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Toxicities of the thrombopoietic growth factors

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Abstract

The thrombopoietic growth factors (TGFs) are a novel class of compounds for the treatment of chronic immune thrombocytopenia (ITP). The first of these agents to receive regulatory approval, romiplostim and eltrombopag, have demonstrated impressive efficacy and tolerability in randomized controlled trials and open-label extension studies of several years duration and stand poised to revolutionize the management of ITP. Nonetheless, critical questions regarding the safety of these agents, particularly after long-term administration, remain partially unanswered. The objective of this review is to describe the reported and potential toxicities of the TGFs including bone marrow fibrosis, thrombosis, rebound thrombocytopenia, hematologic malignancy, neutralizing antibody formation, hepatotoxicity, cataract formation, and common adverse events. The incidence and clinical implications of these toxicities as well as strategies for patient safety monitoring are examined.

INTRODUCTION

Immune thrombocytopenia (ITP) is an autoimmune disorder characterized by antiplatelet antibody-mediated platelet destruction and anti-megakaryocyte antibody-mediated impairment of platelet production. The thrombopoietic growth factors (TGFs) are a novel class of compounds that enhance platelet production by binding to and activating c-Mpl, the thrombopoietin (TPO) receptor, on megakaryocytes and their progenitors. The first of these agents to receive regulatory approval, romiplostim (Nplate®; Amgen; Thousand Oaks, CA) and eltrombopag (Promacta®, Revolade®; GlaxoSmithKline; London, UK), are indicated for the treatment of adults with chronic primary ITP.

Eltrombopag is an orally bioavailable small molecule that is formulated for once daily oral administration. Because its absorption is affected by foodstuffs and metals, it is recommended that eltrombopag be taken on an empty stomach and at least 4 hours removed from other medications, foods, and supplements containing iron, calcium, or other polyvalent cations. Romiplostim, in contrast, is formulated for weekly subcutaneous injection. Its absorption and mechanism of action are not known to be influenced by dietary factors or other drugs.

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CONFLICTS OF INTEREST

The author declares that he has no conflicts to disclose.

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In randomized controlled trials of up to 12 months duration (Table 1), romiplostim and eltrombopag were well-tolerated and effective in raising the platelet count in a majority of adult subjects, many of whom had been refractory to multiple previous ITP therapies.¹⁻⁷ Ongoing open-label extension studies of romiplostim and eltrombopag have enrolled approximately 300 patients each for a median duration of therapy of 48 and 29 weeks, respectively. Subjects approaching as many as 5 years of treatment on romiplostim and 2.5 years of treatment on eltrombopag have demonstrated sustained platelet responses without evidence of cumulative toxicity.^{8,9} Indeed, in the short time since their entry into the marketplace, romiplostim and eltrombopag have changed the treatment paradigm in ITP. However, important questions regarding their safety, particularly with long-term administration, remain partially unanswered.

The primary objective of this article is to review the incidence and clinical implications of reported and theoretical toxicities of TGF therapy including bone marrow fibrosis, thrombosis, rebound thrombocytopenia, hematologic malignancy, neutralizing antibody formation, hepatotoxicity, cataract formation, and common adverse events in adults with ITP (Table 2). Although several additional TGFs are currently in clinical development, significant safety data have been reported only for romiplostim and eltrombopag and will therefore serve as the focus of this review.

TOXICITIES

Bone marrow fibrosis

The bone marrow stroma is comprised, in part, of a structural framework of connective tissue fibers on which hematopoiesis occurs.¹⁰ Among these fibers are reticulin and collagen. Reticulin is a normal component of the bone marrow and is detectable by silver staining methods in 73% to 81% of healthy subjects.^{11,12} Increased reticulin deposition in the bone marrow (reticulin fibrosis) is associated with a number of benign and malignant conditions and is frequently reversible. In contrast to reticulin, any amount of collagen deposition in the bone marrow (collagen fibrosis), detected by trichrome staining, is pathologic. Collagen fibrosis is most often associated with myeloproliferative disease or solid tumors metastatic to the bone marrow and is characteristically irreversible.¹⁰

Several different grading systems have been devised to quantify reticulin and collagen deposition in the bone marrow. In an analysis of bone marrow specimens from healthy individuals using the modified Bauermeister scoring system, 19% were found to have no reticulin (grade 0), 76% had occasional fine reticulin fibers (grade 1), and 5% had fine fibers throughout (grade 2). No subjects had grade 3 (diffuse fiber network with scattered coarse fibers) or grade 4 (collagen deposition) fibrosis.¹¹ A retrospective analysis of bone marrow specimens from 40 patients with ITP, none of whom had received TGF therapy, showed a similar distribution of reticulin grades.¹³

