

# Long-term management of chronic immune thrombocytopenic purpura in adults

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**Abstract:** Chronic immune thrombocytopenic purpura (ITP) is generally a more benign disease than previously thought. Currently it is recommended that only those patients with severe and/or symptomatic thrombocytopenia definitely require treatment. Additional factors, such as age, lifestyle, and uremia can also influence the hemorrhagic risk and should be carefully assessed before decision-making on the appropriate management of patients with less severe forms of ITP. The recent introduction of new classes of therapeutic agents such as rituximab and the thrombopoietic growth factors has had a major impact on the management of ITP. Updated treatment guidelines have recently been made available but they are based largely on expert opinion rather than on high-quality clinical trial evidence. This structured review is focused on the management of adults with chronic ITP, including the use of new classes of agents.

**Keywords:** corticosteroids, splenectomy, romiplostim, eltrombopag, rituximab

## Introduction

According to the recent international consensus report,<sup>1</sup> primary immune thrombocytopenia (ITP) is an acquired immune-mediated disorder characterized by isolated thrombocytopenia, defined as a platelet count  $<100 \times 10^9/L$ , and the absence of any obvious initiating and/or underlying cause for thrombocytopenia. It can be classified by duration into newly diagnosed, persistent (3–12 month duration), and chronic ( $\geq 1$  year duration).

The pathogenic mechanism of thrombocytopenia in ITP was classically interpreted as increased platelet destruction mediated by autoantibodies. However, today it is well known that more complex mechanisms are involved including both impaired platelet production and T-cell-mediated effects.<sup>2–6</sup>

The natural history of untreated ITP shows differences between adults and children. Typically, ITP in adults exhibits an insidious onset and normally follows a chronic course,<sup>7</sup> whereas in children it is usually preceded by a viral infection and more than 60% of patients spontaneously achieve normal platelet counts within 6 months. A survey by the Intercontinental Childhood ITP Study Group (ICIS-1)<sup>8</sup> involving more than 2,000 children showed a peak age of 1–5 years, platelet counts at presentation  $<20 \times 10^9/L$ , and slightly more in boys (55%) than girls. Initial treatment of children with glucocorticoids, intravenous immune globulin (IVIG) or anti-D immunoglobulin (anti-D) may cause a more rapid increase of the platelet count compared with no therapy.<sup>9</sup> However, it is not well established whether an early therapeutic intervention decreases morbidity from bleeding or increases complete remission rates.<sup>10</sup>

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ITP during pregnancy have particular management needs closer to those of patients who develop acute thrombocytopenia and are outside the scope of the present review.

Spontaneous remissions occur rarely in adults. In general, adults with severe symptomatic thrombocytopenia are given treatment, most often with glucocorticoids. However, most patients do not maintain normal platelet counts after glucocorticoids are stopped.<sup>7–12</sup>

In general, ITP in adults is more prevalent in women (30–60 years).<sup>9,13</sup> Signs and symptoms vary widely. Many patients have either no symptoms or minimal bruising, while others experience serious bleeding episodes that may include gastrointestinal (GI) bleeding, extensive skin and mucosal hemorrhage or intracranial hemorrhage (ICH). The severity of thrombocytopenia correlates to some extent with bleeding risk.<sup>13,14</sup> Additional factors including age, lifestyle, and uremia can also influence the risk and should be carefully assessed before making a decision about the appropriate management. On the other hand, adults presenting with mild and asymptomatic thrombocytopenia, with platelet counts between  $30 \times 10^9/L$  and  $50 \times 10^9/L$ , seem to have a stable and benign course without treatment.<sup>7,13,15,16</sup> Data from case series suggest that fewer than 20% of such patients eventually develop more severe thrombocytopenia and require treatment after 3–7 years of follow-up.<sup>7</sup>

Results from some long-term follow-up series suggest that ITP is a more benign disease than previously thought, and should be treated by a conservative approach, reserving aggressive treatment for patients with severe and symptomatic thrombocytopenia.<sup>7,13,16</sup> The most relevant information from these series is: (i) most patients (42%) have a platelet count  $>50 \times 10^9/L$  and remain untreated; (ii) the spontaneous remission rate is 9%; and (iii) patients with a platelet count  $<50 \times 10^9/L$  had a good outcome, with only 12% presenting with frank bleeding, while 28% were asymptomatic, 19% did not need specific treatment, and 55% needed only first-line treatment.

