Immune thrombocytopenia: No longer ‘idiopathic’

■ ABSTRACT

Immune thrombocytopenia (ITP) is a common hematologic disorder. Its pathogenesis involves both accelerated platelet destruction and impaired platelet production. First-line agents are usually effective initially but do not provide long-term responses. Splenectomy remains an effective long-term therapy, as does rituximab (Rituxan) in a subset of patients. Thrombopoietic agents offer a new alternative, although their place in the overall management of ITP remains uncertain.

■ KEY POINTS

ITP is defined as an isolated platelet count of less than 100 × 10^9/L (100,000/µL) and usually presents without symptoms. Patients without symptoms who have a platelet count above 30 × 10^9/L should generally not be treated unless they have an increased risk of bleeding. Recent studies suggest that viruses and other pathogens play an important role in secondary ITP. Initially, corticosteroids are usually given as prednisone (1–2 mg/kg/day, then tapered), though recent studies suggest that dexamethasone pulses (40 mg/day for 4 days) may provide more durable responses when used in this setting. Thrombopoietic agents are important new treatments, although their place in the overall therapy of ITP has not been established.

O nce regarded as idiopathic, immune thrombocytopenia (ITP) is now understood to have a complex pathogenesis, involving the evolution of antibodies against multiple platelet antigens leading to reduced platelet survival as well as impaired platelet production. For this reason, multiple therapies with different mechanisms of action are available to treat ITP, though not all of them are effective for individual patients.

In this article, I discuss the pathogenesis, demographics, manifestations, diagnosis, and management of ITP.

■ THE NAME AND THE CUTOFF HAVE CHANGED

The term ITP formerly was used to refer to “idiopathic” or “immune” thrombocytopenic purpura. However, although not all aspects of the pathogenesis of ITP are understood, the disease can no longer be considered idiopathic. In addition, many patients do not have purpura at the time of diagnosis. Though the abbreviation “ITP” remains the same, it now refers to immune thrombocytopenia, which can be either primary or secondary.1

ITP is defined as a platelet count of less than 100 × 10^9/L (100,000/µL) with no evidence of leukopenia or anemia. This cutoff point is new: in the past, ITP was defined as a platelet count of less than 150 × 10^9/L, which is the threshold for a normal platelet count in most laboratories.

The platelet threshold of 100 × 10^9/L was based on a study by Stasi et al,2 who followed 217 otherwise healthy people who had an incidental finding of mild thrombocytopenia (platelet count 100–150 × 10^9/L). Within 6
months, the platelet count rose to more than $150 \times 10^9/L$ in 23, while three had either worsening thrombocytopenia or were diagnosed with other conditions. During long-term follow-up (median 64 months), 109 of the remaining 191 individuals remained stable, 13 developed counts greater than $150 \times 10^9/L$, 12 developed ITP, 13 developed an autoimmune disorder, 18 developed other disorders, and 26 were lost to follow-up. The 10-year probability of developing ITP, defined as a platelet count persistently below $100 \times 10^9/L$, was only 6.9%, indicating that the chances are small that a person with an isolated finding of mild, stable thrombocytopenia will develop ITP.

**Categories of ITP**

An international working group designated to standardize terminology has divided ITP into two major diagnostic categories. The proportion of patients within each is not well established and varies by region and demographic characteristics.

- **Primary ITP** accounts for the majority of cases in most studies; other conditions associated with thrombocytopenia are absent.
- **Secondary ITP** can be due to infection with a number of agents, including hepatitis C virus (HCV), human immunodeficiency virus (HIV), and *Helicobacter pylori*. Other causes include underlying autoimmune and lymphoproliferative disorders such as systemic lupus erythematosus, Wiskott-Aldrich syndrome, chronic lymphocytic leukemia, antiphospholipid syndrome, and common variable immunodeficiency, as well as drugs such as quinine and trimethoprim-sulfamethoxazole.

