ABSTRACT

Immune thrombocytopenia (ITP) in adults is a chronic disease resulting from increased platelet destruction and impaired platelet production. Splenectomy remains the most effective and durable treatment in cases that are refractory to first-line therapy, but its use has declined because of the availability of alternate medical therapy, the associated risk of infection, and concern for surgery-related complications. Rituximab (Rituxan) may be an effective alternative but carries the risk of immunosuppression.

KEY POINTS

Secondary ITP can be drug-induced or be a manifestation of human immunodeficiency virus (HIV), hepatitis C virus (HCV), a lymphoproliferative disorder, or systemic lupus erythematosus.

Nonautoimmune conditions should also be considered, including pseudothrombocytopenia (a laboratory artifact induced by EDTA), thrombotic thrombocytopenic purpura, thrombocytopenia in pregnancy, and myelodysplastic syndrome (common in the elderly).

Treatment is indicated to keep the platelet count above $30 \times 10^9/L$ or to control bleeding.

Initial treatment usually begins with glucocorticoids, with the duration limited by side effects.

Patients for whom glucocorticoids fail generally require splenectomy, rituximab, or thrombopoietin receptor agonists.

Immune thrombocytopenia (ITP), formerly known as idiopathic thrombocytopenic purpura, is an autoimmune disorder characterized by a low platelet count and increased risk of mucocutaneous bleeding. During the last decade its management has changed, with the advent of new medications and with increased awareness of treatment side effects. This article will focus on the pathophysiology, diagnosis, and management of ITP in adults.

A SLIGHT FEMALE PREDOMINANCE UNTIL AGE 65

The estimated age-adjusted prevalence of ITP in the United States is 9.5 to 23.6 cases per 100,000. In a recent study in the United Kingdom, the incidence was 4.4 per 100,000 patient-years among women and 3.4 among men. A slight female predominance was seen until age 65; thereafter, the incidence rates in men and women were about equal.

INCREASED PLATELET DESTRUCTION AND DECREASED PRODUCTION

ITP is a complex immune process in which cellular and humoral immunity are involved in the destruction of platelets as well as impaired platelet production. Several theories have emerged in the last decade to explain this autoimmune process.

Autoantibodies form against platelets

The triggering event for antibody initiation in ITP is unknown. Autoantibodies (mostly immunoglobulin G [IgG] but sometimes IgM and IgA) are produced against the platelet membrane glycoprotein GPIIb-IIIa. The antibody-
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coated platelets are rapidly cleared by the reticuloendothelial system in the spleen and liver, in a process mediated by Fc-receptor expression on macrophages and dendritic cells. Autoantibodies may also affect platelet production by inhibiting megakaryocyte maturation and inducing apoptosis.4,5

Patients with ITP also have CD4+ T cells that are autoreactive to GPIIb-IIIa and that stimulate B-cell clones to produce antiplatelet antibodies. Although autoreactive T cells are present in healthy individuals, they appear to be activated in patients with ITP by exposure to fragments of GPIIb-IIIa rather than native GPIIb-IIIa proteins.6 Activated macrophages internalize antibody-coated platelets and degrade GPIIb-IIIa and other glycoproteins to form “cryptic” epitopes that are expressed on the macrophage surface as novel peptides that induce further proliferation of CD4+ T-cell clones. Epitope spread thereby sustains a continuous loop that amplifies the production of GPIIb-IIIa antibodies.7

Defective T-regulatory cells appear to be critical to the pathogenesis of ITP by breaking self-tolerance, allowing the autoimmune process to progress.8 This, together with several other immune mechanisms such as molecular mimicry, abnormal cytokine profile, and B-cell abnormalities, may lead to enhanced platelet clearance.9

In addition to destroying platelets, antibodies may impair platelet production.10 Good evidence for platelets being underproduced in patients with ITP is that treating with thrombopoietin agonists results in increased platelet counts.

A DIAGNOSIS OF EXCLUSION

ITP is defined as isolated thrombocytopenia with no clinically apparent associated conditions or other causes of thrombocytopenia.11 No diagnostic criteria currently exist, and the diagnosis is established only after excluding other causes of thrombocytopenia.

