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EXPERT REVIEW

Eltrombopag Thrombopoietin Receptor Agonist for Treatment of Immune Thrombocytopenia: Current and Future Considerations

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Abstract

Summary: Chronic immune thrombocytopenia (ITP) is an autoimmune disorder characterized by a low platelet count that has persisted for more than 12 months. Patients may be asymptomatic but those with severe, disease may have significant morbidity and require treatment. Historically, the pathogenesis of ITP was believed to be increased platelet destruction by anti-platelet antibodies. Treatment options were therefore primarily aimed at reducing platelet autoantibody production or inhibiting macrophage-mediated platelet destruction. These treatments usually have only a transient effect and are often associated with serious treatment related adverse events. Recently, impaired platelet production and inappropriately low serum thrombopoietin levels were observed in many chronic ITP patients. Therefore, stimulation of platelet production by growth factor or growth factor analogues may be useful in ITP treatment. This article presents data on the pharmacology, clinical efficacy, safety profile of Eltrombopag, a novel orally active, thrombopoietin-receptor agonist, in the treatment of ITP.

Keywords: immune thrombocytopenia (ITP), eltrombopag

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Introduction

Immune thrombocytopenic (ITP) is an immune-mediated acquired disease of adults and children characterized by transient or persistent decrease of the platelet count to less than 100×10^9/L.[1] The term "newly diagnosed ITP" is used to describe all cases at diagnosis. Persistent ITP is defined as ITP lasting between 3 and 12 months from diagnosis while chronic ITP is defined as cases lasting for more than 12 months. Secondary ITP includes all forms of immune-mediated thrombocytopenia except primary ITP.

The major goal for treatment of ITP is to provide a safe platelet count, rather than correcting the platelet count to normal levels.[2–5] Most fatal bleeding in ITP occurred in adults with platelet counts lower than 30×10^9/L.[6,7] Therefore, most guidelines suggest that treatment should be considered with counts less than 30×10^9/L in symptomatic adults. A platelet count of $\geq 50 \times 10^9$/L is considered clinically "safe" for surgery and other invasive procedures.[2–4] The incidence of adult chronic ITP is 1.6–3.9/100,000[8] with a prevalence of 236 adult cases per million population in the US.[9] Bleeding complications range in severity from bruises, petechiae, to life-threatening intracranial hemorrhage. Patients who fail to response to first line therapy and splenectomy are considered as having refractory ITP. The percentage of patients with refractory ITP varies from 11% to 35% of adult chronic ITP patients. Refractory, adult-onset ITP is associated with a relative risk of death of 4.2 compared with the general population. The underlying cause of ITP was believed to be immune mediated platelet destruction by anti-platelet antibodies.[5,10] Treatment options were therefore aimed at reducing platelet autoantibody production or inhibiting macrophage-mediated platelet destruction. Corticosteroids are the standard initial treatment.[11,12] Unfortunately, the adverse effects of long term steroids use outweigh the benefits.[11–13] IVIG and anti-D are effective in raising the platelet counts but the effects are usually transient and are recommended mainly for use in emergency situations.[14,15]

In many centers, splenctomy is the recommended second line therapy for chronic ITP patients who failed to respond to corticosteroids or who have severe adverse effects from corticosteriods. Many patients were able to maintain a satisfactory platelet counts after splenectomy.[16,17] However, about 15%–20% of patients do not respond and another 15%–20% of responders relapse weeks, months, or years later.[16,17]

Rituximab at doses of 375 mg/m^2, weekly for 4 weeks may produce durable response of more than 1 year in ITP patients.[18,19] Rituximab may cause flare up of hepatitis B infections and result in fulminant hepatitis.[20] Therefore, it is contraindicated in patients active hepatitis B infection and prohy;axis with lamuvidine is required in hepatitis B carrier without active infection. More than 50 cases of progressive multifocal leukoencephalopathy associated with rituximab treatment have been reported in lymphoma and SLE patients.[21] Additional long-term safety data are required before rituximab can be recommened as a frontline therapy.

