blood advances

Eltrombopag for use in children with immune thrombocytopenia

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Eltrombopag is currently the only US Food and Drug Administration–approved thrombopoietin receptor agonist for the treatment of chronic immune thrombocytopenia (ITP) in children. This oral, once-per-day therapy has shown favorable efficacy and adverse effect profiles in children. Two multicenter, double-blind, placebo controlled clinical trials (PETIT [Efficacy and Safety Study of Eltrombopag in Pediatric Patients With Thrombocytopenia From Chronic Idiopathic Thrombocytopenic Purpura (ITP)] and PETIT2 [Study of a New Medication for Childhood Chronic Immune Thrombocytopenia (ITP), a Blood Disorder of Low Platelet Counts That Can Lead to Bruising Easily, Bleeding Gums, and/or Bleeding Inside the Body]) demonstrated efficacy in raising platelet counts, reducing bleeding, and reducing the need for concomitant ITP therapies with relatively few adverse effects. The most commonly reported drug-related adverse effects include headache, nausea, and hepatobiliary laboratory abnormalities. Long-term safety data in children are limited, and studies in adults have not revealed a clinically significant increased incidence of thrombosis, marrow fibrosis, or cataract formation. Eltrombopag has also been approved for treating refractory severe aplastic anemia (AA) and has potential for expanded use in ITP and severe AA as well as in other conditions associated with thrombocytopenia.

Introduction

Immune thrombocytopenia (ITP) is the most common autoimmune cytopenia in children and is defined as an isolated low platelet count ($<100 \times 10^9$/L) in the absence of an underlying cause. The majority of children with ITP will not have significant bleeding symptoms and will experience spontaneous resolution of thrombocytopenia within 12 months of diagnosis. However, up to 25% of these children develop chronic ITP, and some have significant bleeding symptoms or bleeding risk that requires continuing therapy. There is no consensus on the management of chronic ITP in children. Therapeutic options for managing chronic ITP include rituximab, oral immunosuppressive agents, thrombopoietin receptor agonists (TPO-RAs), and splenectomy. The oral TPO-RA eltrombopag was approved by the US Food and Drug Administration (FDA) for use in children with chronic ITP in 2015.

Biology of TPO-RAs

TPO

In 1958, Kelemen and colleagues postulated the existence of a factor that regulated platelet number and production.[1] In 1994, 4 study groups independently identified and cloned TPO.[2-4] The *TPO* gene is located on chromosome 3q27[5] and encodes a 353-amino-acid precursor protein, which is synthesized primarily in the liver.[2,3] Posttranslational modification results in removal of the 22-amino-acid C-terminal portion of the protein and glycosylation.[6] The resultant protein is a 4-helix-bundle cytokine that shares

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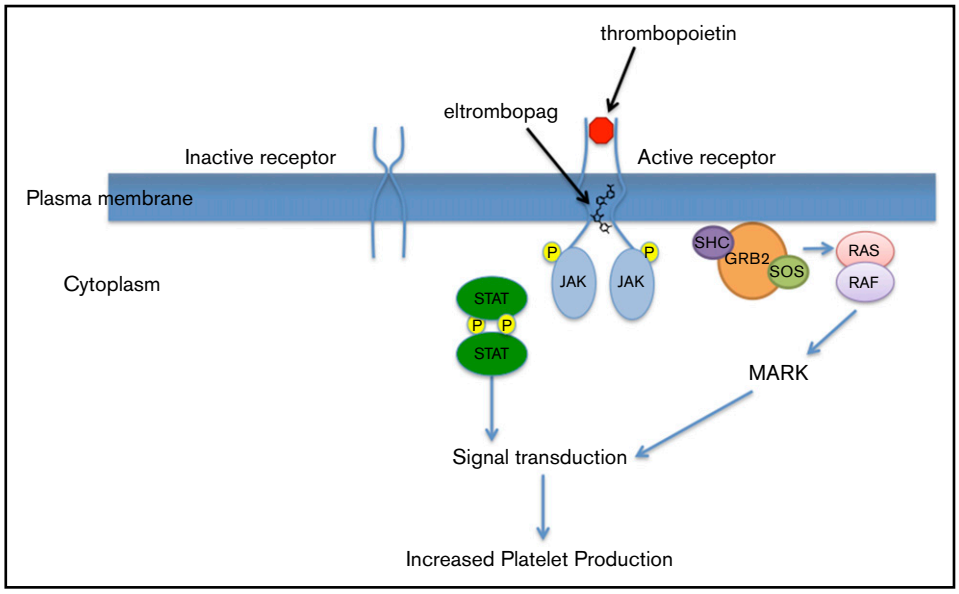

