Chapter 17
Eltrombopag

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Abstract The current concepts and the management of ITP have significantly changed in the past decade. Decreased use of cytotoxic therapy and the introduction of new selective modalities of drug such as TPO-r mimetics are the landmarks of this change. Discovered in the middle of last decade, followed by experiments in mice and then approved in humans, Eltrombopag is the first TPO-r mimetic available. It has been used and validated in several clinical studies in different etiologies of thrombocytopenia, including primary ITP (chronic Immune ThrombocytoPenia) and secondary ITP, due to hepatitis C and more recently in bone marrow failure as myelodysplastic syndromes. Good tolerability and low side effects are the strengths of this drug, contrasted with issues regarding administration (it must be taken every day apart from specific meals containing high levels of calcium, which leads to problems with compliance). We review the first clinical studies with this agent, emphasizing the significant findings.

Introduction

Human use of eltrombopag (SB-497115-GR, Promacta®) was first reported in 2007 in normal volunteers. Subsequently a number of studies have pursued its use in patients with ITP and in those with thrombocytopenia associated with liver disease caused by hepatitis C. Thus far three large, randomized controlled trials have been reported and an additional such trial in ITP has been presented in abstract form only. Of note, published animal data are limited since eltrombopag is only known to be active in humans and chimpanzees and, therefore, safety data are only available for a small number of chimps in whom the platelet count increased (J. Jenkins, personal communication).

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Biochemistry

Eltrombopag ($C_{25}H_{22}N_4O_4$) (Fig. 17.1) is a small molecule (molecular weight 442 Da), member of the biarylhydrazone class of compounds, which are non-peptide agonists of the thrombopoietin receptor (TpoR). The activation of TpoR occurs as eltrombopag associates with metal ions (Zn^{2+}) and specific amino acid domains in the juxtamembrane and transmembrane portions of the receptor. When bound to TpoR, eltrombopag initiates a sequence of events through phosphorylation and activation of the receptor. Once the TpoR is phosphorylated, it triggers activation of the cytoplasmatic tyrosine kinases as Janus Kinases (JAK)2 and tyrosine kinase 2, which in turn activate signal transducers and activators of transcription (STAT)5, phosphoinositide-3 kinase, and Ras-mitogen-activated protein kinase (MAPK) thereby promoting megakaryocyte duplication and differentiation into platelets.

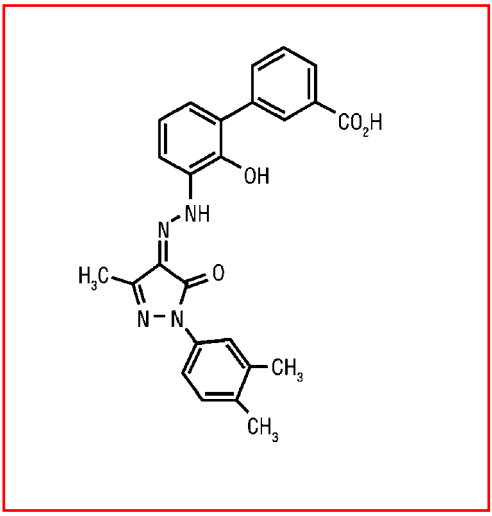

Fig. 17.1 Structure of eltrombopag

Preclinical Activity of Eltrombopag

Previous in vitro studies have demonstrated that the activity of eltrombopag is dependent on expression of TpoR and that a selective interaction with TpoR is responsible for the thrombopoietic activity of the drug. Erickson-Miller et al. [1] analyzed the molecular structure of the drug and the specificity of binding and activation of the TpoR, including second messenger signaling pathways (Fig. 17.2). They also investigated possible anti-apoptotic activity through lowering caspase-3 and caspase-7 cleavage activity. Effects such as induction of stimulation, proliferation, and differentiation in mammalian cells were compared with those seen with rhTpo.

Eltrombopag is known to have specificity for the TpoR and it is unable to activate JAK/STAT signaling pathways on cells expressing other hematopoietic growth