Cyclosporin A, danazol and a variety of immuno-supressive/cytotoxic drugs such as vincristine, cyclophospamide, aziathioprine, dapsone, myco-phenolate mofetil either alone or in combination had been used to treat patients with refractory chronic ITP with response rate of 20%–80%.[22–27] However, most of the studies with immunosupressive agents were not randomized clinical trials and patients may have serious infection complications from prolonged use.

Recently, impaired platelet production was observed in many ITP patients.[28–31] Inappropriately low levels of serum thrombopoietin levels had also been reported in ITP patients including those with severe disease. Therefore, stimulation of megakaryopoiesis by thrombopoietin or thrombopoietin-mimetic agents may be useful in the treatment of ITP. Recombinant thrombopoietin had been shown to increased platelet counts in ITP patients,[32,33] but were associated with production of cross-reacting antibodies that neutralize endogenous thrombopoietin, leading to severe thrombocytopenia.[34,35] These led to the development of novel agents that activated the thrombopoietin receptor but had no homology to native thrombopoietin. Romiplostim (AMG-531, Nplate; Amgen, Thousand Oaks, CA, USA) and eltrombopag (Revolade, Promacta; GlaxoSmithKline, Brentford, UK) are two thrombopietin receptor agonists that had been licensed for the treatment of Chronic ITP.[36,37] This article reviews data on the pharmacology, clinical efficacy and safety profile of eltrombopag, in the treatment of ITP.

Chemistry and Mechanism of Action

Eltrombopag is an orally bio-available, low molecular weight synthetic non-peptide thrombopoietin receptor agonist.[38] Each film-coated tablet contains 25 mg or 50 mg of eltrombopag olamine. Eltrombopag selectively binds to the transmembrane domain of the thrombopoietin receptor present on the surface of platelets, megakaryocytes and megakaryocyte precursor cells. Eltrombopag showed in vitro and in vivo specificity for human and chimpanzee thrombopoietin receptors. It has no known activity against cell lines that did not express the thrombopoietin receptor. Eltrombopag stimulated proliferation of BAF3/Tpo-R cells ([EC50] 30 nmol/L) and CD41+ cells (EC50 100 nmol/L) in human bone marrow cell lines.[47] It acts via the Janus Kinase/Signal Transducer and Activator of Transcription (JAK/STAT) signaling pathway, inducing proliferation and differentiation of megakaryocytes from bone marrow progenitor cells. Eltrombopag did not affect agonist-induced platelet aggregation or activation in vitro and ex vivo studies using platelet samples from healthy volunteers and patients with chronic ITP.[38]

Pharmacokinetics

This is based on data plasma from 111 healthy adult subjects as well as 88 ITP subjects from TRA100773A and TRA100773B studies.

A two-compartment model with dual sequential first-order absorption and lag time best describes the pharmacokinetic profile of oral eltrombopag.[39] Eltrombopag was absorbed with a peak concentration occurring 2–6 h after oral administration and pharmacokinetics were dose proportional over a dose range of 5–75 mg.[39] A 75 mg single solution dose of Eltrombopag was associated with 52% oral absorption with area under the concentration-time curve (AUCt) estimated to be 146 mg/h/mL. Eltrombopag is highly bound to human plasma proteins (>99%).

Absorption and distribution

The plasma elimination half-life of eltrombopag was approximately 21–32 hours.[39] The predominant route of eltrombopag excretion was via feces (59%) with unchanged eltrombopag accounting for approximately 20% of the dose. Urinary excretion accounted for 31%. Eltrombopag is metabolized in the liver with cytochrome P450 isoenzymes (CYP1A2 and CYP2C8) and uridine diphosphate-glucuronosyltransferase (UGT1A1 and UGT1A3) as the major pathways Eltrombopag is not a substrate for P-glycoprotein or organic anion transporting polypeptide (OATP) 1B1, but was an inhibitor of this transporter. When Eltrombopag was administered with rosuvastatin (an OATP1B (substrate), a 2-fold increase in plasma rosuvastatin concentration was observed.[39] Interactions were also expected with other HMG-CoA reductase inhibitors, including pravastatin, simvastatin and lovastatin. In ITP patients taking eltrombopag, a reduction in the dose of concomitant statins with careful monitoring for statin side effects should be undertaken.

