuIL-11 for the treatment of ITP may be helpful (198,199) and appears promising. Indeed, in a mouse model of ITP, it was shown that inhibition of IL-11 using a neutralizing antibody partially prevented the IVIg-mediated amelioration of the ITP. Also, when using recombinant IL-11 instead of IVIg, partial amelioration of the ITP was achieved. Thus, the mechanism of IVIg in amelioration of ITP may involve induction of IL-11 which then acts on megakaryocytes to increase thrombopoiesis (183). This possibility needs additional exploration.

To summarize, the mechanism as to how IVIg ameliorates ITP remains uncertain and because IVIg also ameliorates a number of autoimmune, inflammatory and neuropathy conditions, its mechanism of action is likely

complex and involves multiple mechanisms (169,200-202).

Therapies for adult ITP

Therapies for the treatment of adult ITP have advanced considerably over the years (203-208). Today, there are a number of first- and second-line therapies available as well as a number of potential therapeutics in various stages of development. IVIg has become a first-line therapy for ITP in adults. It is of interest to have an overview of ITP first-line therapies and understand how IVIg has become one of the main therapeutics for treatment of this condition. Below, we will explore the history of first-line therapy for ITP.

First-line therapy for ITP

Splenectomy

Historically, the standard first-line therapy for ITP was splenectomy, which is very effective and relatively inexpensive (203,204). Splenectomy for ITP was first performed by Kaznelson in 1916 (203). It has a good track record in the treatment of ITP and was shown to have an approximate 80% response rate, inducing complete remission in approximately 50–70% of patients (204-211); although, relapse of ITP can occur years after the procedure (212). Splenectomy, however, requires surgery under anesthesia and, therefore, has the possibility of severe complications due to the surgery (212-216). With the advent of therapies having fewer potential complications compared to splenectomy, such as immune suppressants, IVIg and RhIg anti-D therapies, splenectomy was relegated to a last-resort second-line therapy. Today it is recommended to only be used in adults with ITP for ≥ 3 months who are glucocorticoid-dependent or have no response to these steroids (9).

Glucocorticoids

Commonly referred to as “steroids”, corticosteroids comprise two groups of adrenal cortex-produced steroids, some of which are used clinically. Glucocorticoids (GCs) represent the most important and frequently used class of drugs in the management of many inflammatory and immunologic conditions (217). The glucocorticoid prednisone was first used to treat ITP in 1958 (218). Because of its efficacy for amelioration of ITP (82) and less significant side effects compared to splenectomy, prednisone became a first-line therapy for ITP in 1982 in Japan and in 1996 in the USA (82). Prednisone

and dexamethasone are the glucocorticoids of choice for first-line therapy of ITP (9,82,219-221). GCs are known to enter many different cell types through a receptor-mediated mechanism or passage directly into the cell. Once inside the cell cytosol, GCs bind to glucocorticoid receptors. This interaction results in significant effects on signal transduction, which in turn affects the normal function of cells. The final result is a profound effect of glucocorticoids on the immune response and immune cell function, such as macrophage phagocytosis and antibody production (222) (*Figure 1B*). Unfortunately, glucocorticoids are also associated with serious side effects. Adrenal suppression, dyslipidemia, hyperglycemia, Cushing's syndrome, cardiovascular disease, osteoporosis, psychiatric disturbances, and immunosuppression are among the most important side effects of glucocorticoids (223). These side effects are especially noticeable at high doses for prolonged periods. Despite these drawbacks, glucocorticoid therapy remains a first-line therapeutic approach to the resolution of ITP. However, there remains cases of resistance to glucocorticoids; therefore, other additions to the first-line of therapy were needed and this was solved by the serendipitous discovery that immunoglobulin therapy was highly efficacious at amelioration of ITP (158,224) (*Figure 1C*).

IVIg and anti-D

The use of IVIg for the treatment of ITP was first described in 1981 by Imbach *et al.* (127,158). High-doses of IVIg (1 to 2 g/kg) were first used in a pediatric patient having secondary immune deficiency complicated with ITP (127,158). Surprisingly, this patient and the subsequent patients, showed an increase in platelet numbers following the IVIg therapy (139,159,225,226). Later studies used high-dose IVIg therapy in adult ITP with some mixed results but, generally, it worked and, along with glucocorticoids and anti-D, IVIg is now a standard first-line therapy for adult ITP (205-212,226) (see below about anti-D and combination therapy).

Although IVIg has been shown to be well tolerated with few and mild side effects, with headache the primary complaint, it does, nevertheless cause some rare but significant AEs that include thrombosis (227,228) and hemolysis due to the anti-A and anti-B iso-agglutinins contained in the product (229). IVIg-associated hemolysis is more common than thought and can result in life-threatening hemolysis following high-dose therapy

(229,230).