Mortality attributable to thrombocytopenia is low (1%–4%), usually caused by severe bleeding and, more importantly, infections associated with immunosuppressive therapy. Splenectomy is associated with postoperative complications and may result in significant morbidity and costs derived from prolonged hospitalization or readmission in a sizable proportion of patients that has been reported up to 26%.<sup>16</sup>

In this article we will review the long-term management of chronic ITP in adults, including the role of rituximab and the new thrombopoietic growth factors.

## Treatment strategies

### General therapeutic principles

Because severe bleeding is rare in patients with ITP and normally occurs when platelet counts are  $<10,000/\mu L$ ,<sup>17</sup> the main goal of therapy is to maintain a safe platelet count (not necessarily a normal count) to prevent major bleeding, while withholding drugs, when possible, to avoid adverse effects of therapy that often exceed any problems caused by the ITP.<sup>1</sup> Keeping these criteria in mind, patients with mild, asymptomatic thrombocytopenia should not be treated unless they have a risky lifestyle (sports etc)<sup>18</sup> or they are at risk for bleeding because of associated conditions (hypertension, cerebrovascular disease),<sup>15,19</sup> have disorders requiring treatment with anticoagulant or antiplatelet agents, or a need for surgery or other invasive procedures. If patients have moderate or severe thrombocytopenia and bleeding symptoms, treatment must be started but should be limited in duration unless symptomatic thrombocytopenia persists.

The treatment decision-making in ITP should be shared between the clinician and the patient. As has been repeatedly emphasized, for some patients, the morbidity associated with side effects of therapy may exceed any problem caused by the ITP. Patients with life-threatening bleeding require immediate intervention. This situation is uncommon but more frequent in elderly patients (10%–13%).<sup>7,15,19,20</sup> Platelet transfusion is usually accepted as the initial therapy because it can provide critical temporary support, maintaining platelet counts above  $20 \times 10^9/L$  in a number of cases (42%).<sup>21,22</sup> Transfusions must be combined with IVIG (1 g/kg, repeated the following day if the platelet count remains  $<50 \times 10^9/L$ ) and with intravenous pulse methylprednisolone (1 g, repeated daily for 3 doses). If previous treatments fail, intravenous recombinant human factor VII can be successfully used.<sup>23–25</sup>

### First-line treatment

Accurate initial diagnosis of ITP is necessary because some adults may have a self-limited thrombocytopenia caused by an infection or an adverse drug effect.<sup>13</sup> Thus, treatment of concurrent infections or withdrawal of the implicated drug must be considered in the initial phases of ITP management. Among the acute and chronic bacterial and viral infections that have been associated with thrombocytopenia, the following microorganisms must be considered: hepatitis C virus, human immunodeficiency virus, cytomegalovirus, Epstein–Barr virus, parvovirus, and *Helicobacter pylori*.<sup>26</sup> In these cases, treatment of concomitant infection may improve the thrombocytopenia and steroids or immunosuppressive agents should be avoided because they may worsen the infection.<sup>27,28</sup>

Since spontaneous remissions are uncommon in adults with ITP, the administration of glucocorticoids is the recommended treatment when necessary. Prednisone (1 mg/kg per day orally) or high-dose dexamethasone (HDD), 40 mg/day orally for 4 days, repeated every 14–28 days as needed, are the regimens most commonly used. However, only 20% of patients receiving prednisone as first-line treatment have a sustained complete remission lasting more than six months after maintenance therapy is discontinued.<sup>7</sup> The role of HDD in first-line treatment of ITP in adults is well known.<sup>12,29,30</sup> The best results with HDD are 85% initial response and, among responders, 50% will have a sustained response for up to 2 years. Advantages of this regimen are the short and defined duration of treatment compared with the more prolonged duration of daily oral prednisone treatment.<sup>31</sup>

### Second-line treatment and management of refractory ITP

In case of glucocorticoid treatment failure (refractoriness or early relapse following withdrawal), a second-line treatment can be given when necessary. Treatment choice includes IVIG, anti-D in RhD-positive individuals (both can be used as a first option and classified as first-line treatment), splenectomy, and immunosuppressive drugs, including rituximab. Splenectomy remains the most effective option, with the highest rate of durable complete remissions,<sup>32</sup> and provides long-lasting responses for the majority of cases. However, there are no randomized studies that give guidance on the most convenient order of using these distinct alternatives that will be discussed below.