Although the pathophysiology of bone marrow fibrosis remains incompletely understood, a growing body of evidence supports the central role of megakaryocytes. When megakaryocyte growth is stimulated, the cells elaborate transforming growth factor- β (TGF- β) and other cytokines, which promote synthesis of collagen by bone marrow fibroblasts.^{14,15} In rodent models, megakaryocyte stimulation by TGF administration¹⁶⁻¹⁸ or by over-expression of TPO in the bone marrow¹⁹ induces dose-dependent marrow fibrosis.

TGF therapy also has the capacity to induce reticulin fibrosis in humans. In a study of 15 subjects with acute myeloid leukemia (AML), 9 patients were given recombinant human thrombopoietin (rhTPO), a first generation TGF, in combination with granulocyte-macrophage colony-stimulating factor (GM-CSF) following induction chemotherapy and underwent serial bone marrow examination to monitor the leukemia. Six control subjects undergoing the same

induction regimen with GM-CSF support but without rhTPO were also studied. Increased reticulin fibrosis was noted in 8 of the 9 subjects that received rhTPO and in 2 of 6 subjects in the GM-CSF alone group. All 8 rhTPO-treated subjects showed resolution of reticulin fibrosis within 42 days of their last dose.²⁰

Reticulin fibrosis has also been observed in trials of romiplostim and eltrombopag. In a prospective subgroup analysis of patients in the romiplostim extension study, 10 subjects underwent prespecified bone marrow biopsies before beginning treatment and after 3 to 9 months of therapy. Of the 6 patients with evaluable baseline and follow up biopsies, one demonstrated a mild increase in reticulin after 3 months of treatment.¹⁸

Among all clinical trials of romiplostim, an additional 11 subjects underwent bone marrow examinations while receiving romiplostim. These biopsies were performed at the discretion of the clinical investigators, some owing to the appearance of new abnormalities on the peripheral blood film. Nine of these biopsies were centrally reviewed using the modified Bauermeister scale: one showed no reticulin, one showed a peak reticulin grade of 1, 2 exhibited a peak grade of 2, 4 demonstrated a peak grade of 3, and one showed grade 4 fibrosis. Of the 5 subjects with an available pre-treatment biopsy for comparison, 4 exhibited an increase in reticulin deposition on treatment. Four patients underwent repeat bone marrow examination after discontinuation of romiplostim. In 3 of these patients, follow up biopsy was performed 8 to 12 weeks after discontinuation of romiplostim and showed reduced reticulin. In one subject with grade 2 reticulin deposition on treatment, a biopsy performed 68 weeks after stopping romiplostim was unchanged. None of the biopsy specimens in the prospective or retrospective analyses demonstrated evidence of a clonal disorder.¹⁸

The eltrombopag extension study protocol has been amended to include a bone marrow biopsy after 12 and 24 months of treatment. Specimens are scored using the European consensus guidelines for grading bone marrow fibrosis.²¹ In a recent interim analysis of the extension study, 83 patients had evaluable biopsies. Thirty (36%) showed loose networks of reticulin (grade 1), 5 (6%) showed diffuse and dense increases in reticulin (grade 2), and 3 (4%) exhibited collagen fibrosis (grade 3). New cytopenias or abnormalities on the peripheral blood smear were not reported in any of the subjects.²²

Taken together, the data from the romiplostim and eltrombopag studies suggest that a minority of patients may develop bone marrow fibrosis within a year of initiating TGF therapy and that this fibrosis may be reversible after short-term administration. However, important questions regarding the risk of bone marrow fibrosis remain unanswered. Most fundamentally, little is known about the baseline incidence and severity of bone marrow fibrosis in patients with ITP, how these parameters are affected by various ITP therapies, and how they change over the course of the disease. This information is necessary for defining a baseline level of fibrosis in ITP against which the impact of TGF therapy on bone marrow histology may be judged.²³

Our understanding of the incidence and clinical implications of TGF-induced bone marrow fibrosis is similarly limited. Because pre- and on-treatment bone marrow biopsies have not been performed routinely in TGF studies to date, the incidence of increased reticulin and collagen deposition with these therapies is unknown. Moreover, owing to limited follow up time and a dearth of post-treatment biopsy specimens, the natural history of TGF-induced marrow fibrosis is uncertain.

