Review: Clinical Trial Outcomes

CLINICAL INVESTIGATION

# Eltrombopag for the treatment of chronic immune thrombocytopenia

**Clin. Invest.** (2011) 1(2), 295–303

**Stavroula Tsiara[1,2] & Nichola Cooper[†2]**

[1]Department of Internal Medicine, University of Ioannina, School of Medicine, Ioannina, Greece
[2]Department of Haematology, Imperial Health Care Trust, Hammersmith Hospital, Du Cane Road, London, W12 0HS, UK
[†]Author for correspondence:
E-mail: n.cooper@imperial.ac.uk

Immune thrombocytopenic purpura (ITP) is an immune-mediated platelet disorder. Although early studies suggest that the main feature is antiplatelet antibody production and increased platelet clearance, more recent evidence implies that defective platelet production and suppressed maturation and differentiation of megakaryocytes also occurs. In this context, second-generation thrombopoietic agents, romiplostim and eltrombopag, have been developed for patients with chronic resistant/relapsing ITP. Eltrombopag has shown safety and efficacy in three double-blind randomized placebo-controlled multicenter studies. In these studies, a dose-dependent platelet increase to over 50 × $10^9$/l was achieved in 58–60% of the patients. Bleeding episodes were significantly less in patients receiving eltrombopag relative to placebo. Platelet counts returned to baseline within 2 weeks of discontinuation of eltrombopag. Adverse events were mild and similar in eltrombopag- and placebo-treated groups. Transaminases increased, and withdrawal thrombocytopenia and bleeding occurred in a minority of patients. Although not statistically significant, some parameters of quality of life estimation improved following eltrombopag treatment. These findings suggest that eltrombopag may allow patients with chronic resistant ITP to achieve safe platelet count, alleviate bleeding symptoms and improve ability to perform daily activities. Although significant toxicity was not observed in these patients, and lifestyles have been significantly improved, the potential need for long-term treatment and the cost of therapy are the main controversies for the widespread use of this therapeutic option.

**Keywords:** B cell • chronic immune thrombocytopenic purpura • cMPL • cytokine • eltrombopag • megakaryocyte • platelets • T cell • thrombopoietin • thrombopoietin mimetics

Immune thrombocytopenia (ITP) is an acquired autoimmune platelet disorder that is characterized by immune destruction of platelets. Diagnosis is established when thrombocytopenia is isolated, in the absence of other causes that may lead to decreased platelet counts [1–5].

The incidence of ITP in the general population is not well defined. In a recent UK registry derived from the General Practice Research Database, the incidence of ITP has been determined as 3.9 cases/100,000 person-years [6–8]. The incidence is higher among women (4.5 cases/100,000 person-years) than in men (3.2 cases/100,000 person-years). In the same study incidence was found to increase with aging [6–8]. In older individuals, disease typically runs a relapsing–remitting course [9].

The cause of ITP is unknown [10,11]. However, antiplatelet antibody production, phagocytosis of the antibody-coated platelets by the reticuloendothelial system, decreased thrombopoietin (TPO) levels and decreased megakaryocyte maturation have all been proposed as mechanisms of disease pathogenesis [10–16].

FUTURE SCIENCE part of fsg

Although ITP is often asymptomatic, clinical manifestations of the disease range from mild cutaneous bleeding lesions, such as petechiae and ecchymoses, to rare severe complications such as gastrointestinal or intracranial bleeding [9]. The risk of hemorrhage is at least partially related to the platelet count, typically occurring when the platelet count is lower than $30 \times 10^9$/l [9]. In these cases treatment is mandatory [9]. Standard first-line treatment options for ITP are corticosteroids, intravenous IgG immunoglobulins (IVIg) and anti-Rh [1–5,17–19]. Approximately 30% of adults with ITP will go into remission following first-line therapy. In patients with relapsing disease steroid-sparing agents are required. Second-line interventions include immunosuppressive agents, such as azathioprine and mycophenolate mofetil, or potentially curative treatments such as rituximab or splenectomy [1–5,20,21]. In those refractory to second line therapy, treatment remains limited. Typical third-line treatment options such as danazol, dapsone, immunomodulatory drugs (azathioprine, mycophenolate mofetil and cyclosporine A) or cytotoxic agents, as cyclophosphamide or vinca alkaloids can be unsatisfactory [1–5]. Cytotoxic and immunosuppressant agents exert significant toxicity, especially in heavily pretreated patients, response rate ranges between 25 and 60% and it may be apparent for only a few weeks (Table 1) [1–5]. Existing treatment options aim to decrease the antiplatelet antibody production, inhibit T-cell-mediated disease and to inhibit the phagocytosis of platelet-antibody complex [1–5]. In this context, the administration of a new class of drugs, the TPO mimetic agents has been proposed as an alternative therapeutic option targeting defective megakaryocyte and platelet production.

**Table 1. Approximate response rate of immune thrombocytopenic purpura patients on several treatments.**

| Treatment | Approximate response rate (%) |
|---|---|
| Corticosteroids | 70–95 |
| IVIg | 80 |
| Anti-D | 80† |
| Rituximab | 50–60 PR, 30–40 CR |
| Immunosuppressants (azathioprine, cyclosporine, cyclophosphamide and mycophenolate) | 25–60† |
| Splenectomy | 60–70 |
| Eltrombopag | 60–81† |

†Response rate depends on the administered dose.
CR: Complete response; IVIg: Intravenous IgG immunoglobulins; PR: Partial response.