Of interest is the fact that early IVIg products contained various alloantibodies to red blood cells that were not iso-agglutinins. Antibodies such as anti-Rhesus (RhD), anti-D, were rather common contaminants of IVIg (231,232). These antibodies, especially anti-D, were thought to be responsible for the low to modest hemolysis that was routinely seen when using IVIg to treat ITP patients (233). This antibody-induced hemolysis was perceived by Mueller-Eckhart's team to be mostly due to anti-D contained in the IVIg product and led these investigators to try anti-D itself as a therapy for ITP (233). Their thinking was that the mechanism of IVIg amelioration of ITP may involve an antibody-RBC interaction that results in hemolysis. These investigators were the first to use RhIg containing high levels of anti-D to treat ITP patients; and it worked (233-235). Thus, use of RhIg (anti-D) became a first-line of therapy for ITP patients (9). One limitation of this approach was, as indicated above that it only was efficacious in Rh(D)-positive patients. However, a larger limitation was the fact that in some patients treated with anti-D that were Rh(D)-positive, the anti-D resulted in significant morbidity due to associated problems resulting from the hemolysis, forcing the food and drug administration to issue a "black box warning" for using anti-D to treat ITP, especially in pediatric patients (236-239). Anti-D is, nevertheless, still used in the treatment of both pediatric and adult ITP (9,206-212). However, the AEs associated with IVIg, anti-D and glucocorticoids have prompted investigators to explore replacement of IVIg and other alternatives for the treatment of ITP.

Combination therapy

In cases where first-line therapy with IVIg is unsuccessful, a combination of IVIg with glucocorticoids is often used (157). In one study, it was found that use of IVIg plus glucocorticoids was more efficacious than glucocorticoids alone having significantly higher response rates (240). In another case, use of IVIg plus dexamethasone was found to be effective at resulting in a favorable outcome in a patient having coronavirus disease 2019 (COVID-19) and severe ITP (241). When patients are refractory to first-line therapeutics or combinations, splenectomy is still practiced as a "last resort" in some adult patients, especially if also refractory to second-line therapeutics.

Summary

IVIg is a biologic manufactured from tens of thousands

of human plasma donations and had become a first-line treatment modality for amelioration of ITP. It has been used for more than 40 years in both pediatrics and adult patients. In adult ITP, IVIg 10% had often been the treatment of choice over glucocorticoids due to the lesser AEs associated with IVIg therapy. Although anti-D (RhIg) therapy continues to be used, the much harder to produce product from a small population of Rh-negative donors as well as the significant AEs associated with its use have enhanced the use of glucocorticoids and IVIg in the treatment of ITP over the years.

Recently, treatment guidelines for adults with ITP have evolved to favor glucocorticoids over IVIg for first-line therapy. This is primarily due to the less cost of glucocorticoids compared to IVIg and the fact that, in adults with ITP, glucocorticoids are very effective first-line therapy (208,209). However, IVIg and RhIg continue to be used by some institutions as first-line treatment and, especially, where patients may be bleeding (10,208,209). Although some recommendations continue to include IVIg and RhIg in their approach to adult ITP (208,209), more consensus is emerging that IVIg is best saved for adults who have active bleeding or at high risk for bleeding, who require a surgical procedure, or those adults who are unresponsive to glucocorticoids (10). In recent recommendations from the American Society for Hematology, IVIg is not included in first-line therapy (9,25). Thus, in many situations due to recent recommendations, IVIg has been relegated to second-line therapy for adult ITP (see *Table 1* for a comparison of therapy for pediatrics versus adult ITP patients).

Acknowledgments

Funding: Dr. Ruqayyah J. Almizraq is supported by a Post-doctoral Fellowship from the Canadian Blood Services.

Footnote

Provenance and Peer Review: This article was commissioned by the Guest Editors (John W. Semple and Rick Kapur) for the series “Treatment of Immune Thrombocytopenia (ITP)” published in *Annals of Blood*. The article was sent for external peer review organized by the Guest Editors and the editorial office.

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/aob-20-87>). The series “Treatment of

Immune Thrombocytopenia (ITP)” was commissioned by the editorial office without any funding or sponsorship. Dr. DRB reports other from CSL Behring Ltd., outside the submitted work. RJA has no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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doi: 10.21037/aob-20-87

Cite this article as: Almizraq RJ, Branch DR. Efficacy and mechanism of intravenous immunoglobulin treatment for immune thrombocytopenia in adults. *Ann Blood* 2021;6:2.