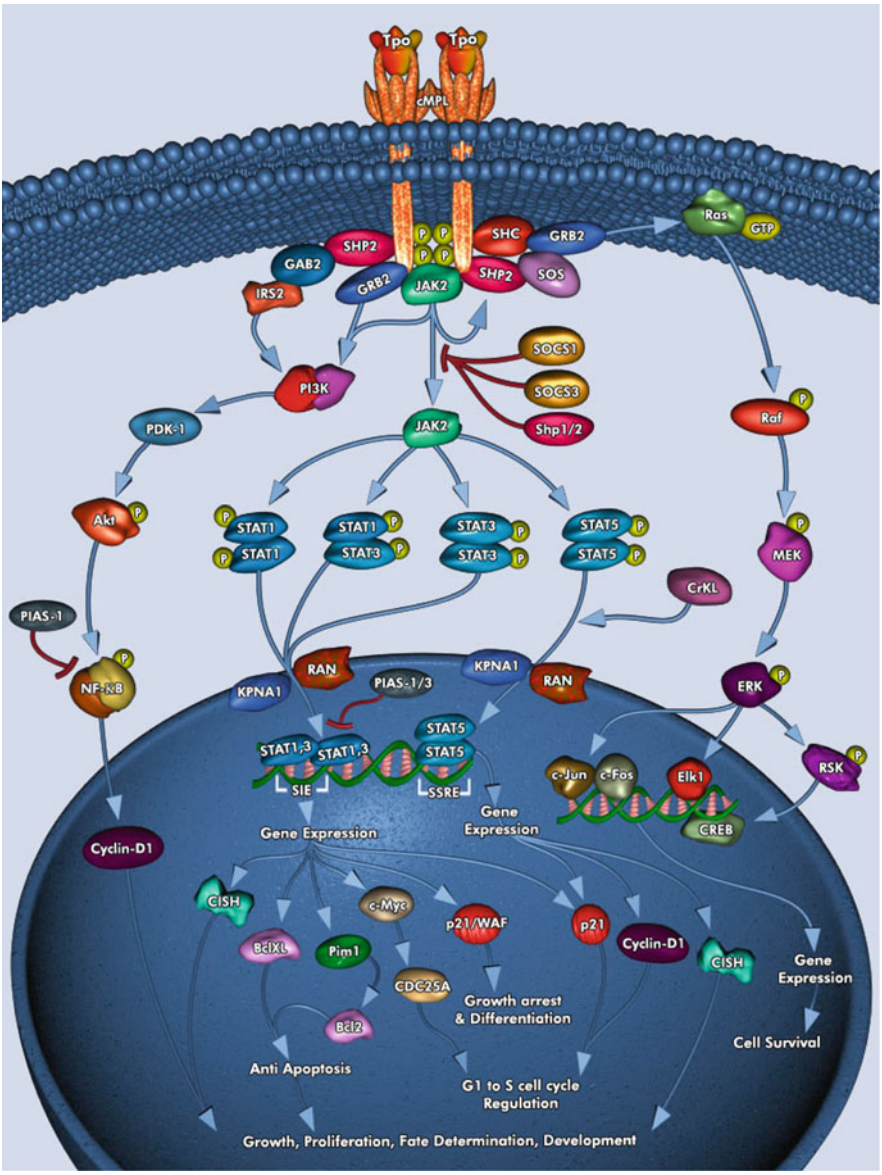

Fig. 17.2 Thrombopoietin signaling pathway

factor receptors (such as receptors for cytokines as EPO, G-CSF, INF-α, INF-γ, and IL-3). Similarly, studies with Tpo-dependent human cell lines (N2C-Tpo cells that endogenously express the TpoR) incubated with eltrombopag demonstrated that the proliferative effect was dependent on the expression of the TpoR.

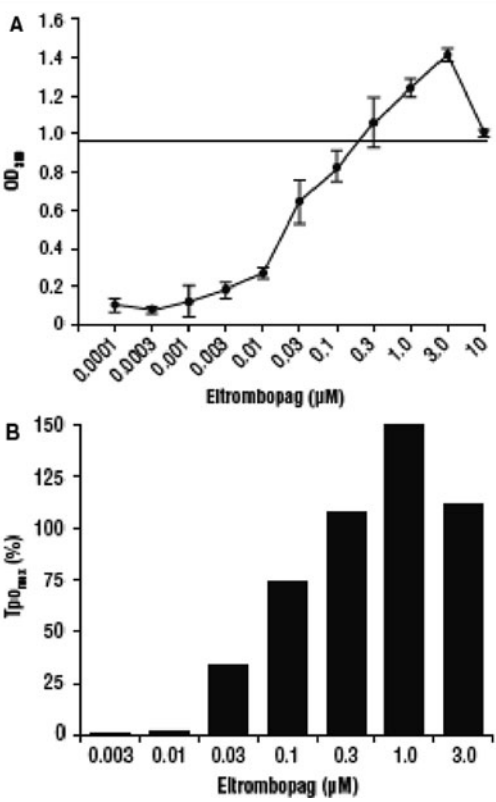

Fig. 17.3 Proliferation and differentiation induced by eltrombopag. **a** Proliferation of BAF3/hTpoR cells induced by eltrombopag after 48 h of treatment; the *dotted line* represents the activity of cells treated with 100 ng/mL of recombinant human thrombopoietin. OD, optical density. **b** Representative example of megakaryocyte differentiation of $CD34^+$ cells after 10 days of eltrombopag treatment; similar results were obtained with six independent marrow samples. **Panel b** was printed from Duffy and Erickson-Miller [2]

Eltrombopag was able to promote the proliferation and differentiation of CD34-selected bone marrow stem cells into committed megakaryocyte lineage $CD41^+$ cells in a dose-dependent manner (Fig. 17.3).

Eltrombopag lowered caspase cleavage to a similar degree as rhTpo illustrating an anti-apoptotic mechanism. The same study demonstrated that eltrombopag is able to activate Tpo signaling pathways (STAT5 and p42/44 MAPK) with kinetics similar to rhTpo, although to a lesser degree. When combined with rhTpo, eltrombopag displayed an additive rather than antagonistic effect (Fig. 17.4).

This additive effect was observed when eltrombopag was added to either suboptimal amount of rhTpo or in the presence of rhTpo at a concentration that causes a plateau in cell proliferation rates. These data suggest that Tpo and eltrombopag have different binding sites on the TpoR and may have an additive effect on cell signaling.

Their conclusions were that eltrombopag has a Tpo mimetic activity that is dose-dependent, has an agonistic effect additive to that of rhTpo, and, similarly to thrombopoietin, interacts specifically with the Tpo receptor triggering initially the JAK/STAT and subsequently, activating the MAPK signaling pathways.

