


# Management of Adult Patients with Immune Thrombocytopenia (ITP): A Review on Current Guidance and Experience from Clinical Practice

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**Abstract:** Immune thrombocytopenia (ITP) is an autoimmune process resulting in increased destruction and inadequate production of platelets that can result in bleeding, fatigue, and reduced health-related quality of life. While treatment is not required for many patients with ITP, the occurrence of bleeding manifestations, severe thrombocytopenia, and requirement for invasive procedures are among the reasons necessitating initiation of therapy. Corticosteroids, intravenous immunoglobulin, and anti-RhD immune globulin are typical first-line and rescue treatments, but these agents typically do not result in a durable remission in adult patients. Most patients requiring treatment therefore require subsequent line therapies, such as thrombopoietin receptor agonists (TPO-RAs), rituximab, fostamatinib, splenectomy, or a number of other immunosuppressive agents. In this focused review, we discuss management of adult ITP in the acute and chronic settings.

**Keywords:** platelets, immune thrombocytopenia, ITP, treatment, corticosteroids, IVIG, splenectomy, thrombopoietin receptor agonist, rituximab, fostamatinib

## Introduction

Immune thrombocytopenia (ITP) results from autoimmune destruction of platelets in the reticuloendothelial system due to platelet autoantibodies and other immune mechanisms, resulting in increased platelet turnover as well as inadequate platelet production.<sup>1–5</sup> Primary ITP is defined as an isolated thrombocytopenia  $<100 \times 10^9/L$  in the absence of other causes or disorders that may be associated with thrombocytopenia, as distinguished from secondary ITP, which is associated with other conditions such as infections, drug effects, rheumatological diseases, or lymphoproliferative disorders.<sup>6,7</sup> The incidence of ITP in the US population is approximately 6.1 per 100,000 persons per year, or 13.7 per 100,000 persons per year in those 65 years or greater, and results in significant economic burden.<sup>8</sup> Clinical presentation can vary between asymptomatic to severe bleeding complications, and prior to 2010, fatal bleeding rates were estimated at 1.62–3.89 cases per 100 patient-years and predicted 5-year mortality rates varied from 2.2% for persons  $<40$  years up to 47.8% for those aged  $>60$  years.<sup>9</sup> Although many laboratory studies can support diagnosis or guide treatment selection, ultimately diagnosis is clinical, after ruling out other etiologies of thrombocytopenia.<sup>7,10,11</sup>

Given the wide variation in presentation, not all patients require treatment immediately after diagnosis. The American Society of Hematology (ASH)

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Immune Thrombocytopenia Clinical Guideline provides a grading system for severity of ITP, defining severe ITP as clinical bleeding requiring treatment.<sup>7</sup> Of note, the degree of thrombocytopenia is not reliably indicative of bleeding risk when platelets are above  $10 \times 10^9/L$ .<sup>12–15</sup> Factors thought to increase risks of bleeding include reduced platelet count, female sex, and exposure to NSAIDs.<sup>16</sup> There is also concern of increased frequency of intracranial hemorrhage in elderly patients aged  $\geq 70$  years when platelets are less than  $20–30 \times 10^9/L$ , so clinicians should also consider age when deciding on a threshold for treatment.<sup>17</sup> The goal of treatment of ITP is to reduce bleeding risks by raising platelet counts. Treatment must be individualized, accounting for an individual patient's risks of bleeding given their history of bleeding, trauma risks, and the risk of adverse events from therapeutics.

In this focused review article, we will discuss the treatment of adult ITP, incorporating the most recent evidence as well as expert opinion.

