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Review Article

PRIMARY IMMUNE TRHOMBOCYTOPENIA IN ADULTS: UPDATED REVIEW ON DIAGNOSIS AND TREATMENT

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ABSTRACT

Primary immune thrombocytopenia (ITP) is an auto-immune disorder resulting in the premature destruction of platelets, and in a defect in their production; this process is characterized by isolated thrombocytopenia, defined as a peripheral blood platelet count below 100 x 10^9/dL without an apparent cause. It is estimated that the annual ITP incidence in adults is similar for both sexes, representing 2 to 4 cases per 100,000 people approximately, however, there is a higher incidence in women among young patients. The treatment of choice should be evaluated by the physician and the patient, considering general recommendations. First-line treatment includes corticosteroids, anti-D immunoglobulin, and immunoglobulin IV; second-line therapy includes splenectomy, rituximab, azathioprine, cyclosporin, cyclophosphamide, mofetil mycophenolate, vincristine or danazol, and more recently due to the need of more effective treatments, and less adverse effects, the thrombopoietin receptor agonists have been developed. New therapeutic strategies increase platelet counts, decrease hemorrhagic events, and have no significant adverse effects, however, they do not offer a cure. New approved thrombopoietic agents for ITP, such as romiplostim and eltrombopag have demonstrated treatment efficacy and safety. This review is intended to offer a general overview of the new therapeutic options for this pathology that is under constant study.

INTRODUCTION

Primary immune thrombocytopenia (ITP) is an auto-immune disorder resulting in the primary destruction of platelets as well as in a defect on its production; this process is characterized by isolated thrombocytopenia, defined as a peripheral blood platelet count of < 100 x 10^9/dL without an apparent cause. This process associates with a 1% mortality during the individual´slife-time. Deaths in this disorder are predominantly caused by a hemorrhage that may be fatal, and/or due to complications caused by the treatments administered, specially, those used to treat infections[1,2].

ITP annual incidence in adults is estimated to be similar for both sexes, approximately 2 to 4 cases per 100,000 inhabitants, however, in young patients there is a higher incidence in women[4]. ITP clinical presentation is very variable, since it may go from asymptomatic patients, as well as those with minimal purpura manifestations such as ecchymosis and petechia, to those with severe bleedings that rarely result in intracranial hemorrhage[5]. ITP is classified into three phases according to

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their duration: initial or newly diagnosed when it lasts up to the first three months, persistent when symptomatology is not resolved in 3- 12 months, and chronic when it lasts more than 12 months[1,3].

The platelet count threshold is 100,000/dL for the ITP diagnosis. On the other hand, the classification was modified based on the ITP natural history during childhood, where approximately two thirds of the subjects recover spontaneously in the first six months, and the remission possibilities are high between the 3 and 12 months, or even later. Severe ITP is reserved for patients with clinically relevant hemorrhagic manifestations[6].

Up to now, the diagnosis is still done by exclusion, since there are no other paraclinic or analytic parameters to allow a certain diagnosis, because symptoms and clinical signs are very variable. The main problem is the increased risk for hemorrhage. There is not always, an exact correlation between the platelets count and hemorrhagic manifestations, although they are more frequent below 10,000/dL. Most patients are asymptomatic or present petechia, bruising or skin or mucosal isolated ecchymosis. However, some cases may experience more severe hemorrhages that may occur at the cutaneous, mucosal, gastrointestinal or even intracranial levels (0.1 to 0.5%)[5,8].

Splenectomy was used as ITP treatment until 1950, however, in the last 10 years, advancements in the knowledge of the disease have grown along with the availability of new therapeutic agents, leading to an era of treatment options based on the pathophysiology of the disease[7,9].

ITP in Mexico

Actual ITP incidence in Mexico is unknown, nevertheless, a review of the Mexican Association for Study of Hematology (AMEH), reveals that ITP is one out of ten causes of attention in third level hospitals, with an average of 1 case per month (Figure 1)[10-12]

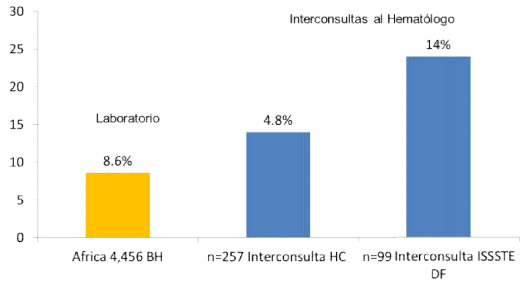

Figure 1 Thrombocytopenia frequency

Cross consultation with a hematologist, and frequency of thrombocytopenia findings in lab services may be observed.