The appropriate screening for and management of increased marrow reticulin is not known. At present, the US Food and Drug Administration requires at least monthly monitoring of cell counts and the peripheral blood smear in all patients on TGF therapy. If new morphologic abnormalities or cytopenias are noted or if there is a loss of response to treatment, a bone marrow biopsy with staining for reticulin and collagen is recommended. How best to apply

this recommendation to the management of asplenic patients, in whom abnormal blood cell morphology is commonplace, is unclear. Furthermore, it is not known whether the finding of increased reticulin deposition in the marrow mandates discontinuation of treatment or whether close monitoring of blood counts and the peripheral blood film and serial bone marrow examinations will suffice.

To better understand the clinical impact of TGF-induced bone marrow fibrosis, larger studies with long-term follow up, serial bone marrow examinations at prespecified intervals, central review of specimens, and utilization of a validated grading system for bone marrow fibrosis are needed. Assiduous post-marketing surveillance and an ongoing prospective 3-year study of the effects of romiplostim on the bone marrow of subjects with ITP will begin to provide much needed answers to these questions.

Thrombosis

Epidemiologic evidence suggests that ITP patients may be at increased risk for venous and arterial thromboembolism (TE), even in the setting of concomitant thrombocytopenia.^{24,25} Several conventional therapies for ITP including intravenous immune globulin²⁶ and splenectomy²⁷ have also been associated with a small increase in thrombotic risk. In theory, ITP patients with pre-existing atherosclerosis or prothrombotic risk factors may enjoy a measure of protection from thrombosis that is lost during a response to any effective platelet-raising therapy.²³

TGF administration has likewise been theorized to increase the thrombotic risk in ITP patients. There is evidence in primates that the platelet count achieved on TGF therapy may be an independent predictor of thrombosis. In TGF-treated baboons with extravascular shunts, increasing platelet counts were associated with a proportional rise in platelet deposition in the shunt.^{28,29} In addition to their effect on platelet number, TGFs may also affect platelet function. At concentrations substantially higher than those achieved with clinical use, the first generation TGFs, rTPO and pegylated human megakaryocyte growth and development factor (PEG-rHuMGDF), as well as romiplostim have been shown to reduce the threshold for activation by specific platelet activators.^{29,30} Interestingly, eltrombopag seems to lack this effect on the platelet activation threshold.³¹ The relevance of these findings *in vivo* is unknown.

Notwithstanding the theoretical concerns regarding the thrombotic risk of TGF therapy, clinical studies have been largely reassuring. Studies of the first generation agents suggested that thrombocytosis did not increase the rate of thrombosis, even in patients with cancer.³²⁻³⁴ In the romiplostim extension study, 25 TEs occurred in 17 (5.8%) patients. Eight events were venous, 15 were arterial, and 2 were of unreported location. The majority of the 17 patients had pre-existing thrombotic risk factors. Nineteen of the 25 events occurred at a platelet count $<400 \times 10^9/L$.⁸ In a pooled analysis of all romiplostim studies in ITP, the incidence of thrombosis did not differ among patients receiving romiplostim and those treated with placebo (8 events per 100 patient-years vs. 10 events per 100 patient-years, respectively).³⁵

In the controlled trials of eltrombopag, 1 TE was reported among eltrombopag-treated subjects and none were observed in patients who received placebo.⁴⁻⁷ TEs have been observed in 13 subjects in the eltrombopag extension study. Platelet counts at the time of the events ranged between $14 \times 10^9/L$ and $407 \times 10^9/L$.⁹ In a pooled analysis of all prior studies of eltrombopag in ITP, 17 out of 446 eltrombopag-treated patients experienced 22 TEs over a total of 377 patient-years of exposure. None of the 129 patients treated with placebo suffered a TE, though the exposure of this cohort was limited to only 26 patient-years. All subjects experiencing a TE had at least one pre-existing thrombotic risk factor and most had multiple risk factors. The most common TEs were deep vein thrombosis (8), pulmonary embolism (6), cerebrovascular

accident (3), and myocardial infarction (3). Only 2 patients had platelet counts $>400 \times 10^9/L$ proximal to their event, and half had platelet counts $<150 \times 10^9/L$.³⁶