## Treatment of ITP Response Criteria

The International Working Group (IWG) defines complete response (CR) to ITP treatment as a platelet count  $\geq 100 \times 10^9/L$  and absence of bleeding and response (R) as platelet count  $\geq 30 \times 10^9/L$  and  $>2$  fold increase in platelet count from baseline and absence of bleeding, both measured on 2 occasions greater than 7 days apart.<sup>6</sup> No response (NR), per the IWG definition, is characterized by a platelet count  $<30 \times 10^9/L$  or a less than 2-fold increase in platelet count from baseline, or the presence of bleeding.<sup>6</sup>

## First-Line/Rescue Treatments Corticosteroids

The standard first-line treatment and most common rescue therapy in newly diagnosed ITP are corticosteroids, often with prednisone (0.5–2 mg/kg daily for a 4–8 week tapering course) or high-dose dexamethasone (40 mg daily for 4 days for 1–4 cycles).<sup>7,10,18</sup> Corticosteroids have been shown to decrease capillary permeability, reduce platelet autoantibody production, increase platelet production, increase myeloid-derived suppressor cells, and change T cell subsets to decrease platelet destruction.<sup>19–24</sup>

Overall, the choice of corticosteroid agent should be made in consideration of adverse event risk and the need for a rapid response. In a meta-analysis comparing prednisone with dexamethasone in previously untreated adult

primary ITP, one to three courses of high dose dexamethasone, compared with prednisone 1 mg/kg for 4 weeks with taper, showed a platelet count response (79% vs 58%) at 14 days, but there was no difference in overall platelet response at 6 months (54% vs 53%) or rates of sustained response.<sup>25</sup> High-dose dexamethasone may be more likely to precipitate acute psychotic complications in the elderly or those with a history of psychiatric disease, however, and this should be considered upon agent selection.

## Intravenous Immunoglobulin (IVIG) and Intravenous Anti-RhD Immune Globulin

Intravenous immunoglobulin (IVIG) is another common first-line or rescue therapy often employed when a patient presents with significant bleeding. It can be administered when a more rapid increase in platelet count is required, and also be added to corticosteroid therapy or when corticosteroids are contraindicated.<sup>7</sup> IVIG is recommended to be given at a dose of 1 g/kg daily for 1–2 days (high-dose) or 0.4 g/kg daily for up to 5 days (low-dose).<sup>10</sup> IVIG has many complex mechanisms of action in decreasing inflammatory processes by multiple pathways, including inhibition of the IgG Fc receptor, which is crucial to link the adaptive and innate immune systems, inhibiting phagocytosis and suppression and/or elimination of platelet autoantibodies.<sup>26–30</sup>

In one meta-analysis, effect rate, time of cessation of bleeding, and rate of development of chronic ITP was not statistically different between high-dose and low-dose IVIG for acute ITP and low-dose IVIG was associated with decreased risk of side effects.<sup>31</sup> In a case-control study by Zhou et al., there was no difference in therapeutic response in groups receiving IVIG doses between 0.2–0.4 g/kg/day, which suggests that ITP patients could be treated more cost-effectively by lower conventional dosages of IVIG.<sup>32</sup>

Intravenous anti-RhD immune globulin (administered at a dose of 50 mcg/kg to 75 mcg/kg daily)<sup>33,34</sup> is an alternative to IVIG for non-splenectomized, Rh (+) patients. It is thought to saturate macrophage Fc receptors with anti-D coated RBCs to prevent destruction of autoantibody-coated platelets.<sup>35</sup> In one study, IVIG and IV anti-RhD immune globulin treatments of patients with ITP yielded no statistical difference in cumulative response and remission rates.<sup>36</sup> Anti-RhD immune globulin induces a controlled hemolysis, with a majority of patients experiencing a decrease in hemoglobin concentration of 0.5–2.0 g/dL 3–7 days after infusion, with recovery

to baseline within 3 weeks of administration.<sup>37</sup> Rarely, this hemolysis can degenerate into life-threatening disseminated intravascular coagulation.

## Second/Subsequent Line Therapies

An estimated 68% of adult patients develop persistent ITP despite first-line treatments including corticosteroids and IVIG.<sup>38</sup> There are no randomized controlled trials directly comparing the different second-line therapy options, so the results of placebo-controlled trials of second-line therapy are examined. The choice of second-line therapy is primarily based on patient values and priorities as well as available resources.