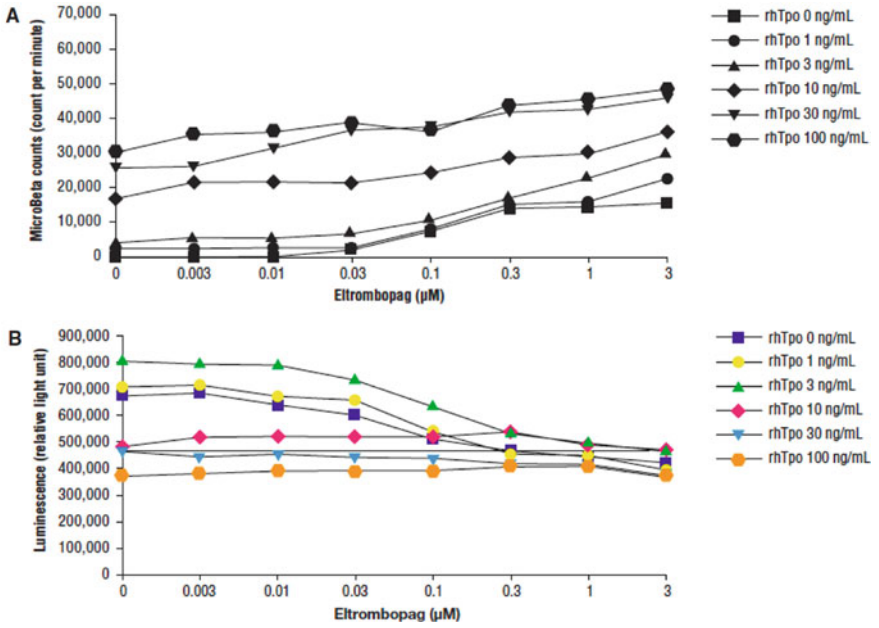

Fig. 17.4 Additive effects of eltrombopag and rhTpo. **a** Proliferation, as measured by thymidine incorporation, of N2C-Tpo cells by eltrombopag (0.003–3 μM) in combination with recombinant human thrombopoietin (rhTpo 1–100 ng/mL). **b** Activation of caspase-3 and caspase-7 by eltrombopag (0–3 μM) in combination with rhTpo (0–100 ng/mL) in N2C-Tpo cells

First Phase 1 Clinical Study of Eltrombopag

Eltrombopag was first analyzed in terms of safety, tolerability, pharmacokinetics, and pharmacodynamics in a phase 1 placebo-controlled clinical trial performed in healthy human volunteers by Jenkins et al. [3] (published in *Blood*, February, 2007). The results of this phase 1 trial set the stage for the subsequent randomized controlled trials described below.

In this study eltrombopag was administered as an oral capsule once-daily for 10 days at escalating doses of 5, 10, 25, 30, 50, and 75 mg in 73 healthy male volunteers who were blinded to medication. The investigator and sponsor were not blinded. The mean baseline platelet count was 239,000/mm^3 (range 134,000–347,000/mm^3). Safety, tolerability, pharmacokinetic, and pharmacodynamic assessments were made at several time points during and after the 10-day dosing phase.

The preclinical data were confirmed as eltrombopag was shown to have oral bioavailability with a serum concentration displaying a dose-dependent and linear pattern. Despite limited clinical activity, increase in platelet counts were seen at 30 mg daily and a platelet count 20% above the baseline was achieved in all patients who took 50 mg and 75 mg daily. The mean platelet count increase was 42.9% and 50.4%, respectively.

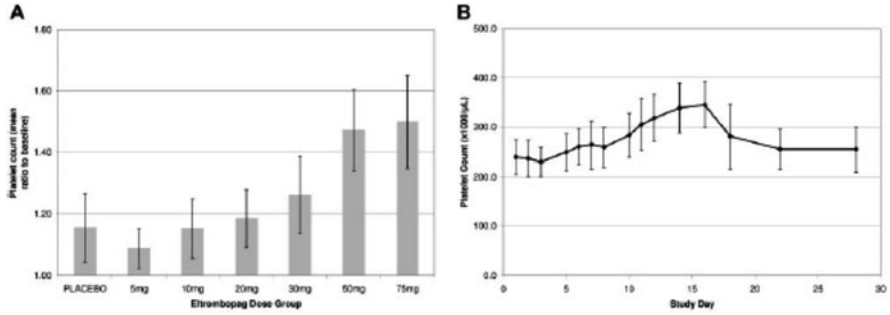

Fig. 17.5 Eltrombopag pharmacodynamics in normal volunteers. Pharmacodynamic data. **a** Platelet response in healthy male subjects following oral dosing with eltrombopag (once per day) for 10 days. Increases are apparent at 30, 50, and 75 mg. Values in graph indicate mean and 1 SD. **b** Kinetics of platelet response in healthy male subjects following 10 days oral dosing of 75 mg eltrombopag. The platelet number began rising at 5 days and peaked at day 15. Values in graph indicate mean and 1 SD

A consistent increase in platelet count started after 8 days of repeated doses of 75 mg of eltrombopag, with a peak on the 16th day returning to baseline values 12 days after the last dose (Fig. 17.5). Following discontinuation of treatment, there was no evidence of rebound thrombocytopenia, as platelet counts remained above baseline levels. Neither abnormal platelet function nor side effects of the administration of drug were reported in the normal controls.

