Recent advances in treatments of adult immune thrombocytopenia

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Abstract

Immune thrombocytopenia (ITP) is isolated thrombocytopenia characterized by auto-immune-mediated disruption of platelet without other etiologies. Treatments for chronic ITP consist of corticosteroids, intravenous immunoglobulins, anti-D immunoglobulin, rituximab, thrombopoietin receptor agonists, immunosuppressants and splenectomy. Although current therapies are effective in over two-thirds of patients, some patients are refractory to therapies or fail to achieve long-term responses. Recently, great advance has been made in identifying various mechanisms involved in ITP pathogenesis, and new treatments targeting these pathways are being developed. Novel agents such as splenic tyrosine kinase inhibitor, Bruton kinase inhibitor, plasma cell targeting therapies, neonatal Fc receptor inhibitor, platelet desialylation inhibitor, and inhibition of the classical complement pathway are expected to be effective for ITP treatment. This review summarizes current strategies and emerging therapies of ITP.

Key Words Immune thrombocytopenia, Platelet, Treatment, Pathogenesis, Thrombopoietin receptor agonist

INTRODUCTION

Immune thrombocytopenia (ITP) is isolated thrombocytopenia characterized by autoimmune-mediated disruption of platelet without other etiologies. The incidence of ITP was approximately 3.3/100,000 person-years in adults and 1.9–6.4/100,000 person-year in children [1]. While approximately 80% of children has remission within 1 year, but most adults (70–80%) show a chronic course [2]. Current therapies for chronic ITP [e.g., corticosteroid, thrombopoietin receptor agonists (TPO-RA), rituximab and splenectomy] are successful in improving platelet count to a stable level in over two-thirds of adult patients. However, some patients still have an inadequate response with current treatments, so there is a great need for other therapies. The exact mechanism of the immune response leading to ITP are incompletely understood. For a long time, it was thought that the thrombocytopenia is solely caused by enhanced destruction of platelets opsonized by antiplatelet antibodies [3]. However, recent studies have demonstrated that T-cell cytotoxicity and impaired megakaryopoiesis are additional pathophysiology of ITP [4]. Recently, great advance has been made in identifying various mechanisms involved in ITP pathogenesis, and new treatments targeting these pathways are being developed. The purpose of this review is to summarize current strategies and emerging therapies of ITP.

CURRENT TREATMENTS

Initial therapy

Initial treatment of newly diagnosed ITP is recommended at a platelet count $<20–30\times10^9$/L in adult patients without symptoms [5-7]. The experts also recommended that treatment goals should be individualized to each patient and aimed at both preventing bleeding as well as minimizing toxicity and optimizing quality of life [6]. Currently recommended treatments are summarized in Fig. 1.