Based on these data, it is not apparent whether TGF use confers a significant increase in the thrombotic risk in patients with ITP, even in the setting of transient thrombocytosis. Nonetheless, the platelet count should be monitored regularly during therapy and the minimum TGF dose necessary to maintain a platelet count $\geq 50 \times 10^9/L$ should be employed. Given that almost all TEs in the aforementioned studies occurred in patients with pre-existing thrombotic risk factors, TGFs should be used cautiously in such patients with dose titration to achieve the minimal platelet count necessary to maintain hemostasis. An antithrombotic agent such as aspirin should be considered if the platelet count exceeds the desired range. It should also be noted that patients with the greatest thrombotic risk, for example those with known atherosclerotic disease or a history of venous thromboembolism, have been excluded from many of the TGF trials. Therefore, an increase in thrombotic risk with TGF therapy in this population cannot be excluded on the basis of available data.

Rebound thrombocytopenia

In clinical trials of both romiplostim and eltrombopag, rebound thrombocytopenia, a transient worsening of thrombocytopenia below baseline following discontinuation of study drug, has been observed. For the purpose of these studies, rebound thrombocytopenia was defined as a platelet count obtained within 4 weeks of study drug cessation that was both $<10 \times 10^9/L$ and at least $10 \times 10^9/L$ below the baseline platelet count. A proposed mechanism for this phenomenon is the increased clearance of endogenous TPO by the expanded megakaryocyte and platelet mass induced by TGF therapy.¹ In addition, some patients in whom rebound thrombocytopenia was observed may have discontinued or had a dose reduction of concurrent ITP treatment, though the relative contribution of these changes in therapy has not been determined.

In the phase I/II trials of romiplostim, 4 of 41 romiplostim-treated patients developed rebound thrombocytopenia. Two patients required rescue therapy. Platelet counts returned to baseline within 3 to 17 days.¹

In a pooled analysis of 3 placebo-controlled studies of eltrombopag, 8% (10/128) of placebo-treated subjects and 8% (20/241) of eltrombopag-treated subjects had rebound thrombocytopenia in the 4 weeks following discontinuation or interruption of treatment. None of the 10 patients in the placebo group and 3 of the patients in the eltrombopag group had bleeding events.³⁷ In an interim analysis of the eltrombopag extension study, 168 patients had a dose interruption or discontinuation of study drug. Rebound thrombocytopenia occurred in 14 (8%) of these subjects, two of whom experienced worsening bleeding symptoms.⁹

In summary, rebound thrombocytopenia occurs in approximately 8–10% of patients who discontinue romiplostim or eltrombopag and appears to be associated with an increased risk of bleeding. Because this rate is similar to that observed in placebo-treated patients, it is not clear whether rebound thrombocytopenia is a true epiphenomenon of withdrawal of TGF therapy or whether it merely reflects random variation in the platelet counts of patients with ITP. Nonetheless, it is recommended that platelet counts be monitored on a weekly basis for at least 4 weeks after TGF cessation. In patients with severe thrombocytopenia and bleeding, it may be prudent to reintroduce or increase the doses of concomitant ITP medications prior to discontinuing TGFs.²³ In theory, tapering the dose of TGF prior to discontinuation may prevent or ameliorate rebound thrombocytopenia, but such an approach has not been systematically investigated.

Hematologic malignancy

Epidemiologic studies suggest a possible association between ITP and hematologic malignancy.^{38–40} Given that some hematopoietic cancers express c-Mpl, it is theorized that TGF administration may further potentiate the risk of hematologic neoplasm in ITP patients. This concern is supported in part by a laboratory investigation of the *in vitro* effects of eltrombopag on leukemia and lymphoma cell lines. At low concentrations, eltrombopag modestly increased proliferation of the HEL92.1.7 and N2C-Tpo cell lines, both of which express c-Mpl and other megakaryocytic markers. Eltrombopag did not enhance proliferation of non-megakaryocytic leukemia and lymphoma cells.⁴¹ In a study of bone marrow mononuclear cells from patients with myelodysplastic syndrome (MDS) and AML, eltrombopag did not increase proliferation, clonogenic capacity, or self-renewal across a wide range of concentrations.⁴²

TGFs have been investigated in patients with thrombocytopenia due to chemotherapy and MDS. In placebo-controlled studies of PEG-rHuMGDF as an adjunct to chemotherapy in patients with AML, there was no evidence that the drug increased the blast count or undermined treatment response.⁴³ In patients with low or intermediate risk MDS, trials of romiplostim lasting 3 to 16 weeks in combination with supportive care, lenalidomide, azacytidine, and decitabine have been conducted.^{44–47} Overall, 113 patients in these trials received romiplostim and 5 (4%) progressed to AML. Several additional subjects experienced a transient increase in the blast count during treatment that returned to pre-treatment levels after discontinuation of romiplostim. One of 39 (3%) placebo-treated patients underwent leukemic transformation while on study. Additional placebo-controlled studies as well as an ongoing extension study of romiplostim in MDS patients will provide further information on whether TGFs increase the risk of leukemic transformation in this population.