Categories of ITP have also been established to facilitate management decisions, as follows:

- **Newly diagnosed ITP** refers to ITP diagnosed within the preceding 3 months.
- **Persistent ITP** refers to ITP diagnosed 3 to 12 months previously, and includes ITP in patients not reaching spontaneous remission and in those not maintaining a complete response off therapy. (When ITP spontaneously remits in adults, it usually does so within the first 12 months after the condition is diagnosed.)
- **Chronic ITP**: Lasting for more than 12 months.

**Severe ITP** is defined by bleeding at presentation sufficient to mandate treatment, or new bleeding symptoms requiring additional therapeutic intervention with a different platelet-enhancing agent or an increased dosage of a current agent.

**ITP IS COMMON IN OLDER ADULTS**

We previously believed that ITP was a disorder that primarily affected women in their third and fourth decades. However, this was not borne out in recent epidemiologic studies, which have demonstrated that the highest age-specific incidence of ITP occurs in the elderly. This may potentially reflect the development of immune dysregulation as a consequence of aging. There is a female preponderance in the incidence of ITP throughout adulthood until around age 60, after which the overall incidence increases in both sexes, and the ratio of affected women to men is about equal. Thus, even though thrombocytopenia in the elderly may reflect myelodysplasia in some individuals, ITP is much more common than previously appreciated.

Previous guidelines from the American Society of Hematology suggested that a bone marrow examination be strongly considered in patients over age 60 with suspected ITP. With the realization that ITP occurs more commonly in the elderly, it is apparent that bone marrow examination is not necessary in this group if there are no other cytopenias present and the physical examination and blood smear are consistent with ITP.

In children, ITP has a peak incidence between ages 5 and 6, and behaves differently from the adult syndrome. ITP in children usually follows an apparent viral infection and tends to be self-limited, with approximately 80% of cases resolving spontaneously within 6 months. In contrast, adult ITP usually develops into a chronic disease.

**BLEEDING MAY NOT BE PRESENT AT DIAGNOSIS**

ITP is now recognized as a diverse syndrome with a constellation of signs and symptoms. Petechiae are pinpoint microvascular hem-
IMMUNE THROMBOCYTOPENIA

orhages that do not blanch with pressure. This distinguishes them from small hemangiomas, which look similar but blanch transiently with pressure. Petechiae tend to occur on dependent areas, particularly the hands and feet, when the platelet count drops below approximately 15 × 10^9/L.

Ecchymoses (dry purpura) appear as large bruises.

Mucosal bleeding (wet purpura) involves the oral mucosa. Particularly in children, wet purpura tends to be associated with systemic bleeding complications, involving the gastrointestinal tract for example. The incidence of intracranial hemorrhage, though very low, may also be increased in patients with wet purpura.

Other bleeding manifestations may include heavy menstrual bleeding, oral bleeding, and epistaxis.

Bleeding is generally but not entirely proportional to the platelet count. In a study of adults with newly diagnosed ITP and a platelet count of less than 50 × 10^9/L,4 the presenting symptom was hemorrhage in 12% and purpura in 58%.4 Remarkably, 28% of cases were asymptomatic, with some patients remaining free of symptoms for years despite very low platelet counts. More than half of patients with a platelet count of 30 to 50 × 10^9/L have no symptoms.3,4

A PARADOXICAL RISK OF THROMBOSIS

Although ITP is primarily a bleeding disorder, it is paradoxically also associated with thrombosis. Sarpatwari et al,5 in a study in the United Kingdom, found that the 4-year incidence of thromboembolic events was about 1.3 times higher in patients with ITP than in matched controls.

The reason for the increased risk of thrombosis is not clear. It is possible that in some patients, antiphospholipid antibodies may contribute to the development of thrombosis, although this has not been confirmed in all studies.

