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MINIREVIEWS

Immune thrombocytopenia in adults

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Core tip: In this manuscript we evaluate all aspects of immune thrombocytopenia (ITP). We outline the etiology, pathogenesis, diagnosis and treatment of ITP. We describe the first and second-line therapies in detail. Also, the mechanism of the actions of drugs is described.

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Abstract

Immune thrombocytopenia is an autoimmune disease resulting in the destruction of platelets. It is classified as acute, thrombocytopenia occurring for < 6 mo and usually resolving spontaneously, and chronic, lasting > 6 mo and requiring therapy to improve the thrombocytopenia. The underlying defects leading to autoantibody production are unknown. Molecular mimicry appears to play a role in the development of self-reactive platelet antibodies after vaccination and certain viral infections. Platelet life span is reduced as a consequence of antibody-mediated clearance by tissue macrophages in essentially all patients. Diagnosis is based on the exclusion of the other causes of thrombocytopenia. Steroid is the first choice of the treatment, often followed by splenectomy in unresponsive cases. Intravenous immunoglobulin, anti-Rho(D) immune globulin, azathioprine, cyclosporine A, cyclophosphamide, danazol, dapsone, mycophenolate mofetil, rituximab, thrombopoietin receptor agonists and vinca alkaloids are other choices of treatment.

Key words: Immune thrombocytopenia; Splenectomy; Intravenous immunoglobulin; Autoimmune thrombocytopenia

INTRODUCTION

Immune thrombocytopenia (ITP) is an autoimmune disease involving antibody and cell-mediated destruction of platelets and suppression of platelet production that may predispose to bleeding which may be even fatal. Recent recommendations from an international working group suggest that ITP be used to designate all cases of immune-mediated thrombocytopenia, whether occurring as a component of another clinically evident disorder or drug exposure, secondary ITP or, in the absence of a clear predisposing etiology, primary ITP[1,2].

The international working group also recommends that a platelet count below 100×10^9/L, rather than 150×10^9/L, be required for diagnosis. This threshold is based on observational evidence that fewer than 10% of otherwise healthy individuals with a stable platelet count between 100 and 150×10^9/L develop more severe unexplained ITP over the ensuing 10 years. This review focuses on primary ITP in the adult population but includes certain aspects of secondary forms and pediatric ITP where pertinent[3].

INCIDENCE AND PREVALENCE

The annual incidence of ITP in the United States is estimated to be 1.6/100000. Acute ITP, defined as thrombocytopenia occurring for < 6 mo and usually resolving

spontaneously, most often affects children and young adults. The incidence peaks in the winter and spring, following viral infections. Acute ITP is most common between 2 and 6 years of age. Approximately 7% to 28% of children with acute ITP develop the chronic form. Chronic ITP, lasting > 6 mo and requiring therapy to improve the thrombocytopenia, occurs most commonly in adults, as emphasized in the oldest reported series in the literature. In the reported series, both acute and chronic ITP cases were reviewed, 67% of 271 patients and 45% of 737 patients were below 21 and 15 years of age, respectively. In chronic ITP in adults, the median age is usually 40 to 45 years, although in one large series, 74% of 934 cases were younger than the of age 40. The ratio of female to male is nearly 1:1 in acute ITP and 2 to 3:1 in chronic ITP[4].

Estimates of the incidence of adult-onset ITP range from approximately 1.6 to 3.9 per 100000 persons per year, with a prevalence ranging from 9.5 to 23.6 per 100000 persons, based on diagnostic codes in the United Kingdom health registry[5,6]. Estimates based on the International Classification of Diseases, 9th revision codes at hospital discharge in the United States are somewhat lower[7]. However, in light of the vagaries of diagnosis and diagnostic coding, as well as the likelihood that some affected patients may not seek medical attention, the actual frequency of ITP and the number of individuals requiring therapy is uncertain.

ETIOLOGY

The underlying defects leading to autoantibody production are unknown. Heritability is uncommon, although predisposing polymorphisms in cytokines and Fcγ receptors have been described. A Th1/Th0 cytokine profile, a reduction in suppressor T-regulatory cells, and an increase in B-cell-activating factor may predispose to emergence of autoantibodies in response to exogenous antigens. Molecular mimicry appears to play a role in the development of self-reactive platelet antibodies after vaccination and certain viral infections[8-12]. Thrombocytopenia can be caused by a myriad of conditions, including systemic disease, infection, drugs and primary hematological disorders (Table 1)[2].