Eltrombopag Use for the Treatment of Chronic Idiopathic Thrombocytopenic Purpura

The first multicenter, randomized, placebo-controlled trial in ITP [4] assessed whether and at what dose eltrombopag could increase platelet counts in patients with chronic disease. In this trial eltrombopag was administered to 117 subjects with at least a 6-month history of ITP, a platelet count of less than 30,000/mm^3 at enrollment and at least one prior treatment for ITP. The patients were at least 19 years old, with a median age of 50 years old. 38% were men and 79% were white. The four groups of patients received either placebo or eltrombopag at doses of 30, 50, or 75 mg/day for up to 6 weeks.

All patients were assessed weekly for safety, tolerability, and efficacy of the treatment during the 6-week treatment period and at 2-week intervals for 6 weeks after the study medication had been discontinued. Patients receiving stable maintenance immunosuppressive regimens, primarily glucocorticoids, were eligible but the dose had to remain unchanged throughout the study. Any other treatment for ITP must

have been completed at least 2 weeks before the enrollment. Values within the normal range were required for neutrophils, reticulocyte count, creatinine, and liver enzymes. Exclusion criteria included secondary causes of immune thrombocytopenia such as HIV, Hep C virus, or SLE; comorbidities such as hemoglobin levels less than 10 g/dL, congestive heart failure, arrhythmia, thrombosis within 1 year before enrollment, or myocardial infarction within 3 months before enrollment. Pregnant or nursing women were also excluded and contraception was required during the study if patients were of childbearing age. Treatment was discontinued when platelet counts exceeded 200,000/mm^3.

Forty-eight percent of patients had a platelet count of 15,000/mm^3 or less and 47% had undergone splenectomy. Seventy-four percent of patients had at least 2 previous treatments for ITP (e.g., glucocorticoids, intravenous immunoglobulins, or danazol); and 32% were taking concomitant medication for ITP.

The primary endpoint, a platelet count of 50,000/mm^3 on day 43, was achieved in 81% of patients given 75 mg, 70% given 50 mg, and 28% given 30 mg compared to 11% on placebo group. The median platelet count approached the normal range and remained relatively stable in the group who continued the drug (median between 100,000 and 200,000/mm^3). These counts returned to levels near baseline within 2 weeks after discontinuation of therapy. The increase in platelet counts happened in a time and dose-dependent manner because both the increase of platelet counts and the velocity at which the platelets increased were greater with 75 mg than with 50 mg. A small effect was seen in the 30-mg group and even less in placebo (Fig. 17.6).

Multiple variables such as race, age, presence of concomitant ITP medication, previous splenectomy, and baseline platelet count (>15,000/mm^3 vs $\leq$15,000/mm^3) had no significant effect on the response to treatment. Patients receiving concomitant ITP medication, usually corticosteroids, responded similarly to patients receiving eltrombopag alone. In particular, after discontinuation of eltrombopag but while continuing concomitant medication, the platelet counts returned to at or near the previous baseline in that group. These findings indicate that eltrombopag was the drug responsible for the increment in platelet counts.

In the patients receiving doses of 50 or 75 mg, the incidence of bleeding as assessed by the WHO bleeding scale, decreased and then gradually returned to baseline levels within the 6 weeks of follow-up as the platelet count also returned to baseline (Fig. 17.7). The incidence of bleeding was the lowerst (regardless of the grade or cause) in the 75-mg group (4% compared to 14% placebo) indicating hemostatic efficacy of the newly produced platelets.

The incidence and severity of adverse effects were similar in all study groups including placebo and the most common side effect was mild-to-moderate headache. There was no evidence of any dose-limiting toxicity.

Thrombopoietin levels (measured by ELISA) remained normal (26–209 ng/L) and unchanged regardless of treatment. Health-related quality of life (based on the

physical and mental component scores of the SF36v2 survey) was similar at the baseline and remained unchanged at the end of the study.

From this dose-ranging study it can be concluded that, at doses of 50 and 75 mg, eltrombopag is an effective, apparently safe, short-term treatment for patients with chronic ITP.