## Definition of the disease & terminology

ITP may be classified on the basis of the disease duration and severity. When disease lasts for more than 3 months from the time of diagnosis is called 'newly diagnosed ITP'. ITP occurring between 3 and 12 months from diagnosis is called 'persistent ITP', while ITP lasting for more than 12 months is called 'chronic ITP'. The term 'severe ITP' is used for patients who develop bleeding symptoms. Patients with severe ITP require urgent treatment or modification of the previously administered therapy [4].

## Pathophysiology

The essential underlying pathophysiologic disorder in ITP remains unknown [1–5,10,11]. Exclusion of pseudothrombocytopenia is essential in avoiding useless investigations [22]. Although bacterial and viral infections have been proposed as predisposing factors for the disease pathogenesis, several studies demonstrate an altered immune response [10,11,23–31]. The production of autoantibodies directed against both the platelet and the megakaryocyte are the major feature of ITP [10–12]. These antibodies target platelet and megakaryocyte membrane glycoproteins (mainly GPIIb/IIa and Ib/IX) [12]. Fcγ receptors of the mononuclear cells in the reticuloendothelial system of the spleen liver or bone marrow clear immune complexes of antibody-coated platelets [14,17,32–34]. Specific genetic polymorphisms of the Fcγ receptors observed in patients with ITP may result in enhanced clearance of the antibody-coated platelets [32]. More recent studies have established a role of T-lymphocytes in ITP pathogenesis [27]. A number of studies have shown that T-helper cells are skewed towards a Th1 immune response with increased production of inflammatory cytokines IL-2, IFN-γ and TNF-α [28]. By contrast, there is a reduction in both Th2 and Tc2 response [29]. Consequently, anti-inflammatory cytokine (IL-4, -5, -6, -9, -10 and -13) production is altered [27–29]. Activated T cells increase the biogenesis of B cells producing antiplatelet antibodies [13,27]. In addition, CD8 cell-mediated direct cytotoxicity against platelets and megakaryocytes results in megakaryocyte and platelet depletion [13,27]. The cause of the Th1 skewing remains unknown, although it may result from altered responses to infection [23–25]. Alternatively, loss of suppression of the immune regulatory cells called T-regs may be responsible for disease [21,30]. These cells, which are $CD4^+$, $CD25^+$ and $FOXP3^+$, have been described by a number of groups to be both decreased in number and to have an impaired suppressive function relatively to healthy individuals [21,30]. Other findings such as elevated CD40 and CD40L (CD154) on the surface of B and T cells indicate an interaction process between B and T cells [31]

and increased expression of CD154 on platelet surface in patients with ITP, suggests that the *in vivo* activation of autoreactive B-lymphocytes is driven by platelets themselves [31].

More recently, earlier studies from the 1980s, which suggest that impaired thrombopoiesis contributes to the thrombocytopenia in ITP, have been verified [10,11,16]. Platelet survival studies have revealed low or inappropriately normal, for the degree of the thrombocytopenia, platelet production in patients with ITP [10,11,16]. Antiplatelet antibodies directed against megakaryocytes also likely contribute to poor differentiation of the megakaryocytes, as indicated by electron microscope images and *in vitro* studies, in which plasma-derived antiplatelet antibodies impair megakaryocyte growth and platelet production [35–39]. Additionally, TPO, the growth factor for platelets and megakaryocytes is inappropriately low relative to the level of the platelet count when compared with the TPO levels in patients with other causes of thrombocytopenia, such as aplastic anemia [15].

Taken together, it appears that ITP is characterized by a pathogenetic diversity [10,11]. This diversity leads to a similar variability in the clinical expression of the disease [10,11]. Better understanding of the pathogenesis of the disease has led to treatment targeted to many of these pathophysiologic alterations and resolution of the hemorrhagic tendency.

## Treatment

In adult patients ITP typically runs a chronic relapsing–remitting course [4]. Prognosis is generally good and mortality is related to the severity of hemorrhagic manifestations of the disease [3]. Moreover, when patients have been heavily pretreated with several therapeutic regimens drug-related complications commonly occur [1–3]. The goals of treatment for patients with ITP are the prevention of bleeding and the achievement of safe platelet counts not necessarily within normal values to prevent serious bleeding. More recently there has also been an emphasis on improving the quality of life of these patients, that is, treating the tiredness that can also occur in this disorder [4].

Agents that have been used for the treatment of chronic relapsing and heavily pretreated ITP often result in significant toxicity and limit their administration [1–4]. Corticosteroids, immunosuppressants and cytotoxic agents exert similar modes of action, whereas anti-D immunoglobulins and IVIg decrease platelet phagocytosis. Side effects to treatment include infusion reactions and, more seriously, infections from immunosuppression and the multiple side effects of steroids. Novel treatments working on a different mechanism are, therefore, very promising.

## Thrombopoietin

Endogenous TPO is a potent cytokine that regulates megakaryocyte proliferation and maturation and subsequent platelet production [37,38]. It is mainly synthesized in the liver and to a lesser extent in the spleen and the kidneys [37,38]. After secretion in the circulation, TPO binds to specific TPO receptors (also called cMPL), on the surface of stem cells, platelets and megakaryocytes [37–39]. Activation of TPO receptors initiates signal transduction events that lead to the JAK2-STAT5 kinases phosphorylation and promotion of cell proliferation [37–39]. Subsequent activation of the MAPK pathway promotes cell differentiation and activation of antiapoptotic mechanisms [37–39]. Therefore, TPO receptor activation promotes growth and viability of stem cells and megakaryocyte progenitors and increases megakaryocyte and platelet production [37–39].

