Immune thrombocytopenia in Adults: Modern Approaches to Diagnosis and Treatment

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Abstract

Immune thrombocytopenia (ITP) is an autoimmune bleeding disorder affecting approximately 1 in 20,000 people. Patients typically present with clinically benign mucocutaneous bleeding, but morbid internal bleeding can occur. Diagnosis remains clinical, possible only after ruling out other causes of thrombocytopenia through history and laboratory testing. Many adult patients do not require treatment. For those requiring intervention, initial treatment of adult ITP is with corticosteroids, intravenous immunoglobulin, or intravenous anti-RhD immune globulin. These agents are rapid-acting but do not result in durable remissions in most patients. No corticosteroid has demonstrated superiority to others for ITP treatment. Subsequent treatment of adult ITP is typically with thrombopoietin receptor agonists (TPO-RAs; romiplostim or eltrombopag), rituximab, or splenectomy. TPO-RAs are newer agents that offer an excellent response rate but may require prolonged treatment. The choice between subsequent treatments involves consideration of operative risk, risk of asplenia, drug side-effects, quality-of-life issues, and financial costs. Given the efficacy of medical therapies and the rate of spontaneous remission in the first year after diagnosis, splenectomy is frequently deferred in modern ITP treatment algorithms. Fostamatinib (a tyrosine kinase inhibitor recently approved by the U.S. Food and Drug Administration) and several older immunosuppressive agents (azathioprine, cyclophosphamide, cyclosporine, danazol, dapsone, mycophenolate mofetil, and the Vinca alkaloids) may be useful in patients with disease unresponsive to standard therapies or in specific clinical circumstances. This comprehensive review explores diagnostic considerations and surveys new and old treatment options for adults with ITP.

Keywords

► platelets
► immune thrombocytopenia
► diagnosis
► treatment
► corticosteroids
► intravenous immunoglobulin
► splenectomy
► thrombopoietin receptor agonist
► rituximab
► fostamatinib
deterioration via nonspecific action on the immune system, newer agents target more specifically the pathophysiology of ITP by improving platelet production or decreasing platelet destruction. In this review, we will assess modern practices in ITP diagnosis and treatment synthesizing the best available evidence and expert opinion.

**Diagnosis of Immune Thrombocytopenia**

**Clinical Presentation**

The incidence of ITP is approximately 1 in 20,000 people and increases with age. It is slightly more common in females. The initial presentation of ITP is highly variable, from incidentally discovered asymptomatic mild thrombocytopenia to severe, life-threatening bleeding. Patients who present with profound thrombocytopenia (platelet count < 20 x 10^9/L and usually < 10 x 10^9/L) often have evidence of benign mucocutaneous hemorrhage, such as petechiae, ecchymoses, and oral mucosal blood blisters. Though clinically benign, this frequently brings the patient to clinical attention. Significant musculoskeletal bleeding, as occurs in severe coagulation factor deficiencies, generally does not occur, but there is a low, albeit important, risk of gastrointestinal bleeding and intracranial bleeding in profoundly thrombocytopenic ITP patients. Bleeds may occur secondary to trauma, other pathology (such as a tumor), or spontaneously. Intracranial bleeding typically presents as intracerebral hemorrhage and is the most common cause of ITP-related death, with a 50 to 80% mortality in patients > 60 years of age and up to 20% mortality in patients < 40 years of age. In a meta-analysis of 17 studies, the rate of fatal bleeding in ITP was estimated at 0.0162 to 0.0389 cases per patient-year. Rapid-acting treatment modalities such as corticosteroids and IVIG are administered to treat and prevent such serious bleeding complications in the acute setting.

While numerous factors impact the degree of thrombocytopenia that is likely to cause bleeding, most ITP patients do not present with mucocutaneous bleeding or clinically significant hemorrhage until the platelet count is < 30 x 10^9/L and many patients remain asymptomatic in the 20 to 29 x 10^9/L range or even the 10 to 19 x 10^9/L range. The most common symptom in ITP aside from bleeding is fatigue, which occurs in 20 to 40% of patients. Although the etiology is not entirely clear, fatigue can markedly affect quality of life in ITP patients and may even be an indication for treatment, which may be very effective at alleviating fatigue.

**Diagnostic Testing**

Although there is no test capable of reliably diagnosing ITP, a laboratory evaluation is recommended at diagnosis to screen for potential causes of secondary ITP, uncover infections resulting in thrombocytopenia that may resolve with proper treatment, and rule out other causes of thrombocytopenia. Alternative causes of thrombocytopenia, and the recommended assessments to rule out these disorders, are listed in the Table 1.

All adults presenting with new suspected ITP should undergo a comprehensive history and physical examination with the following laboratory studies: complete blood count, peripheral blood film, human immunodeficiency virus serology, hepatitis C serology, and comprehensive metabolic panel (including transaminases, bilirubin, and alkaline phosphatase). The peripheral blood film should be examined to rule out evidence of other causes of thrombocytopenia as can be seen such as fragmented erythrocytes (suggesting thrombotic microangiopathy or disseminated intravascular coagulation [DIC]) or atypical leukocytes (suggestive of myeloid or lymphoid malignancy). Giant platelets are frequently seen on peripheral blood film in ITP. Quantitative immunoglobulin levels can be obtained in patients for whom a primary immunodeficiency (e.g., common variable immunodeficiency) is suspected or prior to IVIG infusion but are not required in all patients. Bone marrow evaluation is not indicated unless patients have additional unexplained cytopenia, a significant family history of thrombocytopenia or myeloid malignancies, or poor response to typical initial treatment options (corticosteroids, IVIG, anti-D immune globulin). While ELISA-based glycoprotein-specific direct platelet autoantibody testing has been repeatedly demonstrated to have a high specificity in the > 80 to 90% range, it is not recommended for routine diagnosis owing to its poor sensitivity. The sensitivity of platelet autoantibody testing for ITP diagnosis may be improved with adherence to recent laboratory platelet autoantibody testing guidelines, but this remains under investigation. Other methods of platelet autoantibody testing, such as flow cytometric detection of platelet-associated immunoglobulin G, are additionally not recommended.