A recent report12 from an international working group established a platelet count threshold of less than 100 × 10^9/L for diagnosing ITP, down from the previous threshold of 150 × 10^9/L. The panel also recommended using the term “immune” rather than “idiopathic” thrombocytopenia, emphasizing the role of underlying immune mechanisms. The term “purpura” was removed, because many patients have no or minimal signs of bleeding at the time of diagnosis.12

The 2011 American Society of Hematology’s evidenced-based guidelines for the treatment of ITP present the most recent authoritative diagnostic and therapeutic recommendations.13

ITP is considered to be primary if it occurs in isolation, and secondary if it is associated with an underlying disorder. It is further classified according to its duration since diagnosis: newly diagnosed (< 3 months), persistent (3−12 months), and chronic (> 12 months).

In adults, ITP tends to be chronic, presenting with a more indolent course than in childhood, and unlike childhood ITP, infrequently following a viral infection.

Clinical features associated with ITP are related to thrombocytopenia: petechiae (pinpoint microvascular hemorrhages that do not blanch with pressure), purpura (appearing like large bruises), epistaxis (nosebleeds), menorrhagia, gum bleeding, and other types of mucocutaneous bleeding. Other common clinical features include fatigue, impaired quality of life, and treatment-related side effects (eg, infection).14

A low platelet count may be the sole initial manifestation. The patient’s history, physical examination, blood counts, and findings on

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**TABLE 1**

Basic evaluation for immune thrombocytopenia in adults

<table>
<thead>
<tr>
<th>Evaluation</th>
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</thead>
<tbody>
<tr>
<td>Patient history</td>
</tr>
<tr>
<td>Family history</td>
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<tr>
<td>Physical examination</td>
</tr>
<tr>
<td>Complete blood cell and reticulocyte counts</td>
</tr>
<tr>
<td>Peripheral blood smear</td>
</tr>
<tr>
<td>Blood group (Rh)</td>
</tr>
<tr>
<td>Direct antiglobulin test</td>
</tr>
<tr>
<td>Human immunodeficiency virus screen</td>
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<tr>
<td>Hepatitis C virus screen</td>
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</tbody>
</table>

**Current platelet threshold for ITP:**

\(< 100 \times 10^9/L\) (down from \(< 150 \times 10^9/L\) in previous criteria)
blood smear are essential to rule out other diagnoses. Few diagnostic tests are useful in the initial evaluation (TABLE 1). Abnormalities in the blood count or blood smear may be further investigated with bone marrow biopsy but is not required if the patient has typical features of ITP, regardless of age.

Because there are no specific criteria for diagnosing ITP, other causes of thrombocytopenia must be excluded. The differential diagnosis can be further classified as ITP due to other underlying disease (ie, secondary ITP) vs nonautoimmune causes that are frequently encountered in clinical practice.

### SECONDARY ITP

The differential diagnosis of thrombocytopenia due to known underlying immune disease includes the following:

#### Drug-induced ITP

Recurrent episodes of acute thrombocytopenia not explained by other causes should trigger consideration of drug-induced thrombocytopenia. Patients should be questioned about drug use, especially of sulfonamides, antiepileptics, and quinine. Thrombocytopenia usually occurs 5 to 7 days after beginning the inciting drug for the first time and more quickly when the drug is given intermittently. Heparin is the most common cause of drug-related thrombocytopenia among hospitalized patients; the mechanism is unique and involves formation of a heparin-PF4 immune complex.

#### Human immunodeficiency virus infection

Approximately 40% of patients with human immunodeficiency virus (HIV) infection develop thrombocytopenia at some time. HIV infection can initially manifest as isolated thrombocytopenia and is sometimes clinically indistinguishable from chronic ITP, making it an important consideration in a newly diagnosed case of thrombocytopenia.

The mechanism of thrombocytopenia in early HIV is similar to that in primary ITP: as the disease progresses, low platelet counts can result from ineffective hematopoiesis due to megakaryocyte infection and marrow infiltration.

#### Hepatitis C virus infection

Hepatitis C virus (HCV) infection can also cause immune thrombocytopenia. A recent study demonstrated the potential of the HCV core envelope protein 1 to induce antiplatelet antibodies (to platelet surface integrin GPIIIa) by molecular mimicry. Other causes of thrombocytopenia in HCV infection may be related to chronic liver disease, such as portal hypertension-related hypersplenism, as well as decreased thrombopoietin production. Antiviral treatment with pegylated interferon may also cause mild thrombocytopenia.