The first-generation recombinant thrombopoietic factors (recombinant human TPO and pegylated recombinant human megakaryocyte growth and development factor) proved effective in some patients with chemotherapy-related thrombocytopenia in patients with solid tumors, leukemia, myelodysplastic syndromes HIV and ITP [40]. However, the use of these factors was abandoned following the development of autoantibodies that had cross reactivity to endogenous TPO [41]. A number of individuals, including both patients and normal individuals treated with these agents became profoundly thrombocytopenic and even aplastic [41].

## Second-generation thrombopoietic factors: TPO mimetic agents

Owing to the beneficial effects of TPO agents and the understanding of the possible utility of a thrombopoietic agent, a number of novel thrombopoietic factors have been developed during the last years. These factors are TPO peptide mimetics, nonpeptide mimetics and TPO agonist antibodies designed specifically to avoid previous complications [42].

Thrombopoietin mimetic agents activate through the TPO receptor, express similar activity to that of endogenous TPO and increase production and release of platelets and megakaryocytes in the circulation. These agents have been developed to provide safe and effective alternatives to recombinant human TPO [42]. They have no sequence homology to the endogenous TPO and do not form cross-reactive TPO antibodies [42]. Two agents are currently available for clinical use, the TPO mimetic peptide, romiplostim and nonpeptide TPO receptor agonist, eltrombopag [42]. These new thrombopoietic factors have been administered in patients with chronic ITP in Phase I, II and III studies [43–49]. Other drugs with a similar mode of action under development are the TPO peptide mimetics, Fab 59, peg-TPO mp and the

non peptide mimetic AKR-501 [50]. Another category of drugs, the TPO agonist antibodies are currently under evaluation in preclinical studies [42].

Eltrombopag is a nonpeptide TPO receptor agonist. It is a small molecule containing a hydrazone ring [51]. Eltrombopag interacts at the transmembrane region of the TPO receptor, activating JAK2-STAT5 signaling pathways, promoting $CD34^+$ cells to become megakaryocytes and produce platelets [42,51]. It is licensed for use as an oral, once-daily regimen in patients with chronic ITP and is also being studied in other thrombocytopenic conditions [51]. The mode of action of eltrombopag compared with previous therapies is shown in Figure 1.

## Efficacy of eltrombopag in treating ITP

The safety and efficacy of eltrombopag has been assessed in three randomized, placebo-controlled studies (Table 2) [47–49].

In the first study, 88 patients with chronic ITP were enrolled from 44 centers between February and November 2005 into a placebo controlled multicenter dose-finding study. Their ages ranged from 18 to 85 years and they were randomized to receive eltrombopag 30–75 mg daily for up to 6 weeks; placebo was administered in 29 patients. Platelet count on enrolment was less than 30 × $10^9$/l with 48% of patients having platelet counts below 15 × $10^9$/l. Nearly half (47%) of the patients who were randomized to receive eltrombopag had undergone splenectomy. The primary end point of the study was a platelet count increase to over 50 × $10^9$/l on day 43. The follow-up period was extended to 6 weeks after discontinuation of treatment. Response rate was higher among patients on higher doses. Patients on treatment with eltrombopag 75 mg once daily achieved 81% response rate. Patients on 50 mg achieved a 70% response rate [47]. Patients who received eltrombopag 30 mg daily achieved 27.5% response rate. Patients on eltrombopag treatment (any dose) achieved an overall response rate of 76%. Patients on placebo treatment had an 11% response rate and this difference was statistically significant ($p < 0.001$) (Table 3) [47].