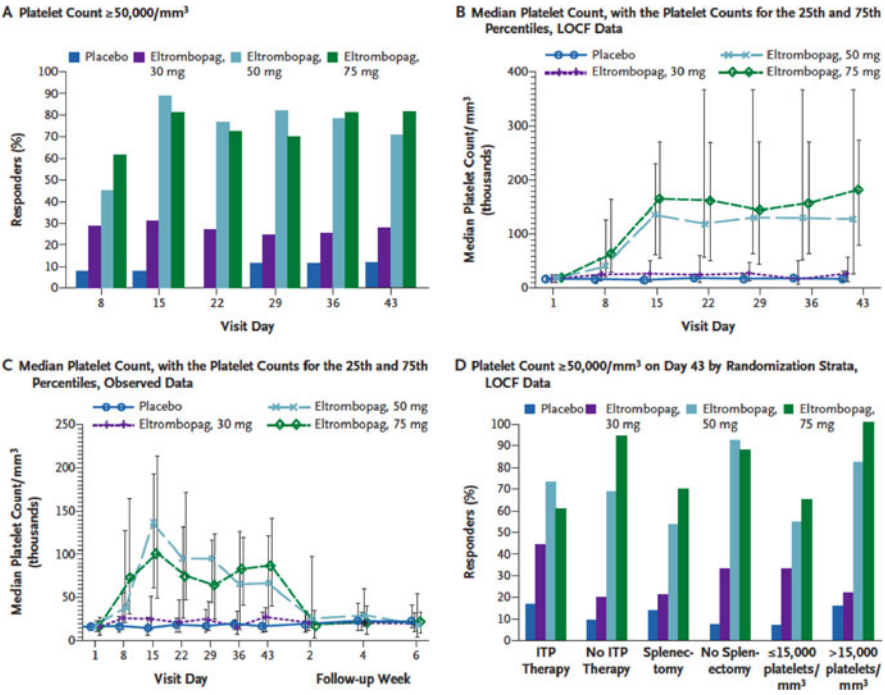

Fig. 17.6 Eltrombopag pharmacodynamics in chronic ITP patients **Panel a** shows the percentage of patients with a response in the four study groups at each weekly treatment visit, on the basis of last-observation-carried-forward (LOCF) data. On day 8, among patients treated with eltrombopag, 44 and 62% of patients receiving 50 and 75 mg, respectively, had a platelet count of more than 50,000/mm^3, and 88 and 81% of patients in these groups had a response by day 15. **Panel b** shows the median platelet counts at each visit, with the 25th and 75th percentiles shown as I bars, on the basis of LOCF data. By day 15, the median platelet counts for the groups receiving 50 and 75 mg of eltrombopag approached the normal range and remained there for the duration of the 6-week treatment period. **Panel c** shows the median platelet count at each weekly visit during the treatment period and at each biweekly visit after the treatment period on the basis of observed data. Patients who withdrew before day 43 were included in the follow-up. Discontinuation of treatment with 50 or 75 mg of eltrombopag before completion of the 6-week treatment period was primarily due to achievement of a platelet count of more than 200,000/mm^3. The median observed platelet counts remained elevated at 50,000 or more per mm^3 for the duration of the treatment in the groups receiving 50 and 75 mg of eltrombopag and returned to or were close to baseline levels within 2 weeks after the cessation of treatment. **Panel d** shows response rates according to the three stratification variables – use or non-use of concomitant ITP therapy (primarily prednisone or prednisolone), splenectomy status, and baseline platelet count (>15,000/mm^3 or ≤15,000/mm^3). A dose–response relationship was observed for each stratification variable

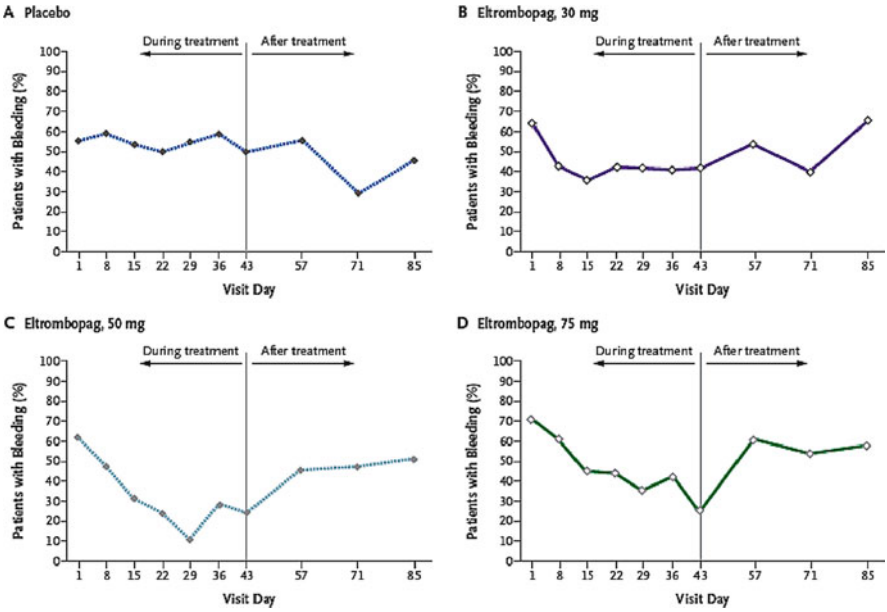

Fig. 17.7 Incidence of bleeding symptoms during and after treatment according to treatment group. The incidence of bleeding symptoms (defined according to the World Health Organization bleeding scale) decreased as platelet counts increased during treatment for patients receiving 50 or 75 mg of eltrombopag. The occurrence of bleeding symptoms gradually returned to baseline levels during the 6 weeks of follow-up, as the platelet counts returned to near-baseline levels

Assessment of an Increased Dose of Eltrombopag in Non-responders

A follow-up study was then performed in order to assess whether using an initial dose of 50 mg with the possibility of an increased dose up to 75 mg in non-responders the outcomes of platelet responses could improve. Fifty milligrams was chosen in preference to 75 mg because of the high rate of patients who started with 75 mg, and subsequently discontinued therapy because their platelet counts exceeded 200,000/μL. Therefore, a phase III randomized double-blinded, placebo-controlled was initiated in which eltrombopag or placebo (2:1) was administered to 114 patients with a median age of 48 years, approximately two-thirds women and three-quarters white [5]. As in the previous study, platelet counts were less than 30,000/mm^3 and most patients had a baseline platelet count of 15,000/mm^3. Additional inclusion criteria were normal creatinine and liver enzyme levels and exclusion criteria were patients who were using drugs or vitamins containing calcium or magnesium because of interference with eltrombopag gastrointestinal absorption. The treatment period was up to 6 weeks and the dose of eltrombopag could be increased to 75 mg after 3 weeks, if platelet counts remained less than

50,000/mm^3. In addition, treatment was discontinued in patients with platelet counts greater than 200,000/mm^3.