BC, blood count, DF: Mexico City, HC, Reference hospital, ISSSTE: Instituto de Seguridad y Servicios Sociales de los Trabajadores del Estado (public hospital for government workers).

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Presently, the study of ITP has grown considerablyin Latin America.

ITP pathophysiology

It affects the whole immune system, where the main feature is the loss of self-tolerance leading to the production of antibodies directed to platelet antigens. These antibodies are mainly immunoglobulin G (IgG) specific type against glycoproteins IIb/IIIa, Ib/IX5 andIb/IX/V. Platelets covered by IgG antibodies accelerate their destruction through Fcγ receptors expressed as macrophages located in the spleen and liver mainly. It has been observed that a compensatory increase in the platelets production occurs in most of the patients. In others, the production is reduced due to the intramedullary destruction of megakaryocytes o by megakaryopoiesis inhibition. Of note, is that the level of thrombopoietin is not increased in any of these patients. Unfortunately, an antibodies test is hard to perform, not routinely available, and a negative result does not exclude the diagnosis, therefore, it is not recommended for the ITP diagnosis[13,14].

New pathophysiology theories suggest that immune cellular mechanisms play a main role in ITP. It is possible that in some cases cytotoxic T lymphocytes take part in the platelet destruction. The triggering factor may be a viral infection, or a toxin, generating the production of immune complexes/antibodies affecting platelets; these platelets covered by antibodies bind to an antigen presenting cell through the internalization and degradation of low affinity receptors. The activated antigen-presenting cell expresses new peptides on the cell surface and this co-stimulatory aid facilitates the proliferation of specific platelet antigens (CD4 +, T cell clones). These T-cell clones lead the production of antibodies by specific platelet-antigen B cells clones. Besides the antigenic stimulation, T-helper lymphocytes (Th) produce a variety of cytokines that modulate the immune response. It has been described that an increase in the Th1 activity, as well as a decrease of the Th2 activity, are present in ITP, leading to a constant pro-inflammatory state that causes an increase of the immune cellular response, and an increase of the IgG antibodies that fix the complex by the inhibition of the regulatory immune response, although it is interesting that the total number of CD4+ CD25+ total cells is not reduced, their function is when compared to healthy controls[16]. T-helper lymphocytes stimulation by the platelet antigens, may originate the production of anti-platelet antibodies, or the production of cytotoxic T-lymphocytes, that manifest as platelet destruction or the inhibition of their production[15].

The increased platelet destruction plays a key role in the ITP pathogenesis. Today, it is recognized that a decrease of the platelet production is, in many cases, very important as well. There is evidence that platelet auto-antibodies also inhibit magakaryocytes decreasing the platelet production. Besides, circulating thrombopoietin levels are not modified by this decrease of the production. Therefore, there is a growing evidence stating that chronic ITP thrombocytopenia is due to the platelet destruction and to a production supression[17].

ITP diagnosis

ITP diagnosis is established by the systematic exclusion of other causes of thrombocytopenia. The initial approach is based

on the clinical history, physical examination, blood cytometry, and a peripheral blood extension test. The bleeding characteristics should be evaluated, if cutaneous or mucosal, its severity, extension and time of evolution. Concomitant conditions increasing the bleeding risk should be identified. All of this will allow a better assessment for a safer and more effective treatment. Approximately 20% of immune thrombocytopenias are associated with other underlying processes, so a complete diagnostic approach should be followed to rule out other possible etiologies[17]; it is essential to evaluate: prothrombin time (PT), activated partial thromboplastin time (PTa), thrombin time (TT) and fibrinogen; The examination of peripheral blood smears is essential to confirm thrombocytopenia, to exclude pseudo-thrombocytopenia by ethylene-diamine- tetra-acetic acid (EDTA) and other thrombocytopenias associated with myelodysplasia, leukemia, megaloblastic anemia, microangiopathy or other of congenital origin. In ITP, platelets may have a slightly increased mean platelet volume (MPV), but the detection of excessively large, agranular or very small platelets should alert to the existence of other diseases. Along with other supplementary routine tests, the administration of immunoglobulins to discard an IgA deficiency or a status of immunodeficiency should be requested; as well as a control of microscopic hematuria and study of viral infections, such as cytomegalovirus (CMV), Epstein Barr virus (EBV), parvovirus B19, herpes simplex, herpes 6, human immunodeficiency virus (HIV), hepatitis B virus (HBV) and HCV[19].