Administration of eltrombopag concomitantly with polyvalent cations significantly reduced eltrombopag absorption. Time to maximum concentration was increased by 1 hour and Cmax and AUC from time zero to infinity (AUC) were decreased by 65% and 59% respectively. Eltrombopag should be taken at least 4 h before or after antacids, dairy products, other food products or mineral supplements containing polyvalent cations.

Co-administration of eltrombopag with lopinavir/ritonavir (LPV/RTV) may cause a decrease in the concentration of eltrombopag. Therefore, platelet counts should be monitored carefully when lopinavir/ritonavir therapy is initiated or discontinued.

Clinical Efficacy Studies

Dose response study (TRA100773A)

The objective of the TRA100773 A study was to determine the optimal dose of eltrombopag.[40] One hundred and eighteen patients who had a 6-month or longer history of ITP and a platelet count $<30 \times 10^9$/L at baseline were randomized in a 1:1:1:1 ratio into 4 groups receiving 30, 50, 75 mg of eltrombopag or placebo daily for six weeks. Study patients, had either not responded to at least one prior therapy, including splenectomy, or had relapsed within 3 months of previous therapy. Within each treatment arm, patients were stratified according to use of concomitant ITP therapy, platelet count $<15 \times 10^9$/L or $>15 \times 10^9$/L and splenectomy status. The primary end point was the proportion of subjects achieving a platelet count greater than 50×10^9/L or more at the day 43 visit. If a patient's platelet counts was $>200 \times 10^9$/L, treatment was discontinued, but the patient would continue to

be followed up over the full trial duration. The subject was counted as a responder. Secondary endpoints assessed the incidence and severity of bleeding events (rated using the WHO Bleeding Scale) Seventy and eighty-one percents of the subjects in the 50 mg eltrombopag (n = 30) and 75 mg Eltrombopag group (n = 28) respectively were responders, as compared with only 11% response rate in subjects (n = 29) on placebo (P values <0.001 for both groups). Recipients of Eltrombopag 30 mg/day (n = 30) did not significantly differ from placebo recipients in response rate (28% versus 11%). The median platelet counts on day 43 in subjects on eltrombopag 50 or 75 mg/day were 128×10^9/L and 183×10^9/L respectively as compared with only 16×10^9/L in the placebo group. The improvement in platelet counts in patients in the eltrombopag 50 mg or 75 mg/day groups was accompanied by a significant reduction in bleeding symptoms compared with baselines and the placebo group. Thrombopoietin levels were within the normal range at baseline in all four groups (54–57 ng per liter) and were unaffected by response to eltrombopag therapy.[40]

Based on the results of this dose finding study, eltrombopag 50 mg daily was selected as the starting dose for subsequent phase III trials.

Phase III study TRA100773B

114 patients were randomized in a 2:1 ratio into receiving eltrombopag 50 mg/day or placebo.[41] Inclusion criteria, primary response were similar to the phase II dose finding TRA100773A study.[40] In this trial, patients who had not responded to Eltrombopag 50 mg/day after 3 weeks of treatment could have their dosage increased to 75 mg/day for the remaining 3 weeks. Again, within each treatment arm, patients were stratified according to use of concomitant ITP therapy, platelet count $<15 \times 10^9$/L or $>15 \times 10^9$/L and splenectomy status. Subjects were allowed to receive ITP medications (corticosteroids, azathioprine, danazol, cyclosporine A or mycophenolate mofetil) during the study, provided that the dose had been stable for at least one month. Significantly more subjects in the eltrombopag group (n = 73) demonstrated a response with platelet counts greater than 50×10^9/L on day 43 when compared with patients (n = 37) on placebo (59% versus 16%; $P < 0.0001$). The eltrombopag dosage was increased to 75 mg/day on or after day 22 of the study in 34 eltrombopag recipients because of no response to a 50 mg/day dosage. Of these, 10 patients (29%) achieved a platelet counts $>50 \times 10^9$/L. Eltrombopag recipients had lower risks of bleeding when compared with placebo recipients (odds ratio 0.27; 95% CI 0.09, 0.88; $P = 0.029$). Severe bleeding events during the 6 weeks of treatment were infrequent and occurred only in patients who did not respond to eltrombopag, or who received placebo. No clinically significant bleeding (WHO grade 2–4) occurred while patients had platelet counts $>50 \times 10^9$/L.