A DIAGNOSIS OF EXCLUSION

The evaluation of any patient suspected of having ITP should include the following:

- Personal history, with special attention to drugs and to medical conditions that could cause thrombocytopenia.
- Family history. ITP may occasionally be mistaken for an inherited cause of thrombocytopenia. The presence of the latter can often be confirmed by review of the peripheral blood film of the patient as well as other family members with thrombocytopenia. ITP is generally not considered to be an inherited disorder, although some HLA alleles may be more prevalent in ITP patients.
- Physical examination, with special attention to lymphadenopathy or splenomegaly, which may suggest an underlying malignancy such as a lymphoproliferative disorder. In general, patients with ITP have a normal physical examination, except for signs of bleeding or bruising in some.
- Laboratory tests, including a complete blood cell count, blood smear, reticulocyte count, Rh typing, and direct antiglobulin (Coombs) test.

In ITP, the peripheral blood smear should appear normal except for the presence of thrombocytopenia, although platelets may be mildly enlarged in some individuals. Red cell and leukocyte morphology is normal. It is important to exclude the presence of schistocytes (red cell fragments) and nucleated red blood cells, which often indicate a microangiopathic hemolytic anemia caused by disorders such as thrombotic thrombocytopenic purpura.

International guidelines suggest that testing for reduced immunoglobulin levels (as seen in common variable hypogammaglobulinemia) and HIV, HCV, and H pylori infections should also be considered. Coincident HCV infection is particularly high in some regions. Other cytopenias or abnormalities in the history or physical examination may prompt bone marrow examination. Testing for antiphospholipid antibodies, antinuclear antibodies, parvovirus, and cytomegalovirus may also be indicated in specific individuals. Testing for antiplatelet antibodies is not commonly performed in the current era because of its relatively low sensitivity and specificity.

Ultimately, the diagnosis of ITP is clinical, however, and cannot be established by any specific laboratory assay. Perhaps the best diagnostic study is assessment of the patient’s response to ITP therapy.
ITP INVOLVES ACCELERATED PLATELET DESTRUCTION

In 1951, William Harrington, a fellow at Washington University, infused blood from a patient with ITP into himself and, subsequently, into normal volunteers.6 The majority of recipients demonstrated significant reductions in the platelet count, sometimes severe. This fascinating and bold experiment provided the first demonstration that ITP was caused by a factor that circulates in blood. What is often not emphasized, however, is that some recipients did not develop thrombocytopenia, suggesting an alternative mechanism.

Later, Luiken et al7 and Hirschman and Shulman8 demonstrated that the transmissible agent in the blood was immunoglobulin, primarily immunoglobulin G (IgG). We now understand that much of the pathogenesis of ITP is caused by antibodies against platelet glycoproteins, most commonly platelet glycoprotein IIb/IIIa, the platelet fibrinogen receptor. Most patients, especially those with chronic ITP, also have antibodies against other platelet glycoproteins, including glycoprotein Ib/IX (the receptor for von Willebrand factor), and glycoprotein Ib/IIa, a collagen receptor. It is commonly believed that ITP may begin with antibodies against a single glycoprotein, which leads to accelerated clearance of antibody-coated platelets in the spleen. Degradation of cleared platelets by splenic macrophages leads to the release and subsequent presentation of antigenic peptides from proteolyzed platelet components, including glycoproteins, on the macrophage or dendritic cell. This may lead to recruitment and activation of specific T cells that in turn interact with and stimulate B cells to produce new antibodies against the platelet-derived peptides. This phenomenon, known as epitope spreading, may be responsible for the fact that most patients with long-standing, chronic ITP develop autoantibodies against multiple platelet glycoprotein targets.9

Several agents used in the treatment of ITP may work by impairing clearance of antibody-coated platelets by the reticuloendothelial system. One of many potential mechanisms underlying the therapeutic efficacy of intravenous immunoglobulin (IVIG) may be its ability to interact with a specific type of Fc gamma receptor, Fc gamma RIIb. IVIG therapy stimulates increased expression of this receptor, which in turn may impair the function of other “activating” Fc gamma receptors responsible for platelet clearance.10,11