Corticosteroids: The preferred first-line therapy for patients with chronic ITP is oral corticosteroids, unless there is a contraindication to corticosteroids or need for more rapid platelet increase due to acute bleeding. Most-commonly used corticosteroids are oral prednisone at 0.5–2 mg/kg/day for 2–3 weeks and should be tapered aiming to stop by 6–8 weeks [5-7]. Initial response rates range from 70 to 80%, but relapse rates are high and long-term remission rates are low [8]. Dexamethasone at higher doses (40 mg daily for four days) has also been suggested, with the goal of providing a higher total amount of corticosteroid over a shorter exposure period. In systemic review and meta-analysis of nine randomized trials (N=1,138) to compare high-dose
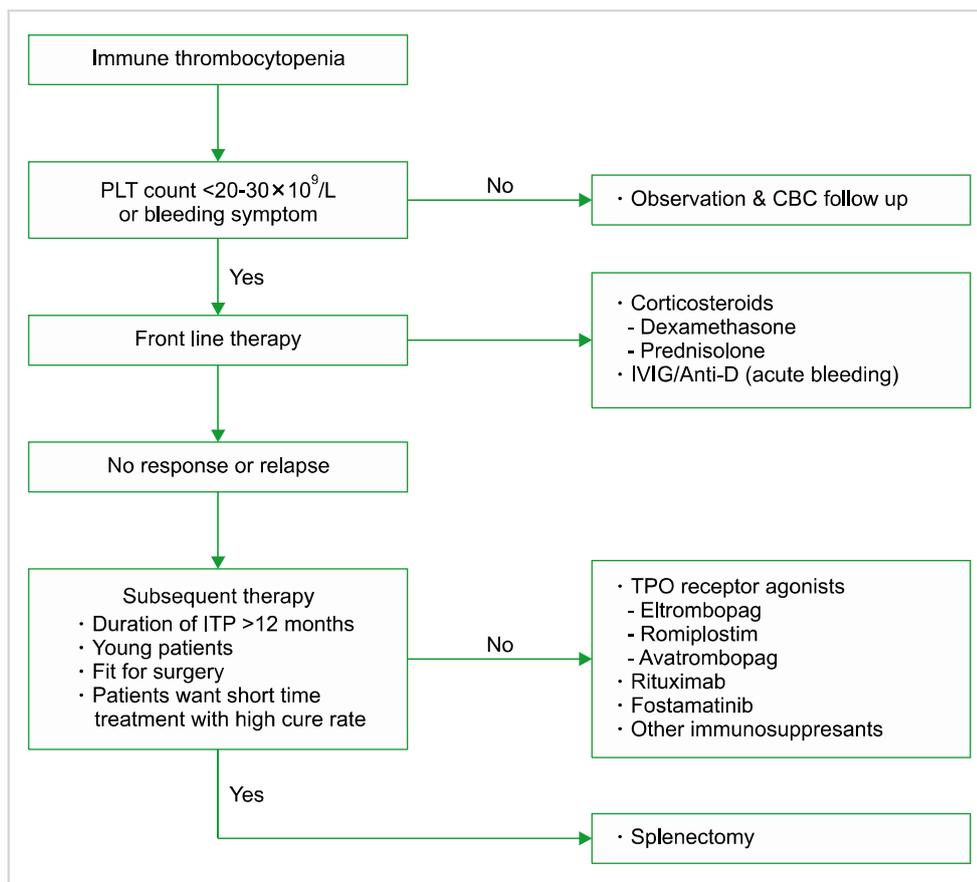
Fig. 1. Treatment approach of immune thrombocytopenia.

dexamethasone with oral prednisone, no difference in overall platelet response at 6 months (54% vs. 43%, P=0.44) and long-term response rates [9]. However, overall platelet response at 14 days was higher with dexamethasone (79% vs. 59%, P=0.048) and adverse events were fewer in dexamethasone group (24% vs. 46%). As both type of corticosteroid has efficacy, treatment of choice should be based on individual characteristics (patient's preference, profiles of side effects and need for rapid response).

Intravenous immunoglobulin: Intravenous immunoglobulin (IVIG) has been widely used as first-line anti-ITP therapy with or without corticosteroids since its effectiveness in treating ITP was first demonstrated in 1981 [10]. The mechanisms of action of IVIG are wide and not completely understood. IVIG is thought to inhibit Fc-mediated phagocytosis of antibody coated platelets by reticuloendothelial system [11]. Usual recommended dose is 1 g/kg/day for 1–2 days (high-dose) or 0.4 g/kg/day for up to 5 days (low-dose) [6]. In one meta-analysis with 13 randomized trials, efficacy is not statistically different between high-dose and low-dose IVIG for acute ITP and low-dose IVIG was associated with lower risk of side effects such as headache, nausea, vomiting and fever [12]. IVIG treatment is generally thought to have more rapid platelet response than corticosteroids, thus IVIG therapy is recommended for use in patients who need a rapid increase of platelet count due to acute bleeding.

Anti-D immunoglobulin: Anti-D immunoglobulin is an im-

mune globulin directed against the D antigen of the Rh blood group system. It acts through competitive occupation of Fc receptors on macrophages by anti-D-coated erythrocytes and inhibit the destruction of antibody-coated platelets [13]. Therefore, it is only effective in Rh-positive patients with an intact spleen. Generally recommended a single intravenous infusion with dose of 50 to 75 µg/kg and response occurred within 48 hours. Overall response rate is around 65% and generally sustains for 3–4 weeks [14, 15]. The major concern of anti-D immunoglobulin therapy is that the incidence is very low, but life-threatening severe intravascular hemolysis have been reported [16, 17].

Second line treatments

Most of ITP patients respond to primary treatment such as glucocorticoids or IVIG, but a significant number of patients eventually require secondary treatment because the maintain of long-term responses are difficult. Such patients may consider medical therapy (TPO-RA, rituximab) or surgical option (splenectomy).