Response to treatment in both the phase II TRA 100773A and phase III 100773B trials were not affected by stratification factors. Similar response rates to Eltrombopag were observed irrespective of the splenectomy status, whether the subjects were on concomitant ITP medications and whether the baseline counts were less than 15×10^9/L or not. In responding patients, the platelet counts started to increase after one week of treatment, peaked around the second week and maintained throughout the remaining weeks. For most patients, platelet count returned to baseline levels within 2 weeks of discontinuing eltrombopag therapy. Transient decreases in platelet counts to both less than 10×10^9/L and at least 10×10^9/L below baseline (rebound thrombocytopenia) were observed in 11% and 13% of eltrombopag and placebo recipients following treatment discontinuation in this phase III trial.[40] Similar incidences of bleeding were observed in the 6 week post treatment period in both the eltrombopag and placebo groups. Therefore, no increased incidence of rebound thrombocytopenia was observed.

Study TRA102537 (RAISE)

RAISE (Randomized placebo controlled ITP Study with Eltrombopag)[42] was a randomized, double-blind, placebo-controlled, phase III study to address the safety and efficacy of a prolonged 6-month treatment of ITP with eltrombopag. Adult patients with chronic ITP who had previously responded to at least one ITP treatment and had platelet counts of $<30 \times 10^9$/L at time of enrollment were eligible for the study. Concomitant ITP medications could be continued if the dosage had been stable for at least 1 month. Again, within each treatment arm, patients were stratified according to use of concomitant ITP therapy,

baseline platelet counts $<15 \times 10^9$/L or $>15 \times 10^9$/L and splenectomy status. A total of 197 patients were randomized in a 2:1 ratio to treatment with eltrombopag (n = 135) or placebo (n = 62). Study patients started with initial dosage 50 mg/day of either Eltrombopag or placebo. At the end of 3 weeks treatment, if the platelet counts were $<50 \times 10^9$/L, the dose could then be adjusted to 75 mg/day. On the other hand, if subjects had platelets counts $>200 \times 10^9$/L, the study medication was reduced to 25 mg per day. Reduction or discontinuation of concomitant ITP medications were permitted after six weeks of therapy provided the platelet counts were $>100 \times 10^9$/L on two successive visits. The primary endpoint of the study was the odds of responding with platelets between 50, and 400×10^9/L in the Eltrombopag group as compared with placebo. Bleeding symptoms were prospectively evaluated using the WHO Bleeding Scale. Other secondary endpoints included median platelet counts, reduction of baseline ITP medication, use of rescue medication, health-related quality of life (HRQOL), and safety.

Median age was 52 years in the placebo arm and 47 years in the eltrombopag group. There were a higher percentage of females (69%) in both groups and 70% patients were of white origin.

Approximately half of the subjects in the placebo and eltrombopag groups (50% and 47%, respectively) were receiving ITP medication at randomization or had baseline platelet counts of less than 15×10^9/L (48% and 50%, respectively) Similar percentages of subjects (34% and 37%, respectively) had prior splenectomy. Most of the subjects had more than one prior ITP therapy. Eighty-one percent of placebo-treated subjects and 78% of eltrombopag-treated subjects had received at least 2 prior therapies, and more than 50% of subjects in each group had received 3 or more prior therapies.