Figure 1. Important molecules for thrombopoietin signaling, including the site of eltrombopag binding. GRB2, growth factor receptor-bound protein 2; RAF, rapidly accelerated fibrosarcoma; SOS: son of sevenless.

sequence homology with an erythropoietin-like domain in the amino terminus and a unique carboxyl terminus domain. Receptor binding activity seems to reside in the erythropoietin-like domain (Figure 1).

TPO exerts its action by binding to a specific cell surface receptor encoded by *MPL*. This gene was first described as a proto-oncogene for murine myeloproliferative leukemia virus and is expressed on megakaryocytes, platelets, and hematopoietic stem cells. The protein product, c-mpl, is a type 1 homodimeric receptor and is normally inactive. TPO binds to the distal cytokine homology receptor domain at 2 main residues, D261 and L265, with interaction around residue F104 (abnormal in congenital amegakaryocytic thrombocytopenia), and activates the receptor. This results in approximation of the intramembrane portion of the dimers and phosphorylation of pre-associated JAK2 with downstream signaling through STAT, ERK, and PI3K (Figure 1).

Development of TPO as a pharmacologic agent

rhTPO and PEG-rHuMGDF. Starting in 1995, a pegylated form of recombinant human megakaryocyte growth and development factor (PEG-rHuMGDF) was studied in patients with advanced cancer.[7] By 2001, both pegylated and nonpegylated forms of recombinant full-length thrombopoietin (rhTPO) molecules were in clinical trials in both healthy individuals donating platelets and in the setting of chemotherapy-induced thrombocytopenia.[8-11] These studies demonstrated that administration of rhTPO increased platelet counts after a single injection starting around day 5 with peak platelet counts after 10 to 12 days. However, in trials that examined the effectiveness of rhTPO in chemotherapy-induced thrombocytopenia in acute myeloid leukemia and in stem cell transplantation, there was no improvement in time to platelet count of $>20 \times 10^9$/L or in reducing the need for platelet transfusion.[12] Patients treated with less myelosuppressive chemotherapy did demonstrate improved nadir platelet count and reduced duration of thrombocytopenia. However, enthusiasm for rhTPO waned after the lack of success in acute myeloid leukemia and transplantation and with the demonstration of cross-reacting antibody formation to endogenous TPO after administration of PEG-rHuMGDF, which resulted in significant thrombocytopenia in healthy participants.[13] This stalled further development of these drugs and motivated the search for alternative molecules to stimulate platelet production. However, development of rhTPO continued outside the United States, and a full-length, glycosylated protein produced in Chinese hamster ovary cells was approved as first-line therapy for chronic ITP in China.[14] A recent study demonstrated efficacy of this molecule in ITP during pregnancy.[15]

Second-generation TPO-RA. Screening of peptide libraries led to the development of several small molecules that were able to stimulate megakaryocyte proliferation and platelet production. Several thrombopoietin agonists have been developed for clinical use, and both romiplostim (a peptibody consisting of 2 short peptides coupled to an Fc domain) and eltrombopag have been approved by the FDA for use in adults with chronic ITP. Currently, eltrombopag is the only TPO-RA approved for use in pediatric patients with chronic ITP. Additional small-molecule TPO-RAs have also been evaluated in various preclinical and clinical models. All of these molecules work by stimulating the TPO receptor on megakaryocytes and hematopoietic stem cells, which causes increased production of platelets and megakaryocytes[16] but the molecules do not share sequence homology with endogenous TPO.

Molecule structure and mechanism of action of eltrombopag

Eltrombopag is a small-molecule, nonpeptide agonist that binds within the juxtamembrane domain of the TPO receptor (at residue H499), which results in signaling through the JAK/STAT, AKT, and MAPK pathways similar to the signaling mechanism of TPO (Figure 1).[17] Because it binds to H499, eltrombopag does not bind to murine mpl. This residue is not conserved in mice, which means that it is specific to humans and nonhuman primates.