PATHOGENESIS

Platelet life span is reduced as a consequence of antibody-mediated clearance by tissue macrophages in essentially all patients. Accumulating evidence from studies of platelet kinetics also points to the contribution of immune-mediated suppression of megakaryocyte and platelet development in many patients; megakaryocyte apoptosis and suppression of megakaryopoiesis *in vitro* by ITP plasma/immunoglobulin G (IgG) or T-cells, and responsiveness to thrombopoietin receptor agonists (TRAs)[13-19]. Platelet-reactive antibodies are not detected in all individuals with ITP and a subset of patients do not respond to pharmacological or surgical inhibition of antibody-mediated platelet clearance or B-cell suppression, suggesting the possible involvement of other pathogenic mechanisms such as antibody-mediated apoptosis, antigen shedding and T-cell mediated platelet destruction or marrow suppression[20].

Table 1 Frequent examples of differential diagnosis of immune thrombocytopenia and potential alternative causes of thrombocytopenia identified by patient history

Previously diagnosed or possible high risk of conditions that may be associated with autoimmune thrombocytopenia, for example, HIV, HCV or other infection; other autoimmune/immunodeficiency disorders (including systemic lupus erythematosus; malignancy (*e.g.*, lymphoproliferative disorders); recent vaccination
Liver disease (including alcoholic liver cirrhosis)
Drugs (prescription or non-prescription), alcohol abuse, consumption of quinine, tonic water, exposure to environmental toxins
Bone marrow diseases including myelodysplastic syndromes, leukemias, other malignancies, fibrosis, aplastic anemia and megaloblastic anemia
Recent transfusions (possibility of post-transfusion purpura) and recent immunizations
Inherited thrombocytopenia: thrombocytopenia-absent radius syndrome, radioulnar synostosis, congenital amegakaryocytic thrombocytopenia, Wiskott-Aldrich syndrome, MYH9-related disease, Bernard-Soulier syndrome, type Ⅱ B von Willebrand disease

HIV: Human immunodeficiency virus; HCV: Hepatitis C virus; **MYH9**: Myosin heavy chain 9.

Although the initial inciting event resulting in provocation of antiplatelet antibodies remains unknown, platelet autoantibodies are often present by the time of diagnosis. Macrophages and dendritic cells of the reticuloendothelial system function to phagocytose circulating antibody-bound antigens, including antibody-targeted platelets. Opsonization of antibody-platelet complexes facilitates intracellular processing of platelets and can lead to presentation by T cells *via* major histocompatibility complex (MHC) Ⅱ as an array of "foreign" platelet peptides. Presentation of platelet peptides by MHC Ⅱ in a stimulatory context activates T cells, leading to enhancement of the antiplatelet immune response and the possibility of epitope spread to additional platelet antigens[21].

In patients with ITP, autoantibodies frequently appear to be directed against Gp Ⅰb/Ⅸ and GP Ⅱb/Ⅲa, although specificity for other platelet antigens can occur. Although antiplatelet autoantibodies appear to play a central role in the pathogenesis of ITP, some patients have no detectable antibodies at the time of diagnosis. This may be explained by limitations inherent to laboratory testing methods and the biology of ITP: Brisk clearance of some types of antibody-platelet complexes may reduce circulating antiplatelet antibody titers to below the threshold of detection; tightly bound antiplatelet antibodies may be difficult to dissociate for study; antibodies with specificity to minor or cryptic antigens on platelets or antigens that reside primarily on megakaryocytes may be missed; and there may simply be a subset of patients in which antiplatelet antibodies are not present. Therefore, although the majority of ITP patients present with features consistent with antibody-mediated autoimmunity

as a central feature of their disease, there exists considerable heterogeneity in the types, titers and likely biology of antiplatelet antibodies in ITP[22,23].

As discussed in more detail in a recent review, the presentation of secondary ITP is often more complex than primary ITP. Similar to the antiplatelet antibodies provoked during *Helicobacter pylori* (*H. pylori)* infection, human immunodeficiency virus (HIV) can provoke anti-HIV antibodies that cross-react with platelet glycoproteins and form immune complexes, as hepatitis C virus (HCV) does. Additional mechanisms of platelet destruction also become apparent from studies in virus-associated ITP[24]. In both HIV and HCV, suppression of viral replication can result in improvement in thrombocytopenia. Interestingly, HIV-associated ITP tends to occur early in HIV infection, whereas non-ITP tends to predominate in more advanced HIV when the immune system has suffered from greater effects of the infection. One possible explanation is that the immune system of HIV patients is more capable of developing autoimmunity in the earlier phases of the disease.

An acute infectious event has long been suspected to be a trigger in the initiation of primary ITP. Acute infection remains a plausible candidate to induce ITP either by providing an opportunity for molecular mimicry or similar targeting of the immune system to platelets or by the mere presence of an acute inflammatory response tipping the balance in a predisposed patient to break tolerance[21].