In the primary efficacy analysis, the odds of responding over the six month treatment period were greater (OR = 8.20, 99% CI: 3.59, 18.73, $P < 0.001$) for eltrombopag-treated subjects compared to placebo-treated subjects. While baseline median platelet counts were 16×10^9/L in both groups, they never exceeded 30×10^9/L in the placebo group. This is in contrast to median platelet counts rising to 36×10^9/L in the eltrombopag group after one week of treatment and ranging from 52 to 91×10^9/L for the remainder of the study. Similar responses were observed irrespective of splenectomy status, baseline platelet count, or baseline ITP medication use.

Like the observation in the two 6-weeks trial, the platelet counts started to increase by the end of the first week of treatment, peaked at the second week and were maintained throughout the 6-month study period. After stopping eltrombopag, the platelet counts usually returned to baseline levels two weeks.

Bleeding symptoms were similar in both groups at baseline. From day 15 onwards, patients in the eltrombopag group had less bleeding symptoms. Bleeding (Grades 1 to 4) was reported in 79% of the patients receiving eltrombopag versus 93% receiving placebo. Bleeding (Grades 2 to 4) was reported in 33% of the patients receiving eltrombopag versus 53% receiving placebo. In the placebo group, four patients (7%) experienced 11 grade 3 or higher bleeding events, including one patient who had a fatal brain stem haemorrhage. In contrast, only three grade 3 or higher adverse bleeding events were reported by three eltrombopag-treated patients (2%) who had platelet counts <50,000 per μL at the time of their event.($P = 0.03$). The eltrombopag and placebo groups had similar incidence of rebound thrombocytopenia. No increased incidence of serious bleeding episodes was observed in the eltrombopag group in the post treatment period (4%; n = 6 in the Eltrombopag arm compared with placebo 10%; n = 6).

Compared with placebo, more eltrombopag patients reduced or discontinued concomitant ITP medications (32% [n = 10/31] versus 59% [n = 37/63]; $P = 0.02$), and fewer eltrombopag patients required rescue medication (40% [n = 25/62] versus 18% [n = 24/135]; $P = 0.001$). Significantly greater improvements in HRQOL from baseline were demonstrated for patients receiving eltrombopag compared with placebo.

Extend study

EXTEND is an ongoing, global, multicenter, open-label extension study.[43] Patients with chronic ITP who had completed treatment and follow-up periods with either eltrombopag or placebo in a prior Eltrombopag clinical study are eligible. Patients must not have experienced any eltrombopag-related serious adverse event (SAE) or drug intolerance during the prior eltrombopag study and must have a washout period of 4 weeks. Eltrombopag treatment is initiated at 50 mg

once daily. The dose of eltrombopag is adjusted to identify the minimal dose of Eltrombopag (between 75 mg once daily to 25 mg once daily, or less) necessary to maintain platelet counts $\geq 50 \times 10^9$/L in conjunction with the minimal dose of concomitant ITP medication. Patients will be followed until withdrawal or commercial availability of treatment to assess the long-term safety and efficacy. Patients who do not achieve platelet counts $\geq 50 \times 10^9$/L, but do experience clinical benefit from eltrombopag without significant adverse effects are permitted to remain on treatment. Long-term safety and tolerability is assessed by clinical laboratory tests, and frequency of adverse events (AEs). Secondary endpoints include the proportion of patients who achieve platelet counts $\geq 50 \times 10^9$/L at least once during treatment and the maximum duration of platelet count elevation $\geq 50 \times 10^9$/L during treatment with eltrombopag.