#### Helicobacter pylori

The association between H pylori infection and ITP remains uncertain. Eradication of infection appears to completely correct ITP in some places where the prevalence of H pylori is high (eg, Italy and Japan) but not in the United States and Canada, where the prevalence is low. The different response may be due not only to the differences in prevalence, but to different H pylori genotypes: most H pylori strains in Japan express CagA, whereas the frequency of CagA-positive strains is much lower in western countries.

In areas where eradication therapy may be useful, the presence of H pylori infection should be determined by either a urea breath test or stool antigen testing.

#### Lymphoproliferative disorders

Secondary forms of ITP can occur in association with chronic lymphocytic leukemia, non-Hodgkin lymphoma, and Hodgkin lymphoma. These diagnoses should especially be considered in patients presenting with thrombocytopenia accompanied by systemic illness. ITP occurs in at least 2% of patients with chronic lymphocytic leukemia and is usually difficult to distinguish from thrombocytopenia secondary to marrow infiltration or from fludarabine (Fludora) therapy.

It is especially important to determine if a lymphoproliferative disorder is present because it changes the treatment of ITP. Treatment of ITP complicating chronic lymphocytic leukemia is challenging and includes corticosteroids and steroid-sparing agents such as cyclosporine (Gengraf, Neoral, Sandimmune), rituximab (Rituxan), and intravenous immunoglobulin.
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Systemic lupus erythematosus and other autoimmune diseases

Thrombocytopenia is a frequent clinical manifestation of systemic lupus erythematosus, occurring in 7% to 30% of patients, and is an independent risk factor for death. Lupus should be suspected in patients with ITP who have multiorgan involvement and other clinical and laboratory abnormalities. A small percentage of patients with ITP (about 2%–5%) develop lupus after several years.

Thrombocytopenia can also result from other autoimmune disorders such as antiphospholipid antibody syndrome and autoimmune thyroid diseases as well as immunodeficient states such as IgA deficiency and common variable immunodeficiency with low IgG levels.

Nonautoimmune thrombocytopenia

Thrombocytopenia can also be caused by a number of nonautoimmune conditions.

Pseudothrombocytopenia

Pseudothrombocytopenia can occur if ex-vivo agglutination of platelets is induced by antiplatelet antibodies to EDTA, a standard blood anticoagulant. Automated counters cannot differentiate the agglutinated platelet clumps from individual cells such as red cells. This can frequently be overcome by running the counts in a citrate or ACD reagent tube. A peripheral blood smear can demonstrate whether platelet clumps are present.

Thrombotic thrombocytopenic purpura

Thrombotic thrombocytopenic purpura presents with thrombocytopenia, purpura, and anemia. Associated clinical abnormalities (fever, neurologic symptoms, and renal failure) and the presence of fragmented red cells on blood smear help to distinguish it from ITP. Plasma exchange is the treatment of choice.

Gestational thrombocytopenia

Five percent of pregnant women develop mild thrombocytopenia (platelet counts typically > 70 × 10⁹/L) near the end of gestation. It requires no treatment and resolves after delivery. The fetus’ platelet count remains unaffected.

ITP does not necessarily require treatment, and the initial challenge is to determine whether treatment or observation is indicated. Treatment is based on two major factors: the platelet count and degree of bleeding. The goals of management are to achieve a safe platelet count to prevent serious bleeding while minimizing treatment-related toxicity. Adults with platelet counts of less than 30 × 10⁹/L are usually treated. In multiple large cohort studies, patients with platelet counts above that level have been safely observed without treatment.

Table 2 outlines a comprehensive approach to therapy.

Initial treatment: steroids and immunoglobulins

Oral corticosteroids are the initial agents of choice

Oral prednisone 1 mg/kg/day in tapering doses for 4 to 6 weeks is the most common initial regimen. Other regimens, such as high-dose dexamethasone (Decadron) (40 mg daily for 4 days per month) for several cycles, have been reported to be more effective but have not been studied in head-to-head trials with oral prednisone.
decreases once the dose is tapered or stopped; remission is sustained in only 10% to 30% of cases. Continuation of corticosteroids is limited by long-term complications such as opportunistic infections, osteoporosis, and emotional lability.