Thrombopoietin receptor agonists: TPO-RAs are small molecule that stimulates thrombopoietin to increase the production of platelets by megakaryocytes in bone marrow [18]. Currently, there are three agents (eltrombopag, romiplostim and avatrombopag) that have been approved by the U.S. Food and Drug Administration (FDA) for the treatment of chronic ITP. The overall response rate of TPO-RA is expected

to be 60–90% [19-21], but it is not generally thought to be curative because long-term remission after treatment of TPO-RA have been reported in around 15% of cases [22, 23].

Eltrombopag is a synthetic non-peptide molecule TPO-RA that can be taken orally. The starting dose was 50 mg, but the use of 25 mg can be considered in East Asian, due to an ethnic difference in eltrombopag pharmacokinetics. It can be increased up to 75 mg with the target of maintaining the platelet count $50–200×10^9$/L. In previous studies, platelet response was 59–79% and the frequency of bleeding and other comorbid drug use was significantly decreased [20, 24, 25]. Hepatotoxicity, headache, diarrhea, and upper respiratory tract infection were frequently reported adverse events. The inconvenience of eltrombopag is that it should be taken 2 hours before or 4 hours after meals and drugs which containing polyanions (calcium, mineral supplements, antiacids) for its maximum absorption [24]. Since the half-life is 26–35 hours, recent studies have reported that alternative intermittent dosing of eltrombopag less frequently than once daily, which has been shown to be effective [26, 27].

Romiplostim is a peptide TPO-RA that is administered subcutaneously on a weekly schedule. It starts at dose of 1 μg/kg and increase to a maximum dose of 10 μg/kg. In previous trials, platelet response was 71–92% and durable platelet response was about 38–56% [19, 21]. Although subcutaneous injection therapy is a disadvantage compared to oral TPO-RA, recent studies have demonstrated that self-administration of romiplostim by patients has no significant difference in safety profile compared with administration by healthcare professionals [28, 29].

Avatrombopag is an oral small molecule TPO-RA. It was approved by the US FDA for the treatment of thrombocytopenia in patients with chronic ITP or liver disease who are scheduled to undergo a procedure. It is started at dose of 20 mg/day, and it can be increased up to 40 mg/day. Unlike eltrombopag, avatrombopag does not require a strict diary restriction or dose adjustment for race of patients. It has also been reported less hepatotoxicity. In several randomized studies, avatrombopag was superior to placebo in long term platelet response rate and rates of reduced concomitant medications [30-32].

To date, there are no randomized controlled trials head-to-head direct comparing between TPO-RAs. In retrospective studies or meta-analysis, no differences between drugs have been identified in overall platelet response rate, duration of response, bleeding incidence, and safety profiles [33, 34]. In case of switching to another TPO-RA agents after the failure of one TPO-RA, the response rate was demonstrated to be around 77.5% [26].

Because of the mechanism of action, TPO-RA is generally thought to only help platelet maintain until patients get a spontaneous remission rather than to achieve cure for ITP. To date, there are no clear guidelines for discontinuation of TPO-RA, but in a single center retrospective study, the two-year treatment free remission rate was 66.4% in patients with TPO-RAs discontinuation and the cumulative incidence

of response loss ($<30×10^9$/L) at 2 years was 34.0% [35]. In Meta-analysis, the probability of remission after discontinuation of TPO-RAs was 18.4% (5.4–36.3%) during a median follow-up of 106 weeks [36]. However, there is still controversy over the predictive factors for sustained response, and further studies are needed to identify predictive factors for decision TPO-RAs discontinuation.

Rituximab: Because B-cell plays an important role in pathogenesis of ITP, rituximab, chimeric monoclonal antibody against CD20 on the surface of B-lymphocyte has been proposed for many years to treatment of ITP. Anti-CD20 targeting therapy depletes CD20+ B cells and reduce the production of anti-platelet antibodies. Studies with standard dose of rituximab (375 mg/m^2/wk for 4 wk) in ITP have showed response rate of 60-80% at 6 to 12 months, and 20–30% at 2–5 years [37-40]. The effectiveness and safety profiles of low-dose rituximab (100 mg or 100 mg/m^2/wk for 4 wk) were also studied to avoid treatment related adverse events. A systematic review found that the pooled overall response rate and complete response rate were 63% and 44% in ITP patients treated with low-dose rituximab [41]. Low-dose rituximab therapy has a satisfactory efficacy and safety profile.