A total of 301 patients were enrolled in the ongoing EXTEND study. Median duration of follow up was 121 weeks. More than half (58%) of the subjects were followed for more than 104 weeks, 28% (84/301) for more than 3 years and 8% (23/301) over 4 years. Seventy—nine percents of the subjects were white and 15% (45/301) were Asians. About one third of the subjects had splencetomy (38%, n = 115) or were on concomitant ITP medications (34%, n = 101). Overall, 88% of patients (264/301) achieved platelet counts $\geq 50 \times 10^9$/L at any time on study. Median platelet counts increased to $\geq 50 \times 10^9$/L by week 2, and remained consistently $\geq 50 \times 10^9$/L throughout observation. At baseline, 56% of patients reported bleeding symptoms (WHO grades 1–4) compared with 16%, 19% and 9% of patients at 52,104 and 156 weeks, respectively. At week 52,104 and week 156, the proportion of patients with clinically significant bleeding (WHO grades 2–4) was reduced from 16% at baseline to 3%, 5% and 0% respectively. At baseline, 101/301 patients reported the use of concomitant ITP medications. Of those, 69% attempted to reduce or discontinue their ITP medication and 43% had a sustained reduction (defined as a reduction in dose and/or frequency from baseline which maintained for 4 weeks) or permanently stopped at least 1 concomitant medication without receiving on-treatment rescue therapy. Late resistance to eltrombopag was not observed. In some patients, the platelet counts dropped following reduction or discontinuation of concomitant medications and required rescue therapy. It is difficult to decide whether the loss of response was due to resistance to eltrombopag or reduction of concomitant ITP medications.

Safety Issues

This are based on toxicity studies in rats, mice, rabbits dogs[44] and those reported from clinical trials.[51–54]

Hepatocyte degeneration or necrosis, often accompanied by increased serum liver enzymes, was observed in mice, rats and dogs at doses that were associated with morbidity and mortality.[44] No hepatic effects were observed after chronic dosing in rats (28 weeks) or dogs (52 weeks) at exposures up to 4 or 2 times, respectively, the human clinical exposure based on AUC.[55] In the RAISE study,[42] elevations of alanine aminotransferase (ALT) ≥ 3 times the upper limit of normal occurred in 9 (7%) patients receiving eltrombopag compared with 2 (3%) in the placebo group ($P > 0.05$). Among the 9 eltrombopag subjects with elevated ALT, the abnormalities resolved in 6 patients while continuing treatment with eltrombopag. In the other 3 patients, the elevated ALT returned to normal levels after treatment was interrupted or discontinued. Elevations of total bilirubin >1.5 times the upper limit of normal occurred in five (4%) patients receiving eltrombopag compared with none on placebo. Of these, three patients had Gilbert's syndrome, one had an isolated elevation that resolved while on therapy, and one patient had pre-existing liver disease. In EXTEND,[43] 11% (34/301) of patients had hepatobilary laboratory abnormalities (HBLAs) that met ≥ 1 FDA Drug-Induced Liver Injury screening criteria. All bilirubin elevations were indirect bilirubin, which is not indicative of serious liver injury. In 30 out of the 34 subjects, the HBLA resolved while the subjects continue on treatment or following discontinuation. Moreover, the HBLAs observed during the EXTEND study were not always the same HBLA experienced by the patient during the previous eltrombopag study. Some subjects who had experienced HBLAs during the RAISE study, did not had recurrence of the HBLAs when retreated with Eltrombopag in the EXTEND study. So far there is no clinical evidence that Eltrombopag, at the recommended dose would result in serious irreversible liver damage. However, liver function tests should be monitored regularly, and if there is progressive

increase in serum aminotranferases, the drug should be stopped. For patients with underlying liver failure, the drug should be used with caution.

Thrombopoietin receptor agonists may increase the risk for developing or progressing reticulin fiber deposition in bone marrow.[45] In the EXTEND study,[43] over 180 on-treatment bone marrow biopsy were performed on more than 100 patients, who had been dosed for 1–4 years. Thirty nine subjects had 2 or more bone marrow biopsies. No significant increase in fibrosis was observed. None of the patients had an abnormal karyotype of bone marrow cells, increased bone marrow blast count >3%, or any clinically relevant bone marrow abnormality other than those compatible with ITP.