### Splenectomy

The decision to perform a splenectomy should take into account both the severity of bleeding and thrombocytopenia, as well as the risk of major bleeding. Splenectomy may not be appropriate for patients with mild or moderate thrombocytopenia and minor bleeding, except for patients with a lifestyle estimated to be at high risk for bleeding (police officers, firefighters, sports, high probability of accidents). The indication for splenectomy must be deferred until failure of first-line treatment for ITP is well documented and spontaneous recovery is judged to be unlikely. If necessary, splenectomy can be performed 4–6 weeks after diagnosis of treatment failure.<sup>1</sup> If rituximab is used as a therapeutic alternative before splenectomy, the response should be evaluated after a minimum follow-up because responses can occur up to 6–8 weeks later.<sup>60</sup>

The effectiveness of splenectomy is well known, and the main case series reported (not controlled studies, with heterogeneous patients and different follow-up)<sup>33,34</sup> have comparable results: approximately two-thirds of patients recovered to a normal platelet count that persisted for the duration of observation.<sup>31,32,35</sup> In 14 case series reporting only adults, 456 (64%) of 707 patients had a complete response with a median follow-up of 7.25 years (range, 5–12.75 years).<sup>32</sup> There is a lack of reliable tools to accurately predict the response of ITP to splenectomy. In general, younger patients respond better,<sup>32,33,36,37</sup> but a specific age cutoff for this observation has not been determined. Splenectomy is considered a low-risk surgical procedure, especially in previously healthy patients, but it must be performed by expert surgeons. Patients should be prepared to have a platelet count  $>50 \times 10^9/L$  before surgery, usually by giving a course of glucocorticoids, IVIG, anti-D, and/or platelet transfusions. Today, with the extent of laparoscopic techniques, the expected morbidity (9.6%) and mortality (0.2%) have dramatically decreased.<sup>32,38–41</sup>

Because splenectomy may predispose to fatal infections by encapsulated bacteria (estimated mortality of 0.73 per 1,000 patient years),<sup>42</sup> a consensus has been reached to recommend vaccination against *Streptococcus pneumoniae* (polyvalent vaccine), *Hemophilus influenzae b*, and *Neisseria meningitides* (conjugate vaccine).<sup>1</sup> Vaccination must be done at least 4 weeks prior to splenectomy or alternatively 2 weeks after this surgical procedure.<sup>81</sup> It should be noted that vaccines may not be effective in patients treated with rituximab within the previous 6 months.<sup>81</sup>

Approximately 20% of patients relapse after splenectomy and exhibit severe ITP or have a risk of bleeding that requires additional therapy. In these refractory ITP patients, apart from reconsidering other potential causes of thrombocytopenia, the development of accessory spleens should be ruled out. The management of refractory ITP is a challenge and several therapeutic options can be considered. In addition, some refractory patients not meeting the criteria for severe ITP can face clinical situations with increased risk of bleeding, such as surgery, bucco-dental interventions or trauma in which there is a need for a rapid and temporary response. Corticosteroids, IVIG or thrombopoietic growth factors (see below) can be useful in these situations.

### Corticosteroids

Both low-dose (prednisone 5–10 mg/day) and high-dose corticosteroids in brief courses have been used to maintain a safe platelet count in refractory patients. Experiences have

been disappointing with failure to achieve complete remissions, short response times, and/or increased toxicity.<sup>43-46</sup>

### IVIG and anti-D

Both agents increase the platelet count within several days in most patients with ITP, with an effect that may last for several weeks.<sup>10,36,47</sup> However, neither modality is expected to induce a long-term remission. Nevertheless, these agents may be valuable in patients with life-threatening bleeding or prior to splenectomy or other surgical procedures.