Based on the available data, the most recent American Society of Hematology ITP clinical guidelines conditionally recommend TPO-RA rather than rituximab and rituximab is recommended over splenectomy, though choice of treatment should be individualized, e.g. depending on patient goals of avoidance of surgery, achieving durable response, or avoidance of long-term medications.<sup>39</sup>

### Splenectomy

Splenectomy is an effective treatment as the spleen is a site of platelet destruction as well as a site of antibody production. Splenectomy has been shown to help 74% of patients achieve sustained CR lasting more than 6 months<sup>40</sup> and 64% after a minimum of 5 years.<sup>41</sup> Previous studies have shown that mortality was 1.0% (48 of 4955 patients) with laparotomy and 0.2% (3 of 1301 patients) with laparoscopy.<sup>42</sup> Splenectomy also increases infection risk as well, with reports of sepsis in 2.1% of splenectomized patients<sup>43</sup> as well as a 2-4-fold risk of venous thromboembolism.<sup>44,45</sup> Given risks of the surgery and potential for spontaneous remission of ITP within the first year, splenectomy as a treatment option should be deferred until the patient is confirmed to have chronic ITP (ITP lasting for more than 12 months), when the rate of spontaneous remission is much lower.

### Rituximab

Rituximab is a monoclonal anti-CD20 antibody that decreases anti-platelet antibody production by B cells and has been an off-label treatment for ITP for many years. Overall response rates of 40–70% were seen in patients given four weekly doses of 375 mg/m<sup>2</sup> of rituximab, though remission is rarely sustained, decreasing to only 21% at 5 years.<sup>46–49</sup> Despite the relapse rate, patients treated with rituximab had a longer duration of response

compared with placebo (median 8.2 months vs 1.8 months).<sup>50</sup> Studies examining different dosages of rituximab, including a lower dose of 100 mg/week for four weeks<sup>51</sup> and a dose of 1000 mg on days 1 and 15 did not show significant differences in response rate or infection risks.<sup>52,53</sup> Rituximab has also been studied in combination with other therapies such as high-dose dexamethasone in newly diagnosed ITP, with an initial strong overall response though sustained response after 12 months of follow up decreased to 61.5%, with an 11.1% incidence of adverse effects.<sup>54</sup> In a meta-analysis of randomized controlled trials, rituximab plus standard of care was shown to have a higher complete response rate (46.8% vs 32.5%) by 6 months than standard of care alone.<sup>48</sup> Infection is an important safety concern of rituximab: in a large ITP patient registry, the incidence of infection was 23.8% after 34 months, with 8.5% being severe (grade III to IV) infections.<sup>46</sup> Some clinicians use anti-infective prophylaxis for patients undergoing rituximab treatment, though evidence to support its use is lacking.<sup>55</sup> Given the ongoing COVID-19 pandemic, clinicians also must take into consideration the B-cell depletion effect of rituximab, which may impair vaccine response for at least 6 months after administration.<sup>56</sup>

### Thrombopoietin Receptor Agonists

Thrombopoietin receptor agonists (TPO-RA) mimic endogenous TPO function to increase megakaryocyte maturation and platelet production.<sup>57</sup> In a large systematic review, treatment failure was seen in 21% of TPO-RA treated patients compared with 47% of control patients, with a lower risk of significant bleeding and all-cause mortality.<sup>58</sup> There are currently three TPO-RAs approved for treatment of ITP: romiplostim, eltrombopag, avatrombopag, described below and summarized in Table 1.<sup>59</sup> Thrombosis is the major potential adverse event of concern with TPO-RA use and though clinical trials have not found an increased thrombotic risk of TPO-RA agents compared with placebo, uncontrolled observational data suggest an increase in thrombotic risk on the order of 2-3-fold.<sup>60</sup>

Romiplostim is a peptide TPO-RA approved by the US FDA for ITP following the failure of a first-line treatment and is administered subcutaneously on a weekly schedule, starting at 1 mcg/kg, increased weekly to a maximum dose of 10 mcg/kg until platelet count is consistently 50–200 × 10<sup>9</sup>/L.<sup>61</sup> In two parallel phase III trials, durable platelet response was achieved in 38–56% of patients with overall