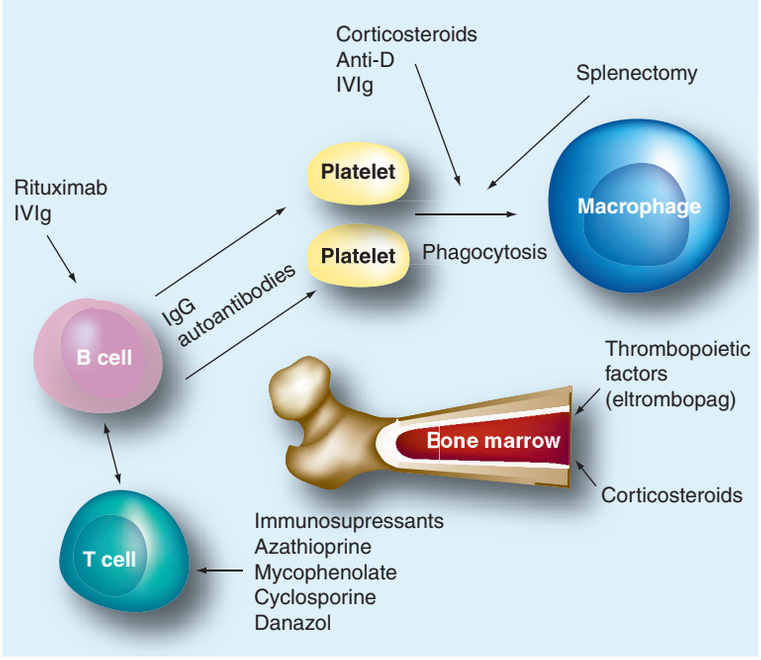


**Figure 1. Mechanisms of action of immune thrombocytopenic purpura therapies.**

The second study was a multicenter, Phase III placebo-controlled randomized study in 63 sites across 23 countries. Eltrombopag 50 mg was administered orally, once daily, for up to 6 weeks, in 76 patients with chronic ITP. The primary end point of the study was a platelet count increase of over 50 × $10^9$/l on day 43 after initiation of treatment. Overall response rate in the eltrombopag-treated patients was 59% ($p < 0.0001$) (Table 3) [48]. Age, splenectomy status, the number and type of previous ITP therapies and platelet count on enrolment did not significantly affect response. Patients who had undergone splenectomy achieved a 62% response rate, whereas in patients without splenectomy the response rate was 57%. This difference was not statistically significant. Platelet count returned to pretreatment levels within 2 weeks of discontinuation of treatment [48]. Health-related quality of life (HRQoL) and the risk of hemorrhage have been also assessed in both studies [47,48,52,53].

The third study describes a Phase III randomized placebo-controlled study eltrombopag or placebo administered in 197 patients in an escalating dose from 50 mg to 75 mg daily, orally for 6 months [49]. Patients had chronic ITP with platelet count lower than 30 × $10^9$/l and had been previously treated with several treatments [49]. The primary end point was a platelet count increase above 50 × $10^9$/l and was achieved by 59% of the patients on eltrombopag treatment compared with 16% of patients on placebo treatment ($p < 0.0001$) (Table 3) [49]. Splenectomy status, platelet count on enrolment and previous or concomitant therapy did not predict response to eltrombopag [49]. Hemorrhagic diathesis was reduced with 65% of the patients on eltrombopag describing a reduction in WHO 2–4 bleeding score. Bleeding episodes were reduced even in patients who did not achieve the primary end point of the study [49]. A significantly greater percentage of patients on eltrombopag reduced concomitant medications relative to placebo (59 vs 32%, $p = 0.016$) and significantly less patients on eltrombopag required rescue treatment (19 vs 40%, $p = 0.001$) [49].

**Table 2. Clinical and laboratory characteristics of patients treated with eltrombopag on enrollment and at the end of the study.**

| Study (year) | Number of patients | Age range (years) | Platelet counts on enrollment† | Eltrombopag dose (mg) | Number of patients with >3 prior therapies | Number patients with prior splenectomy | Patients with platelet counts >50 × $10^9$/l (%) | Ref. |
|---|---|---|---|---|---|---|---|---|
| Bussel *et al.* (2007) | 88 (82)‡ | 18–85 | <30 × $10^9$/l | 30–75 | 46 | 41 | 58.50§ | [47] |
| Bussel *et al.* (2009) | 76 (73)‡ | 19–84 | <30 × $10^9$/l | 50–75 | 42 | 31 | 59§ | [46] |
| Cheng *et al.* (2010) | 135 | 18–85 | <30 × $10^9$/l | 50–75 | | | 59¶ | [49] |

†Half of the enrolled patients had platelet count below 15 × $10^9$/l.
‡Numbers in parentheses denote patients included in the efficacy analysis.
§Platelet count on day 43.
¶Platelet count above 50 × $10^9$/l at least once during the study.

### Treatment-related adverse events

The most common observed adverse events in both studies were headache, nasopharyngitis and diarrhea, which occurred in similar percentage to that in the placebo group [47–49]. Over the two first studies, nine patients had increased transaminases, 15 had minor or moderate in severity infections, mainly upper respiratory tract infections, and eight had withdrawal thrombocytopenia and bleeding (Table 4) [47,48]. One death occurred in a patient with chronic obstructive pulmonary disease, from cardiopulmonary failure with no obvious association to treatment (Table 4) [47]. One thrombotic episode occurred in one patient; a transient ischemic attack 2 weeks after initiation of treatment [47]. Although increased bone marrow reticulin has been reported in patients treated with romiplostim, this finding was not assessed [47,48].

Although a few cases of cataracts (four cases in total, three in the eltrombopag arm and one placebo) have been described following eltrombopag administration, the association with treatment is controversial because nearly all patients on eltrombopag had been treated in the past and during current studies with corticosteroids and the finding was also described in one patient on the placebo arm [47,48].

### Impact of treatment on bleeding

Patients treated with eltrombopag or placebo were assessed for bleeding episodes during the study period at every visit. The incidence and severity of hemorrhagic events were assessed according to the WHO bleeding scale as follows: grade 0: no bleeding, grade 1: petechiae, grade 2: mild blood loss, grade 3: gross blood loss, grade 4: debilitating blood loss [48].

Fewer patients (61%) on eltrombopag had bleeding episodes during all treatment periods compared with placebo (79% hemorrhagic episodes); this difference was statistically significant (p = 0.021). On day 43, fewer of the patients on eltrombopag (39%) had hemorrhagic diathesis relative to patients on placebo (60%; p = 0.029) [48].

### Impact of eltrombopag on quality of life.

Patients with chronic ITP frequently complain of bleeding symptoms, fatigue and treatment-related side effects [9]. Severe hemorrhagic complications and treatment related side effects have a significant impact on HRQoL. These include lifestyle adjustments, frequent physician visits, fear of life-threatening bleeding and of infections related to several treatments, especially splenectomy as well as a negative body image related to multiple bruising episodes.