ITP associated with infection may arise due to molecular mimicry. HCV, HIV, and H pylori contain amino acid sequences that may have structural similarity to regions within platelet glycoproteins. Thus, antibodies directed against the pathogen may cross-react with the glycoprotein, leading to thrombocytopenia.12–15 HCV has been found in up to one-third of cases of ITP in some centers.16–20 H pylori-associated ITP is very common in some regions, particularly in Japan, and may often resolve after eradication of the infection. However, in the United States, eradication of H pylori generally does not improve the course of ITP. This may reflect antigen mimicry, in particular the fact that different cagA proteins are expressed by different strains of H pylori in certain regions of the world.

Our understanding of the immunologic basis of ITP has greatly expanded over the last decade. Although it has long been known that B cells produce autoantibodies, T cells have more recently been shown to play a critical role in regulating B-cell-mediated autoantibody production in ITP. In some situations, T cells may directly lyse platelets, or suppress megakaryopoiesis. This may explain why some patients who do not respond to standard B-cell-targeted therapy may respond to cyclosporine or other T-cell-directed agents.

ANOThER MECHANISM OF ITP: REDUCED PLATELET PRODUCTION

In addition to accelerated platelet destruction, ITP is also associated with decreased platelet production by megakaryocytes in the bone marrow.21–25 Increased platelet destruction and reduced platelet production are likely two ends of a spectrum of ITP, and most patients likely have some degree of both processes. This concept helps explain why different drug strategies are more effective in some patients than in others.
It is important to understand the natural history of ITP to determine whether the risks of therapy are justified. A 2001 study from the Netherlands followed 134 patients with primary ITP for 10 years: 90% had taken prednisone or had had a splenectomy. Within 2 years, 85% of these patients had platelet counts above $30 \times 10^9/L$ off therapy. Although this group likely experienced more bleeding and bruising than the general population, the mortality rate was not increased. Another 6% also achieved a platelet count above $30 \times 10^9/L$, but required chronic maintenance therapy (usually steroids) to do so. This group led a nearly normal life but had more hospitalizations. The remaining 9% of patients had refractory ITP, with platelet counts remaining below $30 \times 10^9/L$ despite therapy. This group had a death rate 4.2 times that of age-matched controls. About half died of bleeding and the others died of opportunistic infections to which they were susceptible because of long-term steroid therapy.

This study was influential in the general opinion that $30 \times 10^9/L$ is a reasonable cutoff for treating ITP. An international consensus report states that treatment is rarely indicated in patients with platelet counts above $50 \times 10^9/L$ in the absence of bleeding due to platelet dysfunction or other hemostatic defect, trauma, or surgery. Although this number is not supported by evidence-based data, it is a reasonable threshold endorsed by an international working group. Individual factors must be weighed heavily: for example, an athlete involved in contact sports requires a higher platelet count in order to play safely.

Recommendations regarding thresholds for safe platelet counts for specific medical interventions vary widely. Guidelines from the British Committee for Standards in Haematology are somewhat arbitrary but reasonable (Table 1).

### TABLE 1

<table>
<thead>
<tr>
<th>Medical Procedure</th>
<th>Platelet Count Threshold</th>
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<tbody>
<tr>
<td>Dentistry</td>
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</tr>
<tr>
<td>Extractions</td>
<td>$30 \times 10^9/L$</td>
</tr>
<tr>
<td>Regional dental block</td>
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<tr>
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<tr>
<td>Major surgery</td>
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</tr>
<tr>
<td>Vaginal delivery</td>
<td>$20 \times 10^9/L$</td>
</tr>
<tr>
<td>Cesarean delivery</td>
<td>$50 \times 10^9/L$</td>
</tr>
<tr>
<td>Spinal, epidural anesthesia</td>
<td>$80 \times 10^9/L$</td>
</tr>
</tbody>
</table>

ADAPTED FROM DATA IN BRITISH COMMITTEE FOR STANDARD IN HAEMATOLOGY, GUIDELINES FOR THE INVESTIGATION AND MANAGEMENT OF IMMUNE THROMBOCYTOPENIC PURPURA IN ADULTS, CHILDREN AND IN PREGNANCY. BR J HAEMATOLOGY 2003; 120:574–596.