Eltrombopag is a biphenyl hydrazone and is structurally distinct from endogenous TPO (Figure 2). Therefore, eltrombopag noncompetitively activates the TPO receptor by binding within the transmembrane domain to initiate the signaling cascade, which results in both proliferation and differentiation of megakaryocytes and

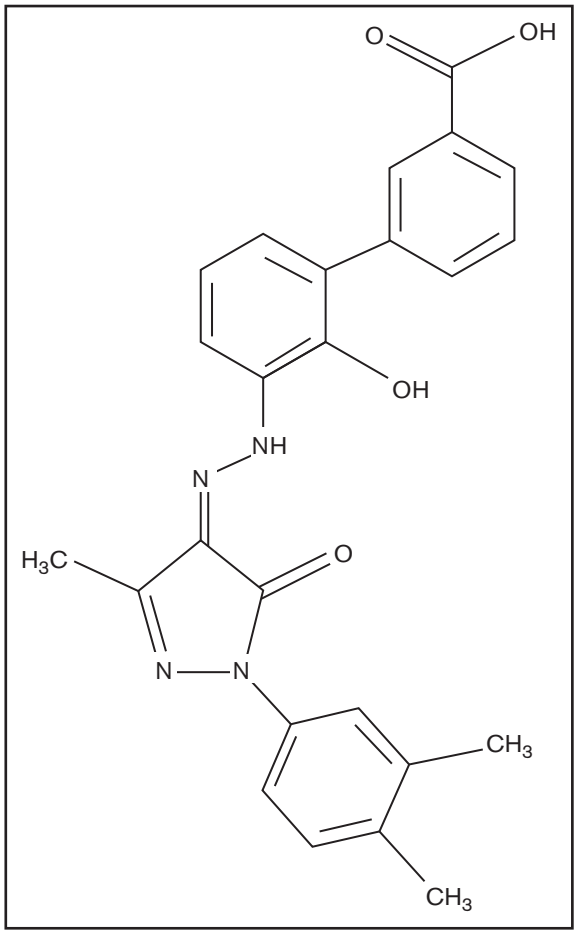

Figure 2. Molecular (2D) structure of eltrombopag olamine.

leads to production of increased numbers of platelets.[17] Because eltrombopag binds to a site that is distinct from endogenous TPO on c-mpl, the effects of eltrombopag in the presence of TPO signaling may be additive, as suggested by additional proliferation even in the presence of plateau concentrations of TPO in megakaryocyte cell cultures.[18]

Drug metabolism

Eltrombopag is predominantly excreted into the feces after oral administration, which suggests that the major organ of elimination is the liver. Some studies suggest that liver uptake is mediated by organic anion transporting peptide 1B1 (OATP1B1),[19] and intestinal uptake may be partially mediated by breast cancer resistance protein.[20] Eltrombopag is metabolized primarily through the CYP1A2 and CYP2C8 enzymes (to form a mono-oxygenation product) and UGT1A1 and UGT1A3 (to form a glucuronide conjugate), although in humans, most of the circulating eltrombopag is excreted as unchanged drug.[21] These characteristics may help explain the observed hepatoxicity (the drug is primarily metabolized and cleared by the liver), as discussed below.

The concentration of eltrombopag in blood cells is ~50% to 79% of plasma concentrations, and plasma eltrombopag is highly protein bound (>99%). The plasma elimination half-life is ~21 to 32 hours in healthy individuals and 26 to 35 hours in individuals with ITP.

Clinical development and current indications

Eltrombopag in adult patients with chronic ITP

Eltrombopag was first assessed in a trial in adult patients with chronic ITP. Bussel et al[22] first evaluated the efficacy and safety of eltrombopag in adult patients with refractory chronic ITP and demonstrated a dose-dependent rise in platelet count.