To avoid the confusion in the diagnosis due to the heterogeneity of terms used at the beginning of this pathology, a new terminology was established, including:Primary ITP defined as an autoimmune disease characterized by isolated thrombocytopenia with a count <100,000 platelets/dL in the absence of other problems or diseases to justify it. This is an exclusion diagnosis that presents with an increase in the risk of hemorrhage, although there might be no clinical bleeding. Secondary ITP includes all forms of autoimmune mechanism thrombocytopenias, except for the primary ITP.

Disease temporality, is classified in three phases

- Recent diagnosis ITP, which is applicable to all the patients at the beginning of the symptomatology.
- Persistent ITP, refers to all the patients who continue with thrombocytopenia 3 to 12 months after the diagnosis, even if they did not reach a spontaneous remission or if the remission achieved during this period is not maintained.
- Chronic ITP, patients with thrombocytopenia of >12 months of evolution.

By consensus, the term serious ITP is only considered applicable to patients with hemorrhage requiring treatment, or an increase of the dose of the treatment used, independently of the platelet count, and the evolution time[13].

ITP treatment

The treatment primary objective is to maintain a platelet count above 20,000/dLand to decrease the risk of hemorrhage, however, in most of the patients, it is allowed to maintain a watchful behavior, as long as they are asymptomatic, with a platelet count above 30,000/mm^3, without signs of major bleeding or risk factors (use of anticoagulants, antiplatelet agents, history of traumatic brain injury or recent polytrauma, coagulopathy, lifestyle or occupational risk, age extremes of life, renal failure, vasculitis, etc.) Patients with this type of risk factors should receive prophylactic therapy before special situations such as surgery, dental extractions or other invasive procedures

Table 1 Treatment response criteria[19.]

Treatment Response Criteria	
Complete remission (CR)	A count greater than or equal to 100,000/dL for more than six weeks after treatment withdrawal.
Partial remission (PR)	Elevation above baseline with a count between 30,000 and 100,000 /dL maintained for more than six weeks after treatment withdrawal.
Absence of response (AR)	No clinical or biological change
Transitory response (TR)	Initial improvement (clinical or biological) with a new clinic or count below 30,000/dL before six weeks after the end of treatment
Relapse (REL)	Count below 30,000/dL after six weeks of treatment completion, having had a previous complete (RC) or partial remission (PR).
Steroid dependence	Need for repeated or sustained doses of corticosteroids to maintain a platelet count greater than 30,000/dL and / or avoid bleeding
Refractory	Cases where no response is achieved, or the loss of response after splenectomy, with the need of continuous treatment to decrease the risk of bleeding.

It is important to adequately assess the patient general condition at the time of the diagnosis, and to consider hospitalization in patients with active bleeding, bleeding risk factors, or platelet counts equal or lower to 20,000/dL. It has been proposed that early intensive treatment can reduce symptoms and even cure patients with ITP[20]. First-line treatment includes corticosteroids, anti-D immunoglobulin, and intravenous immunoglobulins; Second-line therapy includes surgical measures such as splenectomy, other drugs such as rituximab, azathioprine, cyclosporine, cyclophosphamide, mycophenolate mofetil, vincristine or danazol, and more recently, in view of the need for more effective treatments and fewer adverse effects, agonists of the thrombopoietin receptor, whose mechanism of action is to stimulate production to achieve an increase in platelet count, which is a new concept of therapeutic approach in the history of ITP[21].

Although splenectomy still provides the highest cure rate (60-70% in five years), it does not interfere with the response to other treatments; in addition to the laparoscopic technique that is safer, there is more experience and it has the lowest overall cost; Despite this, more and more doctors prefer other treatment options. Splenectomy is considered the second line treatment and soon it will be considered the third line approach since this is an invasive, irreversible procedure associated to post-surgery complications, and the long-term outcome is still unpredictable[19,22]. However, most of the physicians in Mexico still consider this as the first option when corticosteroids fail[1].