Table 1 Phase III Trials of TPO-RAs in ITP

Study	Patient Number (n)	Location	Study Population	Major Results (Compared with Placebo)
Bussel 2009 <sup>68</sup>	Eltrombopag n=76 Placebo n=38	Worldwide (63 sites)	Adults with ITP for $\geq 6$ months and a pretreatment Plt $< 30 \times 10^9/L$ 39% splenectomized	Significantly higher rate of platelet response <sup>a</sup> Significantly less bleeding
Cheng 2011 <sup>68</sup>	Eltrombopag n=135 Placebo n=62	Worldwide (75 sites)	Adults with ITP for $\geq 6$ months and a pretreatment Plt $< 30 \times 10^9/L$ 36% splenectomized	Significantly higher rate of platelet response <sup>a</sup> Reduced use of concomitant ITP medications Reduced need for rescue therapy
Tomiyama 2012 <sup>69</sup>	Eltrombopag n=15 Placebo n=8	Japan	Adults $\geq 20$ years old with ITP for $\geq 6$ months and a pretreatment Plt $< 30 \times 10^9/L$ 70% splenectomized	Significantly higher rate of platelet response <sup>a</sup> Significantly less bleeding Lower doses of eltrombopag were effective in Japanese patients
Yang 2014 <sup>70</sup>	Eltrombopag n=104 Placebo n=51	China	Adults with ITP for $\geq 12$ months and a pretreatment Plt $< 30 \times 10^9/L$ 16% splenectomized	Significantly higher rate of platelet response <sup>a</sup>
Kuter 2008 <sup>62</sup>	Romiplostim n=83 Placebo n=42 (patients from two parallel studies)	United States and Europe	Adults with ITP for $\geq 12$ months and a screening mean Plt $< 30 \times 10^9/L$ 50% splenectomized	Significantly higher rate of platelet response <sup>a</sup> Reduced use of concomitant ITP medications
Kuter 2010 <sup>63</sup>	Romiplostim n=157 Standard of care n=77	North America, Europe, and Australia	Adults with ITP for $\geq 12$ months and a pretreatment Plt $< 50 \times 10^9/L$ 0% splenectomized	Significantly higher rate of platelet response <sup>a</sup> Reduced use of concomitant ITP medications Lower rate of treatment failure Lower rate of splenectomy Significantly less bleeding and transfusions Significantly improved quality of life
Shirasugi 2011 <sup>109</sup>	Romiplostim n=22 Placebo n=12	Japan	Adults $\geq 20$ years old with ITP for $\geq 6$ months and a screening Plt $\leq 30 \times 10^9/L$ 44% splenectomized	Significantly higher rate of platelet response <sup>a</sup> Reduced need for rescue therapy
Jurczak 2018 <sup>79</sup>	Avatrombopag n=32 Placebo n=17	Europe, Asia, and Australia	Adults with ITP for $\geq 12$ months and a screening mean Plt $< 30 \times 10^9/L$ 33% splenectomized	Significantly higher rate of platelet response <sup>a</sup> Reduced use of concomitant ITP medications

**Notes:** Each trial was a prospective, multicenter, randomized, placebo-controlled, double-blind study except Kuter et al. (2010) which was open label. Reproduced with permission from Al-Samkari and Kuter<sup>59</sup>. <sup>a</sup>Platelet response defined as a platelet count  $\geq 50 \times 10^9/L$  at a given assessment on treatment with TPO-RA or placebo.

**Abbreviations:** ITP, immune thrombocytopenia; Plt, platelet count.

platelet response rate of 79–88% in patients given romiplostim, with platelet counts to  $\geq 50 \times 10^9/L$  for 13.8 weeks, compared with 0.8 weeks in the placebo group.<sup>62</sup> In another open-label study, comparing romiplostim to the medical standard of care in patients without history of splenectomy, patients who received romiplostim were 2.3 times as likely to have a platelet response as those who received the standard of care (71–92% patients who received romiplostim had a platelet response, compared with 51% in the standard of care group).<sup>63</sup> Though romiplostim does not have the ease of administration as oral TPO-RAs, a recent study has found that self-administration of romiplostim by patients did not increase adverse events compared with administration by healthcare professionals.<sup>64,65</sup>