Although mortality is uncommon in patients with chronic ITP, it occurs in an increasing incidence in patients of older age with severe thrombocytopenia resistant to various treatments. The impact of the disease-related symptoms and treatment-associated adverse effects on daily functioning and psychological status affect quality of life. The fear of bleeding dominates the every day activities of older patients whereas younger patients may be troubled by the restrictions on lifestyle. HRQoL has been assessed with the results of a Short-Form 36 questionnaire from patients with

**Table 3. Percentages of patients with platelet count above 50 × $10^9$/l.**

| Study (year) | Eltrombopag (%) | Placebo (%) | p-value | Ref. |
|---|---|---|---|---|
| Bussel *et al.* (2007)† | 76 | 11 | <0.001 | [47] |
| Bussel *et al.* (2009)† | 59 | 6 | <0.0001 | [46] |
| Cheng *et al.* (2010)‡ | 59 | 28 | <0.0001 | [49] |

†Platelet count above 50 × $10^9$/l on day 43.
‡Platelet count above 50 × $10^9$/l at least once during the study.

**Table 4. Significant side effects related to eltrombopag administration.**

| Side effect | % affected | Ref. |
|---|---|---|
| Nonserious infections | 9.10 | [47,48] |
| Rebound thrombocytopenia or hemorrhage | 4.80 | [47,48] |
| Increased liver function tests | 7.60 | [47-49] |
| Deaths | 0.60 | [47] |
| Thromboembolic events | 1.7 | [47,49] |

chronic ITP and compared with the scores of general population of similar age and gender. Overall, patients with ITP scored lower than the general population. Similarly, physical component scores were worse than that of patients with arterial hypertension ($p < 0.0001$), arthritis ($p = 0.0014$) and several forms of cancer ($p = 0.0003$) [52]. Physical component scores of ITP patients were similar to that of patients with diabetes mellitus ($p = 0.52$) and better than that of patients with congestive heart failure and amputated or paralyzed limb [52]. Therefore, HRQoL should be taken into consideration when a doctor makes a decision and recommendation for treatment.

Health-related quality of life in patients treated with eltrombopag was estimated on the basis of the SF 36v2 survey. Physical health, vitality and mental component scores remained unchanged from baseline up to the end of the study [47,48].

Health-related quality of life questionnaires are not specific for ITP and these assessments, along with the short duration of treatment and the small samples size, may underestimate the treatment impact of thrombopoietic agents on HRQoL.

## Conclusion

Immune thrombocytopenic purpura in adults typically runs a chronic relapsing remitting course and may lead to resistant disease, extremely low platelet counts and various bleeding manifestations, such as petechiae, ecchymoses, epistaxis, hematuria or rarely intracranial hemorrhage, which may occur spontaneously or following injury [9,53]. TPO is the main endogenous factor that stimulates thrombopoiesis. Patients with ITP have inappropriately low endogenous TPO levels, for the degree of thrombocytopenia [10,11,15]. Decisions on whether to administer treatment or not depends not only on the occurrence of bleeding episodes and extremely low platelet counts but also on a patient's lifestyle and activities [3,4, 9]. Many patients with ITP remain only on careful monitoring of platelet counts and bleeding status [3,4, 9]. Treatment should be administered in cases with bleeding manifestation and in an attempt to avoid serious bleeding, when risk factors, may include extremely low platelet counts, older age and predisposing factors such as requirement for antiplatelet agents [1–4,53]. Corticosteroids are the cornerstone of treatment in acute disease and relapses [1–3]. They have been proven effective in 50–80% of patients. However, the majority of them relapse on tapering and remission is limited to a small percentage, not exceeding 30% [1–3]. Furthermore, patients treated with corticosteroids usually develop unacceptable short and long-term side effects, especially in older age [1–3]. Intravenous IgG and anti-D immunoglobulins are effective alternatives for first-line treatment of ITP [17,18]. Both have increased early onset but acceptable and easily managed infusion-related reactions [1–3]. Patients who do not achieve response are candidates for splenectomy. Beyond the immediate intraoperative and postoperative complications, splenectomy is related to increased risk of bacterial infections, sometimes life-threatening [1–3]. When splenectomy is contraindicated or not desired, or in patients who relapse after the operation, alternative treatment options, as rituximab, should be considered and in fact may enable patients to avoid splenectomy [1–3]. Response rates to rituximab are satisfactory, usually extended up to 50% [20,21]. Limitations in the use of it are cost, immediate infusion-related adverse reactions and the unknown effect of long-term B-cell depletion [20,21].

Recently a new category of drugs has emerged that stimulate increased production of platelets through activation of the TPO or cMPL receptor [42]. Eltrombopag is a small molecule that acts through the transmembrane region of this receptor, inducing platelet production [42]. Unlike the first studies of TPO, it does not induce the production of neutralizing antibodies to endogenous TPO [42]. It is licensed for use in patients with chronic ITP, in whom previous treatments have failed [47,48]. Response rate exceeds 50–60% [47,48]. Of special interest is the finding that in a significant percentage of treated patients cessation or improvement in hemorrhagic tendency occurs and increased HRQoL [47–49]. Adverse events related to the administration and infections are mild and similar to that in the placebo group [47–49]. A finding that warrants further investigation is the increase in transaminases, observed in treated patients, especially in the context that eltrombopag is metabolized in the liver [47,48].