Other second-line treatment options include immunosuppressants such as vinca alkaloids, mycophenolate mofetil, danazol, cyclophosphamide, cyclosporine, and azathioprine. In relation to vinca alkaloids, a very variable response has been observed between 10 to 75%, with a response time of 5 to 7 days, and a risk for neuropathy, neutropenia, fever, inflammation and thrombophlebitis at the

site of administration. As for mycophenolate mofetil, there are reports of better responses ranging from 45 to 75% with a response time of 4 to 6 weeks and in terms of adverse effects, the most frequently reported are headache, back pain, abdominal distension, anorexia and nausea, and a good sustained response rate has not been proven[7].Regarding danazol, one of its main drawbacks is the need for long-term administration requiring at least six months of treatment to observe responses, the literature reports that its response is 67% on average of complete or partial remissions, its toxic effects include: acne, hirsutism, hypercholesterolemia, amenorrhea, hypertransaminasemia, weight gain, fluid retention; with a remission rate of 46% at 119 months in patients who were treated for at least 37 months.

As for cyclophosphamide, better response rates ranging from 60 to 80% have been observed, with important adverse effects such as neutropenia, deep venous thrombosis, nausea, vomiting, bone marrow suppression, hemorrhagic cystitis, infertility, alopecia and a greater development to neoplasias has been seen anecdotally; its sustained response rate is 20-40% for three years after receiving treatment for 2 to 3 months.

In the case of cyclosporine its main limitation is the dose-dependency, its approximate response has been documented from 50 to 80% in small series and uncontrolled studies, with a response time of 3 to 4 weeks and with important adverse effects such as an increase of serum creatinine, arterial hypertension, fatigue, paresthesias, gingival hyperplasia, myalgias, dyspepsia and hypertrichosis; although it has proven to be the one with the best sustained response rate reaching more than 50% at low doses for at least two years.

It has been documented that azathioprine has an approximate response of 45%, with a slow response time of up to 3 to 6 months. Its adverse effects include weakness, mucosal dryness, transaminasemia, severe neutropenia with significant risks of infection, pancreatitis, secondary malignancy and alopecia; 25% of the patients had no recurrence after treatment[23].

Monoclonal antibodies present another treatment option, the best response has been seen with rituximab, a murine and human chimeric monoclonal antibody, obtained by genetic engineering. It is a glycosylated immunoglobulin specifically targeted against the CD20+ antigen that has been found on the surface of normal and malignant B lymphocytes[24]. Despite being a drug not yet approved by the *Food and Drug Administration* (FDA) as a treatment for TIP, it is widely used, and the most commonly used dose is 375mg/m^2 once a week for four weeks, showing a response rate of 40-60% and a sustained post-treatment response of approximately 15%; the most important adverse effects related to this drug are infections, allergic reactions, multifocal leukoencephalopathy, serum sickness in infants, fever and hypogammaglobulinemia[25]. In a study performed at the University of Copenhagen, a better response was demonstrated by the combination of dexamethasone + rituximab than after rituximab alone[26], for this reason the ideal indications to use rituximab as second-line treatment would be: a contraindication for splenectomy or if the patient refuses the procedure.

There is still little information about a cure for ITP using medical treatment only; however, Cuker, *et al* conducted a study at the University of Philadelphia in which they concluded that the association of dexamethasone + Rituximab had a complete remission at 12 months of 53%[20], other important considerations to administer rituximab will be: age >60 years, high risk of thrombosis, hepatic or mixed platelet sequestration, recent or persistent ITP, exposure to malaria, babesia or similar and a predisposition to lack of adherence.

Due to continuous research on ITP, new therapeutic lines have been developed to stimulate thrombopoiesis. Thrombopoietin receptor agonists have a mechanism of action different to that of treatments used so far for ITP, because they mainly generate an increase in platelet production and perhaps an effect on the immune response. Two new agents, romiplostim and eltrombopag, were approved by the FDA for the treatment of ITP in patients with poor response to corticoids, immunoglobulin, or splenectomy[8]. Among the advantages of these drugs we find that they present a high response rate, they are well tolerated, it is possible to reduce the initial therapy, they have proven a significant improvement in the quality of life, and after months of treatment its administration can be suspended; as disadvantages we can observe that it takes a minimum of 1 to 2 weeks to evaluate the responses, with an indefinite duration of treatment, and despite being better tolerated than other treatment lines still carry side effects and present a progressive decrease of the platelet count after discontinuing its administration.