Eltrombopag is a small molecule TPO-RA approved by the US FDA for ITP following the failure of a first-line treatment and is initiated orally at a dose of 50 mg daily in adults (or 25 mg daily in patients of East Asian descent), titrated to a maximum dose of 75 mg daily to reach a goal platelet count of  $50\text{--}200 \times 10^9/L$ .<sup>66</sup> Multiple studies have found eltrombopag significantly increases platelet response (59–79%) with less bleeding (statistically significant OR 0.49) and reduced use of concomitant ITP treatment.<sup>67,68</sup> Ethnic differences in eltrombopag were noted in patients of East Asian descent, with about 60% responding to a 12.5 mg or 25 mg daily dose.<sup>69,70</sup> Commonly reported adverse effects of eltrombopag include hepatotoxicity (11%), headache (2.9%), diarrhea, and upper respiratory tract infection.<sup>68–71</sup> A disadvantage of eltrombopag is the dietary restrictions (avoidance of dietary fat and divalent cations, such as calcium and magnesium in food) for a 4–6 hour window around taking the medication to prevent dietary and medication interference with adequate absorption.<sup>72,73</sup> Given the half-life of 26–35 hours,<sup>74</sup> one method proposed to address this is alternative intermittent dosing of eltrombopag less frequently than once daily, which has been shown to be effective in observational data.<sup>75</sup>

Avatrombopag is small molecule oral TPO receptor agonist approved for chronic ITP in adults as well as patients with liver disease scheduled to undergo a procedure. In ITP, it is initiated at a dose of 20 mg daily<sup>76</sup> titrated to a maximum dose of 40 mg daily to achieve a goal platelet count of  $50\text{--}200 \times 10^9/L$ . Unlike eltrombopag, avatrombopag does not require strict dietary restrictions for a 4–6 hour window around when it is taken. Also, it does not have a known signal for hepatotoxicity, nor

does it require dose adjustment for the race of the patient. In a phase II double-blind randomized controlled trial in patients with persistent and chronic ITP who failed or relapsed after prior therapy, 75% of patients receiving avatrombopag had an overall response, with the drug overall well-tolerated (common adverse events included fatigue and headache).<sup>77</sup> In a phase III study, avatrombopag was superior to placebo in mean cumulative number of weeks with platelet count  $\geq 50 \times 10^9/L$  during a 6-month treatment period with higher rates of reduced concomitant ITP medication use and durable response compared with placebo. In a post hoc analysis of the 2018 phase III study, avatrombopag was shown to have higher rates of platelet response and complete response in the first 6 months and a reduction in chronic corticosteroid use.<sup>78,79</sup> In addition to treatment of ITP, avatrombopag has also been studied extensively in patients with liver disease and has shown to be efficacious in the peri-procedural setting in patients with thrombocytopenia of chronic liver disease.<sup>80–83</sup>

A fourth TPO-RA, lusutrombopag, is also a small molecule oral TPO-RA, approved for thrombocytopenia due to chronic liver disease prior to an invasive procedure.<sup>84</sup> Its effect in ITP has not yet been well studied. A phase II study of lusutrombopag in ITP was recently terminated early due to results suggesting a higher dose was necessary to elicit an efficacy effect.

Thus far, there have not been any head-to-head randomized controlled trials completed comparing TPO-RAs. The relative potency of these agents is a topic of interest.<sup>85</sup> In a single center retrospective comparison of romiplostim and eltrombopag, there was no significant difference in platelet responses or tolerability.<sup>86</sup> One meta-analysis of nine randomized placebo-controlled trials showed no significant difference in overall response rate, bleeding incidence, incidence of adverse events, or durable response.<sup>87</sup> In a systematic review of 18 retrospective studies, the response rate after switching from one TPO-RA agent to another due to lack of efficacy, adverse events, or patient preference was 77.5%.<sup>74</sup>

There have been no formal guidelines regarding the discontinuation or tapering of TPO-RAs.<sup>88</sup> In a single-center observational study of patients who discontinued TPO-RAs, the 2-year treatment-free remission rate was 66.4% with 46% cumulative incidence of loss of complete response, but there was no clear predictive factor for sustained response.<sup>89</sup> In a meta-analysis, the incidence of remission after TPO-RA discontinuation ranged from 5–36%.<sup>58</sup> Tapering of TPO-RAs is dependent on multiple