Routine direct antiglobulin testing or testing for antinuclear antibodies, antiphospholipid antibodies, antithyroid antibodies, or thyroid function is not recommended, although targeted testing may have utility in certain patients given other medical history and findings on history and physical examination. For example, direct antiglobulin testing is appropriate in patients with a concomitant anemia with an elevated reticulocyte count or in those for whom intravenous anti-RhD immune globulin is being considered for treatment. Routine testing for thrombopoietin (TPO) levels, reticulated platelets, bleeding time, serum complement, or platelet survival is similarly not recommended for diagnostic purposes. There may be a role of serum TPO in predicting response to thrombopoietin receptor agonist (TPO–RA) therapy, which is discussed in more detail later.

**Classification of Immune Thrombocytopenia**

The chronicity of ITP has been defined according to the report of the international ITP working group (IWG). Patients with ITP for less than 3 months are considered to have newly diagnosed ITP; an alternative explanation for their isolated thrombocytopenia (Table 1) supplanting the ITP diagnosis will eventually be found in approximately 50% of these patients. Persistent ITP is defined as disease duration > 3 months but ≤ 12 months, and chronic ITP is defined as disease duration > 12 months. These classifications are relevant as chronicity impacts disease manifestations (e.g., intracranial hemorrhage is much less common in patients with chronic ITP).
The severity of ITP has additionally been defined in American Society of Hematology (ASH) clinical practice guidelines. Patients requiring any disease-directed treatment for clinical bleeding manifestations are designated severe ITP and those requiring additional medical treatment following splenectomy are designated refractory ITP. Patients with refractory ITP have higher rates of mortality. While official terminology defines refractory ITP as failure of splenectomy, in modern practice splenectomy is performed only on a small minority of patients. Therefore “refractory” is often used to describe patients who have failed multiple lines of therapy (one of which may be splenectomy), although this is not a definition present in published guidelines.

Response to treatment has also been defined by the IWG. A “response” (R) is defined as a platelet count between 30 and 100 x 10^9/L and at least double the baseline platelet count and a “complete response” (CR) is defined as a platelet count > 100 x 10^9/L following treatment. There is no widely

<table>
<thead>
<tr>
<th>Alternative diagnosis</th>
<th>Recommended evaluation</th>
<th>Additional testing to consider</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic infections</td>
<td>Serologic evaluation for HIV, HCV, and H. pylori</td>
<td>More sensitive H. pylori testing (e.g., urea breath test, stool antigen) may be considered in patients from high-prevalence locations</td>
</tr>
<tr>
<td>Systemic autoimmunity (especially systemic lupus erythematosus and antiphospholipid antibody syndrome)</td>
<td>History and physical examination</td>
<td>Targeted serologic testing (e.g., antinuclear antibody, anti–double-strand DNA antibody, antiphospholipid antibodies) in patients with concerning findings on history and physical</td>
</tr>
<tr>
<td>Chronic liver disease</td>
<td>History and physical examination, Liver panel (transaminases, bilirubin, alkaline phosphatase)</td>
<td>Liver imaging (e.g., ultrasound) in cases suspicious for occult liver disease</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>History and physical examination</td>
<td>Abdominal ultrasound to assess spleen size</td>
</tr>
<tr>
<td>Malignancy</td>
<td>History and physical examination</td>
<td>Targeted evaluation as indicated based on history and physical examination</td>
</tr>
<tr>
<td>Primary bone marrow disorders (e.g., myelodysplastic syndrome, aplastic anemia, leukemia, Gaucher’s disease)</td>
<td>Complete blood count, Peripheral blood film</td>
<td>Bone marrow evaluation can be considered in patients with unexplained concomitant anemia, leukopenia, or leukocytosis or steroid- and IVIG-nonresponsive patients</td>
</tr>
<tr>
<td>Substances and drugs</td>
<td>History</td>
<td>Targeted laboratory evaluation as indicated based on history</td>
</tr>
<tr>
<td>Heritable thrombocytopenias, e.g., Bernard–Soulier syndrome, MYH9-related disease, type IIB von Willebrand disease, Upshaw–Shulman syndrome</td>
<td>Family history, Peripheral blood film</td>
<td>Specific coagulation or genetic testing in potentially suspicious cases</td>
</tr>
<tr>
<td>Acute viral infections (e.g., Epstein–Barr virus, cytomegalovirus) and immunologic stimuli (e.g., vaccinations, transfusions)</td>
<td>History and physical examination</td>
<td>Viral serologies/PCR if specific viral infection(s) suspected</td>
</tr>
<tr>
<td>Chronic disseminated intravascular coagulation or low-grade thrombotic microangiopathy</td>
<td>History and physical examination, Complete blood cell count, Coagulation studies (prothrombin time, partial thromboplastin time, fibrinogen, D-dimer), Peripheral blood film</td>
<td>Targeted imaging or invasive evaluation as indicated based on initial evaluation</td>
</tr>
</tbody>
</table>

Abbreviations: HCV, hepatitis C virus; HIV, human immunodeficiency virus; IVIG, intravenous immunoglobulin; PCR, polymerase chain reaction. Note: Recommended evaluation to rule out each of these disorders is described.
accepted definition of “remission” in ITP. Most investigations examining ITP variably define “partial remission” and “complete remission” based on arbitrary platelet count thresholds.\(^\text{17}\)

**Initial Treatment of Immune Thrombocytopenia**

ITP treatment can be broadly divided into initial/acute treatment and subsequent treatment, which may require long-term administration. Each treatment has one or more distinct effects on the pathophysiology of ITP (► Fig. 1). Initial/acute treatment is administered on initial presentation or acute relapse in a patient with profound thrombocytopenia and/or bleeding manifestations. Agents in this category (corticosteroids, IVIG, IV anti-D immune globulin) necessarily have a relatively rapid onset of action (typically 1–2 days) and are not generally considered appropriate long-term treatments. Most adults with ITP will not maintain a normal platelet count after initial treatments alone, and those that relapse with bleeding or very low platelet counts proceed to subsequent treatments. Subsequent treatments to achieve long-term disease control or remission include TPO-RAs, rituximab, splenectomy, fostamatinib, and others.