Intravenous immunoglobulin and anti-D immunoglobulin are alternatives

Intravenous immunoglobulin is recommended for patients who have not responded to corticosteroids and is often used in pregnancy. It is thought to act by blocking Fc receptors in the reticuloendothelial system. Intravenous immunoglobulin rapidly increases platelet counts in 65% to 80% of patients, but the effect is transient and the drug requires frequent administration. It is usually well tolerated, although about 5% of patients experience headache, chills, myalgias, arthralgias, and back pain. Rare, serious complications include thrombotic events, anaphylaxis (in IgA-deficient patients), and renal failure.

Anti-D immunoglobulin, a pooled IgG product, is derived from the plasma of Rh(D)-negative donors and can be given only to patients who are Rh(D)-positive. Response rates as high as 70% have been reported, with platelet effects lasting for more than 21 days.

Studies have shown better results at a high dose (75 µg/kg) than with the approved dose of 50 µg/kg.

Anti-D immunoglobulin can also be given intermittently whenever the platelet count falls below a specific level (ie, 30 × 10^9/L). This allows some patients to avoid splenectomy and may even trigger long-term remission.

Common side effects of anti-D immunoglobulin include fever and chills; these can be prevented by premedication with acetaminophen or corticosteroids. Rare but fatal cases of intravascular hemolysis, renal failure, and disseminated intravascular coagulation have been reported, precluding its use for ITP in some countries, including those of the European Union.

Emergency treatment: Combination therapy

Evidence-based guidelines are limited for treating patients with active bleeding or who are at high risk of bleeding. For uncontrolled bleeding, a combination of first-line therapies is recommended, using prednisone and intravenous immunoglobulin. Other options include high-dose methylprednisolone and platelet transfusions, alone or in combination with intravenous immunoglobulin.

SECOND-LINE TREATMENTS

Splenectomy produces complete remission in most patients

Patients who relapse and have a platelet count of less than 20 × 10^9/L are traditionally con-
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Patients who relapse and have a platelet count of less than 20 × 10⁹/L are traditionally considered for splenectomy. Adolescents and adults with chronic ITP (platelet counts < 30 × 10⁹/L) for whom one or more previous treatments have failed receive rituximab infusions and were followed for up to 2 years. A good response (defined as a platelet count ≥ 50 × 10⁹/L, with at least a doubling from baseline) was obtained in 24 (40%) of 60 patients (95% CI 28%–52%) at 1 year and 33.3% at 2 years. The authors concluded that rituximab could be used as a presplenectomy therapeutic option, particularly in patients with chronic ITP who are at increased surgical risk or who are reluctant to undergo surgery. Based on these results, rituximab may spare some patients from splenectomy, or at least delay it. However, it has never been tested in randomized controlled trials to establish its role as a splenectomy-sparing agent in ITP.

Rituximab in addition to or possibly instead of splenectomy

Rituximab (Rituxan) is a chimeric anti-CD20 monoclonal antibody that targets B cells. Although initially approved for treatment of lymphomas, rituximab has gained popularity in treating ITP due to its safety profile and ability to deplete CD20+ B cells responsible for antiplatelet antibody production by Fc-mediated cell lysis. In the largest systematic review of published reports of rituximab use in ITP (19 studies, 313 patients), Arnold and colleagues reported an overall platelet response (defined as platelet count > 50 × 10⁹/L) in 62.5% (95% confidence interval [CI] 52.6%–72.5%) of patients. The median duration of response was 10.5 months (range 3–20), and median follow-up was 9.5 months (range 2–25). Nearly all patients had received corticosteroid treatment and half of them had undergone splenectomy. Rituximab has also been investigated as an alternative to splenectomy. In a prospective, single-arm, phase 2 trial, 60 patients with chronic ITP (platelet counts < 30 × 10⁹/L) for whom one or more previous treatments had failed received rituximab infusions and were followed for up to 2 years. A good response (defined as a platelet count ≥ 50 × 10⁹/L, with at least a doubling from baseline) was obtained in 24 (40%) of 60 patients (95% CI 28%–52%) at 1 year and 33.3% at 2 years. The authors concluded that rituximab could be used as a presplenectomy therapeutic option, particularly in patients with chronic ITP who are at increased surgical risk or who are reluctant to undergo surgery. Based on these results, rituximab may spare some patients from splenectomy, or at least delay it. However, it has never been tested in randomized controlled trials to establish its role as a splenectomy-sparing agent in ITP.