Thirty-nine percent had undergone splenectomy, 43% received concomitant ITP medication (three quarters of them had prednisone on both the placebo and the active treatment arms), and 41% had ITP for at least 5 years. All of them also had received at least one previous treatment for ITP (half of them received 3 or more ITP therapies) including corticosteroids, IVIG, and rituximab. The most common cause for withdrawal from the study was a platelet count above 200,000/mm^3 which occurred in 75% of patients on the active drug arm. 72% of the patients completed the 6 weeks of treatment.

The primary endpoint of this study, responsiveness to the drug defined by an increase in platelet counts to at least 50,000/mm^3 at day 43 of treatment, was achieved in 59% of the treatment group (compared to 16% on placebo). The median peak count for eltrombopag responders ($n = 43$) was 144,000/mm^3 (IQR 92.50–268). The median platelet count increased to 53,000/mm^3 by the second week in the eltrombopag group and remained around this range for the 6-week duration of the treatment period (Fig. 17.8).

One week after the end of treatment platelet counts were still at this range in 51% of patients. However, the counts gradually returned to previous baseline levels by 2 weeks after the end of the treatment period.

Patients responded to eltrombopag irrespective of the number of previous ITP treatments ($p = 0.31$), use of concomitant ITP drugs ($p = 0.77$), splenectomy status ($p = 0.75$), or baseline platelet counts 15,000/mm^3 ($p = 0.45$). Age and sex did not effect the response to treatment. Significantly fewer patients in the eltrombopag group compared to placebo had bleeding symptoms (39% vs 18%) ($p = 0.029$). However, after discontinuation of eltrombopag, a gradual return of platelet counts to baseline followed with proportionally increasing bleeding events, as in the previous study.

Mean scores for health-related quality of life at baseline and at the end of study were similar in placebo and eltrombopag groups. The proportion of adverse events during the treatment phase was 59% ($n = 45$) for the eltrombopag arm compared to 37% ($n = 14$) observed on the placebo arm. The most common were headache 8% (11% placebo) and bleeding 9% (11% placebo). Nausea and vomiting were absent in placebo but present in 5% of patients on the treatment arm.

Rare causes of bleeding (i.e., cerebral hemorrhage, gastrointestinal hemorrhage, and hematuria) caused withdrawal of one patient from the placebo group and one from eltrombopag, both of whom were non-responders. Increase in liver transaminases levels twice the upper limit was found in 6 patients on eltrombopag compared to one control. Abnormal liver function caused withdrawal from the study in one patient on eltrombopag, who was treated concomitant with long-term danazol therapy. No deaths occurred on study. Cataracts have been previously reported in preclinical studies in mice but were found in only two patients on eltrombopag and one patient that took placebo; all three had been previously treated with steroids.

This study confirmed the results of the previous randomized 6-week study demonstrating both efficacy and safety of 6-week therapy of eltrombopag in patients with chronic ITP.

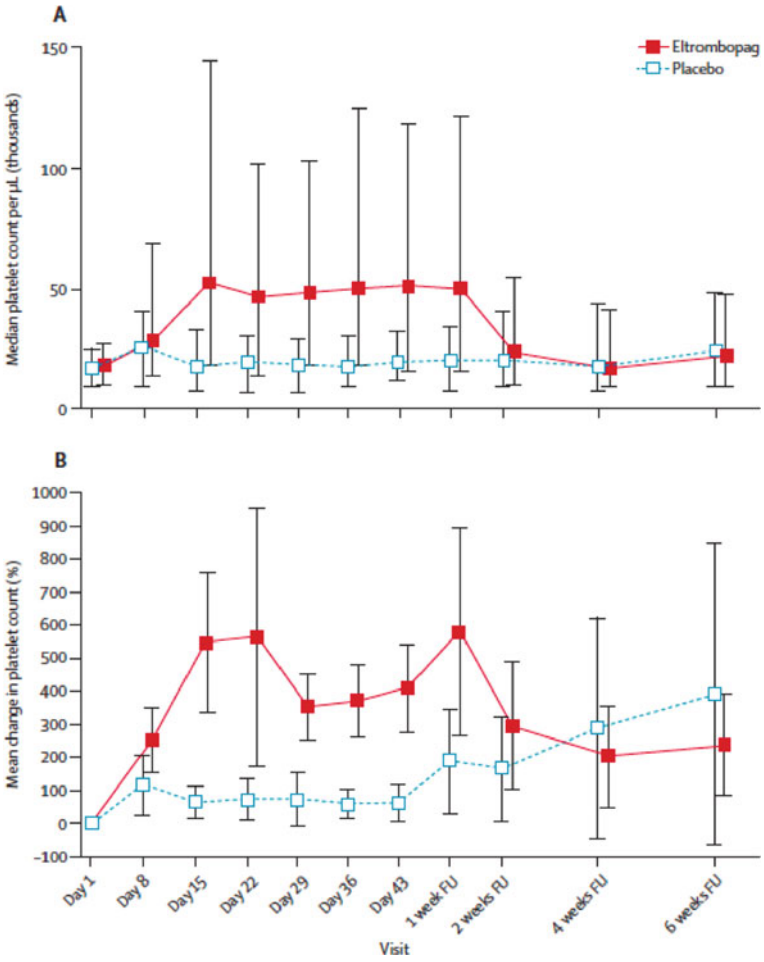

Fig. 17.8 Median platelet counts on ITP patients treated with eltrombopag. Median platelet counts (**a**) and mean changes in platelet counts (**b**) at every visit. (Median platelet counts at every visit are shown with IQR, and mean changes in platelet counts from baseline at every visit are shown with 95% CIs. FU = follow-up.) Four patients who received eltrombopag and two who received placebo were still receiving study medication on or within 3 days before the day 50 assessment and were included in this analysis