Clinical trials in ITP to date are reassuring. In the controlled trials of eltrombopag and romiplostim, the incidence of hematologic malignancy was low and similar in the treatment and placebo groups. In the romiplostim extension study, a 57-year old man was diagnosed with monoclonal gammopathy of undetermined significance.⁸ In the eltrombopag extension study, a 77-year old woman developed NHL.⁹ Longer-term follow up is required to determine if TGF therapy is associated with a distant risk of hematologic malignancy.

Neutralizing antibody formation

The first generation TGFs, rhTPO and PEG-rHuMGDF, raised the platelet count in patients with ITP, chemotherapy-induced thrombocytopenia, and in healthy platelet apheresis donors.^{34,48–49} However, their development was abruptly halted in 1998 when several subjects paradoxically developed thrombocytopenia while receiving PEG-rHuMGDF. The thrombocytopenia was subsequently shown to be due to the development of antibodies against the drug that cross-reacted with and neutralized endogenous TPO.⁵⁰ In most cases, the thrombocytopenia was severe and persisted for many months after the drug was discontinued.

Unlike rhTPO and PEG-rHuMGDF, romiplostim shares no sequence homology with TPO and therefore would not be expected to induce a direct anti-TPO immune response. Indeed, anti-TPO antibody formation has not been observed in any of the trials of romiplostim to date. In the extension study, anti-romiplostim antibodies were detected in two patients. These antibodies showed no cross-reactivity with endogenous TPO and were undetectable several months after drug discontinuation.⁸ Testing for anti-romiplostim and anti-TPO antibodies is available through Amgen and should be considered in patients who have loss of or diminished response to romiplostim during the course of their therapy. Eltrombopag, a small organic non-peptide, is non-immunogenic and would therefore not be expected to induce formation of neutralizing antibodies.

Hepatotoxicity

The risk of hepatotoxicity is cited as a boxed warning in the packaging insert for eltrombopag due to the development of hepatobiliary laboratory abnormalities (HBLAs) in a small proportion of eltrombopag-treated patients in clinical trials. In a pooled analysis of the placebo-controlled trials of eltrombopag, 7% (9/128) of patients in the placebo group and 11% (33/299) of patients in the eltrombopag group met at least 1 of the drug-induced liver injury (DILI) screening criteria (ALT ≥ 3 times ULN, AST ≥ 3 times ULN, alkaline phosphatase >1.5 times ULN, total bilirubin >1.5 times ULN).⁵¹ In the extension study, 24 (8%) patients met at least one of the DILI criteria, 7 of whom had experienced an HBLA in a previous eltrombopag study. HBLAs did not necessarily arise at the outset of therapy. In the extension study, the median onset of HBLAs was 105 days (range 1–482).⁹ Of the 62 eltrombopag-treated patients who suffered HBLAs across the clinical ITP program, 25 had resolution despite continued eltrombopag therapy. None of the 62 patients had clinical symptoms referable to liver impairment.⁵¹

Eltrombopag is being studied in patients with thrombocytopenia secondary to hepatitis C-related liver disease, a population particularly vulnerable to hepatotoxicity. Reassuringly, the drug was well-tolerated in a phase II study of this population with a low incidence of adverse hepatobiliary events.⁵² Nonetheless, eltrombopag should be used with caution in patients with pre-existing liver disease and a reduced starting dose is recommended for those with moderate to severe hepatic impairment. In accordance with the boxed warning, liver function tests should be monitored in all patients prior to initiation of eltrombopag, every 2 weeks during dose titration, and monthly following achievement of a stable dose. The drug should be discontinued if the ALT increases to ≥ 3 times the ULN or clinical symptoms of liver injury develop. Although hepatotoxicity has not been recognized as an adverse event in clinical trials of romiplostim, the drug has not been tested extensively in patients with hepatic impairment and should therefore be used with caution in this population.