## Future perspective

It is now well established that lower than expected TPO levels are observed in patients with ITP. This parameter has a central role in the pathophysiology of ITP. Until recently, the main aim of the clinician has been to inhibit antiplatelet antibody production and decrease clearance of antibody-coated platelets

from reticuloendothelial systems. Corticosteroids, immunosupressants, immunomodulating and cytotoxic drugs have been used alone or in combinations. However, many of these may predispose treated patients to infections and other long-term untoward effects. Eltrombopag, together with other TPO agents, is a promising and effective agent for the treatment of chronic refractory patients with ITP. It is administered orally and has a favorable low toxicity profile. It remains to be determined which patients will benefit from TPO mimetics and when the appropriate time to administer them will be, this is likely to depend on the long-term safety of these agents. It is of special interest that treated patients had a decreased bleeding tendency. It remains to be answered if these agents are eligible for prolonged use in chronic ITP cases and how they may influence survival and quality of life of chronic adult patients.

A number of trials are ongoing in these areas of controversy: The EXTEND trial is aimed at determining the safety and ongoing efficacy of eltrombopag in more than 200 chronic ITP patients for at least 2 years [101]; PETIT is a safety and efficacy study of eltrombopag in children (aged 1–17 years) with chronic ITP [102]; there is a study assessing the effect of eltrombopag on bone marrow fibrosis in a longitudinal 2-year study estimating bone marrow findings in previously treated chronic ITP patients with eltrombopag [103] and response rate to eltrombopag administration is being assessed when the drug is administered in a repeat cyclic dosing schedule [104].

Although there is concern over the cost of this treatment, which may be required for long-term administration, there are early suggestions that some patients may go into a remission and be able to stop therapy [54]. In addition, in those in whom a normal platelet count has been achieved, the decreased requirements for rescue therapy, clinical appointments and hospital admissions, together with a possibility for restoration of a normal working life, may counterbalance this cost.


## Financial & competing interests disclosure

*Nichola Cooper has received honoraria from GSK, Amgen and Eisai pharmaceuticals for talks at educational meetings and for consultation on clinical trials. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.*

*No writing assistance was utilized in the production of this manuscript.*


## Executive summary

- Eltrombopag is a novel agent in the treatment of immune thrombocytopenia (ITP).
- Eltrombopag is a nonpeptide mimetic molecule designed specifically to stimulate the thrombopoietin (TPO) receptor.
- TPO is the main hormone involved in platelet production. Stimulation of the TPO receptor results in increased platelet production.
- ITP is an autoimmune condition in which platelets are prematurely destroyed and patients become sometimes profoundly thrombocytopenic, with bleeding problems.
- In patients with ITP, treatment can become limited, with side effects including immune suppression and long-term steroid toxicity. Novel treatments are required.
- In three randomized placebo controlled studies, eltrombopag has been shown to produce a platelet increment in 58-79% of patients with chronic ITP in a dose dependent manner. This is higher than previous agents.
- In addition to changes in platelet count, treatment with eltrombopag decreases the incidence of bleeding and increases health-related quality of life in patients with ITP.
- Side effects remain minimal and are no different from patients receiving placebo.
- The main considerations of eltrombopag are: interactions with foods and other medications, which can make taking other tablets difficult and increased liver function tests, which appear to resolve, even if treatment is maintained.
- Compared to previous therapies, this agent is very promising.

## Bibliography


1 The American Society of Hematology ITP Practice Guideline Panel. Diagnosis and treatment of idiopathic thrombocytopenic purpura: recommendations of the American Society of Hematology. *Ann. Intern. Med.* 126, 319–326 (1997).

2 British Committee for Standards in Haematology General Haematology Task Force. Guidelines for the investigation and management of idiopathic thrombocytopenic purpura in adults, children and in pregnancy. *Br. J. Haematol.* 120, 574–596 (2003).

3 Provan D, Stasi R, Newland AC *et al.* International consensus report on the investigation and management of primary thrombocytopenia. *Blood* 115, 168–186 (2010).

4 Rodeghiero F, Stasi R, Gernsheimer T *et al.* Standardization of terminology, definitions and outcome criteria in immune thrombocytopenic purpura of adults and children: report from an international working group. *Blood* 113, 2386–2393 (2009).

5 George JN, Woolf SH, Raskob GE *et al.* Idiopathic thrombocytopenic purpura: a practice guideline developed by methods for the American Society of Hematology. *Blood* 88, 3–40 (1996).

6 Abrahamson PE, Hall SA, Feudjo-Tepie M, Mitrani-Gold FS, Logie J. The incidence of idiopathic thrombocytopenic purpura (ITP)

among adults: a population based study and literature review. *Eur. J. Haematol.* 83(2), 83–89 (2009).

7 Schoonen WM, Kucera G, Coalson J, Li L, Rutstein M, Mowat F. Epidemiology of immune thrombocytopenic purpura in the General Practice research database. *Br. J. Haematol.* 145, 235–244 (2009).

8 Frederiksen H, Schmidt K. The incidence of idiopathic thrombocytopenic purpura increases with age. *Blood* 94(3), 909–913 (1999).