For patients on Eltrombopag, peripheral blood smears should be examined for morphological abnormalities such as teardrop, nucleated red blood cells, immature white blood cells, dysplastic cells or cytopenia. If such abnormalities develop or are worsening, a bone marrow biopsy should be performed. A loss of response or failure to maintain a platelet response with eltrombopag treatment within the recommended dosing range should also prompt a search for causative factors such as myelofibrosis.

In the RAISE study,[42] 3 (2%) patients receiving eltrombopag reported on-therapy thromboembolic events (2 with pulmonary embolism, one had deep vein thrombosis) as compared with none in the placebo group. All three subjects had risk factors for venous thrombosis and the platelet counts were less than 50,000/μL around the time of the thrombotic events. In the EXTEND study, 18 patients (6%) experienced 25 confirmed or suspected thromboembolic events with an incident rate of 3.02/100 patient years.[43] Deep vein thrombosis (n = 10) and Cerebral vascular events (n = 7) were the most common thromboembolic events. Majority of these patients (15/18) experienced thromboembolic events at a platelet count lower than the maximum platelet count achieved during eltrombopag treatment. All 18 patients had at least 1 thromboembolic risk factor such as hypertension, smoking, or obesity. The frequency of thromboembolic events in patients treated with eltrombopag in EXTEND study is similar that reported for the ITP patient population.[46] The data so far do not suggest a correlation between high platelet counts and thromboembolism. However, in patients with underlying risk factors of thrombosis, Eltrombopag should be used with caution, and the platelet counts should be monitored very carefully, and aim at the minimal platelet counts adequate to reduce bleeding.

Cataracts were observed in mice and rats, but not in dogs after prolonged treatment with eltombopag at doses that were 2–4 times higher than that used in human.[44] The clinical relevance of these findings is unknown. In the RAISE Study,[42] similar incidences of worsening cataracts were observed in the eltrombopag and placebo group (8% and 10% respectively). Rate of cataract progression across Eltrombopag clinical trials was similar to that observed in steroids treated ITP subjects.[47] However, in view of the observation in rodents, routine monitoring of patients for cataracts is recommended.

One concern about treatment with TPO-R agonist is the possibility of rebound thrombocytopenia upon withdrawal of the drug. In responding patients, endogenous thrombopoetin levels may be suppressed. Withdrawal of TPO-R agonist may therefore result in the platelet counts dropping to lower than pre-treament levels. For eltrombopag treated subjects, thrombopoietin levels were within the normal range at baseline and were unaffected by eltrombopag therapy. Transient decreases in platelet counts to both less than 10×10^9/L and at least 10×10^9/L below baseline (rebound thrombocytopenia) were observed in 11% and 13% of eltrombopag and placebo recipients following treatment discontinuation in the controlled clinical trials.[41] Post-therapy bleeding events were reported by a lower proportion of patients receiving eltrombopag (4%) compared with placebo (10%) in the RAISE study.[42] Nonetheless, platelet counts and bleeding symptoms should bee monitored closely following discontinuation of eltrombopag.

Renal tubular toxicity was observed in studies of up to 14 days duration in mice and rats at doses that were generally associated with morbidity and mortality. Renal effects were not observed in rats after 28 weeks or in dogs after 52 weeks at exposures 4 and 2 times, respectively, the human clinical exposure based on AUC.[44] The clinical relevance of these findings is unknown. Patients with impaired renal function should use eltrombopag with caution and under close monitoring, with monitoring of serum creatinine, platelet counts and urine analysis.

Eltrombopag was not carcinogenic in mice at doses up to 75 mg/kg/day or in rats at doses up to 40 mg/kg/day.[50] These doses were equivalent to 4 times the human clinical exposure based on AUC. Eltrombopag did not affect female fertility, early embryonic development or embryo-fetal development in rats at doses up to 20 mg/kg/day (twice the human clinical exposure based on AUC). Eltrombopag did not affect male fertility in rats at doses up to 40 mg/kg/day, (3 times the human clinical exposure based on AUC). The growth, and development of the offspring are also unaffected. Increased fetal loss and low birth weight were only observed at maternally toxic dose of 60 mg/kg/day (6 times the human clinical exposure based on AUC)[44] The clinical relevance of these findings is unknown. Nonetheless, eltrombopag is not recommended during pregnancy and in women of childbearing potential not using contraception.