Eltrombopag was well tolerated with minimal adverse effects.[22] The Bussel et al study also showed that eltrombopag treatment reduced the need for concomitant therapy and use of rescue therapies as well as improved health-related quality of life.[23] The findings of this pivotal study led to the first FDA approval in 2008 of eltrombopag in adult patients with ITP. Subsequent phase 3 double-blind, placebo-controlled studies in adults have demonstrated that, for the majority of patients with chronic ITP (~70% to 80%), eltrombopag is effective at raising the platelet count and reducing bleeding.[23] Response to eltrombopag was defined in this study as achieving a platelet count of 50 to 400 $\times$ 10^9/L at any assessment point during the study period.[23]

Pediatric trials

The efficacy and safety of eltrombopag was assessed in children in the PETIT trials, which assessed pediatric patients with ITP (PETIT: Efficacy and Safety Study of Eltrombopag in Pediatric Patients With Thrombocytopenia From Chronic Idiopathic Thrombocytopenic Purpura [ITP]; PETIT2: Study of a New Medication for Childhood Chronic Immune Thrombocytopenia [ITP], a Blood Disorder of Low Platelet Counts That Can Lead to Bruising Easily, Bleeding Gums, and/or Bleeding Inside the Body). PETIT and PETIT2 were phase 2 and 3 randomized, multicenter, placebo-controlled trials.[21,24] Children age 1 to 17 years with ITP that lasted for 6 months or more and a platelet count of $<30 \times 10^9$/L at enrollment who had received at least 1 prior therapy for ITP were included. Patients who were receiving stable doses of therapy for chronic ITP were permitted to continue with concomitant therapies.

PETIT was a 3-part, multicenter, phase 2/3 trial. The study enrolled a small number of children in each age cohort into a 24-week open-label, dose-finding phase, and subsequent patients were enrolled into a 7-week randomized, double-blind, placebo-controlled portion of the trial followed by a 17- to 24-week open-label extension.[21] PETIT2 was a phase 3, 2-part randomized, multicenter, placebo-controlled study conducted at 38 centers in 12 different countries across North and South America, Europe, and Asia.[24] That study consisted of a 13-week randomized, double-blind, placebo-controlled portion followed by a 24-week open-label period during which all patients received eltrombopag.[24]

The use of eltrombopag in these studies resulted in improved platelet counts, reduction in bleeding severity, and reduction or discontinuation of concomitant treatments for ITP (Table 1). Overall, eltrombopag proved to be safe and well tolerated. In both PETIT and PETIT2, the primary outcome was achieving a platelet count $\geq 50 \times 10^9$/L without rescue therapy.[21,24] Rescue therapy was defined as dose escalation of a concomitant treatment and the need for additional therapy, platelet transfusion, or splenectomy.[21,24]

Health-related quality of life

The Kids' ITP Tools (KIT) questionnaire is used to assess health-related quality of life in pediatric ITP patients. KIT questionnaires

Table 1. Summary of results of PETIT and PETIT2

	PETIT		PETIT2	
	Eltrombopag, %	Placebo, %	Eltrombopag, %	Placebo, %
Platelet response*	62	32	75	21
Sustained response†	36	0	41	3
Required rescue therapy	13	50	19	24
Able to discontinue or decrease concomitant therapies‡	23	—	46	—
Clinically significant grade 2-4 bleeding	9	32	5	7

PETIT and PETIT2 demonstrated a rise in platelet count, sustained platelet increases, decreased need for other therapies, and reduced bleeding with use of eltrombopag.
*Platelet count of $\geq 50 \times 10^9$/L without rescue therapy during days 8 to 43 in PETIT and during weeks 1 to 12 in PETIT2.
†Platelet count of $\geq 50 \times 10^9$/L without rescue therapy in ≥60% of assessments during weeks 2 to 6 in PETIT and for ≥6 weeks during weeks 5 to 12 of PETIT2.
‡Eltrombopag only phase (no placebo arm).

were completed by study participants in the PETIT trial but not in the PETIT2 trial.[24,25] After 24 weeks of treatment in the open-label portion of PETIT, there were modest increases in KIT scores for those taking eltrombopag, but these improvements were not statistically significant.[21] Eltrombopag has been shown to improve health-related quality of life in adults and certainly warrants further study in pediatric populations.[23]

Adverse events

Overall, eltrombopag is well tolerated. Collectively in PETIT and PETIT2, the most common adverse effects reported during the trial period included headache, upper respiratory tract infection, nasopharyngitis, diarrhea, and transaminitis.[24,26] Clinically significant adverse events were rare in both trials.