**Indications for Treatment**

In ITP, as well as other thrombocytopenic conditions, treatment-triggering platelet count thresholds are frequently sought out or formulated by clinicians. Indeed, thresholds for treatment are described in consensus guidelines; for example, the ASH 2011 ITP guidelines suggest treatment should be given to newly diagnosed patients with platelet counts \(< 30 \times 10^9/L\).\(^\text{4}\) But multiple studies suggest a poor correlation, if any at all, between platelet count and bleeding in ITP in patients with platelet counts \(> 10 \times 10^9/L\).\(^\text{18–20}\) This is consistent with other studies that have demonstrated normal thrombin generation\(^\text{21}\) and bleeding time\(^\text{22}\) in patients with platelet counts as low as \(10 \times 10^9/L\). Additionally, platelets from patients with ITP are often larger and more functional than normal platelets, such that the overall platelet mass is higher than expected for a given platelet count.\(^\text{22}\)

Given this data, we will always treat any bleeding ITP patient (regardless of platelet count), patients with a platelet count \(< 10 \times 10^9/L\), and most patients with a platelet count 10 to \(19 \times 10^9/L\). Beyond this, treatment indications are personalized for individual patients. Most patients with chronic ITP tolerate platelet counts in the 20 to 50 \(\times 10^9/L\) range without spontaneous bleeding events. Consideration of platelet counts during prior bleeding events, activity level, lifestyle/profession (and associated trauma risks), costs and potential side effects of treatment, and patient preferences must be considered in all patients. In those patients with known platelet dysfunction, an additional hemostatic defect, planned surgery, trauma, or need for antiplatelet therapy, anticoagulation, or chemotherapy, higher platelet counts are

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**Fig. 1** Pathophysiology of ITP and impact of ITP treatments. IVIG, intravenous immunoglobulin; BTK, Bruton tyrosine kinase; TPO-RA, thrombopoietin receptor agonist; FcRn, neonatal Fc receptor.
often needed. Finally, ITP-associated fatigue may respond to treatment and resolve with higher platelet counts. Given the debilitating nature of this fatigue in certain patients, treatment may be indicated.\textsuperscript{11}

**Initial/Acute Treatments**

The mainstay of initial/acute treatment is corticosteroids, typically either prednisone (administered over a 4- to 8-week course [including taper] with a starting dose of \(-0.5\text{–}2\) mg/kg daily, to a maximum of \(80\) mg daily) or high-dose dexamethasone (administered as a pulse of \(40\) mg daily for \(4\) days for up to three 4-day cycles).\textsuperscript{4,5} Most responsive patients experience platelet count improvements \(2\) to \(4\) days after initiation of corticosteroids, but response may take \(5\) to \(7\) days or longer in some patients. Patients experiencing a major bleeding event and those with contraindications or nonresponse to corticosteroids should receive IVIG. Intravenous anti-D immune globulin is another agent that can be used in the acute setting in RhD-positive patients, causing mild hemolysis to reduce platelet destruction in the reticuloendothelial system, but it is not available in many countries now because it may precipitate DIC. Each of these agents has response rates in excess of \(70\) to \(80\)% in the newly diagnosed patient.

**Corticosteroids**

How corticosteroids improve the platelet count in ITP remains unclear. Studies have shown that corticosteroids reduce platelet autoantibody production and inhibit Fc receptor-mediated clearance by phagocytic cells\textsuperscript{24} but also increase platelet production.\textsuperscript{25} Additionally, corticosteroids may improve vascular integrity in thrombocytopenic states. Thrombocytopenia results in endothelial thinning and fenestrations which may predispose to bleeding; prednisone has been demonstrated to reverse these changes in a rabbit model.\textsuperscript{26,27}

Prednisone and dexamethasone are the corticosteroids of choice in ITP. Studies comparing dexamethasone to prednisone or prednisolone have not demonstrated clear superiority of any corticosteroid.\textsuperscript{28–30} In a meta-analysis of trials comparing dexamethasone to prednisone, dexamethasone was found to work faster but did not result in a higher rate of sustained remission.\textsuperscript{31} Either agent remains appropriate to use in most patients; in certain patient groups at higher risk of corticosteroid-associated psychiatric side effects (such as very elderly patients), high-dose dexamethasone should be avoided.

Several studies in newly diagnosed ITP patients have explored the addition of rituximab or TPO-RAs to corticosteroids. Several studies comparing rituximab with dexamethasone demonstrated higher remission rates at \(6\) to \(12\) months, but these improved remission rates were not sustained.\textsuperscript{32–37} A study of eltrombopag plus dexamethasone in the upfront setting is potentially promising, but additional follow-up is needed.\textsuperscript{38}

**Intravenous Immunoglobulin**

IVIG reduces Fc receptor-mediated clearance of platelets by the reticuloendothelial system. Several mechanisms have been postulated for this effect, including competition with platelet autoantibodies for FcRn receptor binding, which results in increased platelet autoantibody clearance; binding to FcγRIII on phagocytes, thereby preventing binding of platelet autoantibody immune complexes; and upregulating the inhibitory FcγRIIB on phagocytes.\textsuperscript{39,40}

IVIG can be administered either high dose (\(1\) g/kg daily for \(1\text{–}2\) days) in emergent settings or lower dose (e.g., \(0.4\) g/kg daily for up to \(5\) days).\textsuperscript{5} It should be used in patients with major bleeding (often in combination with corticosteroids) or in patients who require acute treatment and either cannot tolerate or do not respond to corticosteroids.