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**Corticosteroids are standard therapy**

Corticosteroids can be given in one of two ways:

- **Standard prednisone therapy**, ie, 1 to 2 mg/kg per day, is given until a response is seen, and then tapered. Some maintain therapy for an additional week before tapering. There are no guidelines on how to taper: some decrease the dosage by 50% per week, although many recommend going more slowly, particularly at the lower range of dosing.

- Up to 85% of patients achieve a clinical response, usually within 7 to 10 days, with platelet counts peaking in 2 to 4 weeks. Unfortunately, only about 15% of patients maintain the response over the subsequent 6 to 12 months. Restarting prednisone often initiates a vicious circle and makes patients vulnerable to steroid toxicities.

- **“Pulse” dexamethasone therapy** consists of 40 mg per day for 4 days for one to three cycles. (Dexamethasone 1 mg is equivalent to about 10 mg of prednisone.)

- Pulse dexamethasone therapy as an initial approach to ITP has been developed during the past decade and has been used primarily in research studies. This regimen evolved...
Increased platelet destruction and reduced platelet production are likely two ends of a spectrum of ITP

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from studies of patients with multiple myelomas and has the potential to induce more durable remissions in some patients with newly diagnosed ITP. However, high-dose corticosteroids may be associated with increased toxicity, at least in the short term, and should be used cautiously. A study to address the role of high-dose vs standard-dose steroid therapy has recently been opened under the guidance of the Transfusion Medicine–Hemostasis Clinical Trials Network of the National Heart, Lung, and Blood Institute.

Immunoglobulin is useful for very low platelet counts and bleeding

Another primary therapy for ITP is IVIG 0.5 to 2.0 g/kg over 2 to 5 days. Its efficacy is similar to that of prednisone: about 65% of patients achieve a platelet count above 100 × 10^9/L, and 85% achieve 50 × 10^9/L. However, most responses are transient, and a significant minority of cases become refractory to IVIG after repeated infusions.

IVIG is associated with numerous adverse effects, including thrombosis, renal insufficiency, headache, and anaphylaxis in IgA-deficient patients. It also converts the direct antiglobulin test to positive. IVIG is expensive, is inconvenient to administer, and may require lengthy infusions depending on the formulation.

Although IVIG is not a good long-term therapy, it can help raise the platelet count relatively quickly in patients who present with severe thrombocytopenia accompanied by bleeding. Such patients should be treated with high-dose steroids, IVIG, and platelet transfusions. IVIG may also be useful to increase platelet counts prior to interventional procedures.

Intravenous anti-Rho(D)

Anti-Rho(D) is an alternative to IVIG in patients who are Rho(D)-positive and have an intact spleen. Anti-Rho(D) binds to Rh-positive red blood cells, causing them to be cleared in the reticuloendothelial system and blocking the clearance of antibody-coated platelets. In effect, red cells are sacrificed to save platelets, but because there are many more red cells than platelets, the benefits usually outweigh the risks.

The initial dose is 50 µg/kg given intravenously over 2 to 5 minutes. Anti-Rho(D) should not be given to patients whose hemoglobin level is less than 10 g/dL or who have compromised bone marrow function. It is ineffective in Rh-negative patients or those who have undergone splenectomy.

Accelerated hemolysis is a rare but severe possible adverse event associated with this therapy, occurring in slightly more than 1 in 1,000 infusions. About 1 out of every 20,000 patients develops disseminated intravascular coagulation. Its cause is poorly understood, and it is probably an accelerated extravascular rather than an intravascular event. The US Food and Drug Administration has recently issued a black-box warning cautioning that patients who receive anti-Rho(D) should remain in a health care setting for 8 hours after treatment, although most cases of accelerated hemolysis occur within 4 hours. Moreover, it is possible that many of these cases can be avoided by appropriate patient selection.