9 Stasi R, Amadori S, Osborn J, Newland AC, Provan D. Long-term outcome of otherwise healthy individuals with incidentally discovered thrombocytopenia. *PLoS Med.* 3(3), e24 (2006).

10 Cines DB, McMillan R. Pathogenesis of chronic immune thrombocytopenic purpura. *Curr. Opin. Hematol.* 14(5), 511–514 (2007).

11 Cooper N, Bussel JB. The pathogenesis of immune thrombocytopaenic purpura. *Br. J. Haematol.* 133, 364–374 (2006).

12 McMillan R, Tani R, Millard F. Plasma-associated and plasma antiglycoprotein antibodies in adults with chronic ITP. *Blood* 70, 1040–1045 (1987).

13 Chow L, Aslam R, Speck E *et al.* A murine model of severe immune thrombocytopenia is induced by antibody and $CD8^+$ T cell mediated responses that are differentially sensitive to therapy. *Blood* 115(6), 1247–1253 (2010).

14 Crow AR, Lazarus AH. Role of Fcγ receptors in the pathogenesis and treatment of ITP. *J. Pediatr. Hematol. Oncol.* 25(Suppl. 1), S14–S18 (2003).

15 Kosugi S, Kurata Y, Tomiyama Y. Circulating thrombopoietin levels in chronic idiopathic thrombocytopenic purpura. *Br. J. Haematol.* 93, 704–706 (1996).

16 Mc Millan R, Wang L, Tomer A, Nichola J, Pistillo J. Suppression of *in vitro* megakaryocyte production by antiplatelet antibodies from adult patients with chronic ITP. *Blood* 103, 1364–1369 (2004).

17 Cooper N, Heddle NM, Haas M *et al.* Intravenous immunoglobulin and intravenous anti RhD achieve acute platelet increases by different mechanisms: modulation of cytokine and platelet responses to IV anti-D by FcγRIIa and FcγRIIa polymorphisms. *Br. J. Haematol.* 124, 511–518 (2004).

18 Cooper N. Intravenous immunoglobulin and intravenous anti RhD therapy in the management of idiopathic thrombocytopenic purpura. *Hematol. Oncol. Clin. North Am.* 23, 1317–1327 (2009).

19 Song S, Crow AR, Siragam V, Freedman J, Lazarus AH. Monoclonal antibodies that mimic the action of anti-D in the amelioration of murine ITP act by a mechanism distinct from that of IVIG. *Blood* 105, 1546–1548 (2005).

20 Stasi R, Poeta G, Stipa E *et al.* Response to B-cell depleting therapy with rituximab reverts the abnormalities of T-cell subsets in patients with idiopathic thrombocytopenic purpura. *Blood* 110, 2924–2930 (2007).

21 Stasi R, Cooper N, Poeta G *et al.* Analysis of regulatory T-cell changes in patients with idiopathic thrombocytopenic purpura receiving B-cell depleting therapy with rituximab. *Blood* 112, 1147–1150 (2008).

22 Zandecki M, Genevieve F, Gerard J, Gordon A. Spurious counts and spurious results on haematology analysers: a review. Part I: platelets. *Int. J. Lab. Hematol.* 29(1), 4–20 (2007).

23 Takahashi T, Yujiri T, Shinohara K, Inoue Y, Sato Y. Molecular mimicry by *Helicobacter pylori* CagA protein may involved in pathogenesis of *Helicobacter pylori* associated chronic idiopathic thrombocytopenic purpura. *Br. J. Haematol.* 14(1), 91–96 (2004).

24 Wright JF, Blanchette VS, Wang H *et al.* Characterization of platelet reactive antibodies in children with varicella associated acute immune thrombocytopenic purpura. *Br. J. Haematol.* 95(1), 145–152 (1996).

25 Stasi R, Sarpatwari A, Segal JB *et al.* Effects of eradication of *Helicobacter pylori* infection in patients with immune thrombocytopenic purpura: a systematic review. *Blood* 113, 1231–1240 (2009).

26 Brighton TA, Evans PA, Castaldi CN, Chesterman CN, Chong BH. Prospective evaluation of the clinical usefulness of an antigen-specific assay (MAIPA) in idiopathic thrombocytopenic purpura and other immune cytopenias. *Blood* 88, 194–201 (1996).

27 Olson B, Anderson PO, Jernas M, Jacobson S, Carlson B, Carlson LMS, Wadenvik H. T-cell-mediated cytotoxicity toward platelets in chronic idiopathic thrombocytopenic purpura. *Nat. Med.* 9, 1123–1124 (2003).

28 Semple JW, Freedman J. Increased antiplatelet T helper lymphocyte reactivity in patients with immune thrombocytopenia. *Blood* 78, 2619–2625 (1991).

29 Semple JW, Milev Y, Cosgrave D *et al.* Differences in serum cytokine levels in acute and chronic ITP: relationship to platelet phenotype and antiplatelet T-cell reactivity. *Blood* 87, 4245–4254 (1996).

30 Yu J, Heck S, Patel V *et al.* Defective circulating CD25 regulatory T cells in patients with chronic ITP. *Blood* 112, 1325–1328 (2008).

31 Solanila A, Pasquet JM, Viallard JF, Contin C, Grosset C, Dechanet-Merville J. Platelet associated CD 154 in idiopathic thrombocytopenic purpura. *Blood* 105, 215–218 (2005).