Hepatobiliary laboratory abnormalities. Eltrombopag carries a black box warning because of the risk of severe and potentially life-threatening hepatic toxicity. In studies of adults, a minority of patients receiving eltrombopag had increases in alanine aminotransferase (ALT) concentration $\geq 2 \times$ the upper limit of normal (ULN).[24,27] In the RAISE randomized phase 3 trial, indirect hyperbilirubinemia was seen in 5 (4%) of the patients receiving eltrombopag, 3 of whom had Gilbert's syndrome and 1 of whom had preexisting liver disease.[23] All abnormalities in liver function tests and bilirubin levels normalized with cessation of the drug.

In PETIT and PETIT2, increases were seen in both ALT and bilirubin levels.[21,24] Overall, changes in hepatobiliary levels were mild with no clinical consequence and were fully corrected after cessation of the drug. Collectively in the 2 trials, 4.7% of patients developed ALT levels $\geq 3 \times$ ULN.[26] Three percent of patients withdrew secondary to hepatobiliary laboratory abnormalities in the open-label portion of PETIT and in the double-blind portion of PETIT2.[26] Given these results, liver function and bilirubin level tests should be completed before eltrombopag therapy is initiated and should be repeated approximately once per month. The drug should be discontinued for transaminases when the level is more than $3 \times$ ULN.

Cataract formation. Preclinical trials in rats demonstrated the development of cataracts with doses greater than 7 times the predicted human exposure to the drug.[28] Cataract development was directly related to dose and duration of exposure. However, these findings were not replicated in studies with dogs, in which no cataracts developed when the dogs were studied over an extended period of time at 3 times the human dose.[28,29]

Because of the data from animal models, patients were routinely screened for the development or progression of cataracts in the early eltrombopag studies. A new cataract developed in 1 patient and another experienced progression of a preexisting cataract in the PETIT2 study.[24] Both children were also treated with corticosteroids. No patient in the PETIT study developed new or worsening cataracts.[21] Although it seems that eltrombopag monotherapy does not increase risk of cataract development or progression in children, screening and follow-up eye examinations should be considered in patients with significant corticosteroid exposure.

Bone marrow fibrosis. When megakaryocytes are stimulated, they release transforming growth factor-β and other cytokines that promote collagen synthesis by fibroblasts.[29] Prior studies have reported increased formation of bone marrow reticulin in rats treated with romiplostim.[30] This is thought to occur via overexpression of thrombopoietin in the bone marrow followed by megakaryocyte stimulation induced by thrombopoietin agonists.[29] This offers a theoretical mechanism for eltrombopag-induced bone marrow fibrosis. However, as is discussed below, any marrow changes while a patient is receiving eltrombopag have not proved to be of clinical consequence.

Modest reticulin deposition developed in a dose-dependent manner in adult patients who were treated with romiplostim, but it resolved when the drug was stopped.[30] Bone marrow biopsies were not performed as a part of PETIT or PETIT2, but complete blood count derangements indicative of marrow changes were not seen in these trials.[21,24] Studies of eltrombopag in adults with ITP have not demonstrated significant bone marrow fibrosis. The Eltrombopag Extended Dosing Study (EXTEND), which started in 2006, is a recently completed, open-label trial that assessed adult patients with chronic ITP who were being treated with eltrombopag for bone marrow reticulin fibrosis.[31] Initial results from this trial were published in 2015 and showed moderate to marked fibrosis in only 2 patients.[31] One patient's marrow findings reversed after the patient withdrew from the study.[31] The final results of the study (published in December 2017) showed data from 356 biopsy specimens collected from 166 patients treated for up to 7 years with eltrombopag.[32] By using the European Consensus Scale to rate degree of fibrosis, 52% of patients had no fibrosis and 41% increased to marrow fibrosis score of 1.[32,33] Only 1 patient increased to a marrow fibrosis score of 3, the maximum score using