Patients with systemic autoimmune diseases, such as systemic lupus erythematosus (SLE), antiphospholipid antibody syndrome and rheumatoid arthritis, are prone to developing ITP. A diagnosis of secondary ITP in these patients is complex because non-ITP due to underlying disease or related therapies is also common. These observations are consistent with the notion that a patient with one autoimmune disease is at high risk of developing a second. The mechanisms underlying the development of many autoimmune disorders, including ITP, is unknown. It may also be that during the immune dysregulation leading to autoimmunity to one self-antigen, there is a risk of immune presentation of other self-antigens. Interestingly, many of the features of immune dysregulation described in ITP, such as the shift in Th1/Th2 balance, increased Th17 and altered Treg profiles described above, are also common to other autoimmune diseases[25].

DIAGNOSIS

Personal history, with special attention to drugs and medical conditions that could cause thrombocytopenia, is very important. With a 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[26].

Physical examination should be normal aside from bleeding manifestations. Mild splenomegaly may be found in younger patients, but moderate or massive splenomegaly suggests an alternative cause. Constitutional symptoms, such as fever or weight loss, hepatomegaly or lymphadenopathy, might indicate an underlying disorder such as HIV, SLE or a lymphoproliferative disease[27].

ITP is characterized by isolated thrombocytopenia with an otherwise normal complete blood count. Anemia from blood loss may be present but it should be proportional to the amount and duration of bleeding and may result in iron deficiency[2].

In ITP, the peripheral blood smear should appear normal except for the presence of thrombocytopenia, although platelets may be mildly enlarged in some individuals. Both red cell and leukocyte morphologies are normal[26].

Bone marrow examination may be informative in patients older than 60 years of age, in those with systemic symptoms or abnormal signs, or in some cases in which splenectomy is considered. Both bone marrow aspirate and biopsy should be performed. In addition to the morphological assessment, flow cytometry and cytogenetic testing should be considered (evidence level Ⅱb-Ⅳ). Flow cytometry may be particularly helpful in identifying patients with ITP secondary to chronic lymphocytic leukemia[2,27].

International guidelines suggest that testing for reduced immunoglobulin levels and HIV, HCV and *H. pylori* infections should also be considered. 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[26].

MANAGEMENT OF ADULT ITP

Relevant factors that contribute to management decisions include the extent of bleeding, comorbidities predisposition to bleeding, complications of specific therapies, activity and lifestyle, tolerance of side effects, potential interventions that may cause bleeding, accessibility of care, patient expectations, patient's worry or anxiety about disease burden, and patient's need for non-ITP medications that may create a bleeding risk[28,29].

Treatment is rarely indicated in patients with platelet counts above 50×10^9/L in the absence of the following: Bleeding due to platelet dysfunction or another hemostatic defect, trauma, surgery, clearly identified comorbidities for bleeding, mandated anticoagulation therapy, or in persons whose profession or lifestyle predisposes them to trauma. Patient's preference must also be considered when discussing treatment options[30].

FIRST-LINE TREATMENT

First-line therapies for ITP include corticosteroids, intravenous immunoglobulin (IVIg) and anti-Rho(D) immune globulin[2].