**Intravenous Anti-RhD Immune Globulin**

IV anti-RhD immune globulin reduces Fc receptor-mediated clearance of autoantibody-coated platelets by creation of a “controlled” red cell hemolysis. Anti-RhD antibody-coated red cells compete with autoantibody-coated platelets for FcγR on phagocytes of the reticuloendothelial system, reducing platelet destruction. Intravenous anti-D immune globulin is licensed for a \(50\) µg/kg dose but appears to be more effective when administered at a higher \(75\) µg/kg dose.\textsuperscript{41,42} Essentially all patients will have a modest hemoglobin drop of approximately \(1\) g/dL on average. Anti-RhD is effective only in RhD-positive patients who have not been splenectomized. It is an option in the initial/acute setting but has limited availability. Blood group testing, direct antiglobulin testing, and reticulocyte count should be obtained prior to administering IV anti-D immune globulin.\textsuperscript{9} Since DIC is a potential major adverse effect of this drug, patients should be closely monitored.

**Management of Nonresponding Patients in the Initial/Acute Setting**

Patience is important when managing patients in the acute setting. At least \(7\) to \(10\) days from the initiation of treatment should pass before declaring failure of corticosteroids and IVIG.\textsuperscript{4,5} In these situations, several options should be considered. The first is reexamination of the diagnosis, which may include bone marrow examination, to ensure that an alternative diagnosis has not been missed. Additionally, other treatment options can be pursued, generally those deferred to subsequent treatment of patients who relapse after initial therapy (discussed in more detail later). Rituximab can be considered, but it often takes several weeks to work. A TPO-RA can be tried; we favor romiplostim owing to its higher potency\textsuperscript{43–45} and recommend administration of high-dose treatment upfront (\(5\text{–}10\) µg/kg for \(1\text{–}2\) doses). This requires continued patience as TPO-RAs do not work immediately and require a minimum of \(5\) to \(7\) days before an effect is seen. Vinca alkaloids (\textit{vide infra}) might also be considered given their rapid onset of effect, but their use is usually limited by the risk of neuropathy. Emergency splenectomy is another option; this is best reserved for truly treatment-resistant patients and a high degree of confidence that the diagnosis of ITP is correct. Bone marrow examination is advised before performance of emergency splenectomy.\textsuperscript{4,5}

Platelet transfusion achieves a transient improvement of \(>20 \times 10^9/L\) in a significant minority of bleeding ITP patients,\textsuperscript{46} an effect that may be augmented with concurrent
administration of IVIG. Nonspecific hemostatic agents, such as the antifibrinolytic agents tranexamic acid and e-aminocaproic acid, may also be considered in the acutely bleeding patient.

**Management of Pregnant Patients Requiring Treatment**

ITP complicates between 1 in 1,000 and 1 in 10,000 pregnancies, although it requires treatment only in about a third of cases. Pregnancy complications, including maternal hemorrhage, fetal loss, and low birthweight, are more common in women with ITP. Neonatal thrombocytopenia may occur due to transplacental passage of platelet autoantibodies. Treatment should be administered for the purpose of maintaining an adequate platelet count in the mother (>20 x 10^9/L until close to term, with the goal then adjusted based on delivery procedures and potential requirement for neuraxial anesthesia). Either corticosteroids or IVIG is appropriate for treatment. In patients unresponsive to either of these agents alone, a combination of corticosteroids and IVIG is appropriate for treatment. In patients unresponsive to the two agents, one can attempt rituximab or splenectomy. There are inadequate data to recommend other treatments, which in a woman with chronic ITP, corticosteroids and IVIG remain useful as rescue therapy. For patients who do require subsequent treatment, numerous options are available.

**Subsequent Treatment of Immune Thrombocytopenia**

While most adult ITP patients respond to corticosteroids and/or IVIG, the majority will relapse following this response and progress to persistent and often chronic ITP. Many of these patients do not require treatment at the time of relapse because they are able to maintain adequate platelet counts without bleeding manifestations. For those patients who do require subsequent treatment, numerous options are available.

**Choice of Subsequent Treatment**

Most patients who relapse following initial treatment will again respond to corticosteroids or IVIG, but recurrent or long-term use of these agents is generally not recommended. Chronic corticosteroids administered at doses > 5 mg prednisone daily (or equivalent) results in an unacceptable side-effect burden and should not be used in lieu of other treatments, although some ITP patients can do well for years on low doses of prednisone (2.5–5 mg/day). For patients who progress to chronic ITP, corticosteroids and IVIG remain useful as rescue therapies for bleeding or profound thrombocytopenia.

Current and upcoming international consensus report (ICR) and ASH ITP guidelines generally offer wide latitude in the selection of subsequent treatment in the postrelapse setting. The treatments with the most robust evidence in the subsequent treatment setting are the TPO-RAs romiplostim and eltrombopag, the Syk kinase inhibitor fostamatinib, the anti-CD20 agent rituximab, and splenectomy. The proposed ASH 2019 ITP clinical practice guidelines that were unveiled at the 2018 ASH Annual Meeting and Exposition and made available for public comment list TPO-RAs, rituximab, and splenectomy as favored second-line therapies. Implicit in their analysis was the recognition that therapies previously deemed for “chronic” patients could be considered after 3 months of disease, and that splenectomy should be deferred at least that long if possible. TPO-RAs are recommended over rituximab and rituximab over splenectomy. In comparing TPO-RAs with splenectomy, the merits of each approach are stated, but one is not recommended over the other; rather the updated guidelines advise a joint decision-making process between patient and provider. Table 2 summarizes the pros and cons of the major therapies considered in the subsequent treatment setting.