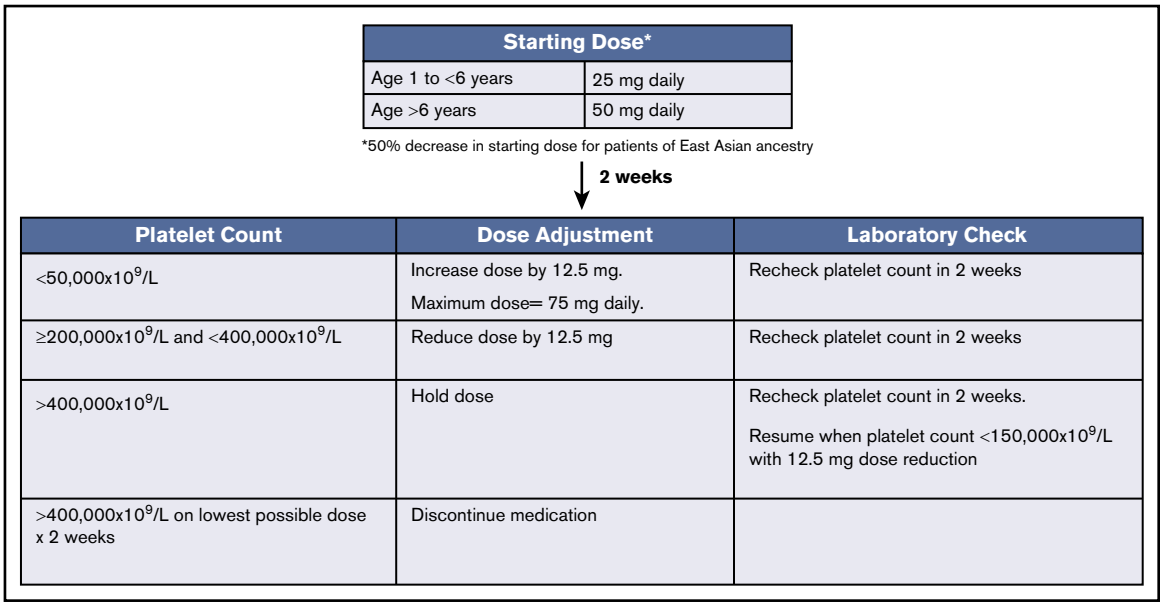

Figure 3. Eltrombopag dosing titration.

this grading system.[32,33] All patients remained asymptomatic and without aberrances in cell count, including those with fibrosis detected on bone marrow biopsy.[32]

Bone marrow biopsies are not routinely required for patients (including children) who are being treated with eltrombopag because marrow fibrosis occurs rarely and is almost always clinically insignificant.[31,34] Although the results of adult studies are reassuring, the impact of long-term eltrombopag therapy on the bone marrow of children has not been studied and remains unknown.

Thrombosis. Venous and arterial thromboses have been reported predominantly in adult patients being treated with eltrombopag. These events occurred in patients with known risk factors for thrombosis and more frequently in patients with hepatitis C. Because ITP is also associated with an increased risk of thrombosis, it is difficult to accurately determine the risk of thrombosis as a result of eltrombopag therapy in patients with ITP, but it does not seem to be significantly elevated in patients without other risk factors and does not clearly correlate with the platelet count. Adolescent patients with ITP may be at similar increased risk of thrombosis in the setting of acquired additional risk factors for thrombosis; the pediatric patients who have been reported with thrombosis have had additional risk factors, including immobilization from a fracture, antiphospholipid antibody syndrome, and use of estrogen-containing birth control.[35,36]

Risk for iron deficiency. The structure of eltrombopag mimics that of currently available iron chelators. Eltrombopag has been shown to chelate intracellular and extracellular iron.[37] It has also been shown to have a significant impact on neonatal iron levels.[38] In children with chronic ITP, there has been some suggestion that use of eltrombopag may increase the risk of iron deficiency.[21] If iron deficiency develops and no other cause is identified, it may be appropriate to continue eltrombopag therapy and give iron supplementation, ensuring that the doses of the 2 medications are spaced as far apart as possible.