Thrombopoietic receptor agonists require continuous treatment

In the early 1990s, recombinant thrombopoietin was tested in clinical studies. These were halted when antibodies developed to recombinant thrombopoietin that cross-reacted with endogenous thrombopoietin, resulting in severe thrombocytopenia. This led to the development of nonimmunogenic thrombopoietin receptor agonists that mimic the effect of thrombopoietin and stimulate the production of platelets. In 2008, the US Food and Drug Administration approved two drugs of this class for treating ITP: romiplostim (Nplate) and eltrombopag (Promacta). They are mainly used to treat patients with chronic ITP who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy.

Although well tolerated and effective in increasing platelet counts, these agents share common drawbacks. They do not modify the course of the disease, they are used only to sus-
tain the platelet count, they require repeated administration, and they must be given for about 7 days to achieve an adequate platelet response, so they cannot be used in emergencies. Long-term adverse effects include bone marrow fibrosis and thrombosis.

**Romiplostim** is a synthetic peptide capable of binding to the thrombopoietin receptor c-Mpl. It has no sequence homology with endogenous thrombopoietin, so does not induce cross-reacting antibodies. It has a half-life of 120 to 160 hours and is usually given subcutaneously 1 to 10 µg/kg weekly.

Phase III clinical trials have shown the effectiveness of romiplostim in attaining a durable platelet response (platelet count > 50 × 10⁹/L) in splenectomized and nonsplenectomized populations. It is well tolerated, and only two uncommon serious adverse effects have been reported: bone marrow reticulin formation and thromboembolism.

A long-term open-label extension study of 142 patients treated with romiplostim for up to 156 weeks showed that 124 (87%) achieved a platelet count of more than 50 × 10⁹/L at some point, and 84% of patients were able to reduce or discontinue concurrent medications for ITP.

Kuter et al, in a randomized controlled trial, confirmed the efficacy of romiplostim in attaining durable increased platelet counts. Patients treated with romiplostim at a mean weekly dose of 3.9 µg/kg ± 2.1 µg/kg demonstrated a higher rate of platelet response, lower incidence of treatment failure, and improved quality of life vs patients treated with standard care.

**Eltrombopag** is a nonpeptide thrombopoietin agonist that binds to the transmembrane domain of the thrombopoietin receptor and stimulates the proliferation and differentiation of megakaryocytes in bone marrow. It is given orally in doses of 25 to 75 mg daily.

Eltrombopag has been shown to be effective in increasing platelet counts in chronic ITP. In a phase III trial conducted by Cheng

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### TABLE 3

**Newer therapies for immune thrombocytopenia refractory to first-line treatment in adults**

<table>
<thead>
<tr>
<th></th>
<th><strong>RITUXIMAB (RITUXAN)</strong></th>
<th><strong>ROMIPLOSTIM (NPLATE)</strong></th>
<th><strong>ELTROMBOPAG (PROMACTA)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drug class</strong></td>
<td>Anti-CD20 monoclonal antibody</td>
<td>Thrombopoietin receptor agonist</td>
<td>Thrombopoietin receptor agonist</td>
</tr>
<tr>
<td><strong>Route</strong></td>
<td>Intravenous</td>
<td>Subcutaneous</td>
<td>Oral</td>
</tr>
<tr>
<td><strong>Dosing</strong></td>
<td>375 mg/m² weekly × 4</td>
<td>1–10 mg/kg weekly</td>
<td>25–75 mg daily</td>
</tr>
<tr>
<td><strong>Approximate platelet count response rate</strong></td>
<td>60%⁴¹</td>
<td>79% (splenectomized patients)⁴⁷</td>
<td>70% (receiving 50-mg dose)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>88% (nonsplenectomized patients)⁴⁷</td>
<td>80% (receiving 75-mg dose) ⁵¹</td>
</tr>
<tr>
<td><strong>Approximate time to response</strong></td>
<td>1–8 weeks⁴⁵</td>
<td>1–4 weeks</td>
<td>2 weeks</td>
</tr>
<tr>
<td><strong>Duration of response</strong></td>
<td>Up to 2 years (median 10.5 months) ⁴³</td>
<td>Platelet count returns to baseline 2 weeks after discontinuing treatment</td>
<td>Platelet count returns to baseline 2 weeks after discontinuing treatment</td>
</tr>
<tr>
<td><strong>Safety concerns</strong></td>
<td>Mild infusion reaction</td>
<td>Bone marrow reticulin formation, thrombosis</td>
<td>Elevated liver enzymes, bone marrow reticulin formation, thrombosis</td>
</tr>
</tbody>
</table>