**Splenectomy**

Splenectomy is effective in ITP by removing the principal site of reticuloendothelial system platelet destruction as well as a major site of platelet autoantibody production. Platelet survival improves over threefold following splenectomy. The early response rate to splenectomy is approximately 85%, with rapid responses in most patients. Unfortunately, 20 to 30% of patients who initially respond to splenectomy will eventually relapse (most in the first year after splenectomy), such that long-term remissions are observed in approximately 60 to 70% of all patients. Patients under consideration for splenectomy should be vaccinated for encapsulated organisms (Streptococcus pneumoniae, Haemophilus influenzae, and Neisseria meningitidis).

Following splenectomy in ITP patients, there is an increased risk of venous thromboembolism (VTE) and sepsis. Since ITP patients already have an increased risk of VTE at baseline relative to the general population, the cumulative VTE risk (including splanchic vein thrombosis) increases approximately threefold following splenectomy occurring in 4 to 5% of patients in one large study. The risk of splanchic vein thrombosis is over fivefold higher in the 3-month period following splenectomy and the rate of portal or splenic vein thrombosis was 74% in one study that employed systematic detection with abdominal CT scans between 3 and 7 days following splenectomy. The incidence of infections leading to sepsis remains persistently elevated by approximately twofold in splenectomized ITP patients relative to their non-splenectomized counterparts. Additionally, splenectomy may have other unforeseen consequences. For example, evidence has emerged that the splenic red pulp is the site of a unique undifferentiated monocyte pool that appears to exit the spleen following ischemic cardiac injury and may be important in repairing injured cardiac tissue. Additionally, splenectomy may alter the balance between the immune and inflammatory system. Although the clinicopathological significance of splenectomy is not fully understood, a recent study has shown a nearly threefold increased cancer risk in patients following nontraumatic splenectomy.

Therefore, while splenectomy offers the promise of long-term remission in approximately two-thirds of patients, patients need to be informed of these risks and splenectomy should be delayed if possible. We favor a delay of at least 1 year in most patients. This is based on the finding that about one-third of adults with ITP will enter remission with medical therapies in the first year after ITP diagnosis. In addition, approximately one-third of patients with chronic disease may attain a remission. With the introduction of novel ITP...
therapies in the past two decades, the rate of splenectomy has declined precipitously, from approximately 30% of ITP patients in the United States in the mid-1990s to less than 10% by 2009.56 Prior studies demonstrating durable remissions in 60 to 70% of patients included many patients undergoing splenectomy as an early treatment following failure of initial corticosteroid-based management. Given that splenectomy is now frequently deferred until several newer medical treatments have been attempted, the population of ITP patients proceeding to splenectomy in modern times may have more treatment-resistant disease. It is unclear if the historic remission rates still apply to these patients.

**Thrombopoietin Receptor Agonists**

Thrombopoietin receptor agonists mimic the action of endogenous TPO on megakaryocytes and megakaryocyte precursors, inducing resistance to platelet autoantibody- and lymphocyte-induced apoptosis, thereby promoting the survival, growth, and maturation of megakaryocytes. Therefore, TPO-RAs augment platelet production to compensate for increased platelet turnover. In addition to their efficacy in ITP, these agents can improve platelet counts in chemotherapy-induced thrombocytopenia, myelodysplastic syndrome, periprocedural thrombocytopenia in chronic liver disease, and aplastic anemia (where eltrombopag can induce trilineage responses).52–66 Three TPO-RAs have demonstrated efficacy in ITP: the peptide agent romiplostim and the small molecule agents eltrombopag and avatrombopag. Table 3 presents an overview of the differences between each of the agents. One or more phase III randomized, controlled trials have been performed evaluating each of these agents; the results of these trials are summarized in Table 4. Regardless of agent, TPO-RAs have a higher overall response rate (70–80%) than other agents used for subsequent treatment of ITP but typically require prolonged durations of use. In patients with refractory ITP (relapse post-splenectomy requiring treatment), the response rate is approximately 40 to 60%.67–69 While extended durations of use are expected, a significant minority of responding patients demonstrate durable, long-standing remissions after prolonged TPO-RA treatment.60,70

**Predicting Response to Thrombopoietin Receptor Agonists**

Evidence has emerged that elevated baseline endogenous TPO levels (which are normal in >75% of ITP patients) may predict response to the TPO-RAs in ITP14,71,72 in as much the same fashion as endogenous erythropoietin levels can predict response to erythropoiesis-stimulating agents. In a study utilizing a well-validated ELISA-based TPO assay with a normal reference range of ≤100 pg/mL, patients with significant TPO elevations (>200 pg/mL) were unlikely to respond well to either eltrombopag or romiplostim, whereas patients with a normal TPO level were very likely to respond to either agent.14 While a study investigating the predictive value of TPO levels for response to avatrombopag in ITP has not yet been published, TPO values do predict response to avatrombopag in patients with chronic liver disease.75 Given the cost and duration of time required to titrate these agents to clinical effect, if validated in additional studies, the use of TPO levels to predict treatment response may emerge as a valuable tool in treatment planning.