Table 2 Summary of dosage and toxicity of drugs

Agent	Typical dosing	Time to response	Selected toxicities
Prednis(ol)one	0.5-2 mg/kg per day 2-4 wk followed by slow taper	Several days to several weeks	Mood swings, insomnia, anxiety, psychosis, weight gain, cushingoid facies, hyperglycemia, decreased bone density, hypertension, skin changes, gastrointestinal distress and ulceration, avascular necrosis, increased susceptibility to infections, cataracts, adrenal insufficiency
Methylprednisolone	30 mg/kg per day 7 d	2-7 d	
Dexamethasone	40 mg/d for 4 d every 2-4 wk for 1-4 cycles	Several days to several weeks	
IVIg	0.4 g/kg per day 5 d or 1 g/kg per day 1-2 d	1-4 d	Headache, aseptic meningitis, renal insufficiency, fever, chills, nausea, thromboembolism, anaphylactoid reactions in patients with IgA-deficiency
Anti-Rh(D)	50-75 mcg/kg	1-5 d	Hemolytic anemia, fever, chills. Rarely, intravascular hemolysis, DIC, and renal failure
Splenectomy	N/A	0-24 d	Adverse effects of surgery and anesthesia, increased risk of infection, long-term vascular complications
Rituximab	375 mg/m^2 weekly 4 wk (lower doses may be effective)	1-8 wk	Infusion reactions, reactivation of hepatitis B infection, rare cases of progressive multifocal leukoencephalopathy
Eltrombopag	12.5-75 mg PO daily	1-4 wk	Increased bone marrow reticulin, rebound thrombocytopenia, thrombosis, eltrombopag also associated with liver function test abnormalities
Romiplostim	(1-10 mcg/ kg) SC weekly	1-4 wk	
Azathioprine	1-2 mg/kg per day (maximum 150 mg day)	1-4 wk	Liver function abnormalities, neutropenia, anemia, infection
Cyclosporine	5 mg/kg per day 6 d, then 2.5-3 mg/kg per day (titrated to blood levels of 100-200 ng/mL)	1-4 wk	Renal failure, hypertension, tremor, infection
Cyclophosphamide	1-2 mg/kg PO daily or 0.3-1 g/m^2 *iv* every 2-4 wk 1-3 doses	1-4 wk	Myelosuppression, infection, secondary malignancy
Danazol	200 mg 2-4 times per day	1-4 wk	Acne, hirsutism, dyslipidemia, amenorrhea, liver function abnormalities
Dapsone	75-100 mg daily	1-4 wk	Hemolytic anemia in patients with G6PD deficiency, rash, methemoglobinemia
Mycophenolate mofetil	1000 mg twice daily	1-4 wk	Headache, back pain, infection
Vincristine	1-2 mg *iv* weekly (total dose 6 mg)	1-4 wk	Neuropathy, constipation, cytopenias, thrombophlebitis at the infusion site

IVIg: Intravenous immunoglobulin; DIC: Disseminated intravascular coagulation; PO: Per oral.

Corticosteroids

Standard prednisone therapy, 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 about 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 d, with platelet counts peaking in 2 to 4 wk. Unfortunately, only about 15% of patients maintain the response over the subsequent 6 to 12 mo. Restarting prednisone often initiates a vicious circle and makes patients vulnerable to steroid toxicities (Table 2)[26].

Pulse dexamethasone therapy consists of 40 mg/d for 4 d 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 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[2].

IVIg

Another primary therapy for ITP is IVIg 0.4 g/kg per day for 5 d or infusions of 1 g/kg per day for 1-2 d[2]. 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, 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[26].

Platelet clearance in ITP mediated by most anti-GPIb antibodies may occur through an Fc-independent process, likely *via* a system that evolved for our innate immunity and for clearance of senescent cells. This type of ITP may not be sensitive to IVIg and other therapies designed based on Fc receptor blockage[31].

Antibody Fc-independent phagocytosis has also been well described in mammals, including Fc-independent opsonization by antibodies[32], as well as antibody and Fc receptor-independent phagocytosis of microbes and other senescent cells[33-36]. In the absence of antibody, specific ligands from bacteria, other foreign microorganisms or the host's senescent cells, may engage receptors directly on phagocytes, such as scavenger receptors, phosphatidylserine counter-receptors, V integrins, com-

plement receptors or C-type lectins[33-38]. In some cases, this engagement can be enhanced by F(ab')2 fragments of antibodies or non-antibody opsonins. These Fc-absent antibodies may bind to receptors on phagocytic cells (*e.g.*, scavenger receptors) or their ligands and induce changes in conformation and affinity of these molecules, which facilitate phagocytosis[32]. Thus, by directly engaging the target, phagocytosis without the need for antibody is an effective mechanism for clearance of microorganisms and senescent cells.

It was demonstrated that the removal of the Fc region of anti-GPIb monoclonal antibodies did not affect the ability of these antibodies to induce thrombocytopenia [*i.e.*, the F(ab')2 portions were as effective as intact antibodies in inducing platelet clearance]. However, when the Fc region of anti-GP Ⅱ bⅢa antibodies was removed, thrombocytopenia was not induced in the same animal model[39].

Intravenous anti-D

An alternative to IVIg for Rh(D)-positive patients before splenectomy is anti-D Ig. At doses of 75 μg/kg, anti-D may increase the platelet count more rapidly compared with the standard dose of 50 μg/kg. Subcutaneous anti-D has been administered to a few patients suffering from chronic ITP who appeared to have the same response rate as those treated with intravenous delivery without relevant side effects. Evidence of hemolysis is present in most patients treated with anti-D. While the decline in hemoglobin concentration rarely exceeds 2 g/dL, several cases of massive intravascular hemolysis and disseminated intravascular coagulation have been reported. Elderly patients, above 65 years of age, with a coexisting infection, autoimmune hemolytic anemia (Evans syndrome), autoimmune disorders or lymphoproliferative disorders appear to be more susceptible to these complications[40].