Romiplostim was the first second-generation thrombopoietic agent to enter a clinical trial and to receive approval for use in adult patients with ITP. It is a mimetic peptide that presents high affinity for the thrombopoietin receptor (TPO-R) but does not show sequence homology with endogenous thrombopoietin (TPO), this being the main difference with thrombopoietic first generation without inducing the formation of neutralizing antibodies against endogenous TPO. Subcutaneous absorption has a peak serum concentration between 12 to 16 hours after administration. The increase in platelet counts occurs between 3 to 5 days, with a maximum between days 12 to 16 of treatment, returning to baseline counts around day 28 after the suspension of the drug. This suggests that both the platelet response and its maintenance and duration depend on the serum concentration of this drug and its clearance from plasma by the endothelial reticulum system. The initial dose is 1 mcg/kg of weight, subcutaneously, weekly[8].

Eltrombopag is a highly specific non-peptidic mimetic of thrombopoietin. The main characteristic of this drug is that it binds at a site other than that of the endogenous TPO in TPO-R, having a non-competitive, additive effect with it; it is a small hydrolyzed molecule and the first thrombopoietic available for oral administration. It has an absorption of 50%, more than 90% is bound to plasma proteins, with a peak plasma concentration between 2 to 6 hours after administration and a half-life of 12 hours. Eltrombopag is mainly metabolized through decomposition, oxidation and conjugation with glucuronic acid, glutathione or cysteine and its elimination is renal and in feces. This drug was approved by the FDA in 2008 for the treatment of chronic ITP. The initial recommended dose is 50 mg with an increase to 75 mg if no adequate response is achieved after three weeks of treatment. The combination of eltrombopag plus dexamethasone has a response of 75% at 6 months[8,27].

Four randomized, controlled trials of eltrombopag on safety and efficacy have been conducted. Compared with placebo, eltrombopag therapy was found to be associated with higher response rates, higher platelet counts, and a significant decrease in all grades hemorrhage; as for adverse effects, a similar incidence was reported during treatment in both groups, placebo and eltrombopag, headache was the most common adverse effect (AE) in both groups, and cataracts (5%) were the serious AE reported more frequently during therapy so, every patient receiving eltrombopag should be periodically checked to prevent the occurrence of cataracts. As a conclusion of the analysis of the published works on its use in ITP, it can be affirmed that the treatment with eltrombopag is effective in 80% of the patients to elevate the platelet count, regardless of their antecedents. In addition, it decreases bleeding events with an acceptable rate of adverse reactions (Table 1)[8]

Table 2 Studies with eltrombopag. [8]

Author	Sample size (n)	Dose	Results
Bussel, 2007	118	30, 50 y 75mg for 6 weeks	Increased platelet count Decreased bleeding Quality of life improvement Good tolerance
Bussel, 2009	114	50 mg for 6 weeks	
Cheng, 2011 (RAISE)	197	50 mg for 6 months	
Saleh. 2013 (EXTEND)	299	50 mg for 2 years	

DISCUSSION

Primary immune thrombocytopenia takes a chronic course in most cases, resulting in important clinical consequences for patients with this condition, including an increased risk of bleeding and a marked decrease in quality of life. Medical therapy for this disease is only a temporary treatment that raises the platelet count with very little evidence of sustained remission upon discontinuation. There is little published information since there are no prospective long-term follow-up studies, especially after one year, besides, the spontaneous remission could be an added confounding factor.