Eltrombopag was detected in the plasma of all offspring rat pups for the entire sampling period following administration of medicinal product to the maternal dams, suggesting that rat pup exposure to eltrombopag was likely via lactation.

Indications and Administrations

The approved therapeutic indication in the USA and EU for Revolade is for adult chronic ITP splenectomized patients who are refractory to other treatments (eg, corticosteroids, immunoglobulins).[48] Currently these patients have limited alternatives. Some centers use rituximab and approximately one-third of patients achieve a relatively durable response. However, rituximab is not licensed for the treatment of ITP and the potential long-term risk of infection and leukoencephalopathy is a real concern.

Eltrombopag may also be considered as second-line treatment for adult non-splenectomized patients who refused surgery or in whom surgery is contraindicated.[48] The choice between splenectomy and eltrombopag may eventually rest with patient's preference and health policy. Some patients have great reluctance for any kind of surgery including laparoscopic splenectomy. If such patients are given the choice of splenectomy or taking an oral medication daily, they may choose eltrombopag treatment. On the other hand, eltrombopag is an expensive long term treatment for many patients, if it is not covered by the government policy or private insurance, the patients may opt for splenectomy first.

The recommended starting dose of eltrombopag is 50 mg once daily. For patients of East Asian ancestry, eltrombopag should be initiated at a reduced dose of 25 mg once daily. After initiating eltrombopag, if no significant increase in platelet counts is observed after 2–3 weeks of treatment, eltrombopag could be increased. After achieving a stable platelet counts on a stable dose, the dose should be further adjusted to the lowest dose sufficient to maintain a platelet count of around 50×10^9/L with minimal bleeding symptoms. Co-adminstration of polyvalent cations (eg, iron, calcium, magnesium, aluminium, selenium and zinc) significantly reduce eltrombopag absorption, therefore it should be taken at least four hours before or after any products such as antacids, dairy products (or other calcium containing food products), or mineral supplements containing.

Eltrombopag is not recommended for use in children and adolescents below the age of 18 years due to insufficient data on safety and efficacy.

Even though no increased incidence of thromboembolic events, myelofibrosis or irreversible hepatic damage was reported in follow-up of over 4 years, one should still monitor patients on eltrombopag closely for such adverse events.

In patients with underlying risk factors of thrombosis requiring eltrombopag treatment, the platelet counts should be monitored very carefully, and aim at the minimal platelet counts adequate to reduce bleeding. For patients with underlying liver failure, the drug should be used with caution, perhaps starting with a 25 mg once daily dose. Peripheral blood smears should be examined for morphological abnormalities such as teardrop, and leucoerythroblastic changes. If such abnormalities develop, a bone marrow biopsy should be performed. A loss of response or should also prompt a search for causative factors such as myelofibrosis.

Author Contributions

Conceived and designed the experiments: NA. Analysed the data: GC. Wrote the first draft of the manuscript: GC. Contributed to the writing of the manuscript: GC. Agree with manuscript results and conclusions: GC. Jointly developed the structure and

arguments for the paper: GC. Made critical revisions and approved final version: GC. All authors reviewed and approved of the final manuscript.

Disclosures and Ethics

As a requirement of publication author(s) have provided to the publisher signed confirmation of compliance with legal and ethical obligations including but not limited to the following: authorship and contributorship, conflicts of interest, privacy and confidentiality and (where applicable) protection of human and animal research subjects. The authors have read and confirmed their agreement with the ICMJE authorship and conflict of interest criteria. The authors have also confirmed that this article is unique and not under consideration or published in any other publication, and that they have permission from rights holders to reproduce any copyrighted material. Any disclosures are made in this section. The external blind peer reviewers report no conflicts of interest. Provenance: the authors were invited to submit this paper.

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