**Agent Selection**

In selecting between the TPO-RAs, numerous factors are considered. Eltrombopag and avatrombopag are orally administered in contrast to romiplostim which requires weekly

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**Table 2** Comparison of the primary treatment modalities used for subsequent treatment of immune thrombocytopenia

<table>
<thead>
<tr>
<th></th>
<th>Splenectomy</th>
<th>TPO-RAs</th>
<th>Rituximab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early response rate</td>
<td>85%</td>
<td>70–80%</td>
<td>50–60%</td>
</tr>
<tr>
<td>Sustained response rate</td>
<td>60–70%</td>
<td>70–80%</td>
<td>20% off treatment</td>
</tr>
<tr>
<td>Remission rate</td>
<td>60–70%</td>
<td>30–40%</td>
<td>20%</td>
</tr>
<tr>
<td>Financial burden</td>
<td>Low</td>
<td>High</td>
<td>Moderate</td>
</tr>
<tr>
<td>Positive clinical aspects</td>
<td>Offers long-term remission in majority of patients</td>
<td>Well tolerated with high response rates</td>
<td>No need for chronic treatment</td>
</tr>
<tr>
<td></td>
<td>No need for chronic treatment</td>
<td>Multiple therapeutic options</td>
<td>Usually well tolerated</td>
</tr>
<tr>
<td></td>
<td>Avoidance of medication side effects</td>
<td>Avoidance of surgery</td>
<td>Avoidance of surgery</td>
</tr>
<tr>
<td>Potential major or important adverse events</td>
<td>Operative complications Immediate and lifetime increased risk of thromboembolism (especially splanchnic vein thrombosis) and infection Lifetime increased risk of malignancy</td>
<td>Headaches Hepatotoxicity (eltrombopag only) Venous thromboembolism (theoretical risk) Bone marrow fibrosis (low risk, reversible)</td>
<td>Infusion reactions B cell depletion and infections Progressive multifocal leukoencephalopathy (rare) Delayed neutropenia (rare)</td>
</tr>
<tr>
<td>Quality-of-life issues</td>
<td>None after initial postsurgical period</td>
<td>Chronic dietary restrictions (eltrombopag) Weekly injections (romiplostim)</td>
<td>None</td>
</tr>
</tbody>
</table>

Abbreviation: TPO-RA, thrombopoietin receptor agonist.
subcutaneous injections. Eltrombopag absorption is dramatically reduced by fat or divalent cation consumption, functionally requiring a 4- to 6-hour fasted window around its administration unless strict dietary restrictions are followed. Avatrombopag, by contrast, absorbs better with food. Romiplostim is considerably more potent than the oral TPO-RAs in healthy volunteers, and may be more potent in ITP patients as well; clinical response to this agent appears to be impacted less by mild baseline TPO level elevations than eltrombopag. Failure of one TPO-RA does not preclude use of another; switching from one TPO-RA to another is successful in many patients.

**Dosing of Thrombopoietin Receptor Agonists**

Per the prescribing information, eltrombopag is initiated at a dose of 50 mg daily in adults (25 mg daily in those of East Asian descent) and dose (12.5–75 mg daily) is titrated to platelet count. This agent has a half-life of 35 hours in ITP patients, so a dose of 1 µg/kg/week per the U.S. prescribing information, which advises up titration by 1 µg/kg/week until an acceptable platelet count is achieved. However, most patients require doses ≥3 mg/kg/week to respond; so, in clinical practice (and in one of the phase III studies of romiplostim), 3 µg/kg/week may be used as the starting dose with low thrombocytosis risk. Avatrombopag was recently FDA-approved for ITP in the United States. Initial dosing is 20 mg once daily, based on data from a phase III clinical trial demonstrating excellent platelet response rates with this dose.

**Adverse Effects of Thrombopoietin Receptor Agonists**

TPO-RAs are generally well tolerated in ITP patients, with mild to moderate headache as the most common side effect. Interval transaminase monitoring is advised for patients on eltrombopag due to the risk of hepatotoxicity. While thrombotic events, bone marrow fibrosis, and leukemogenesis are a theoretical concern with these agents, studies have not found elevated risks of these concerning side effects in ITP patients. Eltrombopag and romiplostim do not result in platelet hyperreactivity or spontaneous platelet aggregation and numerous large randomized, controlled studies of ITP patients have not demonstrated a significantly increased risk of venous or arterial thrombotic events in patients receiving TPO-RAs as compared with placebo. Bone marrow studies in patients receiving TPO-RAs for extended periods show a very low risk (~5%) of marrow reticulin fibrosis (which readily reverses on agent discontinuation) and essentially no risk of irreversible marrow collagen fibrosis. Additionally, there is no evidence of leukemic potential for use of TPO-RAs in any disorder, including myelodysplastic syndrome, where there is no clear increased risk of leukemic progression with several years of follow-up. Therefore, bone marrow examination is not indicated before treatment or for monitoring during treatment.

**Rituximab**

Rituximab is a chimeric anti-CD20 monoclonal antibody that depletes the B-cells that produce platelet autoantibodies. It is not FDA approved for use in ITP but has been a commonly employed ITP treatment for nearly two decades. Studies of mostly heavily pretreated patients demonstrate an overall response rate of approximately 40 to 70% with 4 weekly doses of 375 mg/m² of rituximab, although sustained remissions were much less common. A meta-analysis of five trials containing a total of 376 adults with ITP demonstrated a 57% overall remission rate with rituximab, but remission rate at 1 year was 38% and remission rate at 5 years was only 21%. Alternate dosing of rituximab (both higher and lower dosing schedules)

---

**Table 3** Comparison of the thrombopoietin receptor agonists used in immune thrombocytopenia treatment

<table>
<thead>
<tr>
<th>Molecular structure</th>
<th>Romiplostim</th>
<th>Eltrombopag</th>
<th>Avatrombopag</th>
</tr>
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<tbody>
<tr>
<td>Peptide</td>
<td>Small molecule</td>
<td>Small molecule</td>
<td></td>
</tr>
<tr>
<td>TPO receptor site of action</td>
<td>Extracellular domain</td>
<td>Transmembrane domain</td>
<td>Transmembrane domain</td>
</tr>
<tr>
<td>Route of administration</td>
<td>Subcutaneous</td>
<td>Oral</td>
<td>Oral</td>
</tr>
<tr>
<td>Dosing frequency</td>
<td>Weekly</td>
<td>Daily</td>
<td>Daily</td>
</tr>
<tr>
<td>Relevant food interactions</td>
<td>N/A</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Average U.S. wholesale price</td>
<td>$2,230.30 per 250 µg vial</td>
<td>$197.06 per tablet (12.5 mg or 25 mg)</td>
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<td></td>
</tr>
<tr>
<td>Current indications</td>
<td>Chronic ITP (adults and children)</td>
<td>Chronic ITP (adults and children)</td>
<td>Periprocedural thrombocytopenia in chronic liver disease patients</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Chronic ITP (adults)</td>
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Abbreviations: CLD, chronic liver disease; FDA, United States Food and Drug Administration; ITP, immune thrombocytopenia; N/A, not applicable; TPO, thrombopoietin.