Cataracts

In preclinical toxicology studies of eltrombopag, cataracts developed in juvenile rodents in a dose-dependent and time-dependent fashion at doses 5 to 7 times the human clinical exposure. Cataracts were not detected in dogs after 52 weeks of treatment at 3 times the human clinical exposure. In the controlled trials of eltrombopag, ophthalmic examinations were performed on all subjects at baseline, at the end of treatment, and 6 months after the last dose of study drug. Over this interval, cataracts developed or worsened in 5% of eltrombopag-treated patients and in 3% of patients treated with placebo.^{4–6} Although eye examinations are not mandated in the eltrombopag extension study, 4% of subjects participating in the study who underwent ocular examination prior to initiation of therapy developed new or worsened cataracts.⁹

Many patients with chronic ITP have other risk factors for cataracts, particularly long-term corticosteroid use. Whether eltrombopag contributes to this risk at clinically approved doses is not known. This question will be addressed, in part, by LENS (Long-term Eltrombopag Observational Study), an ongoing assessment of ocular safety and lens changes over a follow up period of 2.5 years in patients who participated in a previous trial of eltrombopag. In addition, eye examinations are mandated in the ongoing PETIT study, a phase II clinical trial of eltrombopag in children with chronic ITP. Until more is known about the risk of cataract formation, it is recommended that patients undergo ophthalmic examinations prior to initiating eltrombopag and at least annually during therapy.

Common adverse events

Both romiplostim and eltrombopag were well-tolerated in clinical trials of ITP. Table 3 shows the most common non-bleeding adverse events and their incidences in clinical trials of

romiplostim^{1–3,8} and eltrombopag.^{4–7,9} In general, reactions occurred at a similar frequency in the treatment and placebo groups, were mild, and did not require discontinuation of therapy.

CONCLUSION

The TGFs are a powerful new option for the treatment of chronic ITP. To date, clinical experience with these agents has demonstrated impressive efficacy and tolerability. However, this experience is limited to a relatively small number of patients and fairly short-term follow up. It is conceivable that rare adverse reactions and cumulative toxicities associated with long-term TGF use have yet to be identified. Moreover, the incidence and clinical implications of recognized toxicities such as bone marrow fibrosis remain poorly understood. For these reasons, meticulous safety surveillance is of paramount priority as clinical experience with these compounds accumulates. This purpose will be served, in part, by the ongoing extension studies of romiplostim and eltrombopag and by mandatory risk evaluation and mitigation strategy (REMS) programs, which are linked to the restricted distribution programs for both drugs.

Most conventional therapies for ITP have a low benefit to risk ratio in the chronic setting owing to limited efficacy, immunosuppressive effects, and a host of agent-specific toxicities. Indeed, the treatment-related morbidity associated with these agents may be comparable to or greater than the morbidity associated with the disease itself.⁵³ From this observation has emerged an axiom of ITP management – that therapy be administered only when the bleeding risk outweighs the risk of treatment-related toxicity. Far more information on the safety of TGFs will hopefully be gleaned in the coming years through scrupulous safety monitoring and pharmacovigilance in order to properly uphold this maxim.

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Table 1
Randomized controlled trials of romiplostim and eltrombopag in adults with ITP.

Drug	Study Design [Reference]	Number of Subjects	Percentage of Subjects with Splenectomy (n)	Treatment Arms (n)	Duration of Study	Primary Endpoint
Romiplostim	Phase II [1]	21	67 (14)	Placebo (4) Romiplostim 1 µg/kg (8) Romiplostim 3 µg/kg (8) Romiplostim 6 µg/kg (1)	6 weeks	Safety and tolerability
	Phase III [2]	62	0	Placebo (21) Romiplostim 1 µg/kg (41) ^a	24 weeks	Platelet count $\geq 50 \times 10^9/L$ during 6 of the last 8 weeks of treatment
	Phase III [2]	63	100 (63)	Placebo (21) Romiplostim 1 µg/kg (42) ^a		
	Phase IIIb [3]	234	0	Standard of care (77) Romiplostim 3 µg/kg (157) ^b	1 year	Incidence of splenectomy and of treatment failure ^c
Eltrombopag	Phase II [4]	23	70 (16)	Placebo (8) Eltrombopag 12.5 mg (15) ^d	6 weeks	Platelet count between $50 \times 10^9/L$ and $400 \times 10^9/L$ at week 7
	Phase II [5]	117	47 (55)	Placebo (29) Eltrombopag 30 mg (30) Eltrombopag 50 mg (30) Eltrombopag 75 mg (28)	6 weeks	Platelet count $\geq 50 \times 10^9/L$ at week 6
	Phase III [6]	114	39 (45)	Placebo (38) Eltrombopag 50 mg (76) ^e		
	Phase III [7]	197	35 (69)	Placebo (62) Eltrombopag 50 mg (135) ^e	6 months	Platelet count between $50 \times 10^9/L$ and $400 \times 10^9/L$ at any point during treatment

^aRomiplostim could be increased to a maximum of 15 µg/kg based on platelet count.