Rituximab have been investigated in combination with dexamethasone versus dexamethasone alone in patients with newly diagnosed ITP. In randomized trials, sustained response rate (platelet count $≥50×10^9$/L at 6 mo after treatment) were greater in 58–63% of patients in rituximab combination group versus 36–37% in dexamethasone alone [42, 43]. The difference in response rates was maintained at 12 months (53% in rituximab combination group vs. 33% in dexamethasone monotherapy). Adverse events were, in general, mild, and balanced between the two groups. However, there was an increased incidence of grade 3 to 4 adverse events (e.g., hemorrhage, hypersensitivity, pneumonia, fever, and transaminases increased) in the rituximab combination group than dexamethasone group. Recent meta-analysis identified a similar improvement in overall response, complete remission, and long-term sustained response with rituximab combination group compared than dexamethasone alone [44]. This analysis also found that there was no significant difference in relapse rates and adverse effects between the two arms. All the above studies are suggestive that rituximab may enhance remission rates when added to initial corticosteroid therapy, but, considering the cost of rituximab, infection risks and infusion reactions caused by B-cell depletions, more robust data from randomized clinical trials are needed to change the current practice.

Splenectomy: Splenectomy is an effective treatment as the spleen is the major site of platelet destruction as well as a site of anti-platelet antibody production [45]. About 70–80% of patients with splenectomy achieve sustained CR lasting more than 6 months and 60–70% patients show sustained response over 5 years [45, 46]. Nevertheless, preference is decreasing due to the risk of procedure-related complications and the availability of effective non-surgical therapeutic options. Laparoscopic splenectomy is preferred over open splenectomy due to less procedural complications (0.2% vs.

1%) [47]. Splenectomy also increases infection risk with sepsis in 2.1%-, and 2–4 folds risk of venous thromboembolism [48, 49]. Therefore, splenectomy should be considered only after the confirmation of chronic ITP, considering the risk of irreversible complications caused by surgery and the possibility for spontaneous remission of ITP within the first year.

NEW THERAPEUTIC PERSPECTIVES

Although current treatments of ITP have shown significant responses, some patients have no response to treatment or failed to achieve long-term remission. Recent advances in understanding of ITP pathophysiology have suggested various mechanisms for ITP development. Current evidence suggests that thrombocytopenia in ITP is the result of multiple mechanisms, including impaired thrombopoiesis and variations in immune response leading to platelet destruction. Recently, various novel treatments targeting these pathways are being developed (Table 1).

Splenic tyrosine kinase inhibitor

Fostamatinib is an oral tyrosine kinase inhibitor that blocks splenic tyrosine kinase (SYK) and is a drug approved by the U.S. FDA for ITP patients who have failed first-or second-line therapy, or intolerable to these therapies. Fostamatinib reduce antibody-dependent cellular phagocytosis by inhibiting FcγR transduction signal, which plays an important role in platelet phagocytosis by macrophage [50]. In two parallel, phase 3 clinical trials (FIT1 and FIT2) included 150 chronic ITP patients, patients were randomized 2:1 to fostamatinib (N=101) or placebo (N=49) [51]. In this trial, overall responses (defined as a platelet count $\geq 50 \times 10^9$/L within the first 12 wk of treatment) was achieved in 43% on fostamatinib vs. 14% on placebo (P=0.0006). However, stable response

(defined as a platelets count $\geq 50 \times 10^9$/L at ≥ 4 of 6 biweekly visits, wk 14–24) occurred only 18% on fostamatinib and 2% on placebo (P=0.0003). Post hoc analysis of the phase 3 trials showed higher benefits in terms of platelet response (78% vs. 48%) and bleeding events (28% vs. 45%) when fostamatinib was used as second line therapy (N=32) compared to third- or later-line (N=113) therapy [52]. Most common adverse events were diarrhea (31%), hypertension (28%) and elevation of liver enzymes has also been reported in 10% of cases [51].