Second-line Therapies

Second-line therapies, as designated by the international working group, include azathioprine (Imuran), cyclosporine A, cyclophosphamide (Cytoxan), danazol (Danocrine), dapsone, mycophenolate mofetil (CellCept), rituximab (Rituxan), splenectomy, thrombopoietin receptor agonists, and vinca alkaloids. Only the most commonly used therapies will be briefly discussed below.

The evidence for efficacy of the cytotoxic agents, ie, cyclophosphamide, the vinca alkaloids, and azathioprine, comes from small, non-randomized studies. Although these agents are useful in some patients, they may be associated with significant toxicities, and they are used less commonly than in the past.

Splenectomy has a high success rate

Splenectomy probably offers the best response of any treatment for ITP. About 80% of patients with ITP respond rapidly—often within 1 week. Of those, 15% relapse within the first year, and after 10 years, two-thirds remain in remission.
Because there is no well-accepted predictor of a short- or long-term response to splenectomy, and because more medical options are currently available, the use of splenectomy has declined over the past 10 years. Nevertheless, splenectomy remains a useful option for therapy of ITP. Whether and which second-line drugs should be tried before splenectomy is still controversial and should be determined on a case-by-case basis. Some patients are poor candidates for splenectomy because of comorbidities. If possible, splenectomy should be delayed until at least a year after diagnosis to allow an opportunity for spontaneous remission.

Splenectomy increases the risk of subsequent infection by encapsulated organisms, and patients should be immunized with pneumococcal, Haemophilus influenzae type B, and meningococcal vaccines, preferably at least 3 weeks before the spleen is removed. Splenectomy is associated with pulmonary hypertension and thrombosis, primarily in patients who have had their spleens removed because of accelerated red cell destruction. Whether these risks are applicable to patients with ITP is unknown, but if so they are probably much lower than in patients with red cell disorders.

Rituximab
Rituximab, a humanized monoclonal antibody against the CD20 antigen on B lymphocytes, was developed for treating lymphoma. However, it has been found to have significant activity in a number of immunohematologic disorders. Although many studies of rituximab for ITP have been published, it has never been tested in a randomized controlled study. The response rate is generally around 50%, and it is effective in patients with or without a spleen.

In one study, 44 (32%) of 137 patients with chronic ITP who were given rituximab achieved a complete remission that was sustained 1 year. After more than 5 years, 63% of this group (ie, approximately 20% of the original group) were still in remission.

Potential drawbacks of rituximab include its expense as well as the risk of first-infusion reactions, which may be severe or, rarely, fatal. Rituxan has also been associated with rare cases of progressive multifocal leukoencephalopathy, usually in patients heavily treated with other immunosuppressive agents; however, very rare cases of progressive multifocal leukoencephalopathy have been reported in patients with ITP who received rituximab.

Thrombopoietin receptor agonists increase platelet production
Thrombopoietin receptor agonists are approved for patients with chronic ITP who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy. Rather than inhibit platelet destruction, as do all the other ITP therapies, they enhance platelet production.

Diseases involving bone marrow failure that also involve a low platelet count tend to be associated with very high levels of serum thrombopoietin, which is produced constitutively by the liver. In ITP, thrombopoietin levels tend to be close to normal and not significantly elevated, most likely because of accelerated thrombopoietin clearance when bound to antibody-coated platelets. This provides a rationale for the use of thrombopoietic agents in the treatment of ITP.

Earlier-generation thrombopoietic drugs had significant amino acid homology with natural thrombopoietin, and some patients who were treated with these drugs developed antibodies against them that cross-reacted with endogenous thrombopoietin. In some cases, this led to severe, refractory thrombocytopenia. Because the newer thrombopoietic agents have no sequence homology to natural thrombopoietin, antibody production has not been a significant problem.