Eltrombopag doses in children with ITP

On the basis of results from PETIT and PETIT2, the starting dose is 50 mg per day for patients age 6 years or older and 25 mg per day for patients age 1 to younger than 6 years. Once initiated, eltrombopag dosing should be adjusted to achieve a platelet count goal of 50×10^9/L, not to exceed 200×10^9/L. The dose should not be titrated to achieve normal platelet counts. The dose can be escalated every 2 weeks in increments of 12.5 mg to achieve the goal platelet range. The maximum dose of eltrombopag for the treatment of ITP is 75 mg per day (Figure 3).

Once a stable dose is established, patients should be evaluated by a physician and have a complete blood count performed once per month. Once the platelet count is stabilized, there is no consensus on duration of therapy or when it is best to attempt weaning from or stopping eltrombopag. The current authors have used complete discontinuation of the drug, but other authors prefer to wean by halving the dose every 2 weeks and monitoring for rebound thrombocytopenia. At this time, it is not possible to predict which patients might experience relapse or have a sustained response after discontinuing eltrombopag treatment.[39]

Dosing in special populations

Patients with East Asian ancestry show 43% higher plasma exposure to eltrombopag compared with their white counterparts.[26] Starting doses for children of East Asian descent age 6 years or older should be lower, beginning at 25 mg per day and at 12.5 mg per day for children age 1 to 5 years.[26] Dose escalation is otherwise the same as that for other children and should be based on the platelet count response.

Preexisting hepatic impairment results in increased drug levels. Even in the setting of mild hepatic dysfunction, eltrombopag levels can be 41% higher.[26] In PETIT and PETIT2, patients developed elevated ALT levels although the levels were reversible.[21,24] It is advised that eltrombopag not be used in patients with hepatic

impairment, unless the potential benefits outweigh the risk of adverse effects.

Eltrombopag is available only in tablet form and must be swallowed whole. Eltrombopag should not be cut or crushed. Although a powder was available for oral suspension for children who participated in clinical trials, this formulation is not yet available for commercial use, but it is expected to be available soon.

Diet and drug interactions

Eltrombopag is orally bioavailable, with peak absorption 2 to 6 hours after administration.[21,22] Similar to other iron chelators, eltrombopag binds divalent cations (calcium, iron, magnesium) that significantly decrease its absorption.[21,22] Therefore, this medication should be taken on an empty stomach (at least 1 hour before or 2 hours after any meal) and at least 4 hours before or after other medications, calcium-rich foods (dairy and calcium-fortified juices), or other supplements (particularly iron, selenium, zinc, or magnesium). The dietary restrictions can have a significant impact on patients' ability to take the medication.

Choice of eltrombopag for pediatric ITP patients

First-line therapies for ITP aimed at increasing the platelet count to decrease bleeding or bleeding risk, include intravenous immunoglobulin, steroids, and/or Rho(D) Immune Globulin Intravenous.[40] There are multiple potential second-line agents which can be used to achieve a sustained platelet response. Because there is no way to predict an individual's response to therapy, optimal second-line agents are determined through trial and error. Adverse-effect profiles, necessary laboratory monitoring, and dosing should also be considered when selecting medications. Second-line therapies include splenectomy, rituximab, immunomodulatory agents, and TPO-RAs.[40] Eltrombopag and romiplostim are available in the United States. The use of romiplostim remains off-label for pediatric patients.

For many patients with chronic ITP, eltrombopag is an attractive option for those who elect for treatment. The adverse-effect profiles for the thrombopoietin agonists are significantly better than those for alternatives such as steroids, rituximab, immunomodulatory medications, or splenectomy. The high cost of thrombopoietin agonists must also be considered when selecting treatment options. The current average wholesale price for a 30-day supply of 25 mg tablets of eltrombopag is $4845.11.

Choosing a thrombopoietin agonist

The choice of which thrombopoetin agonist to use is an individual one. Given as an oral medication, eltrombopag may be preferable to romiplostim, which requires injections once per week. For some patients, injections cannot feasibly be given at home, thus necessitating weekly visits to a clinic. However, young children may not be able to receive eltrombopag if they have to avoid dairy intake or if they cannot swallow pills.