Bruton tyrosine kinase inhibitor

Bruton tyrosine kinase (BTK) pathway is also critical for the intracellular transduction signal of FcγR-signaling pathway in phagocytosis. Most familiar BTK inhibitor, iburutinib plays an important role in current treatment of indolent B-cell lymphomas. However, there is reluctance to use of ibrutinib in patients with ITP. Inhibition of BTK by ibrutinib showed an inhibition of platelet aggregation, because BTK is expressed by platelets. Number of new BTK inhibitors that does not interfere with platelet aggregation have been developed. Contrary to ibrutinib, rilzabrutinib, an oral, reversible, covalent molecule highly selective of BTK had no effect on platelet aggregation. It has both non-covalent and covalent binding regions that allow it to bind with high potency and long residence time to BTK but with minimal binding to off-target kinases [53]. Preliminary data of ongoing phase 1/2 study in adults with relapsed/refractory ITP (NCT03395210) are available [54]. The primary endpoint (safety and achievement of ≥ 2 consecutive platelet counts $\geq 50 \times 10^9$/L and increased $\geq 20 \times 10^9$/L from baseline without rescue medication) was met by 18/45 (40%). Responses were rapid with median time to first platelet counts of $\geq 30 \times 10^9$/L was 8.5 (7–134) days. Long-term extension (LTE) study, 16 patients were maintained on rilzabrutinib 400 mg twice daily

Table 1. Novel therapies for treatment of immune thrombocytopenia.

Target	Drug class	Mechanism	Agents	Development status
Macrophage	Syk inhibitor	Decrease in ADCP (inhibition of macrophage phagocytosis)	Fostamatinib	Approved (US)
Macrophage	BTK inhibitor	Decrease in ADCP (inhibition of macrophage phagocytosis)	Rilzabrutinib	Phase 3 (NCT04562766)
Plasma cells	Proteasome inhibitor	Inhibits plasma cell production of anti-platelet antibody	Bortezomib KZR-616	Phase 1 (NCT03013114) Phase 1 (NCT04039477) withdrawn
Plasma cells	Anti-CD38 antibody	Inhibits plasma cell production of anti-platelet antibody	Daratumumab Mezagitamab	Phase 2 (NCT04703621) Phase 2 (NCT04278924)
Antiplatelet antibodies	FcRn blocker	Increase clearance of anti-platelet antibody	Efgartigimod Rozanolixizumab	Phase 2 (NCT03102593) Phase 3 (NCT00718692)
Platelet	Neuraminidase inhibitor	Decrease in platelet desialylation thus reducing their destruction in the liver	Oseltamivir	Phase 2 (NCT01965626)
Classical complement pathway	C1s inhibitor	Decrease in CDC (antibody inhibits C1s activity)	Sutimlimab	Phase 2 (NCT04669600)

Abbreviations: ADCP, antibody-dependent cellular cytotoxicity; BTK, Bruton tyrosine kinase; CD, cluster of differentiation; CDC, complement-dependent cytotoxicity; FcRn, Neonatal Fc receptor; Syk, spleen tyrosine kinase.

and these patients maintained platelet counts of $\geq 30\times 10^9$/L, $\geq 30\times 10^9$/L with $\geq 20\times 10^9$/L above baseline, and $\geq 50\times 10^9$/L, for a median of 100%, 96%, and 90%, of weeks, respectively, during the LTE period. Continued study in the ongoing, randomized phase III LUNA3 trial (NCT04562766) will further assess the magnitude and durability of rilzabrutinib's clinical benefit in ITP.

Plasma cell targeting therapies

Long-lived plasma cells that play an important role in anti-platelet antibody production, cannot be completely removed by anti B-cell therapies (e.g., rituximab) alone [55]. Thus, plasma cell-targeting therapies could be suggested for treatment of ITP. Bortezomib, a proteasome inhibitor, destroys anti-platelet antibody-secreting long-lived plasma cells obtained from ITP patients and reduces the thrombocytopenia in a murine model of ITP [56]. However, there are concerns about thrombocytopenia caused by bortezomib, a frequent complication observed when used to treat multiple myeloma. Based on preliminary results with bortezomib, clinical trial with another proteasome inhibitor KZR-616 (NCT04039477) was initiated to be investigated in ITP, but the study was withdrawn due to the SARS-CoV-2 pandemic [57].

Anti-CD38 antibody, daratumumab is also another candidate for treating ITP because of its capability to eliminate clonal plasma cell in multiple myeloma. Daratumumab has shown its efficiency in a case of post-allogenic transplantation ITP, which was not responding to rituximab [58]. However, one concern is the possibility of severe hypogammaglobulinemia and infectious complications because of its mechanism of action. Mezagitamab (TAK-079) is a fully human, IgG1 monoclonal antibody that binds human CD38 [59]. There are ongoing studies in ITP with daratumumab (NCT04703621) and mezagitamab (NCT04278924).