Two drugs in this class are currently available for treating ITP:
Romiplostim (Nplate) is a peptibody (comprising an IgG Fc region and four peptidomeric regions that interact with the thrombopoietin receptor, c-mpl) that is given subcutaneously once a week.

Romiplostim performed well in several phase I clinical trials. In a 24-week phase III trial that compared romiplostim against placebo in patients with ITP that had been refractory to other primary treatments, 79% of splenectomized patients and 88% of nonsplenectomized patients had an overall response (defined as a platelet count > 50 × 10^9/L for 4 weeks during the study period), and 38% of splenectomized patients and 61% of nonsple-
nectomized patients had a durable response (platelet count > 50 × 10^9/L for 6 of the last 8 weeks of the study).^{42}

In an ongoing long-term extension study of romiplostim that allows dose adjustments to maintain a platelet count between 50 and 200 × 10^9/L, romiplostim dosage and efficacy have remained stable over 5 years.^{42,43}

**Eltrombopag** (Promacta) is a nonpeptide small-molecule c-mpl agonist that is taken orally once daily. A recent randomized, placebo-controlled study in patients with ITP refractory to other primary treatments found that eltrombopag was highly effective in raising platelet counts over the 6 months of the study.^{44} Like romiplostim, it was effective in both splenectomized and nonsplenectomized patients.

Although eltrombopag has not been studied for as long as romiplostim, data over 3 years indicate that increased platelet counts are maintained without the emergence of drug resistance or cumulative toxicity.^{45}

Several other drugs in this class are currently in development.

### Adverse effects of thrombopoietic agents

Thrombopoietic agents have several associated toxicities:

- **Rebound thrombocytopenia** occurs in up to 10% of patients following treatment with either romiplostim or eltrombopag. Rebound thrombocytopenia is defined as a fall in the platelet count that occurs following discontinuation of a thrombopoietic agent that may result in more severe thrombocytopenia, transiently, than before the drug was initiated. Thus, the platelet count must be closely monitored after treatment with these drugs is discontinued.

- **Bone marrow fibrosis**, which consists primarily of increased marrow reticulin content, occurs in less than 10% of treated patients, and all patients on therapy must be monitored for this potential complication by close examination of the peripheral blood film on a frequent basis. Appearance of abnormalities such as teardrop cells or nucleated red blood cells in the peripheral blood smear should prompt at least temporary discontinuation of the drug and consideration of bone marrow examination. There have been no cases of actual irreversible myelofibrosis in which thrombopoietic agents have been clearly implicated in causation. Interestingly, some reports suggest that increased reticulin is a common finding in marrow from ITP patients who have not been treated with thrombopoietic agents.\(^{46}\)

**Thrombosis** must be considered a risk of treatment with thrombopoietic agents, which increase the platelet count in a disease that may already be thrombogenic. However, in the placebo-controlled studies, a significantly increased incidence of thrombosis was not observed in the treatment arms vs placebo. Moreover, even in treated patients who developed thrombosis, there was no clear association with the degree of elevation in the platelet count. Nevertheless, thrombopoietic agents should be used according to the manufacturer’s recommendations, to increase the platelet count to a range of 50 to 200 × 10^9/L, but not to exceed that.

**Progression of hematologic malignancies.** Thrombopoietin receptor agonists act not only on megakaryocytes but also on stem cells and other hematopoietic precursors. Although trials for treating patients with hematologic malignancies and bone marrow failure with thrombopoietic agents are ongoing, there is concern that they could worsen certain hematologic malignancies, though there are no controlled data to either support or refute this concern at present. At this time, these drugs are approved only for ITP and should not be used for other conditions.

**Hepatotoxicity** has been seen with eltrombopag, but it is usually reversible and may resolve with continued therapy. Nevertheless, close monitoring for this potential complication is indicated.

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