Eltrombopag for Secondary Thrombocytopenia Related to Hepatitis C Cirrhosis

McHutchinson, JG et al. published in 2007 a phase 2 clinical trial on eltrombopag in patients with hepatitis C [6]. This multicenter, randomized, double-blinded, placebo-controlled study of thrombocytopenia in patients with hepatitis C mediated liver disease using the same four doses as in the first ITP study. This study enrolled 74 patients with a median age of 51 years (range 30–74 years), with more than 2/3

men from 22 centers in the United States and Europe. These patients had chronic HCV infection (defined as the presence of anti-HCV antibodies and detectable HCV RNA levels) and thrombocytopenia with a baseline platelet count within a range of 26,000–94,000/mm^3 (median 55,000/mm^3). They were described as having compensated liver disease with cirrhosis confirmed by either a liver biopsy specimen or endoscopic evidence of portal hypertension. However, the severity of the liver disease was not formally graded in this study, for example, by Child-Pugh score (used to assess the severity and therefore the prognosis of chronic liver disease). Assessment of liver function monitoring was performed with eltrombopag treatment because the drug has been shown to increase liver transaminases in a small number of patients. Patients were excluded if they were pregnant, co-infected with human immunodeficiency virus or the hepatitis B virus or had a history of thrombosis.

This study consisted of two treatment phases. During the first 4-week treatment phase, prior to initiation of antiviral chemotherapy, the patients received eltrombopag once daily at doses of 30, 50, 75 mg or placebo. Hematologic, biochemical, and safety assessments were measured weekly. The treatment was interrupted when the platelet count was 200,000/mm^3 or more and restarted when this number was 100,000/mm^3 or less.

The second phase consisted of antiviral therapy if a patient had reached a predefined platelet count of 70,000/mm^3 or more for the use of peginterferon alfa-2a or 100,000/mm^3 or more for the use of peginterferon alfa-2b according to the package inserts for these two agents. Antiviral treatment with peginterferon and ribavirin was administered for 12 weeks concomitantly with eltrombopag or placebo. For safety, the dose of peginterferon was reduced by half if platelet counts had decreased to 25,000–50,000/mL^3 for peginterferon alfa-2a and 50,000–80,000 for peginterferon alfa-2b. The dose was stopped if platelet counts dropped below 25,000 and 50,000/mm^3, respectively.

Efficacy was defined by the ability of the drug to keep a consistent increase of platelet counts after the first 4 weeks (from the baseline value 20,000 to <70,000/mm^3) to 100,000/mm^3 or more and by the ability to continue peginterferon without a substantial decrease in the platelet count forcing an interruption or reduction in peginterferon/ribavirin therapy. The secondary endpoints included those related to safety and tolerability.

This study showed that eltrombopag increased platelet counts to 100,000/mm^3 or more in a dose-dependent manner. This effect was observed after each dose of the drug and was absent on the placebo group. An increase in platelet counts of 200,000/mm^3 or more was also observed on 25–52% of patients on eltrombopag (50–75 mg, respectively). These patients had their treatment interrupted until its platelet counts dropped to 100,000/mm^3 or fewer and at that point it was restarted.

The antiviral treatment phase could be initiated in two-thirds of patients, with the highest frequency of enrollment in the group receiving 75 mg of eltrombopag (91%) when compared to the 50-mg group (74%), 30-mg group (71%), or placebo (22%). In the 75-mg group, more patients (65%) were able to complete 12 weeks of the antiviral treatment phase, compared with patients in the groups receiving 50 mg (53%), 30 mg (36%), and placebo (6%). Despite the fact that platelet counts

decreased in all eltrombopag patients during the antiviral treatment phase they remained consistently above baseline values with a nadir of more than 50,000/mm^3. No one in the placebo group had these results.

Platelet counts in the eltrombopag group were higher at all time points (Fig. 17.9) than placebo and remained higher than the level at which a reduction in the peginterferon dose is recommended (<50,000/mm^3), therefore no patient had their antiviral