factors, including platelet count at or above the lower limit of normal, lack of a major bleeding history, low trauma risk, and taking into account antiplatelet or anticoagulant agents the patient is taking.<sup>90</sup> In an expert consensus panel, the duration of ITP, duration on TPO-RA, and timing of platelet response did not affect the panel's recommendations regarding discontinuation.<sup>90</sup> A recent phase II study of sustained remission off treatment after discontinuation from TPO-RAs found that 25% of responders were able to maintain the response during 6 months after tapering from eltrombopag.<sup>91</sup> This study also reviewed biomarkers including TPO levels, which did not have a significant association with response or with sustained remission, and IL-10, IL-4, and TNF- $\alpha$ , each of which had negative predictive response. Other studies have found that TPO levels can predict response to TPO-RAs.<sup>92</sup> More research is needed to identify predictive factors that might be able to guide the tapering of TPO-RAs.

### Fostamatinib

Fostamatinib is a spleen tyrosine kinase inhibitor which inhibits the inflammatory response and clearance of auto-antibody coated platelets by the reticuloendothelial system.<sup>93</sup> It was approved for ITP after the failure of other therapies at an initial dose of 100 mg twice daily, with up-titration to 150 mg twice daily for an inadequate response. Two phase III randomized placebo-controlled trials of fostamatinib in patients with persistent/chronic ITP showed an overall response in 43% of patients on fostamatinib with a median time to response of 15 days.<sup>94</sup> In the follow-up, open-label extension study, responses appeared durable, with 44% of patients achieving an overall response for a median of >28 months.<sup>95</sup> In this study, most adverse events were mild to moderate, with the most common events including diarrhea, hypertension, nausea, epistaxis, and transaminase elevation.<sup>95</sup>

### Therapies Currently Under Investigation

There is ongoing research involving Bruton's tyrosine kinase inhibitors in the potential treatment of immune-related diseases.<sup>96</sup> Rilzabrutinib is an oral, reversible small molecule selective BTK inhibitor that has shown preclinical efficacy in rapidly inhibiting antibody mediated innate immune response as well as antibody production, exhibiting potential for ITP treatment.<sup>96</sup> Rilzabrutinib was also shown to be safe and well tolerated in a phase I trial, with favorable pharmacokinetics that could result in fast onset of effect.<sup>97</sup>

Bortezomib is a proteasome inhibitor that was shown in a preclinical study to improve thrombocytopenia in ITP by inducing apoptosis in long-lived plasma cells which were thought to play a role in corticosteroid resistant ITP.<sup>98</sup> Bortezomib has been shown to have success in treatment of relapsing ITP in a case report,<sup>99</sup> though further clinical trials are needed.

### Salvage Therapies

Other treatments of ITP include immunosuppressants (azathioprine, cyclophosphamide, cyclosporine, mycophenolate mofetil, vinca alkaloids), dapsone and danazol. These agents are typically used after failure of multiple standard second/subsequent-line treatment options. A brief summary of these therapies can be found in Table 2.<sup>11</sup> The management of patients with refractory ITP is discussed in more detail elsewhere.<sup>100–102</sup>

## Special Considerations in ITP Management

### Bleeding Emergencies in ITP

Management of bleeding emergencies in ITP is an important topic which requires further study. In the Updated International Consensus Report, Provan et al. provides a review of recommendations for treatment of life-threatening hemorrhage due to ITP.<sup>88</sup> Recommendations incorporate general supportive care with a combination of treatments, including IV corticosteroids, IVIG, and platelet transfusions in order to increase platelet count rapidly, and in the absence of significant response, the early addition of a TPO-RA should also be considered.<sup>88</sup> Ultimately, aggressive management to provide for a rise in the platelet count which often incorporates the use of multiple agents simultaneously without waiting for a single agent to be effective is appropriate. When TPO-RAs are used, they may be dosed more aggressively (e.g. romiplostim 5–10 mcg/kg to start). This is done with recognition of a potential thrombocytosis risk but with the understanding that the risk of ongoing severe thrombocytopenia and worsened bleeding is greater and requires urgent mitigation.