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<table>
<thead>
<tr>
<th>Study</th>
<th>Number of patients (n)</th>
<th>Location</th>
<th>Study population</th>
<th>Major results (compared with placebo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bussel et al(^69)</td>
<td>Eltrombopag, (n = 76) Placebo, (n = 38)</td>
<td>Worldwide (63 sites)</td>
<td>Adults with ITP for (\geq 6) mo and a pretreatment Plt &lt; (30 \times 10^9)/L 39% splenectomized</td>
<td>Significantly higher rate of platelet response(^a)                                                             Significantly less bleeding</td>
</tr>
<tr>
<td>Cheng et al(^67)</td>
<td>Eltrombopag, (n = 135) Placebo, (n = 62)</td>
<td>Worldwide (75 sites)</td>
<td>Adults with ITP for (\geq 6) mo and a pretreatment Plt &lt; (30 \times 10^9)/L 36% splenectomized</td>
<td>Significantly higher rate of platelet response(^a) Reduced use of concomitant ITP medications Reduced need for rescue therapy</td>
</tr>
<tr>
<td>Tomiyama et al(^104)</td>
<td>Eltrombopag, (n = 15) Placebo, (n = 8)</td>
<td>Japan</td>
<td>Adults (\geq 20) y old with ITP for (\geq 6) mo and a pretreatment Plt &lt; (30 \times 10^9)/L 70% splenectomized</td>
<td>Significantly higher rate of platelet response(^a) Significantly less bleeding Lower doses of eltrombopag were effective in Japanese patients</td>
</tr>
<tr>
<td>Yang et al(^105)</td>
<td>Eltrombopag, (n = 104) Placebo, (n = 51)</td>
<td>China</td>
<td>Adults with ITP for (\geq 12) mo and a pretreatment Plt &lt; (30 \times 10^9)/L 16% splenectomized</td>
<td>Significantly higher rate of platelet response(^a)</td>
</tr>
<tr>
<td>Kuter et al(^68)</td>
<td>Romiplostim, (n = 83) Placebo, (n = 42) (patients from two parallel studies)</td>
<td>United States and Europe</td>
<td>Adults with ITP for (\geq 12) mo and a screening mean Plt &lt; (30 \times 10^9)/L 50% splenectomized</td>
<td>Significantly higher rate of platelet response(^a) Reduced use of concomitant ITP medications</td>
</tr>
<tr>
<td>Kuter et al(^82)</td>
<td>Romiplostim, (n = 157) Standard of care, (n = 77)</td>
<td>North America, Europe, and Australia</td>
<td>Adults with ITP for (\geq 12) mo and a pretreatment Plt &lt; (50 \times 10^9)/L 0% splenectomized</td>
<td>Significantly higher rate of platelet response(^a) 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</td>
</tr>
<tr>
<td>Shirasugi et al(^106)</td>
<td>Romiplostim, (n = 22) Placebo, (n = 12)</td>
<td>Japan</td>
<td>Adults (\geq 20) y old with ITP for (\geq 6) mo and a screening Plt (\leq 30 \times 10^9)/L 44% splenectomized</td>
<td>Significantly higher rate of platelet response(^a) Reduced need for rescue therapy</td>
</tr>
<tr>
<td>Jurczak et al(^84)</td>
<td>Avatrombopag, (n = 32) Placebo, (n = 17)</td>
<td>Europe, Asia, and Australia</td>
<td>Adults with ITP for (\geq 12) mo and a screening mean Plt &lt; (30 \times 10^9)/L 33% splenectomized</td>
<td>Significantly higher rate of platelet response(^a) Reduced use of concomitant ITP medications</td>
</tr>
</tbody>
</table>

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

\(^a\)Platelet response defined as a platelet count \(\geq 50 \times 10^9\)/L at a given assessment on treatment with thrombopoietin receptor agonist or placebo.

Note: Each trial was a prospective, multicenter, randomized, placebo-controlled, double-blind study except that of Kuter et al\(^82\) which was open label.