### Immunosuppressive drugs and miscellaneous agents

Several single agents have been used with marginal efficacy. Azathioprine,<sup>48</sup> cyclosporin A,<sup>49,50</sup> and cyclophosphamide<sup>51,52</sup> are immunosuppressive drugs that have been used after treatment failure in both splenectomized and nonsplenectomized patients. Complete response rates vary from 24% to 85%, but their use is limited because of the development of serious adverse effects such as infections, secondary tumors, hypertension or renal insufficiency. The list of drugs used in ITP also includes danazol,<sup>53</sup> dapsone,<sup>54,55</sup> or mycophenolate mofetil<sup>56,57</sup> all with poorly defined efficacy. Interestingly, a recent retrospective, observational study reported encouraging results using a combination of azathioprine, mycophenolate mofetil, and cyclosporine in a relatively small series of patients with particularly severe and refractory ITP.<sup>58</sup>

### Rituximab

This monoclonal antibody is being increasingly used off-label for refractory chronic ITP. Our main knowledge about efficacy and safety of this agent in this setting comes from a systematic review<sup>59</sup> and a prospective multicenter phase II trial involving 60 patients treated with 4 weekly intravenous injections of rituximab (375 mg/m<sup>2</sup> per dose).<sup>60</sup> Three important conclusions can be made: (i) rituximab achieved sustained platelet counts ( $\geq 30 \times 10^9/L$ ) in 40% of patients; (ii) rituximab was discontinued because of side effects in only 1 patient; and (iii) in nonresponders, a good response was obtained in 60% of patients by splenectomy. Although the most used dose of rituximab in ITP patients is 375 mg/m<sup>2</sup>/week for 4 weeks, the standard dose is not yet established. It seems that lower doses (100 mg/m<sup>2</sup>/week for 4 weeks) could be useful to achieve responses and minimize adverse effects. High response rates have been also reported recently with rituximab combined with high dose dexamethasone.<sup>61</sup> Although we must be cautious with these results, it seems that rituximab can be used without compromising the response to splenectomy in case of rituximab

failure.<sup>60</sup> Nevertheless, since some cases of progressive multifocal leukoencephalopathy have been reported after rituximab treatment in patients with lymphoproliferative or autoimmune disorders, additional long-term safety data are required before recommending the widespread use of this monoclonal antibody in refractory chronic ITP.<sup>62</sup>

### Antifibrinolytics

In patients with severe bleeding in spite of other treatments and supportive measures, the use of antifibrinolytic agents such as oral or intravenous tranexamic acid or aminocaproic acid may be an appropriate adjunct measure.<sup>63</sup>

### Chemotherapy

Vinca alkaloids as single agents,<sup>64,65</sup> or several combinations of different doses of cyclophosphamide, prednisone, vincristine, etoposide, and azathioprine have been used in patients with refractory ITP and have achieved complete responses in 42% of patients.<sup>66-67</sup>

### Hematopoietic stem cell transplantation

Although toxicities associated with stem cell transplantation are potentially fatal, both autologous and allogeneic transplantation have been used in refractory ITP patients. Remissions have been reported but very few have been durable.<sup>69-72</sup> Clearly this approach must be reserved for patients with refractory ITP with severe bleeding complications unresponsive to other modalities.

### Other treatments

Some miscellaneous treatments historically used are no longer justified because of their demonstrated lack of efficacy or excessive toxicity, including vitamin C, colchicine, interferon, *ex vivo* perfusion of plasma using protein A immunoabsorption columns or plasmapheresis as an isolated approach.

### New thrombopoietic growth factors

A better understanding of ITP pathogenesis has led to the development of a novel nonimmunologic therapeutic approach by stimulating platelet production. Several types of thrombopoiesis-stimulating agents (eg, thrombopoietin (TPO) receptor agonists), including recombinant TPOs (which are no longer available), peptide TPO mimetics such as romiplostim, and nonpeptide TPO mimetics such as eltrombopag, have been developed in recent years. Both romiplostim and eltrombopag have been recently approved for clinical use in patients with chronic ITP refractory to corticosteroids, immunoglobulins, or splenectomy.