### ITP in Pregnancy

Pregnancy complications in the setting of ITP include maternal hemorrhage, fetal loss, low birth weight, and may be treated to maintain a platelet level in the mother ( $\geq 30 \times 10^9/L$  until close to term), with the goal then adjusted based on delivery procedures.<sup>10,103,104</sup>

**Table 2** Other Agents for Use in the Subsequent Treatment Setting in ITP

Agent	Mechanism	Time to Response	Response Rate	Response Durability	Major Adverse Effects	Comments
Azathioprine <sup>110</sup>	Prodrug of antimetabolite 6-mercaptopurine; steroid-sparing immunosuppressant	Delayed (weeks to months)	30%	Good	Bone marrow suppression Infection Hepatotoxicity	Thiopurine S-methyltransferase activity should be measured prior to initiation  Accepted as safe in pregnancy
Cyclophosphamide <sup>111,112</sup>	Prodrug of phosphoramidate mustard metabolite; immunosuppressant	Delayed (weeks to months)	30–40%	Good	Bone marrow suppression Hemorrhagic cystitis Infection	Low-dose oral cyclophosphamide typically used
Cyclosporine <sup>113,114</sup>	Calcineurin inhibitor immunosuppressant	Early (1–2 weeks)	30–40%	Moderate	Nephrotoxicity Hypertension, Metabolic side-effects	Trough levels should be monitored
Danazol <sup>115–118</sup>	Attenuated androgenic steroid hormone with glucocorticoid receptor activity	Delayed (weeks to months)	30–40%	Good	Virilization Hepatotoxicity Weight gain	May be combined with azathioprine but evidence for this is poor
Dapsone <sup>119–121</sup>	Antibiotic with immunomodulatory and anti-inflammatory properties	Delayed (weeks)	40–50%	Poor	Methemoglobinemia Hemolysis	Glucose-6-phosphate dehydrogenase activity should be measured prior to initiation
Mycophenolate mofetil <sup>122–124</sup>	Prodrug of mycophenolic acid, a purine synthesis inhibitor causing immunosuppression	Delayed (weeks)	40–50%	Good	Diarrhea Bone marrow suppression Infection	
Vinca alkaloids (vincristine, vinblastine) <sup>125–128</sup>	Microtubule toxin chemotherapeutic agents causing potent immunosuppression	Rapid (within 1 week)	70%	Poor	Vesication at infusion site Neuropathy Constipation SIADH	Administered as multiple weekly intravenous infusions; can be used as a rescue therapy of last resort

**Notes:** These agents are commonly labeled “third-line” treatments, although they may be used earlier or later in the treatment of ITP depending on clinical circumstances (i.e. pregnancy) or availability of more expensive agents (such as TPO-RAs or rituximab). Reproduced with permission from Al-Samkari and Kuter.<sup>11</sup>

**Abbreviation:** SIADH, syndrome of inappropriate antidiuretic hormone secretion.

Recommended treatments include corticosteroids or IVIG, or a combination.<sup>105</sup> In the event that both modalities fail, TPO-RAs can be considered as a salvage therapy in severe cases, on the basis of limited observational data. One multicenter observational study of 15 pregnant women showed a response rate of 77% to TPO-RA (romiplostim or eltrombopag) though mostly in combination with concomitant ITP therapy.<sup>106</sup> And while this study showed no thromboembolic events and aside from one case of neonatal thrombosis, no other fetal complications,<sup>106</sup> more information is needed about other therapies in pregnancy. The management of pregnant patients is discussed in more detail in a review by Gernsheimer et al.<sup>107</sup>

## Conclusions and Future Directions

Modern treatment of ITP in adults involves a number of tried and true first-line therapies, primarily corticosteroids and IVIG, as well as newer therapies in the TPO-RAs and fostamatinib. Though there are many more options for the management of ITP at present than in even the relatively recent past, there remains unmet need in this disease. Thankfully, additional therapies are under development for ITP, including inhibitors of the Bruton tyrosine kinase (e.g. rilzabrutinib), complement inhibitory therapies (e.g. sutimlimab), neonatal Fc receptor antagonists (e.g. rozanolixizumab, efgartigimod), and others. Management of chronic ITP may involve cycling through multiple drug therapies, consideration of splenectomy, and in some patients, reaching for salvage therapies or clinical trials of novel agents. Lastly, bleeding emergencies in ITP require prompt, aggressive management, typically with multiple agents.

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## Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

## Disclosure

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