Neonatal Fc receptor inhibitors

The neonatal Fc receptor (FcRn) is one of the Fc receptors that binds to IgG and is responsible for transporting of IgG between mother and fetus through the placenta. It plays a role in the immune response by presenting IgG antigens to immune cells, causing the production of antiplatelet antibodies. And it is also responsible for the long circulatory half-lives of IgG and albumin [60, 61]. Thus, inhibition of FcRn permits the reduction of pathologic IgG and, consequently, an increase the clearance of antiplatelet antibodies in ITP [60, 61]. In a recent multicenter, open-labeled phase 2 trial (NCT02718716) including 66 adult ITP patients, rozanolixizumab showed a favorable safety profile, with only 15 of the 51 adverse events reported being related to treatment, mostly consistent with mild-to-moderate headaches [62]. The response (platelet count $\geq 50\times 10^9$/L) was achieved in 66.7% and 54.5% of patients receiving a single subcutaneous infusion at 15 and 20 mg/kg, respectively. These data support phase 3 (NCT02718716) development of rozanolixizumab in chronic ITP.

Efgartigimod (APGX-113) is a human IgG1 antibody Fc-fragment, engineered for increased affinity to FcRn, while preserving its characteristic pH-dependent binding. In a phase 2 study (NCT03102593) including 38 ITP patients, patients were randomized 1:1:1 to administered four weekly intravenous infusions of placebo (N=12) or efgartigimod at either 5 mg/kg (N=13) or 10 mg/kg (N=13). Overall response (platelet $\geq 50\times 10^9$/L on at least two occasions) were 46% with efgartigimod vs. 25% with placebo, and stable response (platelet count $\geq 50\times 10^9$/L for at least 10 consecutive days) were achieved in 38% on efgartigimod as compared to none in the placebo [63].

Platelet desialylation inhibitors

Platelet desialylation has been identified as a novel mechanism of Fc-independent platelet clearance in ITP [64]. A study by Li demonstrated that translation of neuraminidase-1 mediated by anti-GPIbα promoted platelet desialylation, which resulted in Fc-independent platelet clearance in the liver via hepatocyte in primary ITP [65]. Oseltamivir is a sialidase inhibitor widely used for prophylaxis and treatment of influenza. Several studies that addition of oseltamivir in patients with influenza infection or sepsis showed that platelets count was significantly increased, and platelet recovery time was reduced [66, 67]. In a phase 2 randomized multicenter trial in 96 patients with newly diagnosed ITP, dexamethasone plus oseltamivir group showed a significantly higher initial response (platelet count $\geq 30\times 10^9$/L) rate than dexamethasone alone group (86% vs. 66%, P=0.030) and 6-month sustained response rate (53% vs. 30%, P=0.032) [68]. Most common adverse events were fatigue (12%), gastrointestinal reaction (19%), insomnia (16%) and anxiety (12%)

Inhibition of the classical complement pathway

The involvement of complement pathway in ITP pathogenesis has been investigate for many years [69, 70]. Compliment pathway is activated by the binding of antibodies to platelet glycoprotein and leading to platelet lysis by complement dependent cytotoxicity. Complement activation also leads to promotes the phagocytosis of opsonized platelets by macrophages in the spleen. Thus, the inhibition of the classical complement pathway has emerged as a potential therapeutic candidate in ITP. Sutimlimab (BIVV009) is a humanized monoclonal IgG4C1s inhibitor that completely inhibits classical complement pathway. Interim results of phase 1B trial with sutimlimab in patients with chronic severe ITP (NCT03275454) showed that overall response (platelet count $\geq 30\times 10^9$/L with at least a 2-fold increase in baseline level) rate and complete response (platelet count $\geq 100\times 10^9$/L) were 42% and 33.3%, respectively [71]. These responses were durable (more than half of the visits between weeks 5 and 21) in all cases and there was no significant treatment related adverse events. A phase 2a study (NCT04669600) is currently enrolling.

CONCLUSION

Current standard therapies for chronic ITP are successful in improving platelet count to a stable level in most patients. However, some patients still have an inadequate response with standard treatments and there is a need for other treatments. Recently, many treatments approaches targeting of various pathway of ITP pathogenesis are being developed. However, since the long-term efficacy and safety profiles of these drugs have not been clarified, they need to be proven through randomized controlled trials.

Authors' Disclosures of Potential Conflicts of Interest

No potential conflicts of interest relevant to this article were reported.

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