^bRomiplostim could be adjusted to a maximum of 10 µg/kg based on platelet count.

^cTreatment failure defined as platelet count $\leq 20 \times 10^9/L$ for 4 consecutive weeks at the highest allowable dose or major bleeding event or change in therapy due to intolerable side effects or bleeding symptoms.

^dEltrombopag could be increased to a maximum of 25 mg based on platelet count.

^eEltrombopag could be adjusted to a maximum of 75 mg based on platelet count.

Table 2

Serious non-bleeding toxicities in trials of romiplostim and eltrombopag.

Toxicity	Romiplostim			Eltrombopag		
	Placebo-controlled trials ^a		Extension study (n = 291) n (%)	Placebo-controlled trials ^b		Extension study (n = 299) n (%)
	Romiplostim (n = 100) n (%)	Placebo (n = 46) n (%)		Eltrombopag (n = 314) n (%)	Placebo (n = 137) n (%)	
<i>TGF class-specific toxicities</i>						
Bone marrow fibrosis	1 (1) ^c	0 ^c	9 (3) ^c	0 ^c	0 ^c	8 (3) ^d
Thrombosis	2 (2)	2 (4)	17 (6)	1 (0.3)	0	13 (4)
Rebound thrombocytopenia	13 (13)	NR	NR	20 (6)	10 (7)	14 (5) ^e
Hematologic malignancy	0	0	1 (0.3)	0	0	1 (0.3)
<i>Romiplostim-specific toxicities</i>						
Neutralizing antibody formation	0	0	2 ^f	NA	NA	NA
<i>Eltrombopag-specific toxicities</i>						
Hepatotoxicity ^g	0	0	NR	33 (11)	9 (7)	24 (8)
Cataract formation/progression	NA	NA	NA	5 (2)	2 (1)	NR

^aIncludes a pooled analysis of the 6-week phase II trial and the 24-week phase III trials of romiplostim.

^bIncludes a pooled analysis of the 6-week phase II trials and the 6-week and 6-month phase III trials of eltrombopag.

^cRoutine bone marrow biopsies were not performed. Therefore, the number of identified cases may underestimate the true incidence of bone marrow fibrosis.

^dBone marrow biopsy, mandated after 12 months of therapy, has been performed in 86 patients.

^e168 patients had a dose interruption or drug discontinuation.

^fTwo patients developed neutralizing anti-romiplostim antibodies. These antibodies did not cross-react with endogenous thrombopoietin.

^gDefined as ALT ≥3x ULN, AST ≥3x ULN, alkaline phosphatase >1.5x ULN, total bilirubin >1.5x ULN.

Table 3

Common non-bleeding adverse events in trials of romiplostim and eltrombopag.

Adverse event	Romiplostim trials ^a		Eltrombopag trials ^b	
	Drug (16,062 patient-weeks)	Placebo (1,032 patient-weeks)	Drug (9,788 patient-weeks)	Placebo (450 patient-weeks)
Nasopharyngitis/URI	1.1 (173)	1.2 (12)	1.1 (112)	0.7 (3)
Headache	0.8 (126)	1.3 (13)	0.8 (78)	2.4 (11)
Fatigue	0.7 (102)	1.2 (12)	0.5 (45)	1.1 (5)
Arthralgia	0.5 (88)	0.9 (9)	0.4 (38)	0.9 (4)
Diarrhea	0.5 (83)	0.7 (7)	0.4 (38)	0.7 (3)

Events per 100-patient weeks are shown with number of events in parentheses. URI, upper respiratory infection.

^aIncludes a pooled analysis of the 6-week phase II and 24-week phase III trials and the extension study of romiplostim.

^bIncludes a pooled analysis of the 6-week phase II trials, the 6-week phase III trial, and the extension study of eltrombopag.