Platelet transfusions with or without IVIg

Platelet transfusion increases the post-transfusion platelet count by more than 20×10^9/L in 42% of bleeding ITP patients and may reduce bleeding. In a retrospective study of 40 patients, concurrent administration of platelet transfusions and IVIg was associated with resolution of bleeding, rapid restoration of adequate platelet counts and minimal side effects[40,41].

Antifibrinolytics

Antifibrinolytic agents, such as oral or Ⅳ tranexamic acid and epsilon-aminocaproic acid, may be useful in preventing recurrent bleeding in patients with severe thrombocytopenia; however, the efficacy has not been evaluated by randomized trials in ITP patients. Tranexamic acid (1 g, 3 times daily orally) and epsilon-aminocaproic acid (1-4 g every 4-6 h maximum dose, 24 g/d) may be of special value in certain dental or surgical procedures[40-42].

SECOND-LINE TREATMENT

Second-line therapies, as designated by the international working group, include azathioprine, cyclosporine A, cyclophosphamide, danazol, dapsone, mycophenolate mofetil, rituximab, splenectomy, TRAs and vinca alkaloids. The evidence for efficacy of the cytotoxic agents, *i.e.*, cyclophosphamide, the vinca alkaloids and azathioprine, comes from small, non-randomized studies[30]. Although these agents are useful in some patients, they may be associated with significant toxicities and are used less commonly than in the past (Table 2)[26,42].

Splenectomy

Splenectomy probably offers the best response of any treatment for ITP. About 80% of patients with ITP respond rapidly, often within 1 wk. Of those, 15% relapse within the first year and after 10 years, two-thirds remain in remission[43,44].

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 wk 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[26].

Rituximab

Rituximab, an anti-CD20 monoclonal antibody, has produced variable objective responses. Rituximab causes selective B-cell lysis *in vitro* and B-cell depletion *in vivo*. Involved mechanisms of action include apoptosis, antibody-dependent cytotoxicity. Recovery of B-cell counts usually occurs by 6 to 12 mo after completion of treatment[45].

Several publications have reported the use of rituximab in ITP patients since previous consensus documents were issued and suggest that about 60% of patients respond, with approximately 40% achieving complete response. Responses generally occur after 1 to 2 wk to 6 to 8 wk and last from 2 mo in partial responders to 5 years or longer in 15% to 20% of initially treated patients. Most patients with a durable (> 1 year) complete response will respond to repeat treatment if they relapse[46-48].

Romiplostim

Romiplostim is a peptibody (comprising of an IgG Fc region and four peptidomimetics 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 wk 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 non-splenectomized patients had an overall response (defined as a platelet count > 50×10^9/L for 4 wk during the study period) and 38% of splenectomized patients and 61% of non-splenectomized patients had a durable response (platelet count > 50×10^9/L for 6 of the last 8 wk of

the study). In an ongoing long-term extension study of romiplostim that allows dose adjustments to maintain a platelet count between 50-200 × 10^9/L, romiplostim dosage and efficacy have remained stable over 5 years[18,49,50].

Dapsone

Dapsone is a moderate corticosteroid-sparing agent that is usually administered orally at a dose of 75 to 100 mg/d. Dapsone may delay splenectomy for up to 32 mo in patients who have not responded to first-line corticosteroid therapy. However, splenectomized patients have a low response rate[2].

Eltrombopag

Eltrombopag 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 mo of the study. Like romiplostim, it was effective in both splenectomized and non-splenectomized 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. Several other drugs in this class are currently in development[51,52].

CONCLUSION

The pathophysiology of ITP is complex and abnormalities of both the B and the T-cell compartments have been identified. The mechanisms of thrombocytopenia involve both increased platelet destruction and, in a significant proportion of cases, impaired platelet production.

Splenectomy has historically been the second-line therapy for adults with ITP in whom achieving a safe platelet count with initial corticosteroid and/or immunoglobulin therapy has failed. Although it still remains the therapeutic modality that offers the highest chance of cure, its position in the therapeutic algorithm of ITP is currently challenged. Rituximab has been shown to have a limited but valuable activity as a splenectomy sparing agent and is generally tolerated very well. The Thrombopoietin-receptor agonists have undergone a formal, systematic investigation and have been licensed for use in adult patients with ITP. These agents appear to be very effective in a high percentage of patients with chronic and refractory disease and appear to have a favorable side-effect profile in the short and medium term. Potential long-term side effects of TPO-receptor agonists remain a concern and suggest their prudent use in young, non-splenectomized patients.

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