32 Breunis WB, van Mirre E, Bruin M *et al.* Copy number variation of the activating FcGR2C gene predisposes to idiopathic thrombocytopenic purpura. *Blood* 111, 1029–1038 (2008).

33 Psaila B, Bussel JB. Fc receptors in immune thrombocytopenias: a target for immunomodulation? *J. Clin. Invest.* 118, 2677–2681 (2008).

34 Siragam V, Crow AR, Brinc D, Song S, Freedman J, Lazarus AH. Intravenous immunoglobulin ameliorates ITP activating Fcγ receptors on dendritic cells. *Nat. Med.* 12, 688–692 (2006).

35 Houwerzijl EJ, Blom NR, Want JJL *et al.* Ultra-structural study shows morphologic features of apoptosis and para-apoptosis in megakaryocytes from patients with idiopathic thrombocytopenic purpura. *Blood* 103, 500–506 (2004).

36 Houwerzijl EJ, Bloom NR, Want JJL *et al.* Increased peripheral platelet destruction and caspase-3 independent programmed cell death of bone marrow megakaryocytes in myelodysplastic patients *Blood* 105, 3472–3479 (2005).

37 Geddis AE, Kaushansky K. Immunology. The root of platelet production. *Science* 317, 1689–1691 (2007).

38 Bartley TD Bogenberger J, Hunt P *et al.* Identification and cloning of a megakaryocyte growth and development factor that is a ligand for the cytokine receptor CMPL. Cell 77, 1117–1124 (1994).

39 Kaushansky K. The molecular mechanisms that control thrombopoiesis. *J. Clin. Invest.* 115, 3339–3347 (2005).

40 Nomura S, Dan K, Hotta T, Fujimura K, Ikeda Y. Effects of pegylated recombinant human megakaryocyte growth factor in patients with idiopathic thrombocytopenic purpura. *Blood* 100, 728–730 (2002).

41 Li J, Yang C, Xia Y. Thrombocytopenia caused by the development of antibodies to thrombopoietin. *Blood* 98, 3241–3248 (2001).

42 Kuter DJ. New thrombopoietic growth factors. *Blood* 109, 4607–4616 (2007).

43 Newland A, Caulier MT, Kappers-Klunne M *et al.* An open label unit dose finding study of AMG 531 a novel thrombopoiesis stimulating peptibody in patients with immune thrombocytopenic purpura. *Br. J. Haematol.* 135, 547–553 (2006).

44 Bussel JB, Kuter DJ, George JN *et al.* AMG 531, a thrombopoiesis-stimulating protein for chronic ITP. *N. Engl. J. Med.* 355(16), 1672–1681 (2006).

45 Kuter DJ, Bussel JB, Lyons RM *et al.* Efficacy of romiplostim in patients with chronic immune thrombocytopenic purpura: a double blind randomised controlled trial. *Lancet* 371, 395–403 (2008).

46 Bussel JB, Kuter DJ Pullarkat V, Lyons RM, Guo M, Nichol JL. Safety and efficacy of long term treatment with romiplostim in thrombocytopenic patients with ITP. *Blood* 113, 2161–2171 (2009).

47 Bussel JB, Cheng, G, Saleh M *et al.* Eltrombopag for the treatment of chronic ITP. *N. Engl. J. Med.* 357(22), 2237–2247 (2007).

48 Bussel JB, Provan D, Shamsi T *et al.* Effect of eltrombopag on platelet counts and bleeding during treatment of chronic idiopathic thrombocytopenic purpura: a randomised, double-blind, placebo controlled trial. *Lancet* 373, 641–648 (2009).

49 Cheng G, Saleh MN, Marcher C *et al.* Eltrombopag for management of chronic immune thrombocytopenia (RAISE): a 6-month, randomised, Phase 3 study. *Lancet* (2010) (Epub ahead of print).

50 Fukushima-Shinani M, Suzuki K, Iwatsuki Y *et al.* AKR-501 a novel orally active thrombopoietin receptor agonist. *Eur. J. Haematol.* 82, 247–254 (2009).

51 Erikson-Miller CL, De-Lorme E, Tian SS. Discovery and characterization of a selective non-peptidyl thrombopoietin receptor agonist. *Exp. Hematol.* 33, 85–93 (2005).

52 McMillan R, Bussel JB, George JN, Lalla D, Nichol J. Self-reported health related quality of life in adults with chronic immune thrombocytopenic purpura. *Am. J. Hematol.* 83, 150–154 (2008).

53 Psaila B, Petrovic A, Page LK, Menell J, Schonholz M, Bussel JB. Intracranial hemorrhage (ICH) in children with immune thrombocytopenia (ITP): study of 40 cases. *Blood* 114, 4777–4783 (2009).

54 Cook L, Cooper N. Eltrombopag – a novel approach for the treatment of chronic immune thrombocytopenic purpura: review and safety considerations. *Drug Des. Devel. Ther.* 4, 139–145 (2010).


## Websites


101 ClinicalTrials.gov identifier: NCT00351468 http://clinicaltrials.gov/ct2/show/NCT00351468

102 ClinicalTrials.gov identifier: NCT00908037 http://clinicaltrials.gov/ct2/show/NCT00908037

103 ClinicalTrials.gov identifier: NCT01098487 http://clinicaltrials.gov/ct2/show/NCT01098487

104 ClinicalTrials.gov identifier: NCT00424177 http://clinicaltrials.gov/ct2/show/NCT00424177