*Platelet count > 50 x 10⁹/L*
and colleagues, 197 patients were randomized to eltrombopag or placebo. Patients treated with eltrombopag were eight times more likely to achieve platelet counts of more than 50 × 10^9/L during the 6-month treatment period (odds ratio 8.2, 95% CI 4.32–15.38, P < .001) vs placebo. Patients treated with eltrombopag had fewer bleeding episodes and were more likely to reduce or discontinue the dose of concurrent ITP medications. The only significant side effect seen was a rise in aminotransferases (seen in 7% of eltrombopag recipients vs 2% with placebo).52

Additional thrombopoietin agonists under investigation include ARK-501, totrombopag, and LGD-4665. MDX-33, a monoclonal antibody against the Fc-receptor, is also being studied; it acts by preventing opsonization of autoantibody-coated platelets.53

■ THIRD-LINE TREATMENTS FOR REFRactory CASES

Patients with ITP that is resistant to standard therapies have an increased risk of death, disease, and treatment-related complications.28,42

Combination chemotherapy
Immunosuppressants such as azathioprine (Imuran), cyclosporine (Neoral, Sandimmune), cyclophosphamide (Cytoxan), and mycophenolate (CellCept) were used in the past in single-agent regimens with some efficacy, but their use was limited due to drug-related toxicity and a low safety profile. However, there is increasing evidence for a role of combination chemotherapy to treat chronic refractory ITP to achieve greater efficacy and fewer adverse effects.54

Arnold and colleagues55 reported that combined azathioprine, mycophenolate, and cyclosporine achieved an overall response (platelet count > 30 × 10^9/L and doubling of the baseline) in 14 (73.7%) of 19 patients with chronic refractory ITP, lasting a median of 24 months.

Hematopoietic stem cell transplantation
Hematopoietic stem cell transplantation has provided remission in a limited number of patients. However, it is associated with fatal toxicities such as graft-vs-host disease and septicemia, and therefore it is reserved for severe refractory ITP with bleeding complications unresponsive to other therapies.26,57

■ THERAPy FOR SECONDary ITP DEPENDS ON THE CAUSE

Treatments for secondary ITP vary depending on the cause of thrombocytopenia and are often more complex than therapy for primary disease. Optimal management involves treating the underlying condition (eg, chronic lymphocytic leukemia or systemic lupus erythematosus).

Drug-induced thrombocytopenia requires prompt recognition and withdrawal of the inciting agent.

Treating ITP due to HCV infection primarily involves antiviral agents to suppress viral replication. If treating ITP is required, then intravenous immunoglobulin is preferable to glucocorticoids because of the risk of increasing viral load with the latter.58 Eltrombopag may effectively increase platelet counts, allowing patients to receive interferon therapy for HCV. However, a recent study was halted due to increased incidence of portal vein thrombosis, raising concerns about the safety of eltrombopag for patients with chronic liver disease.60

Secondary ITP due to HIV infection should always be treated first with antivirals targeting HIV unless thrombocytopenia-related bleeding complications warrant treatment. If treatment for ITP is necessary, it should include corticosteroids, intravenous immunoglobulin, or anti-D immunoglobulin as first-line therapy.

Eradication therapy for H pylori is recommended for patients who are positive for the organism based on urea breath testing, stool antigen testing, or endoscopic biopsies.

■ REFERENCES


Thrombopoietic receptor agonists are mainly used to treat patients with chronic ITP who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy.
antibodies from adult patients with chronic ITP. Blood 2004; 103:1364–1369.


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