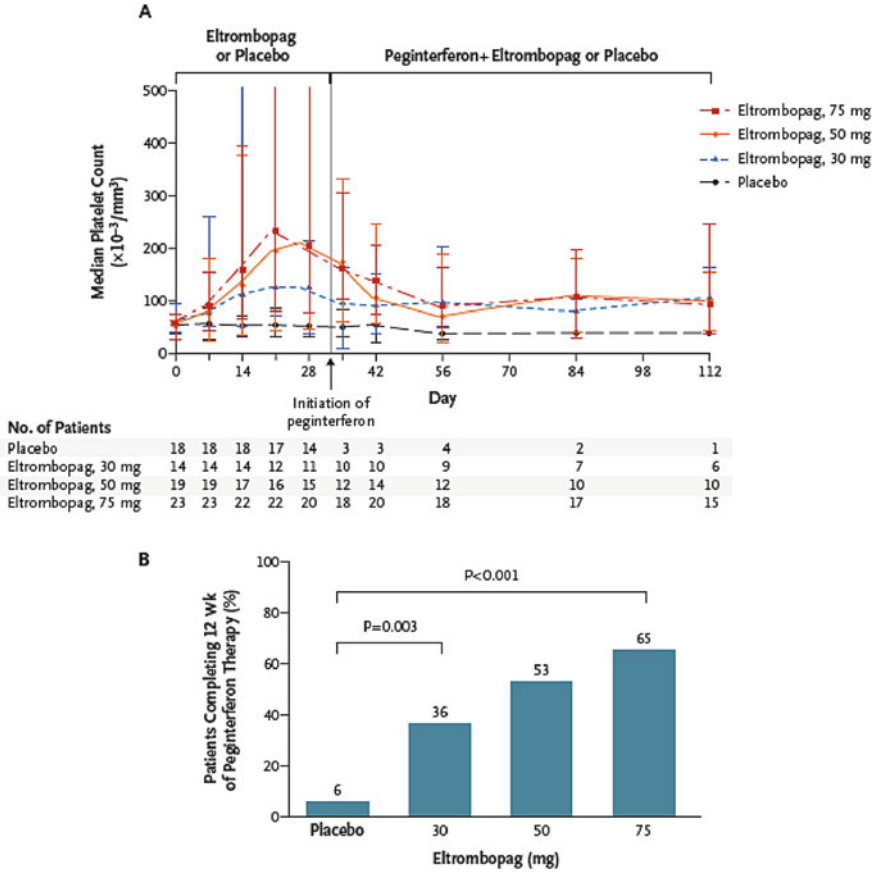

Fig. 17.9 Eltrombopag pharmacodynamics in hepatitis C patients. Median platelet counts and percentages of patients who completed the 12-week antiviral treatment phase. During the initial treatment phase, in which patients received eltrombopag or placebo, the median platelet count for each eltrombopag group was increased relative to the baseline value in a dose-dependent manner (**Panel a**). Counts reached a maximum at week 4, after which antiviral therapy was initiated while the administration of eltrombopag or placebo was continued. As expected, because of the marrow-suppressive effects of peginterferon, counts declined during the antiviral treatment phase and reached a nadir. However, platelet counts in the active treatment groups remained higher than those in the placebo group and those at baseline. I bars indicate the minimum and maximum values. **Panel b** shows the percentages of all patients randomly assigned to each group who completed the 12 weeks of antiviral therapy

treatment interrupted. Some of the patients in the treatment group had platelet counts higher than 200,000/mm^3 and required temporary interruption on eltrombopag therapy.

Side effects were observed, such as headaches (36% with 17% on placebo) and, less frequently, dry mouth, abdominal pain, and nausea, all in low grades of severity. Adverse events during the subsequent antiviral treatment phase were similar in all groups. The most common side effects related to interferon-based therapy were influenza-like symptoms, fatigue, chills, and headache.

In summary, eltrombopag therapy was able to increase platelet counts in patients with thrombocytopenia due to HCV-related cirrhosis, and, at the highest dose, to consistently maintain this effect even when combined with a potential thrombocytopenogenic drug, e.g., peginterferon. The combined use of a TpoR agonist and antiviral drugs including peginterferon and ribavirin would not only enable a greater number of patients to initiate antiviral treatment for hepatitis C, but would also allow a greater number to continue their treatment without dose interruption or reduction. There is a clear consensus that continuing antiviral therapy without interruptions or dose reductions substantially increases the chance of viral eradication.

RAISE Study and Ongoing EXTEND Phase III Study

Finally, the RAISE study [7] has not been published but has been presented in abstract form. It is a 6-month randomized placebo-controlled study of ITP in which standard of care was offered in addition to eltrombopag or placebo (2:1). It demonstrated that eltrombopag could be used for 6 months without loss of platelet effect and that no significant increase in thromboembolic events nor hepatic toxicity were seen. Platelet counts increased, bleeding decreased and health-related quality of life increased.

Similarly there is a large ongoing single-arm phase III study of the long-term treatment of patients with chronic ITP who have been on one of the previous eltrombopag ITP studies. This study, called Extend [8], has been presented in abstract form and suggests that development of tachyphylaxis is rare and that thrombotic and hepatic toxicities are infrequent.

The development of target TpoR agonists has been a landmark development in the management of thrombocytopenia from multiple causes. While the bulk of published data surrounding TPO-R agonists have focused on patients with chronic ITP (see also Chapter 16 by Dr. Kuter, this volume), it is clear that for patients with other diseases eltrombopag may benefit as well. In particular, the use of eltrombopag has been explored in patients with thrombocytopenia secondary to hepatitis C. In addition to the initial study summarized here, three large-scale trials are ongoing all with the intent of allowing better management of these patients. The focus has been on patients with thrombocytopenia prior to the initiation of antiviral therapy but in the future these agents will likely be used in patients who become thrombocytopenic on

therapy. In contrast, studies demonstrating efficacy in chemotherapy-induced thrombocytopenia have not been forthcoming and it remains to be investigated whether TpoR agents, in particular eltrombopag have any important role in this setting.

In summary the availability of TpoR agents has already revolutionized the management of chronic ITP and potentially will do the same for hepatitis C-induced thrombocytopenia and may also prove to have clinical benefit in other thrombocytopenic conditions such as myelodysplastic syndrome, chemotherapy-induced thrombocytopenia, and stem cell transplanted patients. More studies are needed to assess the long-term impact and to address possible long-term risks of chronic exposure to this thrombopoietic drug such as cataracts, liver dysfunction, and a theoretical but potential effect on bone marrow fibrosis.

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