Studies in adults suggest that eltrombopag is as efficacious as romiplostim, but these therapies have yet to be studied head-to-head in pediatrics. Cumulative results from studies of adult patients initially treated with romiplostim and transitioned to eltrombopag after treatment with romiplastim failed showed a 74% success rate with sequential TPO-RA therapy.[41] Adults who initially experienced treatment failure with eltrombopag had an 88% response rate when they were transitioned to romiplostim.[41]

Other indications and future directions

Eltrombopag is also approved in the United States for treating thrombocytopenia associated with chronic hepatitis C, which requires antiviral therapy, and for refractory severe aplastic anemia (AA) in adults. It is currently being evaluated in clinical trials for children with severe AA. In a study of 92 pediatric and adult patients with severe AA refractory to immunosuppression, the addition of eltrombopag resulted in increased bone marrow cellularity and the frequency of hematopoietic progenitor cells.[42] Platelet counts improved at 3 and 6 months when treatment consisted of standard immunosuppression and eltrombopag was compared with treatment for historical controls.[42] Patient's absolute neutrophil counts also improved at these time points, and red blood cell transfusion independence was achieved at a median of 32 days.[42] These findings suggest that eltrombopag has effects on the bone marrow that extend beyond direct stimulation of myeloproliferative leukemia virus receptors on megakaryocytes. Randomized, placebo-controlled trials are underway to validate these preliminary findings.

Studies on the use of eltrombopag for treating qualitative platelet disorders are limited. Case reports have demonstrated successful avoidance of platelet transfusions and bleeding when eltrombopag was given prophylactically to patients with MYH9-related disease who were undergoing surgery or cesarean delivery.[43,44] One study of eltrombopag in Wiskott-Aldrich syndrome or X-linked thrombocytopenia showed improved platelet counts but persistent defects in platelet activation.[45]

Although eltrombopag has been approved for use as a therapy for refractory chronic ITP in children, the authors of this study have used eltrombopag to treat severe, refractory bleeding in patients with acute ITP at the time of presentation. In this setting, eltrombopag was given to help sustain an elevated platelet count while other first-line agents were given for more immediate effect. The patient was then able to be weaned off the drug over a period of weeks as the bleeding subsided and platelet count stabilized.

There are increasing data to suggest that eltrombopag could be disease modifying rather than a temporizing measure used to transiently increase the platelet count while the drug is taken. One study of adult patients with chronic ITP showed that 53% of patients had a sustained remission after stopping eltrombopag at a median follow-up of 9 months.[39] Other studies of AA have also showed durable remissions after a course of treatment with eltrombopag.[46] The ITP Consortium of North America reported on the experience of children with chronic ITP who were receiving TPO-RAs, romiplostim, and eltrombopag. A small percentage of patients demonstrated a sustained response after stopping eltrombopag.[35]

If eltrombopag is potentially disease modifying, it may carry potential as first-line therapy. Treated upfront, patients who may have otherwise gone on to develop chronic ITP may not and the disease course could be shortened for those who would have resolved over time on their own. A small study of newly diagnosed adult patients with ITP who received first-line treatment with 4 days of dexamethasone in combination with eltrombopag showed that 100% of them achieved platelet counts of $\geq 30 \times 10^9$/L at

1 month.[47] Sustained responses with platelets $\geq 100 \times 10^9$/L at 6 months were achieved in 50% of patients.[47] At 1 year, 66.7% had relapse-free survival.[47] Results from multicenter trials studying the outcomes of early eltrombopag therapy for children with ITP are forthcoming.

In conclusion, eltrombopag is the first FDA-approved, oral TPO-RA for pediatric chronic ITP, and it seems to be safe and efficacious. Treatment with eltrombopag requires monthly monitoring and is associated with some modifiable risks (eg, hepatotoxicity and risk of thrombosis), but it can be considered in pediatric patients with chronic ITP who require treatment to modify the platelet count. Although the long-term adverse effects of eltrombopag therapy in children still require further investigation, the use of eltrombopag is expanding to AA, qualitative platelet disorders, and severely affected patients with acute ITP. It may also become a disease-modifying therapy for chronic ITP.

Authorship

Contribution: T.O.K., J.D., and M.P.L prepared and drafted the manuscript, made critical revisions, and approved the final draft.

Conflict-of-interest disclosure: M.P.L. served on advisory boards for Novartis and Bayer and was a consultant for Novartis. J.D. was a consultant for Sanofi-Genzyme. T.O.K. declares no competing financial interests.

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