Despite the significant progress in understanding the pathophysiology and management of the disease over the past 15 years, few controlled, randomized studies have been conducted and management guidelines are limited. In addition, there are few validated risk factors for understanding the outcome or prediction of response to medical therapies and little research has been done to change the paradigm that ITP is an "exclusion diagnosis". Therefore, in order to establish the diagnosis of any thrombocytopenia, an extensive clinical history, peripheral blood smears should be performed to determine if there is pseudo-thrombocytopenia, thrombocytopenia or any association with qualitative alterations in blood cells, as well as the presence or absence of symptomatology. The approach is taken according to age; immunological tests (antinuclear antibodies, anti-DNA, complement, rheumatoid factor, immunoglobulins, group and Rh) should be done to rule out infection (HIV, HCV, HBV, *H. pylori*), also to evaluate exposure to myelotoxic drugs; bone marrow aspirate (BMA) is still a controversial issue. The American Society of Hematology guidelines establish that bone marrow aspiration is not necessary in patients younger than 60 years if the presentation of ITP is typical, however, it is advisable to do so prior to a splenectomy. According to Cines and Blanchette, a BMA is justified in patients over 40 years old with atypical characteristics (additional cytopenias), as well as in patients who do not present a rapid and evident response to treatment. Regarding the performance of a BMA in children with observational treatment or with intravenous immunoglobulins, the evidence rejecting its use in the daily practice is clear. Although not mandatory, many pediatricians recommend performing a BMA prior to initiating corticosteroid therapy to rule out acute leukemia. The strict indications for a BMA are: patients with atypical presentations such as lethargy, persistent fever, myalgias and/or arthralgias, unexplained macrocytosis or neutropenia[24].

Among the multiple therapeutic options to treat ITP is the use of glucocorticoids and IV immunoglobulins as first-line drugs; a platelet transfusion is indicated if the patient presents digestive hemorrhage, central nervous system or hematuria.

For the second line treatment, there is a debate among experts, as for some of them splenectomy should be the choice due to its high rates of sustained remission after the procedure, however, because it is an invasive technique, others prefer treatment with rituximab or thrombopoietin receptor analogues with or without steroids since these drugs are associated with the lower rate of adverse effects.

As a third line treatment, and for patients who have failed to the previous lines, the use of immunosuppressants such as azathioprine or mycophenolate mofetil is suggested, they have shown good remission rates during treatment, but are associated to a large number of adverse effects, also they have failed to achieve satisfactory remission rates after dosing cessation.

A retrospective study conducted at the National Medical Center "20 de Noviembre" concluded that the first-line treatment is sufficient to cure half of the patients, the second line had efficacy of 31% and splenectomy is preferred *vs.* immunosuppression due to the risk of toxicity[28].

Although there are multiple guidelines for the management of patients with ITP, in Mexico, the newly diagnosed patients are treated as chronic patients; in addition, attention is focused on the treatment of platelets, when the main goal of treatment should be to reverse and prevent bleeding by keeping the platelet count at a safe level[29].

Future prospects in the treatment of ITP are vast, the most appropriate treatment for persistent ITP is still not well defined, but there are high expectations that the analogues of thrombopoietin receptors are the most viable option, since the generalized use of these drugs can avoid toxicity caused by the prolonged use of corticosteroids, offering a possible cure option for patients in whom splenectomy is contraindicated or who are not candidates for the application of rituximab. In addition, they may be used in patients with increased cardiovascular risk, as well as in women receiving hormone replacement therapy.

It is clear that, the archetype of ITP in which the destruction of platelets by antibodies was thought to be the only event related to the disease has changed. In consequence, there is a better knowledge of the pathophysiology, allowing the discovery of new drugs that considerably increase the therapeutic possibilities. Treatment should be individualized, considering

the potential benefits that outweigh the adverse effects. A cost-benefit analysis should be performed to find the best therapeutic option.[30,31]

CONCLUSIONS

Primary immune thrombocytopenia is a common pathology that frequently occurs in young, previously healthy adults, which in many cases is usually self-limiting or presents adequate response to first-line treatments, however, if they turn chronic or persistent they become a treatment issue since, although there are multiple therapeutic options, there are no recommendations based on evidence on when to select a particular treatment or when it is better to maintain an expectant attitude. Although higher bleeding rates or bleedings compromising the patient's life are not high, this disease creates obstacles for minor or major surgical practices, altering the quality of life. To date, multiple therapeutic interventions have been tested, splenectomy is the only one that has presented high rates of sustained response, although there are no absolute contraindications for performing this procedure, there are patients in which due to their comorbidities it is not advisable, others with little response, and others who prefer not to submit to it. During the last years, these patients had been treated with corticoids or immunosuppressants on prolonged basis, generating a high number of adverse reactions.

Innovative therapeutic strategies such as the new thrombopoietic agents approved for use in ITP have demonstrated treatment efficacy and safety, although studies to evaluate their use for a long time are lacking. They are an option for patients who do not meet the criteria for performing splenectomy, who do not respond to second line therapies; even if a face-to-face study has not been carried out to ascertain the effectiveness between eltrombopag and romiplostim, clinical guidelines recommend them equally.

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