Source: Reproduced with permission from Al-Samkari and Kuter.\(^107\)
<table>
<thead>
<tr>
<th>Agent</th>
<th>Mechanism</th>
<th>Time to response</th>
<th>Response rate</th>
<th>Response durability</th>
<th>Major adverse effects</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azathioprine&lt;sup&gt;108&lt;/sup&gt;</td>
<td>Prodrug of antimetabolite 6-mercaptopurine; steroid-sparing immunosuppressant</td>
<td>Delayed (weeks to months)</td>
<td>30%</td>
<td>Good</td>
<td>Bone marrow suppression Infection Hepatotoxicity</td>
<td>Thiopurine S-methyltransferase activity should be measured prior to initiation Accepted as safe in pregnancy</td>
</tr>
<tr>
<td>Cyclophosphamide&lt;sup&gt;109,110&lt;/sup&gt;</td>
<td>Prodrug of phosphoramide mustard metabolite; immunosuppressant</td>
<td>Delayed (weeks to months)</td>
<td>30–40%</td>
<td>Good</td>
<td>Bone marrow suppression Hemorrhagic cystitis Infection</td>
<td>Low-dose oral cyclophosphamide typically used</td>
</tr>
<tr>
<td>Cyclosporine&lt;sup&gt;111,112&lt;/sup&gt;</td>
<td>Calcineurin inhibitor immunosuppressant</td>
<td>Early (1–2 wk)</td>
<td>30–40%</td>
<td>Moderate</td>
<td>Nephrotoxicity Hypertension Metabolic side effects</td>
<td>Trough levels should be monitored</td>
</tr>
<tr>
<td>Danazol&lt;sup&gt;113–116&lt;/sup&gt;</td>
<td>Attenuated androgenic steroid hormone with glucocorticoid receptor activity</td>
<td>Delayed (weeks to months)</td>
<td>30–40%</td>
<td>Good</td>
<td>Virilization Hepatotoxicity Weight gain</td>
<td>May be combined with azathioprine but evidence for this is poor</td>
</tr>
<tr>
<td>Dapsone&lt;sup&gt;117–119&lt;/sup&gt;</td>
<td>Antibiotic with immunomodulatory and anti-inflammatory properties</td>
<td>Delayed (weeks)</td>
<td>40–50%</td>
<td>Poor</td>
<td>Methemoglobinemia Hemolysis</td>
<td>Glucose-6-phosphate dehydrogenase activity should be measured prior to initiation</td>
</tr>
<tr>
<td>Mycophenolate mofetil&lt;sup&gt;120–122&lt;/sup&gt;</td>
<td>Prodrug of mycophenolic acid, a purine synthesis inhibitor causing immunosuppression</td>
<td>Delayed (weeks)</td>
<td>40–50%</td>
<td>Good</td>
<td>Diarrhea Bone marrow suppression Infection</td>
<td></td>
</tr>
<tr>
<td>Vinca alkaloids (vincristine, vinblastine)&lt;sup&gt;123–126&lt;/sup&gt;</td>
<td>Microtubule toxin chemotherapy agents causing potent immunosuppression</td>
<td>Rapid (within 1 wk)</td>
<td>70%</td>
<td>Poor</td>
<td>Vesication at infusion site Neuropathy Constipation SIADH</td>
<td>Administered as multiple weekly intravenous infusions; can be used as a rescue therapy of last resort</td>
</tr>
</tbody>
</table>

Abbreviation: SIADH, syndrome of inappropriate antidiuretic hormone secretion.

Note: These agents are commonly labeled “third-line” treatments, although they may be used earlier or later in the treatment of immune thrombocytopenia depending on clinical circumstances (i.e., pregnancy) or availability of more expensive agents (such as thrombopoietin receptor agonists or rituximab).
has been attempted, it is unclear if these approaches are superior to standard-dose rituximab with respect to either effectiveness or safety. Rituximab may result in acute infusion reactions, but the most consequential potential long-term adverse events (especially with recurrent treatment episodes over time) are chronic B cell depletion and hypogammaglobulinemia with attendant infection risk, chronic neutropenia, and progressive multifocal leukoencephalopathy.

**Fostamatinib**

Fostamatinib is a prodrug of the Syk (spleen tyrosine kinase) inhibitor tamatinib (R406). As Syk is active in numerous inflammatory cells including splenic macrophages, fostamatinib inhibits Fc-receptor-mediated clearance of autoantibody-coated platelets in the spleen. In two double-blind randomized controlled trials of heavily pretreated patients with severe or refractory ITP and a median disease duration of 8.5 years, the overall response rate (one or more platelet counts ≥50 × 10^9/L over the 12-week trial period) was 43% in the fostamatinib arm versus 14% in the placebo arm. Responses were durable in over half of patients maintained on fostamatinib. As is the case for several tyrosine kinase inhibitors, hypertension and gastrointestinal side effects (nausea, diarrhea) were common. Fostamatinib is initiated at 100 mg twice daily and can be uptitrated to 150 mg twice daily after 4 weeks if the platelet count is inadequate. If there is no response after 4 weeks at the highest dose, the drug should be discontinued.

**Other Treatment Options**

Numerous other medical therapies with immunosuppressive or immunomodulatory effects have been examined in ITP. Table 5 summarizes these agents. Studies of these agents are typically small and often retrospective; the overall response rate for these drugs is approximately 20 to 50%, depending on the agent and the ITP population, with lower response rates in more heavily pretreated patients with longer disease duration. Prolonged treatment is necessary to maintain responses for all these agents, except Vinca alkaloids.

**Conclusion**

Diagnosis of ITP has changed little in the past decade, as there remains no reliable biomarker or gold-standard diagnostic test. While the search for such a test continues, diagnosis will remain clinical and possible only with exclusion of other causes of thrombocytopenia. ITP treatment has advanced considerably in the past decade, with the introduction of TPO-RAs and fostamatinib. As numerous additional agents are currently under development for ITP treatment, continued advances are likely moving forward.

Authors’ Contributions
H.A. drafted the manuscript, created the tables and figures, and contributed to the concept and design, critical revision of the intellectual content, and final approval. D.J.K. contributed to the concept and design, critical revision of the intellectual content, and final approval.

**Conflicts of Interest**

H.A. reports research funding (Agios, Dova) and consultancy (Agios, Dova, Moderna). H.A. is the recipient of the National Hemophilia Foundation-Shire Clinical Fellowship Award, which provides partial salary support. D.J.K. reports research funding (Protalex, Bristol-Myers Squibb, Rigel, Bioverativ, Agios, Syntimmune, Principia, and Alnylam) and consultancy (ONO, Pfizer, 3SBios, Eisai, GlaxoSmithKline, Genzyme, Shire, Alexion, Amgen, Shionogi, Rigel, Syntimmune, MedImmune, Novartis, Bioverativ, Argenx, and Zalgen).

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