Romiplostim consists of an IgG<sub>1</sub> Fc component linked to a peptide domain with 4 binding sites for Mpl, the TPO receptor.<sup>71,72</sup>

With this structure, the development of antibodies to romiplostim or to endogenous TPO, as it was previously observed with the recombinant TPO polyethylene glycol-conjugated human megakaryocyte growth and development factor (PEG-MGDF), is unlikely. Based on 2 Phase I/II trials,<sup>74,75</sup> a parallel placebo-controlled Phase III trial,<sup>76</sup> and an open-label study,<sup>77</sup> the most important observations regarding the use of romiplostim are the following: (i) romiplostim produces a durable platelet response in both previously splenectomized (38%) and nonsplenectomized patients (56%); (ii) adult patients responding to romiplostim experience an improvement of health-related quality of life;<sup>78</sup> (iii) side effects are very unusual, mild to moderate headache being the most frequent (39%), although transient worsening of thrombocytopenia during the post-treatment period (vaginal hemorrhage) and deep venous thrombosis owing to secondary thrombocytosis have been occasionally reported; (iv) antibodies against endogenous TPO or romiplostim have not been reported.

Similarly, a Phase II dose-ranging trial<sup>79</sup> and a randomized (2:1 drug to placebo), double-blind, placebo-controlled Phase III trial<sup>80</sup> have provided the following information about the use of eltrombopag, which is a TPO nonpeptide mimetic: (i) toxicities and adverse effects of eltrombopag are low and similar to placebo, while patients receiving 50–75 mg/day show a trend toward fewer bleeding events on therapy; (ii) eltrombopag achieves a platelet count  $>50 \times 10^9/L$  at 6 weeks in 59% of splenectomized and nonsplenectomized patients, and platelet counts return to baseline within 2 weeks of the end of treatment; (iii) liver function test abnormalities are present in 13% of patients treated with eltrombopag.

Although most reported adverse effects with both thrombopoietic agents were mild, concerns have been raised over the increased bone marrow reticulin occasionally found in patients treated with romiplostim or eltrombopag. Because the clinical meaning of this observation is not well understood, subsequent long-term clinical trials will address the importance of this finding and whether routine monitoring is required.

Romiplostim is administered subcutaneously once weekly and the dose ranges from 1 to 10  $\mu\text{g}/\text{kg}$ , whereas eltrombopag is orally administered in doses ranging from 25 to 75 mg daily. Doses are chosen in order to achieve platelet counts  $\geq 50 \times 10^9/L$ , considered the optimal threshold to reduce the risk for bleeding. Experience with these drugs is limited but, because of their mechanism of action, both are effective as long as they are

maintained and they might be useful for temporary therapy when remission with other treatments is expected to be delayed or when a splenectomy is postponed.

## Algorithm for the management of ITP

### Conclusions and future research directions

Although it was first described more than two centuries ago, progress in our understanding of the main aspects of ITP has only become significant in the last few years. However, the diagnosis of ITP continues to be one of exclusion, the first-line treatment (glucocorticoids) has been the same for more than 60 years, and the most effective second-line therapy continues to be splenectomy. Moreover, very limited knowledge has been obtained from the few randomized and controlled clinical trials conducted.

Nevertheless, some advances that have been relevant in recent years and that could change the paradigm of ITP management are:

- The introduction of rituximab as second-line treatment (before performing splenectomy), which is an interesting option to avoid or postpone splenectomy in patients with increased surgical risk.
- The new understanding that the pathophysiology of ITP is based not only on the destruction of platelets but on their impaired production in the bone marrow, which gives impetus to the use of the thrombopoiesis-stimulating agents romiplostim or eltrombopag. These agents have demonstrated their efficacy in controlling disease in both splenectomized and nonsplenectomized patients, with few adverse effects.

Finally, as the investigation of ITP has for years been mainly based on noncontrolled studies, recent efforts to achieve an international consensus on terminology, investigation, and management of patients with ITP is to be considered as an attempt to overcome the difficulties of the past and encourage future research focused on randomized trials and large multicenter prospective cohort studies.<sup>79</sup>

## Disclosure

The authors report no conflicts of interest in this work.

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